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Development of a polymer stent with shape memory effect as a drug delivery system

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The article presents a new concept for vascular endoprothesis (stent). Almost all commercially available stents are made of metallic materials. A common after effect of stent implantation is restenosis. Several studies on metal stents coated with drug show, that the use of a drug delivery system may reduce restenosis. The purpose of this work is to develop a new stent for the drug delivery application. The shape memory properties of thermoplastic polyurethane allow to design a new fully polymeric self-expandable stent. The possibility to use the stent as a drug delivery system is described.

1. Introduction

Over 50 000 stents are applied annually in Germany in order to avoid heart attacks. In spite of more than 20 years of research into stent development, none of the currently available products are ideally suited for any clinical situation. The treatment of vascular obstruction diseases (stenosis) with revasculating methods such as catheter dilatation and re-canalization does not always result in the desired outcome. After the expansion of the obstructed vessel, there is the chance of an immediate recoil and a re-constriction of the vessel walls. Furthermore, dilatation leads to hardly controllable hyperplastic intimae reactions, especially in the coronary arteries. This may result in a restriction of the flow volume and thereby may lead to the necessity of further therapies or a bypass surgery (Fig. 1).

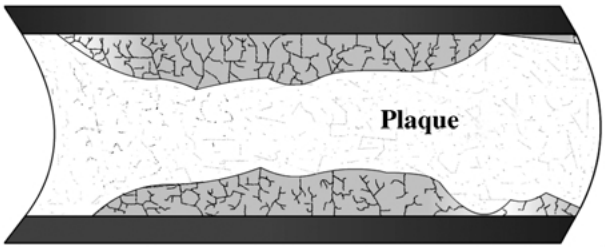

Figure 1 Plaque within a blood vessel.

Therefore, an endoprotheses is being implanted in the vessel after a revasculating treatment in order to avoid these complications, and to ensure a durable enlargement of the flow volume. There are several design of these minimally invasive implanted vascular endoprothesis (''stents'') for coronary application, among which are tubular mesh, slotted tubes or coils [1, 2]. Different materials have been used for stents manufacturing. According to the implantation procedure and the long-term application, these materials must fulfil several rigorous physical, mechanical and chemical properties. Dependent on the stent design, the used material have to have enough plasticity (an expandable stent), sufficient elasticity or shape memory properties (self-expanding stent). Because the stents surface comes into contact with body fluids, which are very aggressive and may cause the corrosion of metal, very high resistance to corrosion and chemical stability is required. Moreover, good biocompatibility is obligatory.

The most recent available stents are manufactured in stainless steel 316L, but tantalum, nitinol, cobalt alloy and platinum iridium are used as well [3]. While the mechanical requirements can be fulfilled to a large extent, undesired side effects with blood or tissue still represent an incompletely solved problem. Third body reactions with ongoing intimae proliferation through the stent grid are, along with recoil, the most frequent reasons for failure. Coating of the stent surface with noble metals (gold, platinum, etc.), biocompatible polymers or biological substances like fibrine or heparine has been applied in order to reduce intimae proliferation and thrombosis [4–10].

However, the stent technology let to avoid heart attacks and reduce the rate of coronary artery disease – stenosis, still there is a danger of re-stenosis complication. The prevention of thrombus formation and neointima development in the stented artery is the challenge of current research. A satisfying solution remains yet to be found. The utilization of the shape memory effect of polymers as developed by the polymer engineering group of TU Berlin allows the application of a fully polymeric stent for the first time, which enhances the use of the stent as drug delivery system and thereby improves the post-surgery course through specific application of medicament. The research aims to manufacture a polymer stent that can be applied with

minimally invasive effects due to the shape memory behavior.

2. Material and method: shape memory effect of polymers

One explanation of the appearance of the shape memory effect by polymers are physical changes in polymer microstructure (Fig. 2). This effect is present by materials, which consist of two phases, a frozen phase and a reversible phase. In some kinds of semi-crystalline polyurethane's the amorphous and crystalline phases are designed to be the reversible and the frozen phase respectively [12]. The deformed shape will be fixed, if the micro-Brownian movement of a polymer chain will be frozen. It appears, when the deformation proceed within the temperature range between glass transition temperature (T_g) of amorphous phase and the melting temperature (T_m) of crystalline phase and the sample is subsequently cooled below T_g, under constant strain afterwards. The reheating of polymer to the temperature range between T_g and T_m results in the original shape recovery.

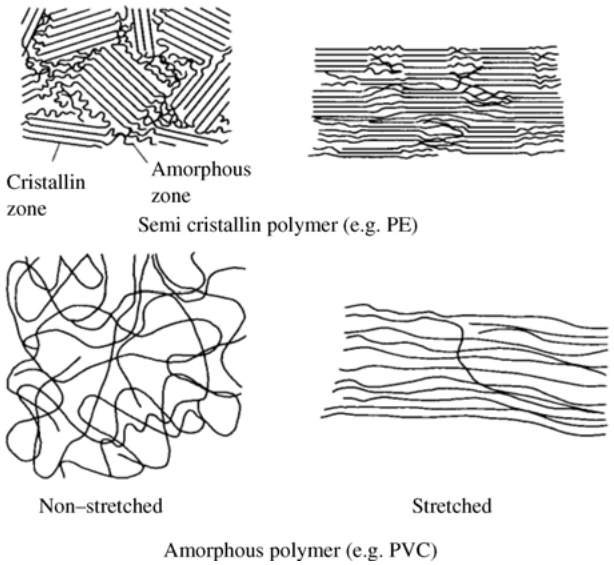

Figure 2 Reorientation of macromolecules due to elongation of a polymer sample.

The fact that through the orientation of macromolecular chains and structures, the shrinking behavior of thermoplastic polymers can be influenced, is being utilized in industry for the manufacture of heat shrinkage products. These products are used, depending on their later application, in the form of foils, tapes, hoses and alike. They will shrink when heated, thereby partially returning to the original, unoriented molecular structure, which they possessed prior to the low-temperature deformation. These products ''memorize'' their original shape and therefore show a shape memory effect. Today's shrink products find their application mainly in the wrapping, textile, heavy electric current, general electronic and construction industry. The activation temperatures of these established applications lie between 80 and 120 °C [13–15].

3. The polymer stent

The field of applications of a polymer stent was demonstrated in pre-trials. Samples from a suitable polymer (thermoplastic polyurethane) were manufactured by injection molding, extrusion and immersing from solution. A deformation in the form of an elongation is then brought upon these samples at activation temperature (the temperature with maximum recoil) by use of a custom-made test-bench. After relaxation and cooling below 8 °C the shape of the tube is stable. The elastic recoil of a sample is activated at its specific activation temperature only (Fig. 3).

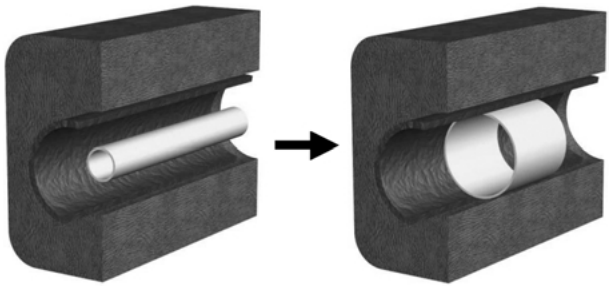

Figure 3 Principle of the shape memory effect: prior to application (left), after reset (right).

The recording of the recoil behavior is conducted within the custom-made test-bench by a PC. By a suitable choice of parameters, the activation temperature can be lowered to temperatures as low as 15 °C. The maximum value of the activation temperature is restricted by the sensitivity of blood. An important aspect of the research is to find the optimum elongation and recoil parameters. On the one hand, a sample with a low activation temperature advantageously recoils faster at body temperature, on the other it requires permanent cooling during storage and application. In the pre-trials an axial deformation of more than 200% was achieved. An increase of approximately 100% of the diameter at activation temperature in tubular samples was reached.

4. Results

4.1. Demonstration of the shape memory effect

In order to demonstrate and optimize the shape memory effect, elongation and recoil tests have been carried out with suitable samples. Such an experiment is presented in Fig. 4.

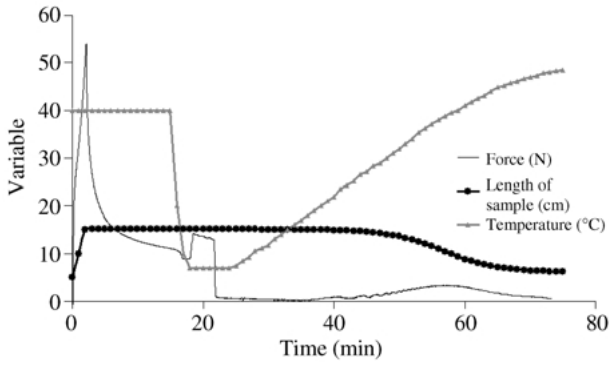

Figure 4 Diagram of a complete test run.

The diagram in Fig. 4 shows a complete test run with the following phases: elongation, fixation and recoil.

Elongation. A sample of thermoplastic polyurethane is elongated at constant temperature to approximately 200%. The resulting force needed for elongation increases continuously with the deformation.

Fixation. After having reached the desired elongation, the sample is held at this length. The stress in the polymer sample relaxes partially, and the resulting force decreases exponentially. After fast cooling of the sample, the residual force is zero, the shape of the sample is frozen in.

Recoil. The temperature is increased with a heat rate of 1 °C/min, and the sample is then recoiling in correspondence with the temperature. In Fig. 4 it is obvious that the retracting stresses reach a peak at the activation temperature. This illustrates that maximum recoil can be expected in this temperature region.

Fig. 5 presents the measured recoil as a function of temperature. Indeed, maximum recoil is seen to occur at the activation temperature. Ideally recoil is restricted to a very narrow temperature window, i.e. recoil mainly takes place at the activation temperature. The optimization of elongation and recoil parameters is one of the research aims of this project.

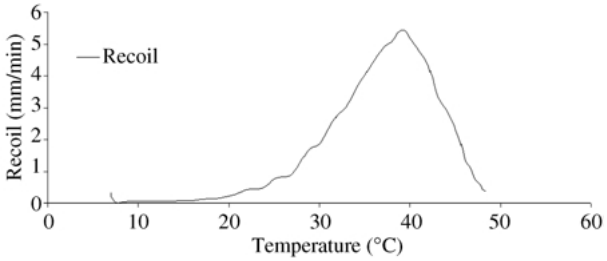

Figure 5 Reset over temperature.

4.2. Relevance for clinical application

The main advantage of a polymer stent is the potential of a having a positive influence on the post-surgery course through specific application of drugs. Among the others, the thrombolytic agents, antiplatelet drugs and anti-coagulants are potential drugs for these application. The controled release of drug in the delivery system is most important, and therefore it is necessary to investigate the loading and release of the medicines.

Loading of medicines. Depending on the various manufacturing methods (injection molding, extrusion, dip-coating), there is a range of possibilities to introduce the drug into the polymer. In principal, the active substance can be added during polymerization or processing. In our case the drug was added to the polymer during the processing by injection molding and dip coating. The handling of the additive, the maximum uptake of medication and the influence on the properties of the polymer were studied. A variety of active agents (anti-coagulants, anti-inflaments, etc.) were examined.

Drug release. In a complying model, drug release as a function of time was investigated. Fig. 6 shows the

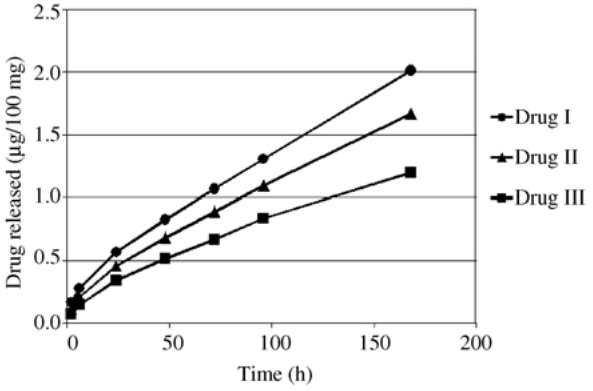

Figure 6 Release rates.

release rates for three different active agents, which had initially a concentration of 10% weight in the polymer.

A continuous release over a long period of time is evident. Further analysis showed that a continuous release can be expected at lower drug concentrations as well, which will result in a positive influence on the healing process.

Another point of interest is the visibility during application. This was achieved through the addition of radiopaque material. After a variety of materials were studied with regard to miscibility, processing and compatibility, barium sulfate was chosen as the preferred material. A sufficient visibility under X-ray was obtained and the influence on the shape memory effect was quantified.

Finally, the implementation of the application in an appropriate model has to be examined. The present method of choice is shown in Fig. 7.

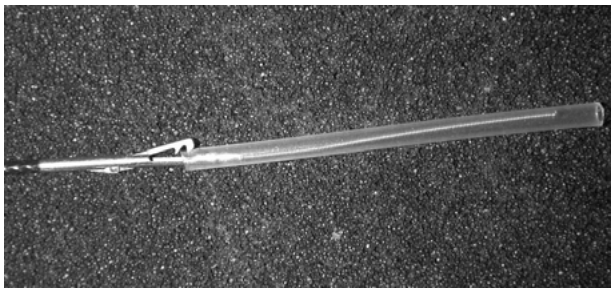

Figure 7 Pre-applied stent.

The elongated stent (length approximately 30 mm) is introduced in a catheter by the means of pliers. Due to the utilization of the pliers it is possible to place the stent exactly at the desired location and to guarantee ideal positioning. This application method is currently studied in detail in *in vitro* trials.

5. Discussion and outlook

The research aims to improve stents, which are used in constricted coronary blood vessels. Future progress and work can be divided into two topics, on the one hand the possibility of specific release of medication in a restricted area within the organism, on the other hand the application of more complex polymer implants with shape memory effect.

The polymer stent represents an innovative alternative

to the conventional stent, due to less costly manufacturing compared to metal stents, as well due to a reduced risk of complications because of drug loading. Therefore, a fast acceptance of the polymer stent by the surgeons can be expected.

The use of the polymer stent as a drug delivery system will lead to a significant reduction of restenosis and thrombosis. An improved biological tolerance in general can be expected when utilizing biocompatible materials, possibly with especially activated or modified surfaces.

Beside anti-coagulation medication or drug with influence on cell growth, completely different active agents may be considered. By imposing less strain on the organism, the range and intensity of side effects can be reduced dramatically.

Active agentus can be added to the polymer in rather high doses. A fraction of up to 35% by weight can be realized. This high dosage and a high release of medication in the blood flow might allow for an application of the polymer stent also as a drug delivery system, for example, in a cancer therapy. A loaded polymer stent may be placed in the very vessel that provides blood to the tumor. Thereby a locally restricted, continuous therapy can be realized, and the organism is less burdened with unwanted side effects. Due to the influence of the specific release of active agents, which impinge on blood coagulation and cell growth at the inner walls of the blood vessel, an increased success rate is expected. Hospital costs can be reduced and the patient is less burdened through the avoidance of secondary surgery (which is typically necessary in the form of bypass surgery after re-stenois) by application of a polymer stent.

The manufacturing of the raw tube by injection molding or dip-coating technology from solution guarantees an economical production. The degree of automation of the elongation process is critical for the productivity of the manufacturing process. Compared to the production of conventional metal stents, which are slotted by laser, the production costs are reduced by more than 50%.

The shape memory effect of the polymer stent is not restricted to the cardial area, but may be applied in other organs too, e.g. trachea, oesophagus, urethra, etc. when troubled by stenosis or tumors.

Furthermore it seems to be possible to place foil elements inside the stent, which unfold when the stent expands, functioning as a check valve. Through this capability of minimally invasive application of a cardiac valve and thereby reduction of strain put on the patient, short term use like bridging the time to a transplant is both possible and useful. A support in the case of insufficiency of the venous cardiac valve may be achieved. A gall bladder implant in order to avoid reflux is also a possibility.

The results so far can be utilized to exactly set the parameters in such a way that allow the optimal result in a clinical application. In order to achieve this, the test bench as well as the deformation process must be optimized further. The processing and the mechanical properties of drug-loaded stents are yet to be examined.

Before trials with animal models can be carried out, the necessary catheter systems have to be modified in order to guarantee reproducibility of the application.

After successful animal experiments, the efficiency of polymer stents with drug delivery applied to a larger patient group must be proven in a clinical study. Furthermore, the concept of polymer stents has to be engineered for industrial production. A production line has to be designed, built, and certified.

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