THERMOPLASTIC POLYURETHANES AND THEIR APPLICATION AS ELECTROSPUN BIODEGRADABLE SOFT TISSUE MEDICAL PROSTHESES

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INTRODUCTION

Cardiovascular diseases are the number one cause of death worldwide.[1] Several surgical interventions are established as treatment methods with a common denominator: the necessity of medical prostheses with a wide range of demanding properties. Prostheses for soft tissues such as vascular grafts or heart valves must be biocompatible, flexible and robust to persevere blood pressure, and appropriately porous. Recent studies have shown that degradation of the artificial material enables and promotes native tissue growth. Therefore, degradability has also become a desirable attribute. Additionally, economic factors such as cost and shelf life are essential for the realization of medical prostheses.[2] Finally, it is also well known that the surface structure of medical prostheses plays a critical role in successful implantation. Segmented thermoplastic polyurethanes (TPUs) are a polymer class which meets many of the above mentioned criteria.[3] The polyaddition of diols and diisocyanates via the establishment of urethane bonds yields linear, thermoplastic polymers. Due to the urethane groups' ability to form hydrogen bonds, a segmented secondary structure can be achieved in which long, linear segments (poly(tetrahydrofuran) (pTHF) or poly(hexamethylenecarbonate) (pHMC) as soft blocks) are responsible for the material's elasticity, while the hydrogen-bonding urethane blocks from isocyanates (hexamethylenediisocyanate (HMDI), 4,4'-methylene-bis(cyclohexylisocyanate) (H_{12}MDI), 1,3-bis(iso-cyanatomethyl)cyclohexane (BIMC), or isophoronediiso-cyanate (IPDI)) and diol-chainextenders (CE: bishydroxyethyleneterephtalat (BHET), bishydroxypropane-carbonate (BHPC), or CEs from biogen substances as hard blocks) achieve mechanical stability. For the introduction of degradability of the material we aim to introduce cleavable bonds such as esters or carbonates, both in the soft and hard segments of the TPU polymer chains. Therefore, the design of cleavable chain extenders (CCE) is of special interest.

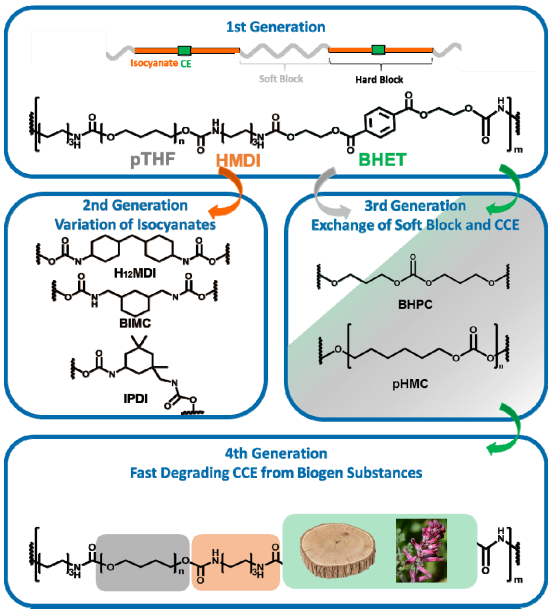

Figure 1: Schematic overview over the four TPU generations for soft tissue medical grafts

MATERIALS AND METHODS

The synthesis of linear TPUs requires the use of the prepolymer method. In order to analyze the polymers' properties, size exclusion chromatography and dynamical mechanical analysis are

conducted. Tensile testing is performed with specimens made by an optimized method for solvent casting. Biocompatibility and -degradability are tested *in vivo* and *in vitro*. Electrospinning has been chosen as processing method to create vascular grafts and heart valves from the designed TPUs because the technique provides an appropriate surface structure for such prostheses.[4] During this process a continuous polymer solution stream is converted into a nanofiber through the application of an electrical field between the tip of the syringe holding the polymer solution and a rotating rod on which the spun fiber is collected.

RESULTS AND DISCUSSION

So far, three generations of materials have been developed, a summary over the chemical composition of each TPU generation is given in figure 1.[5-7] The first generation of degradable TPUs was superior to the non-degradable commercial TPU Pellethane due to better *in vivo* vascularization of the material.[4] The design of the second generation aimed to enhance mechanical stability of the grafts by using more rigid isocyanates in the hard block. The introduction of carbonate-moieties in the third generation of TPUs decreased inflammatory responses due to less acidic, non-autocatalytic degradation. This material's enhanced mechanical properties were attributed to the introduction of carbonyl-moieties that contribute to hydrogen bonding. However, degradation speeds decreased for polycarbonate urethanes. After further optimization generations 1 and 3 have been scaled up to make vascular grafts and heart valves for *in vitro* and *in vivo* testing.[4] Currently, a fourth generation with faster degradation speed and biobased compounds is investigated. Fourth generation CCEs exhibit bonds that are prone to biodegradability and the degradation process should release the original reactants that are ideally FDA approved. In the best case, this novel cleavable chain extender concept may lead to an *in situ* long term drug-releasing biomaterial. Furthermore, these CCEs are highly rigid due to conjugation which implies high mechanical stability of resulting polymers.

CONCLUSION

The illumination of the structure-property relationship of the first three generations lead to the conclusion that moieties that contribute to hydrogen bonding (e.g. carbonyl groups) drastically ameliorate the mechanical strength of materials, also if their contribution to the material in weight percentage of the polymer is very low. Furthermore, the rigidity of hard block compounds can be detrimental to mechanical stability if they are sterically demanding due to hindrance of hydrogen bonding. With the gained knowledge about the structure-property relationship, new potential chain extenders have been synthesized and are about to be tested in polymer formulations. This will lead to a new generation of high performance artificial vascular grafts and heart valves with lower inflammation reactions and regenerative stimulus via tunable degradability to enhance long term efficiency of the prosthesis.

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