POLYMERIC MATERIALS AS BIOMATERIALS UNDER PARTICULAR CONSIDERATION OF BIODEGRADABLE POLYMERS

Hartwig Höcker

Textile Chemistry and Macromolecular Chemistry, Center of Competence of Biomaterials and Interdisciplinary Center of Clinical Research, University of Technology Aachen, Germany

Abstract: Biomaterials may be defined as artificial materials which fulfill the mechanical requirements and interact with the biosystem they are in contact with in same way as a natural material would react in the same place. While the requirements of mechanical properties can be reached by suitable organo-polymeric and inorganic materials the interfacial biocompatiblity is neither understood in all its complexity nor can be fulfilled by any of the applied materials. Surface modification and characterization with greatest scrutiny and the observation of the answer of selected parameters of the biosystem are a subject of utmost interest. A few examples will be presented. In the long range, however, it has to be considered that any material is degraded and hence should present continuously a renewable biocompatible surface. On the other hand, materials are desired which deliberately are biodegradable. Presently available materials are polylactides and copolymers. An alternative could be presented by polydepsipeptides because of two reasons, (i) the local concentration of acid formed upon degradation would be reduced as compared to polylactides which in certain cases might be advantageous and (ii) the aminoacid units could carry side groups with bioactive molecules attached. Therefore, a new method of acylation of an aminoacid with a hydroxyacid is presented as well as the cyclisation to result in the cyclic depsipeptide and the polymerisation to yield the polydepsipeptide. The microstructure of the polymers, the thermal properties and the degradation behaviour is presented.

 CCC 1022-1360/98/$ 10.00

INTRODUCTION

Diseases and accidents as well as the increasing expectation of life require replacements of parts of the human body. Transplantations only present a very restricted solution since suitable material is not available in sufficient amounts and ethical constraints reduce the availability further. Another solution is the use of artificial materials or implants which bear the risk of unknown performance. Although implants are used in large numbers the risk cannot be calculated because the interaction of the biosystem with the implant is widely unknown. Hence companies withdraw their material from the market. Thus there is an urgent need to develop knowledge on the interaction between a material's surface and the biosystem.

In reality, all kinds of materials implanted into the body are degraded; thus, eventually a material has to be developed which continuously presents a biocompatible surface to the biosystem, and/or which is deliberately degraded and continuously replaced by natural tissue.

DEFINITION AND SURFACE MODIFICATION/CHARACTERIZATION

Because of the missing knowledge of the response of the biosystem to an artificial material a definition of what generally is called biocompatibility is not available. It is self-evident that an implant material must not provoke thrombogenic, toxic, allergic or inflammable reactions, must not destroy cells and modify plasmaproteins and enzymes, must not provoke carcinogenic effects or modify the surrounding tissue.

A biomaterial rather should have the ability to be integrated into the biosystem, should suppress undesired reactions such as inflammation and should stimulate desired reactions in the respected place. Thus it becomes evident that a biomaterial should be decorated with bioactive substances which are able to provoke a well-defined reaction of the biosystem such as enhancing the endothelial cell growth or in general cell proliferation and in-growth or prohibiting cell adhesion and/or cell proliferation. Thus, according to Ikada, biocompatibility is not confined to mechanical or chemical biocompatibility but also concerns the interfacial biocompatibility[1]. To learn more about the interaction of the biosystem with an artificial material surface modification and characterization might be a useful approach for the beginning.

The surface of a biomaterial after having come into contact with liquors of the body is immediately covered with proteins in a very unspecific way. This causes the adsorption of platelets and eventually the formation of a thrombus when the body liquor is blood. Natural vessels are covered with a monolayer of endothelial cells which in the normal state exclude deformation of a thrombus. They grow on a basal membrane and adhere to proteins, in particular fibronectin which presents an endothelial cell-binding domain consisting of the pentapeptide sequence, GRGDS.

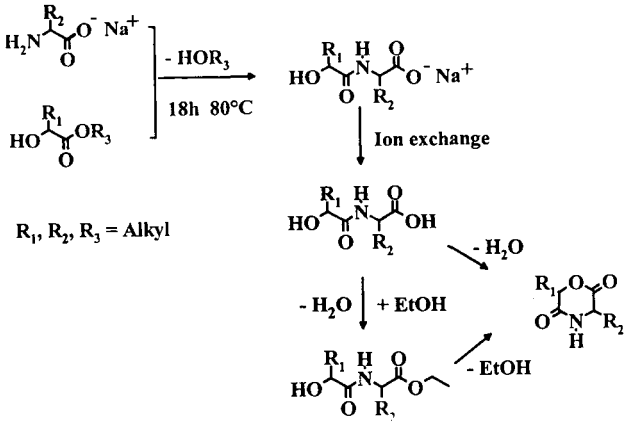
The surface of a material, in particular of a blend or a block copolymer containing hydrophilic and hydrophobic components is determined by the surrounding upon preparing the device. Different parameters of hemocompatibility indicate that there is a certain window of hemocompatibility for materials which are within this window with respect to their ζ-potential and with respect to the ratio of dispersive and polar contributions to their surface tension[2].

A more effective modification of the surface may be achieved by chemical modification or by glow discharge treatment. By these methods a certain hydrophilicity may be generated as well as the presence of oligopeptide sequences and oxidized sulfur groups which provide an excellent basis for the adsorption of fibronectin, and the adsorption of fibronectin shows a linear correlation with the cell-growth on these surfaces[3]. When fibronectin is linked covalently to a polymer surface via a spacer the cell proliferation is enhanced and after seven days even overcomes that of the reference material (thermanox)[4]. A hydrophobic surface such as that of the fully aromatic polyethersulfone tends to strongly adsorb fibrinogen thus being highly thrombogenic. The grafting of hydroxyethylmethacrylate to the surface reduces both the contact angle and the fibrinogen adsorption thus presenting an athrombogenic surface[5].

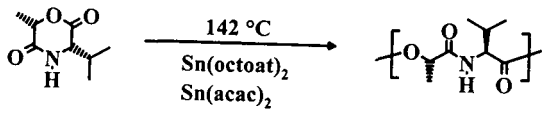
POLYDEPSIPEPTIDES

The most common biodegradable polymer used for medical applications is polylactide and its copolymers. An alternative might be the use of polydepsipeptides. They represent alternating copolymers of α-aminoacids and α-hydroxyacids.

The linear depsipeptide is readily prepared by the reaction of the sodium salt of an amino acid and the



alkylester of a hydroxy acid during 18 h at 80°C (aminolysis of the ester group)[6]. After preparing the free acid of the depsipeptide by using a ion exchange resin the linear depsipeptide is cyclised in the conventional way and the cyclic depsipeptide is polymerised in a ring-opening fashion at 142°C with



$Sn(octanoate)_2$ or $Sn(acac)_2$ as catalyst or initiator to yield the polydepsipeptide. The time conversion curves are shown in Fig. 1 indicating the increase of the reaction rate with increasing catalyst

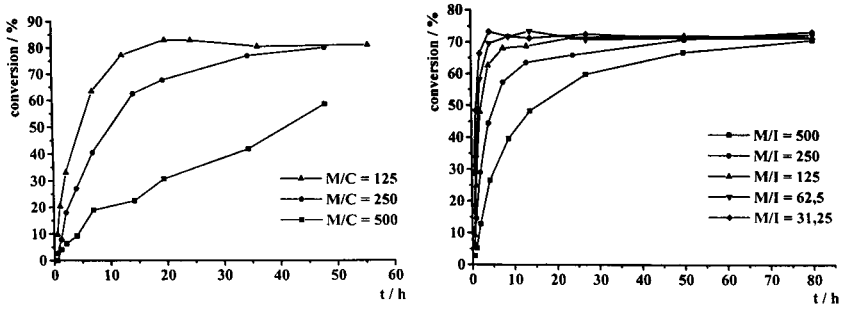


Fig. 1 Time conversion curves for the ring opening polymerization of the cyclic depsipeptide (Lac-Val) with a) $Sn(octanoate)_2$ as catalyst (initiator: ROH) and with b) $Sn(acac)_2$ as initiator

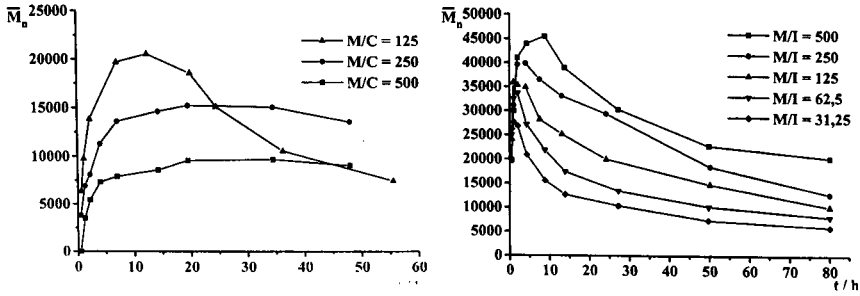


Fig. 2 Molecular weight as a function of reaction time for the systems described in Fig. 1

concentration. Fig. 2a shows that in the initial range of the reaction the molecular weight increases with decreasing molar monomer/$Sn(octanoate)_2$ ratio. This behaviour indicates that tin octanoate is a catalyst rather than an initiator and that the initiator very probably is an alcohol being present as an impurity. Fig. 2b shows that the result is reversed for tin acetyl acetonate; here the molecular weight initially formed increases with decreasing initiator concentration. In both cases, however, the molecular weight after the initial period decreases due to transesterification and degradation reactions.

Starting from monomers with S configuration the polymers obtained show some racemisation of the α-hydroxycarboxylic acid (lactic acid) which occurs both during cyclodepsipeptide as well as polymer preparation. The partial racemisation has some consequences for the morphology of the polymers. The polydepsipeptide consisting of glycolic acid and valin and not being subject to racemisation shows the highest degree of crystallinity (Fig. 3). The polydepsipeptide consisting of lactic acid and valin and obtained with tin octanoate as a catalyst shows a significantly lower degree of crystallinity due to partial racemisation of the lactic acid unit and the same polydepsipeptide obtained with tin acetyl acetonate is completely amorphous due to a higher degree of racemisation of the lactic acid unit.

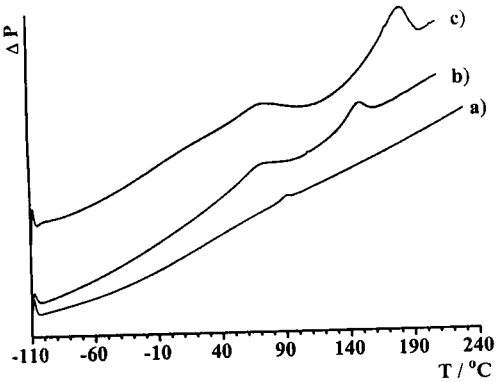
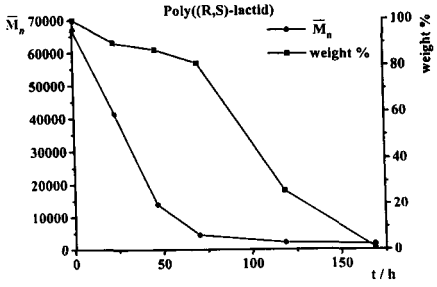
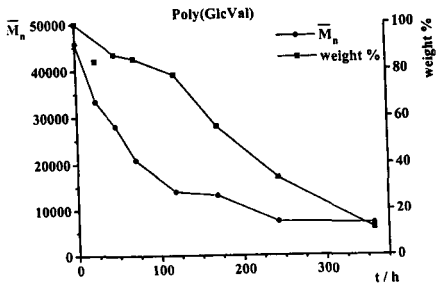


Fig. 3 Thermal behaviour of polydepsipeptides. a) Glyc-Val, b) Lac-Val ($Sn(octanoate)_2$ Lac-Val ($Sn(acac)_2$).

The hydrolytical degradation was achieved in a 0,01M phosphate buffer solution with pH 7,4 at 70°C. Fig. 4 indicates the degradation behaviour of poly(R,L)-lactide as compared with the two polydepsipeptides consisting of glycolic acid and valin and lactide acid and valin. It is clearly seen that there is an increasing stability against hydrolysis in the order of polymers mentioned.
Poly(RS)-lactide is a rather hydrophobic polymer. The polydepsipeptide consisting of lactic acid and valin already has a significantly lower contact angle. Block copolymers consisting of a middle-block of poly(ethylene oxide) and two terminal blocks of a polydepsipeptide consisting of lactic acid and valin show only a further significant decrease of the contact angle if the poly(ethylene oxide) middle-block has a molecular weight significantly larger than 4000, i.e. 8000 in the given example.





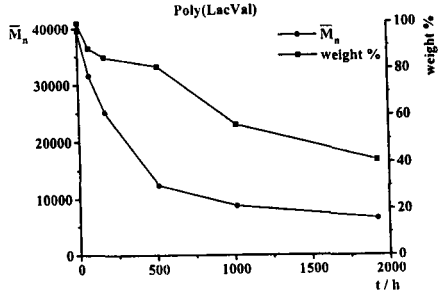


Fig. 4 Degradation of polydepsipeptides as compared with polylactide in 0,01 M phosphate buffer, pH 7.4, 70°C

CONCLUSION

To learn more about the interaction of the biosystem with an artificial material extensive studies with well-defined surfaces have to be accomplished. The surfaces may comprise fully artificial ones with a particular hydrophilic/hydrophobic balance or even surfaces with covalently linked bioactive molecules such as proteins, interleukines, proliferating and antiproliferating agents etc. Biomaterials which are degradable upon demand are desirable in many cases, in particular when they are decorated with bioactive molecules which control the bioanswer to the implantat of the respective material, e.g., cell proliferation and in-growth. Thus, the artificial material may be replaced step by step by biological material. Polydepsipeptides may provide materials which because of their hydrophilicity and retarded hydrolysis will be of some value in the future.

Literatur

[1] B.D. Ratner, *„Biomedical Applications of Synthetic Polymers"*, in: The Synthesis, Characterisation, Reactions and Applications of Polymers, Vol. 7, Pergamon Press, 201 (1989)

[2] D. Klee, B. Severich, H. Höcker, Makromol. Chem., Macromol. Symp. **103**, S. 19-31 (1996)

[3] D. Klee, V.Villari, B. Dekker, H. Höcker, J. of Materials Science: Materials in Medicine, 592-595 (1994)

[4] J. Wirsching, D. Klee, H. Höcker, A. Dekker, C. Mittermayer, Proc. of the 12th European Conf. on Biomaterials, Porto, 10.-13. Sept. 1995 (1995)

[5] H. Thelen, R. Kaufmann, D. Klee, H. Höcker, Fresenius J. Anal. Chem. **353**, S. 290-296 (1995), in press.

[6] DE 19513398, V. Jörres, H. Keul, H. Höcker