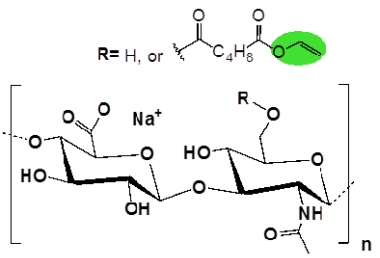
MICROFABRICATED BIOCOMPATIBLE HYDROGELS

Stefan Baudis[a], Elise Zerobin[a], Zuzana Tomášiková[a], Xiao-Hua Qin[a], Marica Markovic[b], Peter Gruber[b], Jürgen Stampfl[b], Aleksandr Ovsianikov[b], Robert Liska[a]

[a]E163 - Institute of Applied Synthetic Chemistry
[b]E308 – Institute of Materials Science and Technology
stefan.baudis@tuwien.ac.at

INTRODUCTION

Lithography-based additive manufacturing technologies ("3D printing") enable the generation of arbitrary, highly complex 3D structures with very high resolution. This was one of the main aspects, which attracted the interest of modern medicine. The vision is to be able to fill defects in tissues or whole organs with tailor-made, patient-specific, biocompatible polymeric constructs, which promote the regeneration of the tissue or the organ. Hydrogels are an ideal basis for soft tissue regeneration as the mechanical properties match with these of natural tissue and nutrients as well as metabolites can migrate through the constructs easily. The concept is to mimic the extracellular matrix (ECM) by modification of the natural components with crosslinkable groups and to encapsulate cells by spatially resolved photopolymerization using the 2-photon-technology.



HAVE

Figure 1: Structure of hyaluronic acid vinyl esters (HAVE).

Hyaluronan (HA) is a major component of the ECM. The introduction of double bonds to the back bone of HA enables the production of photocrosslinked, biocompatible hydrogels. Functionalization with (meth)acrylates is not unfavourable due to inherent cytotoxicity. The low cytotoxicity of vinyl esters in combination with the superior photo-reactivity as thiol-ene system makes vinyl esterfunctionalized HA (HAVE, Figure 1) an interesting candidate for biomaterial constructs for tissue engineering.[1]

EXPERIMENTS / FUNDAMENTAL OF THE PROBLEM / EXAMINATIONS

HAVEs were synthesized from HA with different molecular weights by lipase catalyzed transesterification with divinyl adipate (DVA).[1] Formulations with varied macromer contents were prepared and their reactivity was examined by photorheology (Figure 2). Additionally, the influence of the addition of different thiol-based chain transfer agents was investigated. The slope of the storage modulus from rheometric curves was taken as a measure for the reactivity whereas the final storage modulus was used to calculate the mesh size of the hydrogels as reference value for the crosslink density. The swellability of ready-cured hydrogels was determined as complementary parameter. Cell compatibility of HAVEs were assessed by metabolic as well as DNA assay. An exemplary HAVE based formulation was used for the encapsulation of murine fibroblast cells by 2-photon polymerization (2PP) based microfabrication.[2] The viability of the encapsulated cells was assessed by calcein staining.

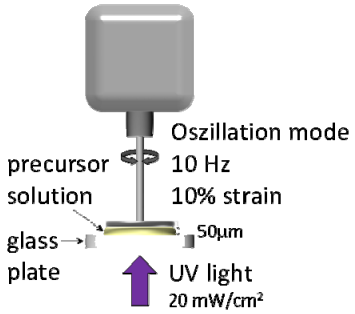


Figure 2: Photorheology (Scheme).

RESULTS AND DISCUSSION

HA can be transformed to biocompatible HAVE by lipase-catalyzed transesterification reaction with DVA in high yields. The degree of substitution (DS) is easily adjusted by variation of reaction time. Macromer content, macromer size, and/or DS determine the material properties on demand (Figure 3).

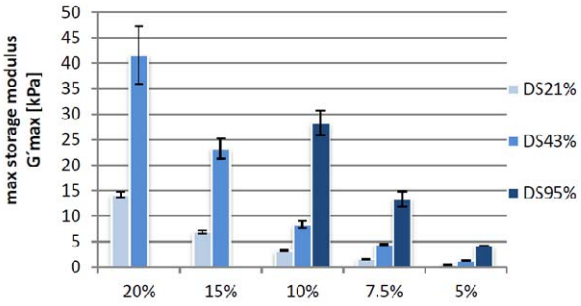


Figure 3: Photorheology results.

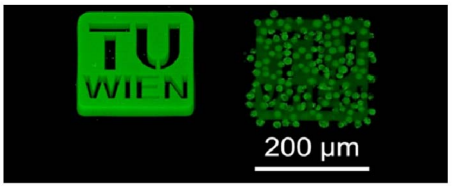


Figure 4: Encapsulated cells in cross-linked HAVE.

Moreover, the variation of the chain length of the thiol component offers an additional adjustment possibility for the properties of the hydrogels.

The cytocompatibility of the synthesized macromeres enables the fabrication of 3D hydrogel constructs with encapsulated cells by laser fabrication using 2PP (Figure 4).

CONCLUSION

HAVEs were found to be a promising modular material platform to engineer 3D hydrogel constructs as environment for living cells. Still, the material is very brittle, therefore ongoing research concentrates on toughening on the hydrogels by reinforcement with collagen fibers.

ACKNOWLEDGEMENT

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