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Resorbable continuous-fibre reinforced polymers for osteosynthesis

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Four institutes from three countries in the European Union have collaborated under the BRITE–EURAM framework programme for the development of processing technologies for resorbable osteosynthesis devices. The devices should be continuous-fibre reinforced, and the technology should offer the possibility of orienting the fibres in the main trajectories. Poly-L-lactide and poly-L–DL-lactides have been synthesized for reinforcement fibres and matrix material, respectively. Melt-spun P-L-LA fibres of a strength of 800 MPa have been embedded in an amorphous P-L–DL-LA 70:30 matrix by compression moulding. Ethyleneoxide sterilized samples have been tested *in vitro* and *in vivo*. A satisfying bending modulus has been reached (6 GPa). Yet with 50% strength retention after ten weeks, fast degradation occurred that could be related to residual monomers. By this fast degradation 70% resorption after one year could be observed in the non-functional animal studies in rabbits. There was only a mild inflammatory reaction, which confirmed the good biocompatibility of the materials even during the resorption period. Further effort has to concentrate on the reduction of initial monomer content. The great advantage of the processing method to orient fibres in the device will be utilized in prototype samples, e.g. an osteosynthesis plate with fixation holes. © *1998 Chapman & Hall*

1. Introduction

Today osteosynthesis implants are mainly made of metals, which are removed after healing. They may evoke allergic reactions by electrical potential differences, and underly corrosion. Their high stiffness may act as stress over-protection, which hinders healing of the bone [1].

Polymeric implant materials have been developed reinforced by carbon fibres [2, 3] or even thermoplastic fibres [4]. The bending modulus can be adjusted by fibre content and orientation; 50 GPa has been given as an example [2]. Additional features of thermoplastic polymeric implants are the chance to form them intraoperatively, and their transparency regarding X-ray beams. But still a second operation for removal is needed.

For the past 30 years, resorbable polymeric materials have been investigated for osteosynthesis, some of these materials were brought to the market in the last decade. Non-reinforced materials on a base of polylactides [5, 6] have low bending stiffness and shear strength. The reported modulus of 4–6 GPa was determined at room temperature, most probably in the dry stage. The selfreinforced materials of the Finnish group [7] and others [8, 9] have quite good mechanical properties (bending stiffness up to 8 GPa at room temperature, but in the wet stage). With selfreinforcement, combination of materials for a retarded degradation time is not possible. Rather complicated structures, like reinforced fixation holes in plates, cannot be produced, because of the unidirectional pultrusion process.

In technical applications thermoplastic polymers are reinforced usually by non-thermoplastic high modulus fibres (glass, carbon, aramide) [10, 11], which are highly temperature stable, a requirement for easy thermal processing. Chopped fibre reinforced polymers are processed economically by injection moulding. Improved mechanical properties can be reached by using continuous fibres. Their processing by pultrusion or compression moulding is more complicated and less economical. Therefore their use is limited to highly advanced technologies. The matrix can be fed to the reinforcement fibres in form of powder, as fibres, by solution or by melt impregnation. Using hybrid yarns, three-dimensional braided

structures are produced for adapted fibre orientation [10]. In the next step the matrix has to be plastified at a temperature above its glass transition or eventually above its melting temperature and at high pressure. Pultrusion and compression moulding are used to enhance the impregnation and to form the device. Using thermoplastic fibres for reinforcement the processing temperature has to be far below the melting temperature of the fibres, but at the same time the viscosity of the matrix has to be low enough for complete impregnation of the fibres. Today technical applications are restricted to sports equipment [12, 13].

The aim of the project was the development of a processing technique for resorbable continuous-fibre reinforced osteosynthesis devices. This covers the synthesis of resorbable polymers, the spinning of high strength fibres, their impregnation with matrix and the formation of samples for characterization of the material and processing. The samples had to be tested in short and long term tests, and in degradation and simulation tests. Implantation of samples in a limited animal study should show the principal biocompatibility and the *in vivo* degradation of unstrained material.

The development should consider polymers of relevant mechanical performance and degradation kinetics and of an appropriate processability. The use of different polymers should be possible to tune the degradation. The processing must enable orientation of the fibres in the main trajectories. Good fibre–matrix adherence and alignment of the fibres were important in the final shaping. The diffusion of tissue fluids at the fibre–matrix interface has to be prevented.

Polymer synthesis and chemical analysis, fibre spinning and a first impregnation was performed at ITV Denkendorf. At ITF Lyon the materials were formed into testing samples. Sterilized samples were tested *in vitro* at BEL Patras, while the *in vivo* studies were performed at OC Patras. The industrial endorsers, Aesculap AG, Tuttlingen and Péters Laboratoire Pharmaceutique, supported the project work by testing and sterilizing samples.

2. Materials and methods

2.1. Materials

The research has been restricted to polymers of α-hydroxycarboxylic acids with known principal biocompatibility. Polyglycolic acids (PGA) have a very short life-time. Therefore polyesters of the lactic acid have been synthesized by ring-opening melt polymerization using tin-octoate catalysts. Pure poly-L-lactide (P-L-LA) has been produced for reinforcement fibres. The inherent viscosity (i.v.) was in the range 1.5–3.5 dl g^{-1}. For the matrix an amorphous copolymer was chosen. The poly-L–DL-lactide (P-L-DL-LA) 70:30 (i.v., 1.5–2.5 dl g^{-1}) was found to have the most appreciable processing and mechanical properties.

2.2. Processing

Based on the literature, the dry spinning method [14] was chosen first for fibre production yielding the highest fibre modulus. The experiments have shown that production of the large amounts of fibres required could not be realized by dry spinning. Residual solvents and a very slow production speed made this process inefficient.

Alternatively, melt spun fibres of considerable high moduli (7–10 GPa) were developed. Melt spinning allows a considerably high take up speed (up to 700 m min^{-1}) and avoids the extraction of solvents.

Impregnation of fibres was best achieved using a low viscous matrix at processing temperatures. A hot melt impregnation process for technical materials [13] was adapted to the resorbable materials. Very promising results were achieved first with PGA-fibres up to 20 °C below the melting temperature of the fibres. Unfortunately P-L-LA fibres turned out to be less temperature stable. At 150 °C the fibres (T_m, ~180 °C) break, even if a low stress is applied. Also the thermal stability of fibres of complexed P-L-LA–P-D-LA blend [15] was poor despite the increased melting temperature.

Therefore, hybrid yarn technology has been introduced using reinforcement fibres intermingled with fibres from the matrix material. P-L–DL-LA 70:30 was spun into fibres by melt spinning and stretched online to the required cross-section (fineness). Multifilament fibres were intermingled by high pressurized air using a special intermingling nozzle.

Samples of 3 × 10 mm; 1.5 × 5 and 3 mm diameter were produced by compression moulding. The fibre–matrix proportion was between 45:55 and 60:40. The testing samples were unidirectionally reinforced, yet it has been demonstrated that other fibre orientations were possible by textile processing, e.g. braiding.

All materials were sterilized by ethyleneoxide (EtO). The sterilization procedure was evaluated regarding the effect on mechanical properties and inherent viscosity. During EtO sterilization the polymer was exposed to temperatures up to 50 °C and to a humid atmosphere to enhance the penetration of EtO. To evaluate the effect of the gas sterilization on the fibre-reinforced materials 10 × 3 mm samples were sterilized. Sterilization without the usual prehumidification was compared with the normal gas sterilization process, where the samples were prehumidified.

2.3. Test methods

The *in vitro* testing consisted of short term four-point bending, torsion and shear testing relaxation (bending and torsion), cyclical loading and a simulation test (bending and torsion). The testing methods are specified in Table I. Except where otherwise stated mechanical tests were performed at 37 °C in a water bath or were wetted continuously by water at 37 °C. In the simulation tests, cyclical loading was applied until break down of the samples.

For the determination of mass loss the samples were washed three times in distilled water and then dried in vacuum until constant weight was reached. Each single sample was weighed separately before and after the degradation process.

TABLE I *In vitro* test methods

Test method	International standards
Inherent viscosity	ISO 1628 (1); 25 °C; 0.1% chloroform; Ubbelohde 0c
Gas chromatography	ISO/DIS 13 741-1 and -2; 1995-12 (Head space–GC)
Bending test (four-point)	ASTM D 790M-82, II, B (related)
Torsional test	ISO 458-1 (related)
Shear test	DIN 50 141 (related) 21 °C, dry
Bending stress relaxation	No standard, design acc. ASTM D 790M-82, II, B displacement 1.4 mm in 0.4 s; relaxation time 15 h
Torsional relaxation	No standard available, design acc. ISO 458-1 torsion 0.3° in 0.4 s; relaxation time 15 h
Degradation test	ISO-DIS 13781-1995, pH 7.4, 37 °C

Explanted plates were tested in the three-point bending test because of their short length. The results were compared with original samples tested by three-point bending as well.

2.4. Animal test

There are many publications on tissue compatibility and the degradation rate of polylactides. But as both of them are dependent on the processing conditions and on physical properties such as crystallinity, information is first necessary on tissue compatibility, chronic toxicity and on the *in vivo* degradation rate of the polymers as synthesized and processed in that project, before functional tests can be started. Dysfunction of an implant will also cause adverse tissue reaction independently from the implant material.

Eighteen mature New Zealand rabbits were used, whose body weights ranged between 3–4.5 kg. On the tibia of each of the 18 rabbits one plate ($5 \times 1.5 \times 40\ mm^3$) was implanted. The skin was incised laterally through the intramuscular septum down to the bone. The periosteum was left intact in place. A polylactide plate was applied and fixed to the bone using two AO (Arbeitsgemeinschaft Osteosynthese) screws with washers (1.5 mm core of the screw) that were inserted outside the plate pressing it firmly to the bone. In this way a "stable mechanical environment" was achieved avoiding mechanical loading. The right tibia was used as a control, the surgical approach performed and the wound closed in exactly the same fashion as on the left side. Through a medial parapatellar incision the medial femoral condyle was exposed. Drilling was performed in a horizontal fashion (mediolateral) using a 3.0 mm drill bit. A 3.0 mm polylactide pin was inserted aided by a special instrument provided by Aesculap AG.

Following routine closure and draping the animals were left to move freely within individual cages. The implants were retrieved after one, six and twelve months and analysed by histology, inherent viscosity and mechanics, where appropriate.

A second group included three animals to show the relationship between soft tissues–plate–bone in one picture for the early stages. These animals, S1, S3, S6, were sacrificed one, three and six months post-operatively and only undecalcified sections were done.

3. Results

3.1. Sterilization

Inherent viscosity and bending modulus were almost uneffected by EtO sterilization (Fig. 1). The strength decreased by about 8% and did not depend significantly on the sterilization method used. Therefore the usual sterilization process was chosen for future samples.

3.2. *In vitro* degradation

3.2.1. Static four-point bending, degradation

Fig. 2 describes the results of a four-point bending test up to 2 mm deflection over a degradation period of up to 26 weeks of both *in vitro* and *in vivo* degradation. Bending stress and bending modulus remain stable for up to eight weeks, followed by a strong decrease after 12 weeks to less than 50% of the original values. At week 26 only 10% of the original data were measured after *in vitro* degradation: the explanted samples had almost no strength left, and this may be the likely

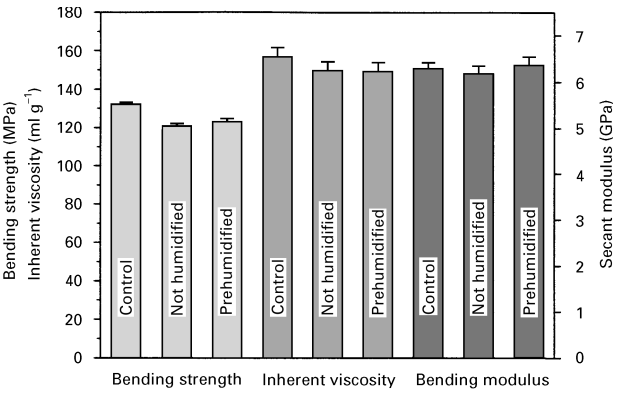

Figure 1 Effect of sterilization method on the material properties of P-L-LA fibre-reinforced P-L–DL-LA 70:30 (sample size, $3 \times 10 \times 60$ mm) following a four-point bending test at 37 °C in water, preconditioned for 1 h.

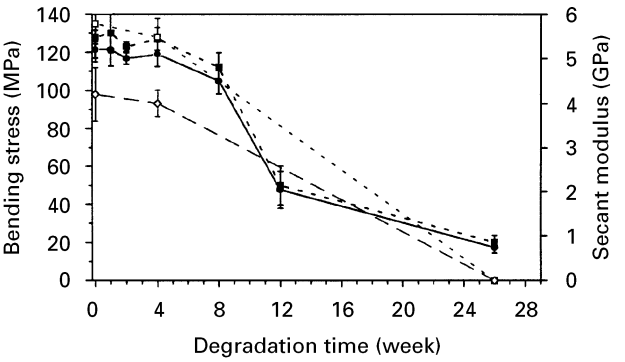

Figure 2 Bending stress (■, □) and secant modulus (●, ○) at 2 mm deflections of sterile P-L-LA–P-L-DL-LA 70:30 (sample size, $1.5 \times 5 \times 48$ mm) conditioned with a buffer solution (pH 7.4, 37 °C). Closed symbols, *in vitro*; open symbols, *in vivo*.

explantation. After 52 weeks all samples had started to disintegrate.

3.2.2. Static torsion, degradation

Fig. 3 shows the change in the secant stiffness in torsion, T (GPa × 10), at 10° torsion, with degradation at the prescribed periods of time.

Torsion modulus of the 3 mm diameter pins increased heavily after immersion for one week in the buffer solution. It remained constant up to eight weeks followed by a decrease to the original value after twelve weeks. At 26 weeks the material could not be measured because it was mechanically degraded.

3.2.3. Relaxation test

Fig. 4 shows the stress (per cent of initial stress S_0) of 1.5 × 5 and 3 × 10 mm plates against time under relaxation loading in a four-point bending test. A displacement of 1.4 mm was between the linear portion of the stress–strain curve.

The very strong relaxation of stress down to 10% of the starting value was very surprising. The pure matrix control measurement (P-L–DL-LA 70:30) showed similar results. Relaxation tests of the pure matrix at room temperature under dry conditions came to a value of 78% after 2 h and decreased further to 65% over 12 h.

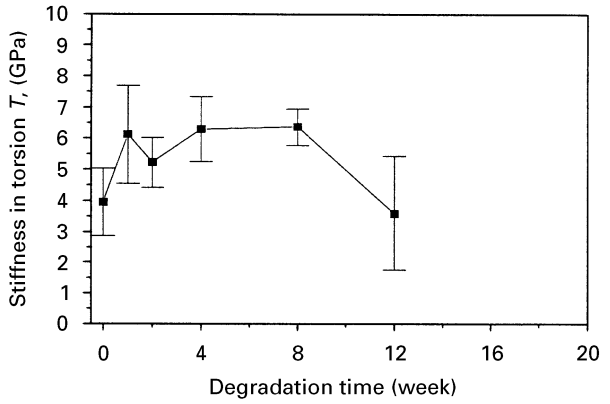

Figure 3 Variation of secant stiffness in torsion, T, at 10° torsion with degradation time (tested in buffer solution, pH 7.4, 37 °C).

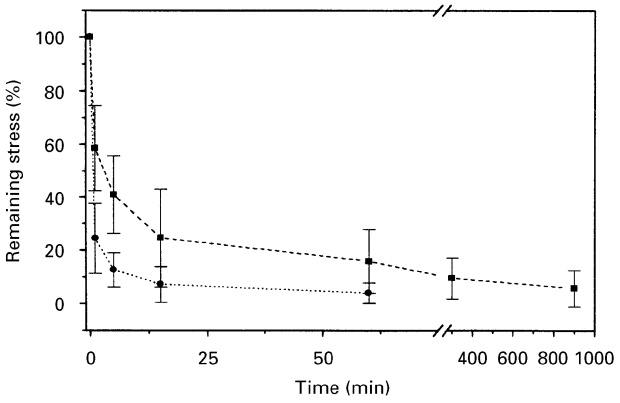

Figure 4 Remaining load during four-point bending relaxation test with time for 1.5 × 5 (●) and 3 × 10 (■) mm plates (buffer solution, pH 7.4, 37 °C; deflection, 1.4 ± 0.2 mm; rise time, 0.2 s). S_{max} = 299.81 ± 117 (n = 4) and 57.35 ± 10.1 (n = 5) MPa for the 3 × 10 and 1.5 × 5 mm plates, respectively.

3.2.4. Shear test

The shear force of the 3 mm pins was tested at room temperature after conditioning at 37 °C in water for 1 h. A shear strength of 104 ± 4 MPa was obtained. Comparing an injection moulded, non-reinforced PLA-pin, this result confirms earlier observations that fibre reinforcement increases the shear strength by a factor of ~2.5.

3.2.5. Inherent viscosity

The inherent viscosity as a measure of the molecular mass decreased very quickly at the beginning, but that decrease was retarded at the eight week period (see Fig. 5). This can be explained by a decrease of the molecular mass of the matrix, which reached a low level after eight weeks, but still remained in place. After 26 weeks the matrix started to resorb. The fibres remained in place, their contribution to the mixed inherent viscosity increased by the resorption of the matrix. It is not possible to measure the reinforcement fibres and the matrix separately as they are solved in the same solvents.

The mechanical and molecular degradation *in vivo* is almost comparable to the *in vitro* results as far as the observation times are the same. The slower decrease of the molecular mass *in vivo* after four weeks is not confirmed at the half-year values, which are almost identical for degradation *in vitro* and *in vivo*.

3.2.6. Resorption: loss of mass

Fig. 6 shows the remaining mass as a percentage of the initial mass after each degradation period. The measured weights of the samples were in the range

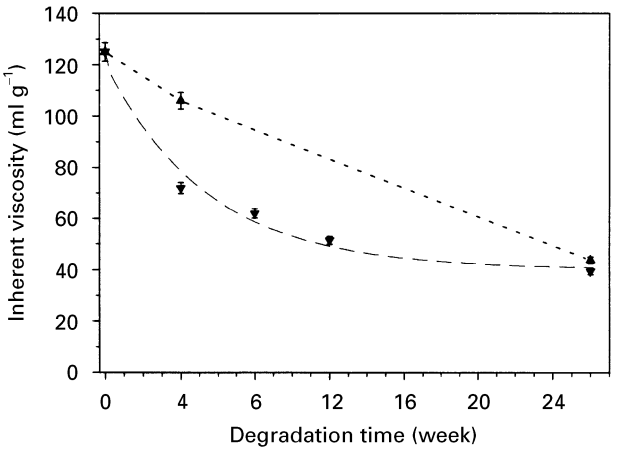

Figure 5 Inherent viscosity of sterile P-L-LA–P-L-DL-LA 70:30 after *in vitro* (▼) and *in vivo* (▲) tests. The *in vivo* test involved implantation in the tibia of the rabbit, the *in vitro* test took place in a phosphate buffer at pH 7.4 at 37 °C.

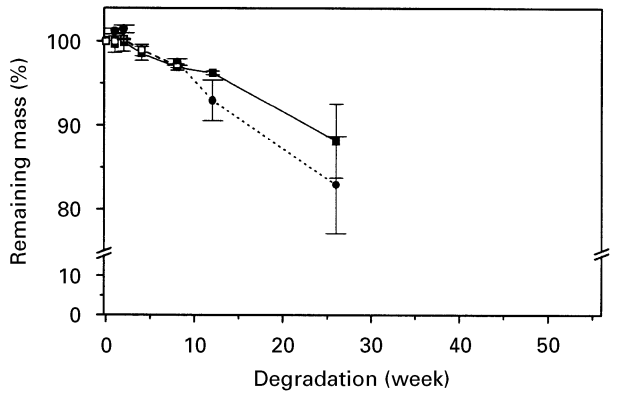

Figure 6 Loss of mass at *in vitro* degradation: (●) 3 mm diameter pins, (■) 1.5 × 5 mm plates, (□) 3 × 10 mm plates.

200–900 mg, while the resolution of the weighting scale was ± 1 mg.

The loss of mass started even at four–eight weeks, which can be related eventually to the extraction of monomers during drying of the samples. The change of mass is in the same magnitude of order as the monomer content.

After 26 weeks the pins started to disintegrate and had a higher mass loss (>15%) than the rectangular samples (>10%). That for these materials the mass is reduced significantly, but still some strength could be measured, can be explained by the fact that the degradation is uneven over the cross-section.

3.3. *In vivo* results

Three of the animals died during general anaesthesia (IV Ketalar) and the remaining 15 were divided in three groups of five each. Unfortunately two more died during the post-operative period and one became infected; the effects on these rabbits were not related to the implants. Hence, at the end four animals in each group were studied.

3.3.1. Histology

3.3.1.1. Around the plate

1. At one month, conventional histology was performed only to the soft tissues surrounding the plate (encapsulation membrane). The plates retrieved were sent for mechanical testing to BEL. Findings:

- fibrous and loose connective tissue;
- no macrophages nor giant cells nor histocytes;
- a few birefrigent particles in only one specimen were identified using polarized light (this was probably due to mechanical damage of the plate during the implantation process).

Undecalcified sections showed fibrous and loose connective tissue ~1.5–2.0 mm wide.

2. At three months, undecalcified sections showed hypertrophy and hypercellularity of the periosteum below the tested material.

3. At six months, conventional histology was performed on the soft tissues around the plate. The plates retrieved were very soft, and two of them were completely destroyed during retrieval. Findings:

- mature connective tissue;
- no macrophages, giant cells or histocytes.

4. At 12 months, undecalcified sections were examined under conventional and polarized microscope using Goldner and Tolouidine blue stains. Findings:

- fibrous connective tissue around the plate (0.8–1.2 mm wide);
- 30–40% of the plate was resorbed;
- the degradation started from both ends of the plate with invasion of vascularized connective tissue;
- macrophages and giant cells appeared phagocytosing the particles of the material (epitheloid type);
- osteolysis around both metal screws;
- for samples S1, S3 and S6: undecalcified sections showing loose connective tissue encapsulation of the plate.

3.3.1.2. Femoral condyles (undecalcified sections)

1. At one month
- fibrous and loose connective tissue around pins;
- new bone formation around the pins within the osseous tunnel.

2. At six months
- fibrous connective tissue with a few macrophages and giant cells;
- approximately 30% of the pin was broken down to fibres and macrophages started phagocytosis of the particles; almost all the matrix has been replaced by fibrous hypercellular connective tissue;
- on the bone-tunnel mixed areas of woven and mature bone were found.

3. At 12 months
- same as at six months, but almost 90% of the pin was broken down to fibres;
- many macrophages and giant cells found around the particles in the phagocytosis process;
- in the tunnel, mixed areas of woven and mature bone; areas of the tunnel started to fill up with newly formed bone.

3.3.2. Resorption in vivo

For the plates
- At one month: no resorption.
- At six months: just started in both ends (sealing defect or mechanical damage)
- At 12 months: 30–40% of the plate (no autocatalytic effect but surface degradation).

For the pins
- At one month: no resorption.
- At six months: 30% resorbed.
- At 12 months: almost 90% resorbed.

4. Conclusions

4.1. Mechanical performance

1. The moduli (bending, torsion) of the devices are satisfying already, but will be increased by higher Young's modulus of the reinforcement fibres.

2. The 2.5 times higher values of the shear strength of the reinforced materials compared with the non-reinforced materials support the importance of fibre reinforcement.

3. Regarding the relaxation behaviour of polylactides, only some literature [16, 17] has been found confirming strong relaxation for polylactide screws. The strong relaxation in humid conditions must be explained by the depression of the glass transition of polylactides by water uptake, which was detected earlier in non-woven materials showing high shrinkage when exposed to water at 37 °C [18].

4. Degradation tests: the increase of modulus and strength after four weeks degradation of the 3 mm pins, the embrittlement after eight weeks, and the fast decrease of inherent viscosity in the beginning is considered to be due to the monomer content. Even the original material has a (relatively) high monomer content (1.0–3.0%). Together with water diffusion into the bulk, an acidic environment is caused showing a so-called autocatalytic effect with a high degradation rate [19–21]. This degradation takes place in the centres of the samples. At the borders of the samples the monomer can migrate to the surrounding area, resulting in a quasi neutral pH in the material, if the immersion solution is buffered. Similar degradation curves reported by other groups suggest, that an accelerated degradation took place as well. Fast degradation of injection moulded P-L-LA samples, but retarded degradation of P-L–DL-LA [22] can be explained by the monomer content in the first material rather than by differences in molecular mass. A reduction of monomer content of the devices as produced will not only increase the initial modulus but also reduce the degradation rate.

5. The early changes in the mass of the sample can be measuring artefacts, for example residual crystals from the buffer solution will increase the measured weight. The decrease of some samples by up to 3% on the other hand can be due to the extraction of dissolved monomer by the drying procedure. Resorption by hydrolysis of homogeneous materials starts usually after complete degradation. Because of inhomogeneous degradation from the centre, significant mass loss can be measured even when some strength is retained.

4.2. *In vivo* study

After *in vivo* tests it was feasible to test mechanical performance only after one month, whereas after six months, the mechanical performance failed and after 12 months the tests were not even attempted. The plates retrieved from the first group killed at one month post-operatively were white with soft edges. All plates retrieved from the second group were white and very fragile, and almost immediately dissolved to the reinforcement fibres alone.

Bioresorption starts in plates after just six months post-implantation and no autocatalytic effect could be observed.

On the other hand, in the pins bioresorption starts after the first three months and the breakdown of the pin is rather uniform (possibly due to an autocatalytic effect).

As far as biocompatibility is concerned it can be concluded that the polymer used is biocompatible because no acute or chronic inflammatory reaction is detected. Encapsulation was done by loose connective tissue and no bone resorption was found to the cortical diaphysis. The hypertrophy and hypercellularity of the periosteum can be related to the not tight fixation of the plate. Whenever the plate is in complete contact to the bone the "encapsulating" membrane is very thin consisting of mature connective tissue, whereas when the contact is incomplete the vacant region is filled with adipose tissue. The osteolysis detected around the metal screws at 12 months post-operatively is of no clinical significance. The only problem was that soft tissues were not firmly attached to the plate but this could be due to the suboptimal block cutting technique.

Comparing *in vitro* and *in vivo* results, no significant difference can be seen from the few comparable data (bending modulus and inherent viscosity), because of the differences of the samples produced. Due to the operational method and the required histology, mass loss could not be quantified with the few samples.

4.3. Future work

The already satisfying bending modulus of about 7 GPa can be increased further by improvement of the spinning processes and by increasing the fibre content. The initial monomers will be avoided in order to have 50% strength retention for up to six months. The great advantage of the process technology in orienting the fibres in the direction of the main load will be exploited in prototype implants first.

Major improvement is required regarding the relaxation behaviour of the matrix. Another resorbable matrix material is needed, which shows a relaxation of less than 30% stress reduction over 24 h approaching asymptotically a constant value. The data confirm very impressively the necessity to measure in general the mechanical data of polymeric devices at the usage temperature and in the respective atmosphere, and to report the testing conditions precisely.

The highly demanding tasks require further precompetitive but applied research. The partners are looking for supplemental industrial partners to follow up the project work.

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