Development of a biodegradable microstent for minimally invasive treatment of Fallopian tube occlusions

Ariane Dierke, Institute for ImplantTechnology and Biomaterials e.V., Rostock, Germany, e-mail: ariane.dierke@uni-rostock.de
Finja Borowski, Institute for ImplantTechnology and Biomaterials e.V., Rostock, Germany
Swen Großmann, Institute for ImplantTechnology and Biomaterials e.V., Rostock, Germany
Christoph Brandt-Wunderlich, Institute for ImplantTechnology and Biomaterials e.V., Rostock, Germany
Claudia Matschegewski, Institute for ImplantTechnology and Biomaterials e.V., Rostock, Germany
Paula Rosam, Institute for ImplantTechnology and Biomaterials e.V., Rostock, Germany
Nico Pilz, Institute for Biomedical Engineering, Rostock University Medical Center, Rostock, Germany
Paul Reister, Institute for Biomedical Engineering, Rostock University Medical Center, Rostock, Germany
Rebekka Einenkel, Department of Obstetrics and Gynecology, University Medicine Greifswald, Greifswald, Germany
Ulf Hinze, Institute of Quantum Optics, Leibniz University Hannover, Hannover, Germany
Jonas Keiler, Department of Anatomy, Rostock University Medical Center, Rostock, Germany
Michael Stiehm, Institute for ImplantTechnology and Biomaterials e.V., Rostock, Germany
Kerstin Schümann, Institute for Biomedical Engineering, Rostock University Medical Center, Rostock, Germany
Andrea Bock, Institute for ImplantTechnology and Biomaterials e.V., Rostock, Germany
Boris Chichkov, Institute of Quantum Optics, Leibniz University Hannover, Hannover, Germany
Niels Grabow, Institute for Biomedical Engineering, Rostock University Medical Center, Rostock, Germany
Andreas Wree, Department of Anatomy, Rostock University Medical Center, Rostock, Germany
Marek Zygmunt, Department of Obstetrics and Gynecology, University Medicine Greifswald, Greifswald, Germany
Klaus-Peter Schmitz, Institute for ImplantTechnology and Biomaterials e.V. and Institute for Biomedical Engineering, Rostock University Medical Center, Rostock, Germany
Stefan Siewert, Institute for ImplantTechnology and Biomaterials e.V., Rostock, Germany

Introduction

Fallopian tube occlusion represents a common cause of female sterility. Success rates of current treatment options such as in vitro fertilisation or minimally invasive catheterization are limited. Within the current work, we developed an innovative therapy concept based on a biodegradable self-expandable microstent.

Materials and Methods

Poly(L-lactide) is used as microstent material. Prototypes are manufactured by means of fs-laser cutting. Scanning electron microscopy and laser measurement methods are used for morphological characterization. For mechanical characterization, bending stiffness and radial force were investigated at 37 °C, respectively.

Results

Tubular semifinished products with reproducible wall thickness of (97.2 ± 6.0) µm were manufactured. Further processing resulted in two microstent prototypes. For both an outside diameter of about 2.3 mm and a strut thickness / width of 114 µm / 103 µm were measured. Lateral bending of both prototypes yield a maximum force of (5.40 ± 0.57) N and (5.30 ± 0.63) N and a bending stiffness of (1.09 ± 0.19) Nmm^2 and (1.07 ± 0.25) Nmm^2, respectively. With decreasing minimum crimping diameter from 2.2 mm to 0.8 mm the maximum radial force increases from 0.32 N to 37.14 N. After crimping to a diameter of 0.8 mm and subsequent release, an acceptable diameter recovery of 77% was found.

Conclusion

The current work represents an initial attempt to develop a self-expandable biodegradable microstent for minimally invasive treatment of Fallopian tube occlusions. Microstent prototypes show low values for bending stiffness, comparable with commercially available biodegadable stents for vascular application. Commercially available drug-eluting stents for vascular application are commonly stiffer by one order of magnitude. The presented analyses of crimping and release behavior strongly indicate feasibility of a polymeric self-expandable microstent for gynecological applications in combination with a micro delivery catheter with an inner diameter of 0.8 mm.

Sensitivity analysis of FDA´s benchmark nozzle regarding in vitro imperfections - Do we need asymmetric CFD benchmarks?

Michael Stiehm: Institute for ImplantTechnology and Biomaterials e.V., Friedrich-Barnewitz-Str. 4, 18119 Rostock-Warnemünde, Germany, michael.stiehm@uni-rostock.de,
Christoph Brandt-Wunderlich, Stefan Siewert, Klaus-Peter Schmitz: Institute for ImplantTechnology and Biomaterials e.V., 18119 Rostock-Warnemünde, Germany,
Niels Grabow, Klaus-Peter Schmitz: Institute for Biomedical Engineering, Rostock University Medical Center, 18119 Rostock-Warnemünde, Germany
Leonid Goubergrits, Titus Kühne: Institute for Imaging Science and Computational Modelling in Cardiovascular Medicine, Charite´ - Universitätsmedizin Berlin, Berlin, Germany
Titus Kühne: Department of Congenital Heart Disease and Paediatric Cardiology, German Heart Center Berlin, Berlin, Germany
Eric K. W. Poon, Andrew Ooi, Peter Barlis: Department of Mechanical Engineering, Melbourne School of Engineering, The University of Melbourne, Melbourne, VIC 3010, Australia
Peter Barlis: Department of Medicine, Melbourne Medical School, Faculty of Medicine, Dentistry & Health Sciences, The University of Melbourne, Melbourne, VIC 3010, Australia

Introduction

Modern technologies and methods such as computer simulation, so-called in silico methods, foster the development of medical devices. For accelerating the uptake of computer simulations and to increase credibility and reliability the U.S. Food and Drug Administration organized an inter-laboratory round robin study of a generic nozzle geometry.

Methods

By using in silico computational fluid dynamics method the influence of in vitro imperfections, such as inflow variations and geometrical deviations, on the flow field were evaluated. Based on literature the throat Reynolds number was varied $Re_{throat} = 500 \pm 50$.

Results

It could be shown that the flow field errors resulted from variations of inlet conditions can be largely eliminated by normalizing if the Reynolds number is known. Furthermore, a symmetric imperfection of the silicone model within manufacturing tolerance does not affect the flow as much as an asymmetric failure such as an unintended curvature of the nozzle.

Conclusion

In brief, we can conclude that geometrical imperfection of the reference experiment should be considered accordingly to in silico modelling. The question arises, if an asymmetric benchmark for biofluid analysis needs to be established. An eccentric nozzle benchmark could be a suitable case and will be further investigated.

Eustachian tube stenting

T. Lenarz*, M. Ezzat*, R. Schuon*, T. Wilfling*, K. Schümann** , N. Grabow**, K.P. Schmitz***, P. Krüger****, T. Stein****, G. Paasche*

*Department of Otorhinolaryngology, Hannover Medical School, Carl-Neuberg-Str. 1, 30625 Hannover, Germany, Lenarz.Thomas@mh-hannover.de; Ezzat.Malena@mh-hannover.de; Schuon.Robert@mh-hannover.de; Wilfling.Tamara@mh-hannover.de; kerstin.schuemann@uni-rostock.de; niels.grabow@uni-rostock.de; klaus-peter.schmitz@uni-rostock.de; p.krueger@besspro.eu; t.stein@bessgroup.com
**Institute for Biomedical Engineering, Rostock University Medical Center, Friedrich-Barnewitz-Str. 4, 18119 Rostock-Warnemünde, Germany
***Institute for Implanttechnology and Biomaterials – IIB e.V., Friedrich-Barnewitz-Str. 4, 18119 Rostock-Warnemünde, Germany
**** bess pro GmbH, Gustav-Krone-Str.7, 14167 Berlin, Germany

Introduction

Chronic otitis media affects about 2 million people in Germany. The main pathophysiology is the impaired function of the Eustachian tube. So for now effective treatment method is available. The development of an Eustachian tube stent aims to address the underlying pathophysiology with an innovative concept

Methods

Current achievements:

1. The dimensions of human Eustachian tube have been measured and models have been developed.
2. Expandable stents based on biomedical Nitinol or polymer have been designed and developed.
3. Prototypes have been tested in cadaver experiments in order to check their feasibility, the placement and the function of these tubes.
4. Appropriate tools for insertion and optic control using mini endoscopes have been developed.
5. An animal model based on the black sheep has been established and chronic implantations using the optimized stent design have been started.

Results

From the previous years of experiments it has been shown that the stents are well tolerated and incorporated into the surrounding tissue while the patency of the Eustachian tube is achieved.

Conclusion

Future developments and next steps:

1. Chronic animal experiments with the definitive stent design that has been defined will be done. Nitinol stents will be used.
2. Additional cadaver experiments using the optimized stent design will be performed.
3. Product development has been started using the data from the different experimental steps for the product definition.
4. Appropriate stent testing on mechanical stability and clinical long term stability, opening force and risk of dislocation will be done within the next period of the project.

Dexamethasone release from photopolymerised PEGDA700 for cochlea drug delivery

Thomas Eickner, Institute for Biomedical Engineering (University Medical Center Rostock, University of Rostock), Rostock, Germany, thomas.eickner@uni-rostock.de
Michael Teske, Natalia Rekowska, Volkmar Senz, Klaus-Peter Schmitz, Niels Grabow, Institute for Biomedical Engineering (University Medical Center Rostock, University of Rostock), Rostock, Germany, michael.teske@uni-rostock.de, natalia.rekowska@uni-rostock.de, volkmar.senz@uni-rostock.de, klaus-peter.schmitz@uni-rostock.de, niels.grabow@uni-rostock.de

Introduction

Sustained local drug release can be obtained by specially designed Drug Delivery Systems (DDS). A high local drug concentration is achieved via the special application of DDS. This results in therapeutic drug amounts at the site of action, by simultaneously providing a very low drug amount in total.

Bodily compartments that contain liquids, such as the cochlea with the perilymph, may be used to transport the drugs from DDS into the tissue, e.g. in the case of cochlea implants [1]. However, predominantly dry environments, such as the middle ear, are lacking such a medium but may deliver enough moisture for the use of swellable DDS through the surrounding mucus membranes. Therefore, DDS with new functionalities are needed to ensure a sustained drug release.

Methods

In this study, the release of dexamethasone out of a photopolymer system is presented. The system is built from UV-polymerized PEGDA followed by the incorporation of dexamethasone via swelling. The drug release is tested *in vitro* with isotonic NaCl solution for specified time periods.

Results

The drug release shows two phases, a swelling phase and a release phase. After the swelling phase the concentration of dexamethasone in the release medium was not controlled by diffusion, although sink conditions were ensured. In contrast, this system can be used to release the drug until equilibrium with a final medium concentration that is far below the solubility of dexamethasone.

Conclusion

Hence, such DDS may be useful for dexamethasone delivery into the cochlea to ensure a constant drug concentration in the perilymph.

[1] Krenzlin, S, Vincent, C, Munzke, L, Gnansia D, Siepmann F. Predictability of drug release from cochlear implants. Journal of Controlled Release. 2012;159:60-68.

Transfer activities for cardiovascular, ophthalmologic and otolaryngologic medical device innovations – Progress report 2020 from the Twenty20 consortium RESPONSE

Niels Grabow, Institute for Biomedical Engineering, University Medical Center Rostock, Germany, niels.grabow@uni-rostock.de
Volkmar Senz, Institute for Biomedical Engineering, University Medical Center Rostock, Germany, volkmar.senz@uni-rostock.de
Klaus-Peter Schmitz, Institute for Biomedical Engineering, University Medical Center Rostock, and Institute for ImplantTechnology and Biomaterials e.V, Warnemünde, Germany, klaus-peter.schmitz@uni-rostock.de

Mission

Since 2012, the research consortium "RESPONSE – Partnership for Innovation in Implant Technology" has been pursuing the identification, implementation and transfer of technology-driven medical device innovations. In its endeavors, the consortium is focusing on widespread diseases with the potential for alleviation through optimized implantable medical devices. RESPONSE has continuously advanced the definition of its scientific, economic and social objectives, as well as its pathway to accomplishment.

Creation of value

In accordance with BMBF funding targets, the creation of value through participating industry partners is ascribed particular importance. Internationally, the sphere of activity is driven by high clinical demands and tremendous potential for industrial exploitation. Against this background, RESPONSE has initiated transfer phase for industrial and clinical translation. This process is guided by the managing and advisory boards to identify product, technology and process innovations suitable for transfer.

Innovations

RESPONSE is centered on pre-competitive R&D in cardiovascular medicine (covered stents/scaffolds, electrospun nonwovens for transcatheter heart valves), ophthalmology (glaucoma microstent) and ENT medicine (Eustachian tube stent). Projects have been started for gynecologic (Fallopian tube) and gastroenterologic (pancreas) stent applications. Technological innovations cover drug delivery for responsive functionalized implants. In silico methods shall enable novel characteristics, such as reduced thrombotic potential of venous and heart valve prostheses. Smart implant concepts are being accessed for novel diagnostic and therapeutic functions. RESPONSE is aiming at participative technology development, integrating perspectives of developers and medical professionals, as well as systems and innovation researchers. Iinternational health markets are being studied regarding regulatory and reimbursement mechanisms, and to determine cost-effectiveness ratios. Another aspect of transfer are standardized test protocols along the entire translation chain in light of increasing regulatory requirements. This portfolio of RESPONSE key innovations takes into consideration the transfer opportunities of new medical devices, technologies and processes, beyond the completion of the funding period in 2021.

Assessing the quality of science: There must be more than the impact factor

Axel Haverich, Department of Cardiothoracic, Transplantation, and Vascular Surgery, Hannover Medical School, Hannover, Germany, haverich.axel@mh-hannover.de
Tobias Schilling, Department of Cardiothoracic, Transplantation, and Vascular Surgery, Hannover Medical School, Hannover, Germany, schilling.tobias@mh-hannover.de

Introduction

The impact factor still seems to be the holy grail when it comes to assessing the scientific work of research groups. For instance, funding significantly relies on the impact factor. Performance-oriented internal funding in the universities is also mainly determined by the cumulative impact factor of the institute or the researcher. However, the impact factor only measures the influence of the journal as intended by its inventor Eugene Garfield in 1955 and not the quality of the scientific work or the researcher. The estimation and comparison of research quality, especially across faculty borders, therefore, requires a more holistic perspective and should include the specific framework of each discipline. In this regard, the development of biomedical implants represents a particular challenge, not least due to the enormous impact of replacement therapies worldwide. Hence, the presented project at hand focuses on detecting, defining, and field-testing of holistic key performance indicators for the research and development of novel biomedical implants.

Methods

First, this project aims to capture the status quo of the parameters to grant performance-oriented funding in different universities. Second, interviews with the universities' representatives are taken to assess the strengths and weaknesses of the respective system. Third, the parameters are cataloged and their applicability on biomedical implant research and development is tested and discussed with surgeons and engineers.

Results and conclusion

There are numerous examples of surgical research over the last five decades that have proved to have a high impact on the therapeutic strategies and outcomes for legions of patients but were published in journals with comparably low impact factor or no impact factor at all. In conclusion, the quality of surgical research should be assessed as a function of scientific influence (impact factor), therapeutic relevance, patient outcome, impact on society, and industry-led market shares.

Micro processing of plastics for biomedical applications

Gábor Jüttner, Kunststoff-Zentrum in Leipzig gGmbH, Leipzig, Germany, juettner@kuz-leipzig.de
Peter Bloß, Kunststoff-Zentrum in Leipzig gGmbH, Leipzig, Germany, bloss@kuz-leipzig.de

Introduction

Medical engineering are facing new challenges due to forward-pressing minimal invasive surgery technologies and functional implants. Micro-plastic processing technologies developed allow to process all kind of plastics which are appropriate for medical applications including implants. Here, several technological sulutions are presented which are successfully applied to R&D projects within the Response.

Methods

To manufacture micro parts in a reproducible high precision, a micro injection moulding machine (MIMM) named formicaPlast based on plunger injection technology was developed. Resulting from its design, the residence time and the accuracy problems for managing small shot volumes are solved. Hence, also sensitive bioresorbable plastics can be processed. Furthermore, a micro extruder (ME) was developed to process in a gentle way also bioresobables.

Results

In the design of our two plastic processing machines, the MIMM and the ME, the thermo mechnanical stress is minimized because of the simple geometry and a minimum residence time. Consequently, a wide variety of materials, including sensitive bioresorbables, highly filled plastics (the so called powder injection moulding, PIM) and all thermoplastics can be processed. This also works in case if only small amouths of material are available.
We have manufactured implants consisting of bioresorbables as parts and pipings, respectively. By using mould inserts manufactured by laser structuring and additive manufacturing, silicon parts with challenging micro structures were made. Here, precise surface structures investigated by electron microscopy we have casted.
By using our ME, we were able to generate an additive manufacturing process also by applying brittle materials.

Conclusion

By applying the new MIMM in its different facets for manufacturing micro parts, a high reproducible precision is achieved in one and tow component technologies for a wide variety of materials including liquid silicons and bioresobables. Also the developed ME allows to process senstitive polymers.

On-demand antimicrobial coatings to combat biofilm formation on blood-contacting materials

Carsten Werner, Leibniz-Institut für Polymerforschung Dresden e.V, Max Bergmann Center of Biomaterials, 01069, Dresden and TU Dresden, Center for Regenerative Therapies Dresden, Germany, werner@ipfdd.de
Juliane Valtin, Leibniz-Institut für Polymerforschung Dresden e.V, Max Bergmann Center of Biomaterials, 01069, Dresden, Germany, valtin@ipfdd.de
André Ruland, Leibniz-Institut für Polymerforschung Dresden e.V, Max Bergmann Center of Biomaterials, 01069, Dresden, Germany, ruland@ipfdd.de

Introduction

Catheter-associated blood stream infections remain a major challenge in global health care. Though antibacterial coatings can effectively reduce bacterial colonization, current strategies mainly base on permanent drug conjugation or continuous release. Limitations of these approaches include early exhaustion and overdosage. We therefore herein report a new concept for bio-responsive antimicrobial in situ coatings. The approach relies on water-soluble, strongly adsorbing anchor-copolymers tethered to enzymatically cleavable peptide-drug conjugates.

Methods

Fabrication: Using ‘click-chemistry’, a bacterial protease-cleavable peptide linker is conjugated to various biocides including trusted antibiotics, antiseptics and antimicrobial peptides. The conjugates are then tethered to the anchor-copolymer via Michael-Type Addition.
Coating characterization: The adsorption of the modified anchor-copolymers on thermoplastic polyurethane (TPU) surfaces was analyzed by quartz microbalance (QCM), AFM and in-situ ellipsometry. The binding stability was shown via fluorescent labeling (Atto647) over two weeks in PBS, 4% BSA-buffer and citrate plasma.
Enzyme cleavable toolbox: The cleavage response of peptide-drug conjugates susceptible to specific, extracellular bacterial proteases (such as Elastases and Collagenases) was tested under realistic conditions.
Antibacterial performance: The antimicrobial activity of the coatings and their components was evaluated by optical density kinetics over 20 hours and Live/Dead-Staining (BacLightTM Viability Kit).
Hemocompatibility: All coupled biocides were tested in human whole blood incubation. Inflammation (e.g. CD11b, C5a) and hemostasis parameters (e.g. F1+2, PF4) were analyzed after an incubation time of two hours. An incubation system to analyze the coatings over 24 hours in the presence of bacteria is in development.

Results

Whole blood incubation experiments showed that peptide-conjugated biocides are similarly hemocompatible as compared to the unmodified biocides. The chosen drug concentrations exceed the minimal inhibitory concentration for relevant bacteria (S. epidermidis, S. aureus, P. aeruginosa, E. coli) at least by a factor of three.

Conclusion

The reported results suggest that bio-responsive anchor-copolymer coatings can effectively reduce biofilm formation on blood-contacting devices.

Acknowledgements

Financial support from the Federal Ministry of Education and Research (Project RESPONSE - Partnerschaft für Innovation in der Implantat-technologie) is gratefully acknowledged.