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Mechanical investigation of newly hybrid dental implants

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Titanium and titanium alloys are common used materials for dental implants, however they have biological limitations for oral use. Ceramics meet the demands of biocompatibility, but their susceptibility to implant fracture is increased. Therefore, a combination of both materials could be an advantage for dental implants. Therefore, a new hybrid implant combining titanium and ceramic components by glass solder fixation was introduced. The aim of the present study was to investigate the static and dynamic mechanical properties of such hybrid implants.
Two different types of hybrid implants were tested, which consisted of a metallic inlay made of titanium grade 4 or grade 5 (primec GmbH) fixed in a thin modified Cercon ceramic (yttrium stabilized zirconium dioxide) shell with a diameter of 4.3 mm (DeguDent GmbH) via glass solder and a titanium abutment fixed with an abutment screw. For each group $n = 4$ were tested according to DIN EN ISO 14801. The static tests were performed displacement-controlled until implant failure with 0.2 mm/s and the dynamic tests with sinusoidal load levels of 20 to 200 N and 24 to 240 N until failure or $5x10^6$ run out cycles.
The Cercon ceramic implant with the Ti grade 5 abutment showed higher fracture loads (298 N ± 42 N) in the static tests compared to the implants with the Ti grade 4 (262 N ± 22 N). During dynamic testing two specimens of both groups reached $5x10^6$ cycles at the load level of 200 N. At the higher load level one specimen with the Ti grade 5 reached the required cycles, none with the Ti grade 4.
The tested hybrid implants showed favourable static and dynamic failure loads comparable to other titanium or ceramic dental implants. Further research has to be performed to determine the *in vivo* performance of hybrid implants.

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Influence of cold atmospheric pressure plasma on biofilms of s*taphylococcus epidermidis* on structured titanium – concerning antimicrobial potential and gentamicin susceptibility

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Adherence to biomaterials and formation of biofilms are important factorsin the pathogenicity of microorganisms, which may result in persistent infections despite aggressive antibiotic therapy. Within biofilms, bacteria are protected from hostdefense mechanisms and administered antibiotics. Cold atmospheric pressure plasma, an ionized electrically discharged gas-flow, might be an alternative for treating biofilms associated with implant-related infections. Our previous research showed the antimicrobial potential of atmospheric pressure plasma in altering the morphology and reducing viability of bacterial biofilms. The objective of the current experimental study was the examination of the influence of plasma on *S. epidermidis* biofilms concerning antimicrobial potential as well as gentamicin susceptibility.
Biofilms of *S. epidermidis* ATCC 35984 were grown on sterile, rough titanium alloy samples (Ti6Al4V, ø11 mm, Rz=20 µm, DOT GmbH) for 24 h in Tryptone-Soy-Broth (TSB, 37 °C, 5 % CO_2). Furthermore an antibiotic sensitivity test of *S. epidermidis* cultures was carried out. Plasma treatment of the biofilms was performed by using an atmospheric pressure plasma source working with argon and 1 % 0_2 admixture (kINPen08, INP, Germany) for 1 and 3 min. Biofilm-bound bacteria were quantified by measurement of viable bacterial counts after plasma-treatment and further cultivation for 24 h in TSB with gentamicin-sulfate.
The antibiotic sensitivity test of control bacteria indicated a resistance against gentamicin. Treatment of bacterial biofilms with plasma by kINPen08 reached a significant reduction of vital bacteria up to two log-units within the biofilm in comparison to the untreated control. After further cultivation of plasma-treated biofilms for 24 h in gentamicin-supplemented TSB, total reduction of vital bacteria to 0 CFU/ml was achieved in contrast to the untreated control with $1.17*10^4 \pm 1.63*10^3$CFU/ml. Our results demonstrate the potential of atmospheric pressure plasma combining major purposes dealing with infected implants: to remove and degrade the bacterial biofilm and simultaneously increase the gentamicin-susceptibility.

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Micro plasma source for the selective treatment of cell cultures

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A miniaturized ceramic atmospheric plasma source for use in life sciences has been developed. It is manufactured using LTCC-technology (Low Temperature Cofired Ceramics). Plasma generation is based on buried electrodes, which provoke a Dielectric Barrier Discharge (DBD). The technology employed allows small feature sizes (electrode width 150 µm, barrier thickness 40 µm) as well as precision in µm range, resulting in very low power consumption of the system (approx. 1 W). Thus, the maximum temperature at the point of use is kept below 40 °C.
The flexibility of the manufacturing process (layer lamination, screen printing, patterning etc.) offers additional features like robust fluidic structures (channels, chambers, gas distribution) as well as the direct implementation of electronic components.
The plasma produced by the system can be tuned depending on the assembly structure of the system and the pattern of electric excitation. The different parts of the plasma characteristics (ozone generation, reactive radicals, ultraviolet radiation) and their effects can be separated. To prove biocompatibility and experimental compatibility with cell cultures (low temperature at the point of use), a method for temperature measurements on the bottom of a multi-well plate is presented. The impact of plasma on cell cultures was evaluated. Keratinocytes and fibroblast cell lines were applied to test the cell tolerability of the treatment with the micro-plasma source while test with bacteria (S. aureus, MRSA und P. aeruginosa) and yeast (C. albicans und M. pachydermatis) investigated its antimicrobial potential.

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Multilayer diffusion-barrier model for experimental determination of coated-implant related drug eluting processes.

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A problem of modern orthopaedic surgery are implant-associated infections. These infections are difficult to treat with conventional methods due to biofilm formations on the implant surface which protects the bacteria colonies against systemically applied pharmaceuticals. Depending on the degree of the disease, removal of the infected implant could be necessary.
A reliable approach to avoid colonisation of the implant surface is a preventative coating of the implant with an antibiotic-releasing covering.
Even infection-uncritical applications could benefit from drug eluting coatings, for example if the implant elutes growth stimulants which supports the healing process after the implantation.
There are no standardized in-vitro measurements for the development of drug eluting implants or drug coatings in general. The mostly used test methods (paddle apparatus and flow-through-cell) are originally developed to determine the dissolve speed of tablets and show poor in-vivo/in-vitro correlation (IVIVC) when applied to coated implants.
We are working on an experimental setup to fills this gap and provide a better testing method for drug eluting implants, to enable faster and cheaper development cycles with reduced need for animal studies.
The experimental setup contains a modified flow-through-cell with fluorescein-sodium as a model drug and an artificial membrane as a replacement for the implant-surrounding tissue. The membrane separates the flow channel (acceptor channel) from the drug solution (donator channel). The concentration is measured spectroscopically inside of the acceptor channel with an UV/Vis spectrometer.
We have shown, that pHEMA (poly(2-hydroxyethyl methacrylate)) based hydrogels are suitable and reproducible substitutes for biological membranes, related to research of diffusive mass transport through membrane layers up to 8 mm thickness.
The diffusion resistance through the hydrogel is tuneable by changing the percentage of crosslinker (EGDMA), photoinitiator (TPO) and dilution. A further possibility to imitate different biological membranes is realized by stacking membranes and create multilayer hydrogels.
By using this options to manipulate the diffusion barrier, we plan to provide a drug eluting measurement method which is comparable to drug eluting processes in the human body.

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96-well plate ultrasonic applicator for high-throughput in-vitro hyperthermia experiments

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While diagnostic ultrasound has been established as standard tool within the medical community for decades, therapeutic ultrasound is only emerging in the last years. While HIFU is based on the delivery of high energy densities allowing coagulation in applications such as tumor therapy, ultrasound hyperthermia produces a soft temperature increase leading to an improved metabolic activity of cells, resulting for instance in a better drug uptake. However, existing setups for hyperthermia experiments on cells do not comply with pharmaceutical standards where parallelization is required in view of producing results with a high level of statistical significance.

In view of overcoming the mentioned limitations of existing systems, we developed a cell applicator allowing to investigate the effect of ultrasound on cells, in particular in the context of hyperthermia. The device is based on a 8 x 12 matrix of single element ultrasound transducers and has been set up in 4 versions with centre frequencies of 0.5, 1, 1.5 and 2 MHz. All transducers allow acoustic dry coupling to the bottom of the well plates. The applicator is driven by a modified version of Fraunhofer IBMT´s multichannel ultrasound platform DiPhAS. A special software interface, that allows adjusting the transmit parameters of individual wells or groups of wells, has furthermore been developed.

The sound field of the applicator has been measured in order to verify that there is no overlap between the beams of individual transducers. Furthermore, the standard deviation of the transducer efficiency has been assessed to 9 %. In another set of experiments, the cross coupling between individual transducers was investigated (damping of 35-40 dB to neighbouring element). Finally, the acoustic intensities for all transmit settings were assessed (max 0,05 W/cm²). Hyperthermia experiments were initially conducted with water filled wells and the ability to acoustically induce a temperature increase was demonstrated.

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A new concept of interconnecting feedthrough-bearing substrates with conducting wires in active implantable medical devices

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The development and application of new active implantable medical devices (i.e. neuromodulators for the treatment of hypertension) require an ever-increasing amount of stimulation and recording sites. In many cases the therapeutic electrical signals generated by the implant penetrate a hermetic enclosure of the involved electronics via feedthrough structures. Typically, a multi-fibre-core cable connects these feedthroughs with the machine-tissue interface. In state-of-the-art applications (with a low amount of channels), i.e. pacemakers or cochlear implants, cables are connected directly to the metal pins or ribbons of the hermetic feedthroughs. This well established and reliable interconnecting technique, however, comes to its limitation when an active implant requires a high amount of channels. For an envisioned packaging concept new ways to connect thin metal wires to the feedthrough-bearing ceramic substrate are developed and characterized. The investigated method uses glass-based screenprinting paste with a gold-filler as a bondpad for metal wires. Sputtered metal connects the fired paste and the location of the feedthroughs on the ceramic substrate. Laser-welding is the method of choice for a long term stable mechanical and electrical connection between the wires and the paste. In this new approach, the paste is applied in laser structured trenches on the ceramic substrate. This allows for rapid prototyping of geometries, since no screen printing mask is needed to apply the paste before firing. Furthermore, the trenches are designed in a way, that the metal wire can be pressed in a cavity, which constrains the movement of the wire in all directions during the laser-welding of the wires. This can enhance the repeatability and speed of the welding process significantly. Since the interconnects between the wire and the paste are located beneath the ceramic surface, high resistance to shear forces is to be expected, which is beneficial for the long term stability of this packaging concept.