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Molecular architecture of biodegradable poly(lactide) alloys and blends.

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Summary

The aim of this research was to develop new biodegradable lactide based materials, with controlled mechanical properties and degradation patterns suitable for biomedical applications. Most of the work described in this thesis deals with amorphous (glassy) lactide stereo-copolymers that are intrinsically brittle materials. The deformation mechanism of polymer glasses is mainly controlled by their entanglement density ν_e and chain stiffness, expressed as the characteristic ratio C_∞ . For poly(L-lactide) (PLLA) Flory proposed that $C_\infty = 2$, which would indicate ductile instead of brittle tensile deformation behavior. To investigate this discrepancy and explore the effect of tacticity, high molecular weight poly(D,L-lactide) stereo-copolymers with varying D-lactide contents were studied with light scattering and DSC. The results of the light scattering experiments indicated that C_∞ of poly(lactide)s depends on the L/D-lactide ratio and increases with the tacticity of the polymer from 9.5 for racemic PDLLA to an estimated 11.8 for isotactic PLLA. These results are consistent with the observed brittle behavior of poly(lactide) stereo-copolymers and agreed well with predictions obtained from group contribution methods.

Furthermore it was found that tacticity also influences the glass transition temperature of poly(lactide)s, which varies from 54°C for racemic to 63°C for isotactic poly(lactide). The first studies on the biomedical applications of poly(lactide)s focused on as-polymerized PLLA, which due to its crystallinity is a strong and stiff material. Clinical trials with as-polymerized PLLA were very successful and showed undisturbed bone healing. However, during the bulk degradation of as-polymerized PLLA a fast decrease of molecular weight and tensile properties was observed, that cannot be explained by the kinetic models for hydrolysis as described in the literature. This work shows that the degradation behavior of poly(L-lactide) is strongly influenced by the typical morphology that is obtained through melt or bulk polymerization. The rapid loss of strength of as-polymerized PLLA during bulk degradation could be explained by the presence of thermal stresses and subsequent generation of micro-cracks.

Furthermore, with as-polymerized PLLA late complications arise after implantation periods of 3 years due to highly crystalline debris. Our studies showed that the lamellar crystallites in as-polymerized PLLA are very stable towards hydrolysis. The resorption time of high molecular weight as-polymerized PLLA *in vivo* was estimated at 40-50 years by extrapolation of molecular weight data, which is unacceptable for the intended application and raises serious questions about its 'biodegradability'.

Also, hot-drawn poly(L-lactide) fiber showed exceptional hydrolytic stability under a static load and retained much of its mechanical properties for more than 5 years. The high perfection

penetration of water and induced surface erosion of the fiber.

These results generally indicate that crystallizable lactide compositions should not be used for biodegradable implants. More importantly however, it may be presumed that densification or orientation will also influence the hydrolytic degradation pattern of amorphous poly(lactide)s. The brittleness of poly(lactide)s poses problems for their successful application in dynamically loaded fracture fixation devices. Rubber modification is a very effective tool for improving the impact resistance of thermoplastic and thermosetting polymers. Semi-crystalline and amorphous copolymers of lactide and glycolide could be modified using two types of fully biodegradable rubbers based on ϵ -caprolactone. Also, linear ABA and star-shaped AB block copolymers have been synthesized using multifunctional alcohols as initiators for the ring-opening polymerization. In this way the influence of crystallinity of the matrix, type of rubber, chain architecture and interfacial adhesion on the impact resistance of lactide copolymers could be investigated. With a poly(L-lactide-co- ϵ -caprolactone) rubber semi-crystalline poly(lactide)s could be impact modified to a greater extent than amorphous non-crystallizable lactide matrices. Blends and linear and star-shaped block copolymers with a more incompatible poly(trimethylene carbonate-co- ϵ -caprolactone) rubber yielded supertough materials that did not break in Izod notched impact testing. At a rubber content of around 20 weight percent a sharp transition from brittle to ductile deformation was observed for the blends.

Star-shaped macromolecular structures display interesting rheological behavior and mechanical properties. Enhanced phase separation in blends and a lower melt viscosities might result in better rubber toughening and easier processing of star-shaped poly(lactide)s. From linear and 6-arm star-shaped poly(D,L-lactide-co-glycolide)s blends with biodegradable rubbers were prepared and their mechanical properties and *in vitro* degradation evaluated in relation to thermal properties and physical aging. It appeared that the tensile and impact properties of these blends are hardly influenced by matrix composition and chain architecture, but predominantly vary with the amount of rubber. The *in vitro* hydrolytic degradation rate of the blends could be enhanced by the incorporation of glycolide into the poly(D,L-lactide) matrix. The opposite effect was noticed when the rubber content of the blends was increased. Surprisingly, blends based on 6-arm star-shaped poly(D,L-lactide-co-glycolide) retain their mechanical properties for a longer period than blends with linear matrices of comparable composition. This could be related to the more severe and faster physical aging of the linear copolymers compared to that of star-shaped copolymers. So, by varying the chain architecture and glycolide and rubber content the degradation pattern (chemical aging) of lactide based blends can be tuned to the requirements of the application in mind.

The starting point in the synthetic route to blocky star-shaped structures (star AB's) is a low molecular weight hydroxyl terminated star-shaped rubber core. This rubber core can be synthesized with polyol initiators. A matter that still needs to be resolved was whether the functionality of the initiator is preserved as end-groups of the rubber macro-initiator on to

which the lactide copolymer branches can be attached. For this purpose we synthesized linear and star-shaped trimethylene carbonate/ ϵ -caprolactone copolymers using different polyol initiators and catalysts. From the results of SEC the structure factor g could be measured and the functionality f of each star-shaped polymer could be calculated. With D-sorbitol star-shaped rubbery copolymers could be synthesized with average functionality between 4 and 6, indicating that the synthesis of true 6-arm stars is very difficult.

Unexpectedly, when dipentaerythritol was used as an initiator for trimethylene carbonate/ ϵ -caprolactone copolymers, cross-linked rubbers were obtained. Possibly, a transesterification reaction between trimethylene carbonate and initiator has led to the 'in situ' generation of cross-linking species.

Furthermore, the synthesis and mechanical properties of some 4- and 6-arm star-shaped block-copolymers have been described. Star-shaped lactide/glycolide block-copolymers with a poly(trimethylene carbonate/ ϵ -caprolactone) rubber core based on D-sorbitol ($f=6$) showed excellent mechanical properties. Even at relatively low rubber contents ductile tensile behavior was observed, indicating extensive toughening.

The heat sensitivity of poly(lactide) constitutes a serious problem for its processing and may obstruct large scale application. Hydroxyl end-groups seem to play an important role in the thermal degradation mechanism. Therefore, the effect of end-group modification on the thermal degradation of poly(lactide)s was investigated. Poly(L-lactide) and poly(D,L-lactide) of different molecular weights could be end-group modified with acetic and benzoic anhydride and with phenyl isocyanate.

Dynamic and isothermal TGA showed that end-capping of poly(lactide) resulted in thermal stabilization, the nature of the end-capping agent being of little significance. Unfortunately, the onset temperature of thermal decomposition could not be increased, but the thermal degradation rate of poly(lactide)s could be lowered by end-group modification. Furthermore, it was found that the tacticity of poly(lactide)s plays a role in thermal stability, causing end-capping to be more beneficial for atactic poly(D,L-lactide) than for isotactic poly(L-lactide). Introduction of ϵ -caprolactone units in the poly(L-lactide) chain by copolymerization resulted in a substantial reduction of thermal stability with increasing comonomer content, indicating that such sequences act as 'weak links'.

As with most scientific research, this thesis presents some answers, but raises more questions. Future research in the field of poly(lactide)s should aim at a thorough rheological characterization of linear and star-shaped poly(lactide) and its (block-) copolymers. Measurement of the plateau modulus could confirm the values for v_e and C_∞ that were established in this work with other techniques.

The presumably lower melt viscosities of star-shaped lactide copolymers and the adverse effect of a higher number of hydroxyl end-groups on their thermal stability create an interesting paradox as far as their processing behaviour is concerned. Hence, if star-shaped structures are going to be used, end-capping will become a very important issue. Also, the

impact of thermal degradation on molecular weight and mechanical properties should be looked into.

An important factor in rubber toughening is the morphology of the blends, which is influenced by the compatibility of the components, rheological behaviour and processing parameters. This requires a more thorough investigation than the preliminary studies carried out with phase-contrast microscopy.

Finally, the concepts proposed here for a new class of tough and biodegradable materials with adjustable properties have to be confirmed clinically. Amorphous linear poly(D,L-lactide) toughened by blending has already been tested in the mandible of dogs with satisfactory short-term results. Further experiments will have to prove whether rubber modified star-shaped lactide/glycolide (block-) copolymers show more favorable characteristics during *in vivo* application.