POLISH - SCANDINAVIAN SYMPOSIUM ON BIOMATERIALS

PROGRAM AND BOOK OF ABSTRACTS

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The Journal Engineering of Biomaterials publishes refereed original articles and review papers on biomedical aspects of engineering. It deals with application of materials engineering principles and methods to problems associated with human health. This includes the design and manufacturing of biocompatible materials, implants, artificial organs, controlled drug delivery systems and various medical devices. The journal encourages to present the research results focused on the areas of biomaterials technology and analysis of interaction between implant surfaces and the biological environment/living tissue to improve the biocompatibility and the biofunctionality of biomaterials.

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To exchange ideas, research results, and perspectives within the field of biomaterials science and engineering. To meet, discuss, seek collaboration, and enhance partnership between Polish and Scandinavian biomaterials scientists.

Program

9:00 - 9:10	Opening remarks – Prof. Elżbieta Pamuła & Prof. Jerzy Jedliński
	Experts' Panel
9:10 – 9:50	Szczepan Zapotoczny *Polymer nanocapsules for drug delivery*
9:50 – 10:30	Hanna Tiainen *Antibacterial strategies for prevention and treatment of peri-implantitis*
10:30 – 10:50	Coffee break/Networking
10:50 – 11:30	Paweł Sikorski *Nanotechnology meets bioengineering with examples from the field of biomaterials*
11:30 - 12:10	Alicja Kazek-Kęsik *Electrochemical and biological methods for titanium implants modification*
12:00 – 13:00	Lunch break/Networking

Straight from the lab – current research wins and struggles of young biomaterial scientists

Short oral presentations of young scientists to see the most up-to-date research results

13:00 – 13:10 **Angelika Banaś**, Kaja Fołta, Dominik Paździorko, Szymon Smołka, Marcin Pająk, Katarzyna Krukiewicz
Electroactive polymeric microspheres as carriers for anticancer drugs in glioblastoma multiforme therapy

13:10 - 13:20 **Kamila Walczak**, Małgorzata Krok-Borkowicz, Elżbieta Pamuła
Mesenchymal stem cells proliferation and osteogenic differentiation on polymeric scaffolds and microspheres for bone tissue engineering

13:20 – 13:30 **Malwina Furgała**, Patrycja Domalik-Pyzik
Derived from nature - bioinspired hydrogels modified with pomegranate peel extract, tea tree oil, and allantoin for wound healing

13:30 – 13:40 **Pavan Kumar Reddy Gudeti**, Armin Amirsadeghi, Marcus Koch, M. Kamperman, Małgorzata Włodarczyk-Biegun
Melt electrowriting of PEOT-PBT copolymers for soft tissue regeneration

13:40 – 13:50 **Iwona Pudełko-Prażuch**, Konrad Kwiecień, Karolina Schickle, Elżbieta Pamuła
Antibiotic-loaded nanoparticles – a chance to obtain an antimicrobial effect on the site of an implant?

13:50 – 14:00 **Joanna Karbowniczek**, Krzysztof Berniak, Urszula Stachewicz
Composite bone scaffolds produced by co-axial electrospinning

14:00 – 14:10 **Stanisław Marecik**, Małgorzata Krok-Borkowicz, Elżbieta Pamuła
Manufacturing of poly(L-lactide-co-glycolide) microparticles with emulsification by mixing and in a microfluidic device

14:10 – 14:20 **Piotr Pańtak**, Joanna P. Czechowska, Aneta Zima
How silane coupling agents influenced the properties of bioactive bone substitutes?

14:20 – 14:30 **Martyna Polak**, Urszula Stachewicz
Osteoblast integration with electrospun PLLA scaffolds with tunable surface potential and piezoelectricity

14:30 – 14:40 **Sara Shakibania**, Małgorzata Skorupa, Katarzyna Krukiewicz
Bioactive betulin and PEG loaded poly(vinyl alcohol) nanofibers as biodegradable coatings for titanium bone implants

14:40 – 14:50 **Alicja Macyk**, Anna Kusibab, Elżbieta Pamuła
Gellan gum-based hydrogels with zinc oxide as potential composite biomaterials for wound treatment

14:50 – 15:00 **Konrad Kwiecień**, Karolina Knap, Katarzyna Reczyńska-Kolman, Daria Niewolik, Joanna Płonka, Alicja Kazek-Kęsik, Przemysław Mielczarek, Katarzyna Jaszcz, Elżbieta Pamuła
Encapsulating drugs in polyanhydrides – a delight or a nightmare?

15:00 – 15:10 Closing remarks – Prof. Elżbieta Pamuła & Dr. Patrycja Domalik-Pyzik

Experts' Panel

Szczepan Zapotoczny

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Szczepan Zapotoczny holds a full professor position at Jagiellonian University in Krakow (Poland) where he also completed his PhD in chemistry working on synthesis and photophysics of polymeric photosensitizers. He joined the group of prof. G. J. Vancso (University of Twente, The Netherlands) as a postdoctoral researcher (1999-2001) working on force spectroscopy and surface chemistry of self-assembled systems. After coming back to Poland his research focused on amphiphilic polymers obtained using controlled radical polymerizations and formation of photoactive polyelectrolyte multilayer films. In the period 2005-2006 he visited the group of prof. Vancso again initiating the studies on surface-grafted polymer brushes. His current interests focus on nanostructural polymeric and hybrid materials including films, brushes (conductive, stimuli-responsive), polymer coated nanoparticles, magnetic nanoparticles, nanocapsules serving as drug carriers and photoreactors. He is a leader of Nanotechnology of Polymers and Biomaterials group, the team of Nanoengineering of Functional Polymeric Materials Group (https://nfpm.chemia.uj.edu.pl) and Polymeric and Hybrid Nanomaterials for Biological Applications group at AGH University of Krakow (https://acmin.agh.edu.pl/2021/06/polymeric-and-hybrid-nanomaterials-for-biological-applications). He has been leading number of projects on a national level and in collaborations with partners from e.g. Germany, China. He is a coauthor of over 160 scientific papers (H= 32, Scopus) and more than 10 patent applications.

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Polymer nanocapsules for drug delivery

Designing and application of nanodelivery systems has been considered as a solution to one of the major challenge in pharmaceutical research - poor bioavailability of lipophilic drugs. Such nanocarriers, based on polymers or assemblies of low molecular weight compounds, have to be not only biocompatible but, among others, robust enough to survive digestive system for the preferred oral administration and characterized by prolonged circulation in blood for efficient cellular uptake.

Nanocapsules with liquid oil cores and shells based on amphiphilic polysaccharides were proposed as robust carriers of hydrophobic active compounds [1]. Hydrophobically modified charged hyaluronates were synthesized and used as stabilizing shells ensuring also biocompatibility of the nanocapsules formed in a simple emulsification process. Importantly, the oil nanodroplets were found to be stably suspended in water for more than 24 months without addition of low molar mass surfactants. Moreover, their size (in the range 100-500 nm) may be tuned by varying the relative content of hydrophobic and hydrophilic groups in the hyaluronate derivatives as well as by changing the applied oil in the cores as it was indicated by dynamic light scattering, nanoparticle tracking analysis as well as electron microscopies. The oil cores of the capsules may be easily loaded with various lipophilic compounds during emulsification.

In vivo studies (mice models) demonstrated that hyaluronate-based nanocapsules after oral administration were accumulated preferentially in liver as well as in lungs and their accumulation was dramatically enhanced in endotoxemic mice (with systemic inflammatory response) [1]. Such nanocapsules were shown as efficient delivery systems of curcumin that only in such a form resulted in hypotensive effect in rats developing hypertension [2]. As an example, anticancer activity of the nanocapsules filled with oleic acid was demonstrated in vitro [3]. The process of their uptaken by the cells and subsequent release of the cargo was followed using confocal fluorescent microscopy. Hyaluronate-based nanocapsules were shown to serve also as protective carriers of garlic oil active components with anticancer activity [4].

Biocompatible hyaluronate-based nanocapsules with liquid oil cores described here represent a promising and tailored nanodelivery system for lipophilic active compounds via both oral and intravenous administration.

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The research experience of Prof. Hanna Tiainen is highly interdisciplinary, but relies strongly on her solid academic background in biomaterials science and materials chemistry. After completing MSc in Materials Engineering at Tampere University of Technology in Finland, she focused on ceramic bone scaffolds and implant surface modification during her PhD at the Department of Biomaterial at the University of Oslo, Norway. After brief postdoc research positions abroad working with bone cements at the RMS Foundation in Switzerland and 3D cell cultures at Texas Southern University, USA, she returned to the University of Oslo, where now she works as an Associate Professor at the Department of Biomaterials, Faculty of Dentistry.

Main research interests of Prof. Hanna Tiainen centre on designing and engineering materials and surfaces for targeted cell-material interactions and biofilm prevention as well as hard tissue regeneration in application where natural tissue regeneration may be hampered by underlying chronic inflammatory diseases. Through collaborative and cross-disciplinary research focus, Prof. Tiainen have accumulated a broad scientific understanding of interactions between both biological molecules and organisms and material surfaces as well as a strong multidisciplinary network of collaborators in the field biomaterials science.

In March 2023, Prof. Hanna Tiainen was elected the President of the Scandinavian Society for Biomaterials.

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Antibacterial strategies for prevention and treatment of peri-implantitis

Despite the decades of research on osteointegration, achieving strong long-term soft tissue integration of dental implants to seal their surface from the oral environment still remains a significant technical and therapeutic challenge. The lack of true biological soft tissue attachment at the transmucosal region compromises the success of dental implant, leaving the implant surface prone to bacterial colonisation and biological complications associated with peri-implant infections. Peri-implantitis is an inflammatory process around an osteointegrated dental implant that is characterised by progressive loss of the supporting bone tissue, and if left untreated, results in loss of the implant. On patient level, the prevalence of peri-implantitis ranges from 20-50% [1,2], depending on the diagnostic criteria, and it is the most common cause for loss of dental implants.

Plant polyphenol solutions containing tannins or flavonoids have previously been associated with antimicrobial properties as well as reduced inflammation and tissue destruction caused by periodontal disease. Our ambition is to combining the antimicrobial and anti-inflammatory potential of tannic acid nanocoatings with the reparative potential and bacteriostatic properties of cationic polypeptides to promote uneventful wound healing and soft tissue integration of dental implants. The reservoir of non-oxidised tannic acid on the implant surface can attenuate the foreign body reaction towards the implant material by curbing inflammation, while the polycations reduce bacterial adhesion and accelerate the sealing of the implant surface from the oral environment.

With no quick solution for infection-resistant implants at hand, peri-implantitis remains a prevalent biological complication affecting large number of patients. As antibiotics are often insufficient in clearing the contaminating bacterial biofilm, mechanical debridement combined with chemical decontamination of infected dental implants with disinfectants such as chlorhexidine or H_2O_2 is essential for successful treatment of peri-implantitis. While these conventional treatments for peri-implantitis can stop the progressive tissue damage around dental implants, the currently used regenerative therapies remain unpredictable and often fail to restore the lost bone tissue, leading to poor functional and aesthetic outcomes. Simple new strategies to facilitate endogenous bone regeneration are therefore needed to fully reverse the loss of supportive peri-implant tissues. We have developed acellular calcium phosphate-hydrogel composites that crosslink and self-mineralise once injected into a bony defect that hold great promise as simple and clinically feasible scaffolds for endogenous bone regeneration in peri-implant defects. By functionalising these composite hydrogels with platelet lysate, we aim to create a synthetic bone-like microenvironment that can be easily remodelled, readily delivering growth factors, chemoattractants, and calcium and phosphate ions required for facilitating cell recruitment and *de novo* bone formation in peri-implant bone defects.

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Pawel Sikorski (born 1974) is a full Professor at the Department of Physics, Norwegian University of Science and Technology (NTNU), where he is a member of the Biophysics and Medical Technology research group. His expertise lies in the fields of biomaterials, biophysics, nanoscale material characterization, and nanofabrication. In his research he uses nano- and microfabrication to create artificial cell culture substrates that are, for example, used to study cell-substrate interactions or control the structure of the engineered neuronal network. Hi is interested in developing new hydrogel-based materials and studying their properties and is experienced in using model systems to explore mineralization in biological and artificial systems. This includes cell-induced mineralization of the extracellular matrix during the development of bone tissue. His group has also pioneered a new technique to form alginate hydrogels compatible with various applications, such as 3D printing, microfluidic-based cell encapsulation, injectable preparations, and large-scale mouldable gels. Prior to his current research, Sikorski has contributed significantly to the field of polymer physics and structural studies of crystalline polymers and biopolymers. Sikorski received his Master's degree in Materials Engineering from the Faculty of Fundamental Problems of Technology, Wroclaw University of Science and Technology, and his Ph.D. in physics from the University of Bristol, UK. After completing his doctoral studies, he worked at the University of Bristol and NTNU before establishing his research group at NTNU in 2005. He has held visiting scholar positions at the Department of Biomedical Engineering at the University of California, Davis, USA. Additionally, he is the leader of the Biophysics and Medical Physics Section of the Norwegian Physics Society and leads a national network that supports Ph.D. education within nanotechnology in Norway.

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Nanotechnology meets bioengineering with examples from the field of biomaterials

In this presentation, my aim is to highlight connections between bioengineering, biomaterials, and nanotechnology. I will introduce nanoscale effects that can be important for bioengineering research and technology development. Nanotechnology has a potential to contribute to biomaterial and biomedical research by providing new tools and new experimental methods. Compared to traditional approaches, these techniques often allow for miniaturization and better control of the experimental system. In our research we are interested in hydrogels and hydrogel-based composites. I will describe how one can study formation of calcium phosphate within a hydrogel matrix. I will show how similar experimental methods can be used to investigate clinically relevant model systems based on 3D cell spheroids. In such systems, one hope to study processes relevant to bone development and bone repair, in particular, the extracellular matrix structure and mineralization.

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Alicja Kazek-Kęsik received her PhD in chemical technology at the Silesian University of Technology in Poland and DSc. in chemical engineering. She is a co-author of more than 70 scientific papers (h-index 19), 14 patents, 2 European Patents and 4 European patent applications.

Prof. Kazek-Kęsik is experienced in metallic biomaterials, surface treatment of metals, coatings characterization including biological and microbiological evaluation. Her laboratory work is focused on electrochemical techniques such as anodization, plasma electrolytic oxidation, electrophoretic deposition and post-treatment techniques. Chemical engineering is close with her scientific interest. She is a co-author of one technology transferred to industry (production of veterinary implants with bioactive ceramic coating).

She managed several scientific projects and was awarded for her scientific achievements. Since 4 years, she has reviewed European projects and now she is a member of Council of the National Science Centre Poland.

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Electrochemical and biological methods for titanium implants modification

Electrochemical techniques like anodization, plasma electrolytic oxidation, electroreduction, electrophoretic deposition are widely used to modify surface of titanium implants [1]. Bioactivity surface enhance integration of the bone tissue with long term implants. Plasma electrolytic oxidation is surface treatment process to form a porous oxide layer promotes osteoblast adhesion [2]. However, the porous morphology of the ceramic layer is also favourable surface for bacteria adhesion. Thus, the additional surface treatment is necessary, of formation a ceramic coating with antibacterial agents.

Bacteriostatic surface could be achieved by formation a polymer layer with selected antibiotics. Amoxicillin, cephalosporin's, clindamycin or doxycycline excellent protect surface against Gram-positive or Gram-negative bacteria such as *S. aureus*, *S. epidermidis*, *P. aeruginosa* or *E. coli*. The antibiotics lose its stability over the time in water based solutions [3]. Thus, fast release from the biomaterials is necessary to protect the surface against bacteria within first hours after material implantation into bone. Polymer like poly(adipic anhydride) or poly(sebacic anhydride) are cytocompatible polymer, easily blend with antibiotic and could be deposited on previously anodized implant surface. The polymer could be deposited on the implants using a simple dip coatings techniques [4]. Polymer concentrations, speed of immersion and withdrawn strongly influence on antibiotic loading into the layer. It is possible to obtain an implant with the bacteriostatic surface, and enough drug concentration release from the implant within 1h to protect the surface against bacteria adhesion. On the other hand, the balance between antibacterial properties and cytocompatibility of the implants must be achieved.

During the Symposium the electrochemical techniques of the titanium implant surface will be presented, and methods for formation of ceramic-polymer coatings loaded with antibiotics. Correlation between surface morphology, surface roughness, adhesion of proteins, cytocompatibility and antibacterial properties will be discussed.

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Straight from the lab

Current research wins and struggles of young biomaterial scientists

Angelika Banaś

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Electroactive polymeric microspheres as carriers for anticancer drugs in glioblastoma multiforme therapy

Cancer is one of the most common causes of death worldwide and, as a result, effective ways of cancer treatment are heavily studied all around the world. One of the most aggressive tumours is glioblastoma multiforme, which is the most common primary brain tumour in adults. e. Despite the widespread use of conventional treatment methods, such as radiotherapy, chemotherapy or surgery, new methods are required to treat tumours that are resistant to traditional treatments. The aim of our project is to develop a carrier for a model anticancer drug (curcumin) based on a conducting polymer, which would allow a specific amount of the drug to be dosed by electrical stimulation. Microspheres of poly(3,4-ethylenedioxythiophene) were chemically synthesized and then characterized by infrared spectroscopy and scanning electron microscopy (Fig. 1). Curcumin was immobilized in two ways: by adsorption to the surface of the microspheres and by electrodeposition. The release of the drug was also carried out in two ways, i.e. spontaneously and electrically-induced, with the concentrations of released curcumin monitored through UV-Vis spectrophotometry The results of the study indicated the great potential of conductive polymers as controlled drug release systems, enabling 'on-demand' drug dosing and realising the concept of regional chemotherapy.

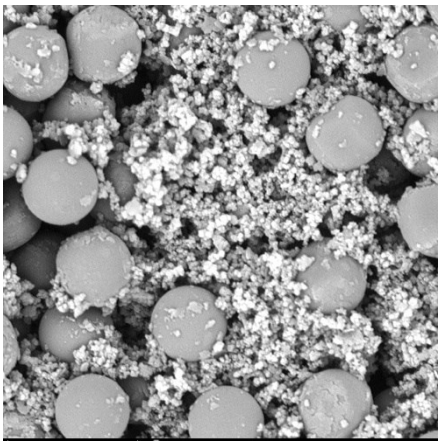

Fig.1.SEM picture of PS and PEDOT matrix (10000x)

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Kamila Walczak

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Mesenchymal stem cells proliferation and osteogenic differentiation on polymeric scaffolds and microspheres for bone tissue engineering

Bone tissue healing and regeneration are effective in the case of small lesions, while in the case of critical-size defects, they should be supported with biomaterials, which can provide cues for osteogenic cell infiltration, adhesion, proliferation and differentiation and thus new bone tissue formation.

In this study, three-dimensional supports were manufactured from degradable poly(L-lactide-*co*-glycolide) (PLGA). They were produced by emulsification and solvent casting/salt particulate leaching and had a form of microspheres and porous scaffolds, respectively. Mesenchymal stem cells were seeded on microparticles, on the scaffolds or control tissue culture polystyrene (TCPS, bottom of the wells) and cultured in basal or osteogenic medium for 1, 3, 7, 14 and 21 days. Cell proliferation and osteogenic differentiation were studied using lactate dehydrogenase (LDH) and alkaline phosphatase (ALP) assays, respectively. Furthermore, cell morphology and viability were analysed after live/dead and phalloidin red/DAPI fluorescence staining.

The results show that optimised emulsification conditions allowed to produce PLGA microspheres with median size of 100 µm. The PLGA scaffolds had a porosity of 82% and a median pore size of 400 µm. Cells cultured on control TCPS in osteogenic medium were more spread and polygonal than those in basal medium. They were characterised with lower proliferation rate, as shown by LDH results, but higher ALP activity. This suggests that osteogenic differentiation was achieved. The same tendency was observed for cells cultured on the microspheres and scaffolds. In general, both the microspheres and the scaffolds promoted cell adhesion, proliferation, and osteogenic differentiation. Cell proliferation was more efficient on the scaffolds in growth medium, while amount of ALP, i.e. a marker of early osteogenic differentiation, was elevated especially for the cells cultured on the scaffolds in osteogenic medium for 14 and 21 days.

In summary, porous scaffolds were found to be more suitable for long-term promotion of cell adhesion, proliferation and osteogenic differentiation, but in clinical condition they would require implantation, which is more traumatic. The application of microspheres can be considered when low-invasive administration of the cell-biomaterial construct is required.

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Derived from nature - bioinspired hydrogels modified with pomegranate peel extract, tea tree oil, and allantoin for wound healing

Wound dressings play a vital role in facilitating wound healing, offering advantages in terms of ease of use, affordability, and extended wound care [1]. Yet, conventional dressings often fall short in effectiveness and require frequent changes, potentially leading to additional harm. Hence, there is a need for new solutions offering balance between material performance, degradation, safety, and tissue regeneration [2]. Nature can serve here as both the inspiration and (almost) endless source of materials.

The aim of the study was to develop hydrogels based on chitosan (CS) and poly(vinyl alcohol) (PVA). The hydrogel systems were further modified by incorporating natural active substances potentially improving wound healing. Three compounds with anti-inflammatory, soothing, and cell proliferation-promoting properties were selected: pomegranate peel extract, tea tree oil, and allantoin. The synthesized biomaterials were subjected to examinations of physicochemical and biological properties. The microstructure, structure (FTIR-ATR), wettability, chemical stability, and water absorption capacity were investigated. Regarding biological properties, the effectiveness of the active substance modification and its release were evaluated, along with an assessment of the proliferation and adhesion of mouse L929 fibroblast cells under *in vitro* conditions. Based on the obtained results, the biocompatibility, biofunctionality, and absence of cytotoxicity of the hydrogels modified with tea tree oil and allantoin were confirmed. However, the cytotoxicity results of the systems containing pomegranate peel extracts were questionable. Therefore, a further detailed investigation is needed. For now, it can be stated that the modification of the CS/PVA hydrogel matrix with certain natural active substances positively affects selected physicochemical and biological properties of the materials intended for wound dressings.

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Melt electrowriting of PEOT-PBT copolymers for soft tissue regeneration

Introduction

Melt electrowriting (MEW) is a promising technique for fabricating scaffolds that enable precise deposition of molten polymers into organized fibers with diameters in the range of a few to tens of micrometers. However, the number of printable polymers for MEW is limited, with polycaprolactone (PCL) being the most commonly used. To address this challenge, we investigated the use of Poly(ethylene oxide terephthalate)-poly(butylene terephthalate) (PEOT-PBT), an elastomeric multiblock copolymer with water-absorbing properties, for MEW scaffold fabrication. We also compared the biological activity of MEW PEOT-PBT scaffolds with MEW PCL scaffolds in terms of their ability to support tissue healing by cultured fibroblasts.

Methodology

PEOT-PBT (PolyVation, the Netherlands) and PCL were printed using a MEW machine (Spraybase, Ireland). The mechanical properties of the fabricated scaffolds with different designs were studied using tensile testing. Simple mesh design with 400µm fiber-to-fiber distance fibrous strands scaffold (random fibers forming thicker well-ordered strands) with 800µm fiber-to-fiber distance obtained by different printing parameters were used for cell culture studies. Biocompatibility was analyzed by culturing NIH3T3 cells on the printed scaffolds, and various cell-based assays were performed. Statistical significance was determined using a two-way ANOVA test with GraphPad Prism 8.0.

Results and Discussion

Our results indicate that PEOT-PBT block copolymer is suitable for MEW, with the ability to easily manipulate fiber diameter and scaffold design by changing printing parameters. The mechanical analysis revealed young'smodulusof1.1±0.2to2.2±0.2MPa with a linear elastic strain above 10%, depending on the printing design.

Biological analysis revealed good biocompatibility with both PCL and PEOT-PBT MEW scaffolds. Immunofluorescence study shown positive staining for collagen-I and alpha smooth muscle actin (α-SMA) on all types of scaffolds after 14 days of culture. Fibroblast proliferation was faster with higher myo-fibroblast contractile activity in PEOT-PBT grid scaffolds. Furthermore, after 28 days culture PEOT-PBT grid scaffolds have significant amount of cell number compared to PCL scaffolds. These results suggest that PEOT-PBT grid scaffolds may exhibit faster tissue healing or regeneration behavior.

Conclusion

Our study highlights the potential of MEW using PEOT-PBT as a printable material for scaffold fabrication in biomedical applications. The mechanical properties of the printed scaffolds are within the required range for soft tissue engineering applications. Additionally, both PCL and PEOT-PBT scaffolds demonstrate good biocompatibility. Overall, PEOT-PBT grid scaffolds are a promising candidate for tissue engineering and other biomedical applications.

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Antibiotic-loaded nanoparticles – a chance to obtain an antimicrobial effect on the site of an implant?

Bone infections associated with implantation are a worldwide problem. They are commonly treated with conventional systemic antibiotic therapy, which is relatively often not sufficient and ends up failing [1, 2]. Some bone infections cannot be healed and surgical intervention is required in order to reconstruct or replace the bone [3]. The delivery of the drug at the implant site appears to be more sufficient than conventional treatment [4]. We manufactured different zirconia (ZrO2) substrates (2D and 3D materials) and coated them with a layer of calcium phosphate (CaP) using a biomimetic co-precipitation method to enhance bioactivity. In order to obtain an antimicrobial effect, poly(lactic-co-glycolic acid) (PLGA) nanoparticles (NPs) loaded with antibiotics were produced by the double emulsion method and immobilised in the CaP layer. Encapsulation efficiency (EE) was dependent on the type of antibiotic and was within the range of approximately 40 to 99% for gentamicin sulphate and modified gentamicin, respectively. Scaffolds were observed after each step of the production process by scanning electron microscopy (SEM). Furthermore, the drug release from the particles themselves and from the substrates was evaluated. Cytocompatibility tests with osteoblast-like MG-63 cells were performed and antimicrobial properties with Staphylococcus aureus were investigated. Both 2D and 3D materials were non-toxic to MG-63 cells and the presence of NPs did not have a significant impact on cell viability. Bacteria growth inhibition zones were observed for both types of NPs and were superior for modified gentamicin. Although the antimicrobial properties of the NPs were confirmed, the antibacterial effect of substrates coated with a CaP layer containing gentamicin-loaded NPs was not sufficient. As expected, the results were superior for modified gentamicin; however, they are still unsatisfactory and may be improved. Nevertheless, the use of antibiotic-loaded NPs to deliver drugs at the implant site, combined with enhanced bioactivity of the substrates, may be an effective way to reduce the possibility of implant-related infections.

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Composite bone scaffolds produced by co-axial electrospinning

Electrospinning is a widely used method of producing meshes with ultra-thin fibers for tissue engineering applications. Electrospun structures are explored for supporting the regeneration of various tissues, especially as bone scaffolds. One of the goals following biomimetic approach for bone regeneration is to successfully combine organic and inorganic phases into fibrous scaffold. This could be achieved by employing advanced electrospinning process using co-axial nozzles, allowing to create polymer fibers coated by ceramic particles.
In the current work fibers based on PHBV (poly(3-hydroxybutyrate-co-3-hydroxyvalerate)) covered with titanium dioxide (TiO_2) nanoparticles were produced by co-axial nozzle electrospinning [1]. Obtained core-shell PHBV+TiO_2 scaffolds were studied by scanning electron microscopy (SEM) techniques to characterize their morphology and nanoparticles distribution within mesh and individual fiber. Furthermore, antibacterial properties were studied and *in vitro* cell culture for up to 14 days was performed. Cells proliferation, morphology and early stages of extracellular matrix (ECM) production by collagen staining were examined.
Importantly, co-axial nozzle in electrospinning allowed to achieve excellent integration of TiO_2 nanoparticles with the polymer matrix; homogenously distributed on fibers surface. Such composite scaffolds also exhibited antibacterial properties and promoted cells proliferation and growth in-between the fibers (Fig. 1 a). Additionally, within 14 days of incubation, osteoblasts started to produce collagen, forming extended network around cells (Fig.1 b). Current study shows that it is possible to produce bioactive scaffold supporting bone regeneration in a single-step process.

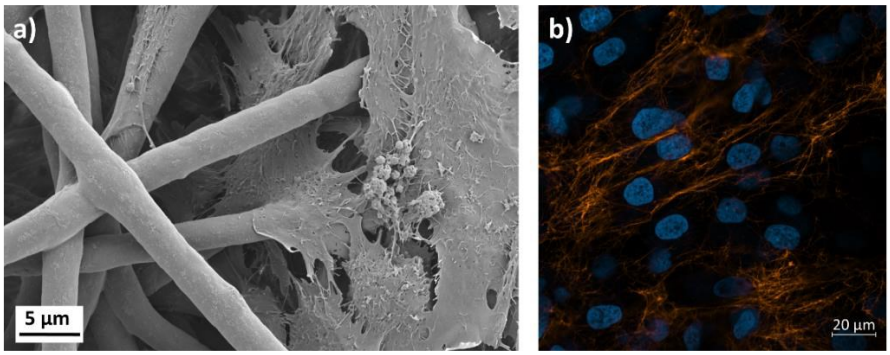

Fig. 1. a) SEM micrograph of cells growing for 7 days at PHBV+TiO_2 scaffold, b) confocal laser scanning microscopy image of cells growing on PHBV+TiO_2 scaffold for 14 days with collagen network (orange) and nucleus (blue).

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Manufacturing of poly(L-lactide-*co*-glycolide) microparticles with emulsification by mixing and in a microfluidic device

Introduction

Producing polymeric degradable microparticles with controlled sizes and properties is of interest in the development of modular scaffolds for bone tissue engineering. The aim of this study was to compare batch versus microfluidic emulsification techniques to produce homogenous and spherical poly(L-lactide-co-glycolide) (PLGA) microparticles with defined size and low polydispersity. Additionally, preliminary *in vitro* tests were performed to assess potential cytotoxicity of produced microparticles.

Materials and Methods

To prepare the oil phase, PLGA (85:15, Mn =100, d = 2.0) was dissolved in dichloromethane (DCM) at concentrations of 1%, 2% and 4% (w/v). As the water phase 0.5%, 1%, 2%, 2.5% and 4% (w/v) aqueous solutions of poly(vinyl alcohol) (PVA, Mowiol 4-88) were prepared. The microparticles were produced by two techniques: emulsification by mixing with a magnetic stirrer and in a microfluidic device (RayDrop, Fluigent). Emulsification parameters were optimised. The microparticle morphology was assessed with an optical microscope (Axiovert, Zeiss), and ImageJ software was used to measure the size of microparticles. MG-63 osteoblast-like cells were cultured in contact with the microparticles for 1, 3, and 7 days, and cell viability was tested with resazurin reduction and live-dead fluorescence staining.

Results and Discussion

The results show that the size of microparticles increases with the concentration of PLGA in the oil phase, while the concentration of PVA in the water phase has a lower impact on the microparticle size. The microparticles produced in the microfluidic device were characterised by lower size and a lower polydispersity than those produced by batch emulsification. For example, for the system: PLGA 2% and PVA 2% the diameter of microparticles produced by classical emulsification was 64.5 ± 12.4 µm, while for those produced in a microfluidic device, it was 43.2 ± 3.2 µm. Cells cultured in contact with both particle types were found alive as shown by live/dead staining. Cell viability assessed by resazurin reduction was similar on days 1 and 3.

Conclusion

Microfluidic technology offers the possibility of manufacturing homogeneous spherical PLGA microparticles which were found to be cytocompatible with osteoblast-like cells.

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How silane coupling agents influenced the properties of bioactive bone substitutes?

Introduction

Among commercially available bone substitutes, calcium phosphate cements (CPCs) stand out as a unique group due to their excellent bioactivity and composition similar to bone [1]. CPCs consist of powder and liquid phases that form a plastic paste upon mixing. Unfortunately, CPCs based solely on α-tricalcium phosphate (α-TCP) are usually brittle and non-injectable. To improve their mechanical and rheological properties, natural polymers can be added. Unfortunately, polymers often disrupt the setting process of CPCs, leading to elongation of their setting times. An innovative approach involves using silane coupling agents (SCAs) as modifiers for α-TCP. SCAs improve adhesion between material components by forming chemical bonds [2,3]. Our hypothesis is that cementitious materials based on α-TCP with added citrus pectin, due to modification of α-TCP with tetraethoxysilane (TEOS) and (3-Glycidyloxypropyl)trimethoxysilane (GPTMS), will achieve an acceptable setting time while maintaining suitable mechanical properties and injectability.

Results and Discussion

The results showed that modification of α-TCP powder with coupling agents led to the development of bone cements with favourable properties compared to the control material (non-modified α-TCP). XRD studies of the resulting materials revealed the presence of two crystalline phases: α-TCP and hydroxyapatite (HA). The setting times of the tested cements varied from 4 ± 1 to 11 ± 1 minutes (initial setting time) and 8 ± 1 to 19 ± 1 minutes (final setting time). It was also established that an increase in the amount of modifier in the material reduced both the initial and final setting times. These phenomena can be explained by chemical interactions that occur between the coupling agent and other components of the cements. Furthermore, the study demonstrated two simultaneous processes within the materials: the hydrolysis of α-TCP into non-stoichiometric hydroxyapatite and the hydrolysis of silane coupling agents. It was established that application of coupling agents, resulted in significant alterations in the physicochemical properties of the materials. The bioactive potential of the obtained CPCs was confirmed *in vitro* tests in simulated body fluid (SBF).

Summary

The use of silane coupling agents as modifiers of the initial α-TCP powder allows the development of new surgically handy cementitious bone substitutes with favourable mechanical properties. The obtained materials combine the beneficial properties of bioceramics and polymers, making them promising bone substitute biomaterials. Initial *in vitro* studies in simulated body fluid (SBF) indicate a high bioactive potential of the obtained biomaterials, paving the way for further *in vitro* and *in vivo* research.

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Osteoblast integration with electrospun PLLA scaffolds with tunable surface potential and piezoelectricity

Biomimetic polymer scaffolds can provide biological cues for cell–material interaction. As mimicked ECM (extracellular matrix) is a microelectrical environment where charges play a pivotal role in cell signaling, the aspect of surface charges and piezoelectric effect in biomaterials for tissue regeneration processes still requires an investigation [1,2]. Our research focuses on the surface potential and piezoelectric tunable effects of electrospun PLLA (poly(L-lactide) scaffolds.

The electrospinning technique has gained popularity in tissue engineering and drug delivery systems thanks to various processing parameters that directly affect fiber morphology, mechanical or electrical properties, scaffold geometry, and many others [3]. In electrospinning, fibers are produced by stretching polymer solution in an electrical field between the nozzle under high voltage and a grounded collector. Depending on the voltage polarity, the polymer solution exerting the nozzle is surrounded by positive or negative charges on the liquid interface. These charges influence the orientation of functional groups in polymer chains, resulting in controlled surface properties of fibers. We electrospun two types of PLLA scaffolds, using positive or negative voltage polarity, showing a relation between surface chemistry, surface potential, and piezoelectricity of PLLA fibers.

We verified the surface potential with Kelvin probe force microscopy (KPFM) and piezoelectricity with piezoresponse force microscopy (PFM). Due to the potential application of PLLA scaffolds in bone tissue engineering, we performed osteoblast cell culture experiments including cells' adhesion, proliferation, and morphology studies using confocal laser microscopy (CLSM). In conclusion, the enhanced initial adhesion of osteoblasts to fibers confirmed the effect of the higher surface potential and piezoelectricity on improved cellular response [4].

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Bioactive betulin and PEG loaded poly(vinyl alcohol) nanofibers as biodegradable coatings for titanium bone implants

Recent findings in the literature reveal that there is a correlation between the nervous and skeletal systems. This association forms a neuro-osteogenic network. Proper skeletal development and fracture healing depend on the accurate innervation of the neural structure.

In this work poly (vinyl alcohol) (PVA) nanofibers containing biodegradable polyanhydrides based on betulin disuccinate (DBB) and dicarboxylic derivatives of poly (ethylene glycol) (PEG) were prepared and their potential for coating on bone implants were investigated. Morphology of the nanofibers and surface properties of the samples were studied using scanning electron microscopy and water contact angle evaluations. Eventually, as a proof of concept it was coated on Ti_4AL_6V samples.

The average diameter of PVA and DBB/PEG-loaded PVA nanofibers were 132 nm and 247 nm, respectively. Surface roughness (Ra) of PVA and DBB/PEG-loaded PVA nanofibers was 96.2 nm and 117.6 nm, respectively, which is in agreement with previous studies on PVA nanofibers. Furthermore, the coating improved the wettability of the surface. All samples were found to be biocompatible, however, DBB/PEG-loaded PVA nanofibers indicated the highest percentage of viable cells when compared with PVA nanofibers and the control sample. The developed coating indicated appropriate adhesion on the Ti surface and it can be considered promising candidate for future application, particularly for the modification of metallic scaffolds used in bone tissue engineering.

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Gellan gum-based hydrogels with zinc oxide as potential composite biomaterials for wound treatment

Composites based on gellan gum with the addition of micro- and nanoparticles of zinc oxide were produced as potential biomaterials for wound dressings. The concentrations of zinc oxide in the samples were 0.01%, 0.02%, and 0.04%, and Ca^{2+} ions in the form of $CaCl_2$ were used as an additional cross-linker. The hydrogel composites were then processed by freeze-drying, to produce highly porous wound dressing prototypes.

All sample types showed high swelling in the phosphate buffered saline, exceeding 2000%. The pH of the extracts was measured after 24 h of incubation in ultrapure water; for hydrogels with the addition of ZnO, the pH was closer to neutral (pH of 7.0 – 7.6) than for control samples (pH of 5.5 - 6.1). Samples with the addition of CaCl2 showed greater stability after 7 days of incubation in ultrapure water than those without crosslinking.

Extracts of the samples with 0.04% ZnO and the control samples were tested for zinc release using atomic absorption spectrometry. Zinc concentrations were more than twice as high for samples with nanometric ZnO (1.94 ± 0.04 mg/l) than for samples with micrometric ZnO (0.92 ± 0.03 mg/l), showing that it is possible to control the amount of released zinc by the size of the zinc oxide particles.

The cytotoxicity of the samples was tested on L929 fibroblasts using resazurin reduction assay. For this purpose, hydrogel extracts were prepared with concentrations of 0.5% and 1% w/v. The highest cell viability was demonstrated in the presence of 0.5% extracts of the cross-linked samples (72.5 ± 6.9% for samples with nanometric zinc oxide and 74.5 ± 1.6% for micrometric zinc oxide) comparable to control conditions (66.4 ± 5.9%). High cell viability was confirmed by live/dead fluorescence staining.

The results show that composites based on gellan gum and zinc oxide particles additionally crosslinked with $CaCl_2$, show the most promising properties as potential materials for wound dressings due to their sufficient dimensional stability, cytocompatibility and the release of zinc species, which can act as an antibacterial agent.

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Encapsulating drugs in polyanhydrides – a delight or a nightmare?

Polyanhydrides are an interesting group of polymers in terms of drug delivery due to their erosive degradation mechanism that can decompose the material in a relatively very short time. However, parameters such as encapsulation efficiency (EE) and drug loading (DL) are crucial for any considered drug delivery system (DDS). Obtaining satisfactory values of EE and DL may be problematic when there are different chemical characters of a drug and a matrix, e.g. hydrophilic antibiotic to be encapsulated within hydrophobic polyanhydride microparticles (MPs).

In our research we are trying to entrap various antibiotics and quorum sensing inhibitors in MPs created from poly(sebacic anhydride) (PSA) to deliver them by inhalation to the lungs. The material we use is highly hydrophobic which is the cause of many issues related to the encapsulation. Despite many approaches (various experimental set ups of solid-in-oil-in-water (SOW) or water-in-oil-in-water (WOW) emulsification techniques), we failed to encapsulate hydrophilic drugs (gentamycin, tobramycin) in our material, obtaining DLs below the detection limit. An interesting solution of this issue is to modify the chemical character of drugs by hydrophobic ion pairing that have been proved to increase EE and DL in other synthetic polymers[1]. Unfortunately, we were able increase the these parameters for PSA by very little – the DLs were not higher than 1%. EE of naturally hydrophobic compounds such as curcumin was able to reach between 20-30%, resulting in DL up to 6% which is satisfactory but still not high.

Surprisingly, we obtained almost complete EE independent from the drug to polymer ratio (hardly any drug was detected in the supernatants that was not entrapped within the MPs) when we used naturally hydrophobic antibiotic azithromycin (AZ) that resulted in DLs up to 23%[2]. A closer examination revealed that the reason for this observation is a chemical reaction between the drug and polymeric chains with creation of the ester bond. The drug remains bioactive, as we were able to prove the reverse reaction in the presence of human microsomes.

In conclusion, we assume that the best application for PSA as DDS is when it is used as a carrier of hydrophobic molecules that have hydroxyl groups that can react with the polymeric matrix. However, this leads to another issue that is evaluation of the drug release profiles, as the bioactive molecules are not released in their free form causing a challenge for the currently used analytical methods.

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