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Release of Tetracycline out of PLLA Foils Functionalized by Adhesive Polyelectrolyte Complexes in the Context of Parodontitis Therapy

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Abstract

For the therapy of parodontitis degradable poly(L-lactide) (PLLA) based threads are envisioned, which can be functionalized by relevant antibiotics. In this context first results on the release of tetracycline (TCL) out of PLLA specimens modified by casting and drying adhesive TCL loaded polyelectrolyte complex (PEC) particles are presented. A significant delay of the TCL release was found for the modification based on PEC/TCL in comparison to that based on pure TCL.

Keywords: Parodontitis; Drug delivery; Poly(L-lactide); Tetracycline; Polyelectrolyte complex

Introduction

Parodontitis appearance

In Germany 50 % of the adults suffer from parodontitis and this percentage is even increasing to 90 % for adults older than 75 years. Severe forms of parodontitis pevail for 10-20 % of the adults and for 40 % of adults older than 75 years. These numbers indicate the high abundance of parodontitis in the population and long for urgent required actions. Additionally, correlations between parodontitis and cardiovascular diseases (hypertension, vessel constriction, heart attack, stroke), diabetes mellitus, rheumatoid arthritis and further systemic diseaeses were found, which manifest the need for dedicated therapies. Parodontitis is an inflammatory disease of the dental hold apparatus leading to teeth loss, if no therapy is lanced and in this case would cause expensive dental substitution. The disease is caused by microorganisms of dental biofilms, which represent a specially resistant form of the organization of microorganisms on the typically not self-renewing dental surface. While in the beginning inflammatory changes are confined to the gums, in the further course the formation of gingival pockets and fibre reduction within dental hold apparatus and jawbone take place [1,2]. Parallely, gingival bleeding, abscess formation, teeth loosening, halitosis and limited quality of life are obtained. Beside genetic predisposition environmental factors like smoking, stress, low socio-economic status and low oral hygiene play a role. Generally, parodontitis may occur either at all or localized at single teeth of the denture. After conventional mechanical therapy single spots or teeth may remain, which due to their specific anatomy or other local and systemic factors do not react and need further treatment. Therapeutic strategies primarily focus on the reduction of the microorganisms, which by both mechanical therapy and application of antiseptic drugs are unspecifically reduced. Furthermore, at severe disease forms antibiotics are used in order to eliminate parodontitis-relevant bacteria (e. g. A. actinomycetemcomitans, P. gingivalis, P. intermedia, F. nucleatum, T. fosythus). Antibiotics can be given either systemically or locally, where in contrast to the systemic application concerning and afflicting the complete organism, the local application in gingival pockets is advantageous with respect to the spatial, temporal and concentrative confinement of the antibiotic and its effect enabling defined therapy and lower systemic side effects. It was proven, that the combination of antibiotic and mechanic therapy revealed better effects compared to single mechanic therapy [3]. Therefore, there is a considerable need for the application of local antibiotics. However, the problem of the local application form concerns the specific situation of the gingival pocket, in which the drug has to withstand the high permanent flow of fluid (SFFR, sulcus fluid flow rate) especially in case of local inflammation. Within one hour the sulcus fluid in a gingival pocket of 5 mm depth is renovated around 40 times [4]. Moreover, microorganisms are embedded and protected within the biofilm and can be eliminated not until they are reached by still sufficient

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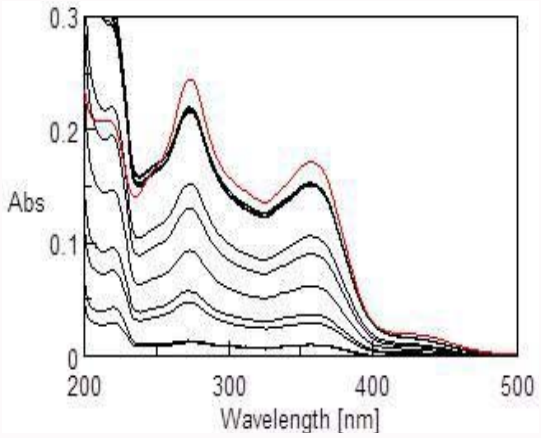

Figure 1: UV/VIS spectra of the release medium (2 ml 0.001M HEPES) adjacent to PLLA foils (2 x 1 cm^2) modified with PEC NP (100 µl of 0.01 M casted and dried) and loaded with TCL (100 µl of 0.001 M soaked dried) recorded between 0 to 46 h.

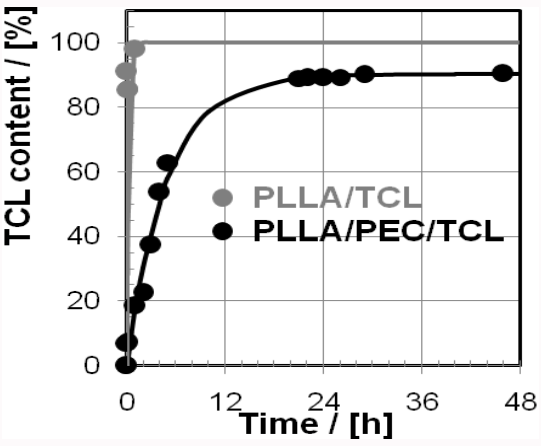

Figure 2: Release kinetics of TCL out of PLLA (grey circles) and out of PEC modified PLLA foils (black circles) into HEPES (0.001 M) buffer based on absorbance values at 360 nm from UV/VIS spectra shown in Figure 1.

antibiotic doses.

Drug-Delivery-Systems for parodontitis

In the past various delivery systems for antibiotics were developed and applied, out of which at present only one product (Ligosan® Slow Release, Heraeus Kulzer) is available on the german market. These systems are based on Metronidazol/Doxycylin gels, Minocyclin micro beads or Minocyclin ointments. The only previously approved textile-based drug, Actisite® a Tetracycline containing hollow fiber, is no longer commercially available. Actisite®, was reported to be very successful in decreasing inflammation and its effectiveness was based on the specific formulation enabling to form a locally stable subgingival depot and maintain a continuous drug concentration en in the gingival pocket. Such thread based "Controlled Release Device" released its drug for 1-7 days [5] and could achieve the best healing results compared to the other products. However, a major disadvantage of this product concerned the removal of the thread, which was non-resorbable. Alternatively, for the local application a gelatine based chip (PerioChip®) is licensed in Germany, which contains Chlorhexidin and causes an antiseptic effect in the gingival pocket.

Finally, concerning research and development of all three *threadlike, resorbable* and *drug eluting* materials, at present are based on an encapsulated drug within fibrous constructs, which are fabricated by wet- or electrospinning [6-10]. At present numerous realizations of nano fleeces up to hollow fibres with release rates of clinical relevance prevail. However, the biomaterial-process-structure correlations are not completely described. Major reservations concern the production conditioned usage of harmful or toxic solvents, the nontrivial applicability of the fragile materials as well as lacking productivity of the process. The specific situation in the periodontal pocket with a high sulcus fluid flow rate and thus short half-lives of incorporated drugs requires special drug delivery systems.

Related to these issues our idea is the usage of threads based on melt spun poly(lactic acid) (PLLA) containing relevant drugs, which are modified by adhesive bio related polyelectrolye complex nanoparticles (PEC NP) loadable by drugs like the common antibiotic tetracycline on the surface. While incorporated drugs can be released slowly within 14 days by erosion of the thread material, surface loaded drugs can be released immediately and may act as temporal buffer until release from the fiber can take place. Moreover, different release patterns and therapeutic agents allow for a well-adjusted healing procedure. PEC NP have been introduced [11-14] and are based on the complexation of polycations and polyanions in aqueous solution and can be irreversibly deposited onto different material substrates varying in size, shape or surface chemistry. Before applying PEC NP at threadlike PLLA materials, herein PLLA foils were subjected. For this commercial PLLA foils were cut into pieces suited for an appropriate analytical access by e.g. UV/VIS spectroscopy.

Experimental

Chemicals

PLLA was obtained from Nature Works, USA (Ingeo™, D6202). TCL was obtained from Carl Roth GmbH Co KG (Karlsruhe, Germany). The polyelectrolyte poly(N-isopropylacrylamide-co-acrylic acid) (PNIPAM-AA) was purchased from Sigma-Aldrich (Darmstadt, Germany) and ethylenediamino-cellulose (EDAC) was from purchased from Thüringisches Institut für Textil- und Kunststoff-Forschung e.V. (TITK, Rudolstadt, Germany). HEPES buffer was from Sigma-Aldrich (Darmstadt, Germany).

Fabrication and analytics of PLLA specimen and PEC coating

PLLA model sheets (200 µm), obtained by means of hot pressing for 3 min at 190 °C, were cut into smaller specimens (2 x 1 cm^2), which were completely coated with 100 µl of EDAC/PNIPAM-AA complex dispersions and dried on a heating stage at T = 50 °C for 10 min. Thereafter, the EDAC/PNIPAM-AA modified PLLA specimens were three times thoroughly rinsed by Millipore water and dried, respectively. Onto the rinsed EDAC/PNIPAM-AA modified PLLA specimens 100 µl of 0.001 M TCL solution was spread and allowed to soak into the EDAC/PNIPAM-AA coating for at least 12 h. TCL release measurements were performed by placing the EDAC/PNIPAM-AA modified and TCL loaded PLLA specimen into a standard 10 mm cuvette (Quartz) filled with 2 ml of 0.001 HEPES solution and measuring subsequently the concentration increase of TCL in the HEPES release medium by UV/VIS (Figure 1). For comparison also 100 µl of 0.001 M TCL solution was spread onto an uncoated PLLA foil and allowed to dry for 12h. The UV/VIS signal of the released TCL in the HEPES release medium at around 360 nm was calibrated by the UV/VIS signal of a TCL solution prepared by dosing 100 µl of 0.001 M TCL solution into 2 ml 0.001 M HEPES solution

corresponding to a TCL concentration of 0.00005 M (TCL calibration solution). This TCL concentration was assumed to be equal to the complete elution (i.e. 100 %) of TCL out of the EDAC/PNIPAM-AA modified PLLA specimen. Ratioing actual UV/VIS absorbance values at 360 nm (A_{ACT}) with those of the TCL calibration solution (A_{CAL}, 0.00005 M) resulted in actual percentage values of the TCL released amount RA according to RA = A_{ACT}/A_{CAL} / [%] (Figure 2).

Results and Discussion

Herein we like to present first results on the release of the antibiotic tetracyclin (TCL), which is relevant for parodontitis treatment, out of PLLA foils as a model for PLLA threads. For that PLLA model sheets were modified by casting PEC nanoparticles onto PLLA foil specimens and drying. As PEC system the synthetic anionic PNIPAM-AA and bio related cationic cellulose EDAC were used. Highly adhesive PEC coatings on PLLA remained, on which data are not shown here. This PEC coating was further loaded with TCL by immersing TCL solutions for at least 12h. The release of TCL from PEC modified PLLA foils was measured by UV/VIS spectroscopy. Typical UV/VIS spectra along the release kinetics of TCL out of PEC modified PLLA foils are given in the (Figure 1) and a typical TCL release curve is given in the (Figure 2). For comparison also a typical TCL release curve for PLLA foils modified by drying pure TCL is shown. For the latter case TCL is immediately released (i.e. dissolved) at PLLA foils with an initial burst of around 80%. For TCL release at PEC modified PLLA foils there is an initial burst of around 10 % within a defined time of 1 h. After around 4 h around 50 % and after 24 h around 90 % of the initial TCL content were released.

Given the requirements on PLLA threads mentioned above, incorporated drugs shall be released slowly within 14 days by erosion of the thread material. However it is the aim, that additionally to this sustained long-term TCL release, also surface (PEC) loaded drugs shall be released immediately and may act as temporal buffer until the long-term release from the fiber can take place. Moreover, beside such multimodal release patterns also additional therapeutic agents shall be considered for a well adjusted yet personalized healing procedure. Hence the shown elution profile of TCL from PEC modified PLLA material is relevant for the immediate phase after implantation of the TCL loaded PLLA thread. Further studies on switching and controlling the kinetic TCL elution profile will be provided in a forthcoming paper.

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