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RESORBABLE CONTINUOUS FIBER REINFORCED POLYMERS FOR THE OSTEOSYNTHESIS

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RESORBABLE CONTINUOUS-FIBER REINFORCED POLYMERS FOR THE OSTEOSYNTHESIS

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Abstract:

Four institutes of three countries of the European Communities have collaborated under the BRITE/EURAM framework programme for the development of processing technologies for resorbable osteosynthesis devices. The devices should be continuous-fiber reinforced, and the technology should offer, the possibility to orient the fibers in the main trajectories.

Poly-L-lactide and poly-L/DL-lactides have been synthesized for reinforcement fibers and matrix material respectively. Melt-spun P-L-LA fibers 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. Satisfying bending modulus has been reached (6 GPa). Yet with 50% strength retention after 10 weeks a fast degradation occurred which could be related to residual monomers. By this fast degradation 70% resorption after 1 year could be observed in the non-functional animal studies in rabbits. Only mild inflammatory reaction confirmed a good biocompatibility of the materials even during the resorption period.

Further effort has to concentrate on the reduction of initial monomer content. The high advantage of the processing method to orient the fibers in the device will be utilized in prototype samples like osteosynthesis plate with fixation holes.

Introduction:

State of the Art: Today osteosynthesis implants are mainly made of metals, which are to be 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 the healing of bone /1/.

Polymeric implant material have been developed reinforced by carbon fibers /2,3/ or even thermoplastic fibers /4/. The bending modulus can be adjusted by fiber 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.

Since 30 years, resorbable polymeric materials are under investigation for osteosynthesis, some are brought to the market in the last decade. Not reinforced materials on the 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 dry stage. The self-reinforced 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 wet stage). With self-reinforcement a combination of

materials for a retarded degradation time is not possible, Rather complicated structures, like reinforcing of fixation holes in plates, can not be produced, because of the unidirectional pultrusion process.

In technical applications thermoplastic polymers are reinforced usually by non-thermoplastic high modulus fibers (glass-, carbon-, aramide) /10,1 1/, which are highly temperature stable, a requirement for easy thermal processing. Chopped fiber reinforced polymers are processed economically by injection moulding.

Improved mechanical properties can be reached by using continuous fibers. Their processing by pultrusion or compression moulding is more complicated and less economical. Therefore their use is limited to high advanced technologies. The matrix can be fed to the reinforcement fibers in form of powder, as fibers, by a solution or by melt impregnation. Using hybrid yarns 3-dimensional braided structures are produced for adapted fiber orientation /10/.,.

[n the next step the matrix has to be plastified by temperature above its glass transition or eventually above its melting temperature and by high pressure. Pultrusion and compression moulding are used to enhance the impregnation and to form the device.

Using thermoplastic fibers for reinforcement the processing temperature has to be far below the melting temperature of the fibers, but at the same time the viscosity of the matrix has to be low enough for a complete impregnation of the fibers. Today technical applications are restricted to sport equipment/12,13/.

Aim of the project: The aim of the project was the development of the processing for resorbable continuous fiber reinforced osteosynthesis devices. This contains the synthesis of resorbable polymers, the spinning of high strength fibers, their impregnation with matrix and the forming of samples for the characterization of the material and processing. The samples had to be tested in short and long term tests, 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 the orientation of the fibers in main trajectories. A good fiber matrix adherence and the alignment of the fibers were to respect in the final shaping. The diffusion of tissue fluids at the fiber-matrix interface has to be prevented.

Partnership: Polymer synthesis and chemical analysis, fiber spinning and a first impregnation has been performed at the ITV Denkendorf. At the ITF Lyon the materials were formed to testing samples. Sterilized samples were tested in vitro at BEL Patras, while the in vivo studies have been performed at the OC Patras. The industrial endorsers Aesculap AG, Tuttlingen and Peters Laboratoire Pharmaceutique have supported the project work by testing and sterilization of samples.

Technical Description

Materials: The research has been restricted to polymers of α -hydroxycarbon acids with known principal biocompatibility. Polyglycolide acids have a very short life time. Therefore polyesters of the lactide acid have been synthesized by ring-opening melt polymerization using tin-octoate catalysts. Pure poly-L-lactide has been produced for reinforcement fibers. The inherent viscosity (iv.) was in the range from 1,5 all/g to

3,5 all/g. For the matrix an amorphous copolymer has been chosen. The poly-L/DL-lactide 70:30 (iv. 1,5 -2,5 dl/g) was found to have most appreciable processing and mechanical properties.

Processing: Based on literature dry spinning method /14/ has been chosen first for the fiber production expecting highest fiber modulus. The experiments have shown, that the production of the needed large amounts of 'fibers could not be realized by dry spinning. Residual solvents and a very slow production speed make this process inefficient.

Alternatively melt spun fibers of considerable high moduli (7 - 10 GPa) were developed. The melt spinning allows a considerable high take up speed (up to 700 m/min) and avoids the extraction of solvents.

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

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

Samples of 3 mm x 10 mm; 1,5 mm x 5 mm and 3 mm diameter were produced by compression moulding. The fiber/matrix proportion was inbetween 45/55 and 60/40. The testing samples were unidirectionally reinforced, yet it has been demonstrated that other fiber orientations are possible by textile processing like braiding.

All material were sterilized by ethylenoxide (EtO) sterilization. The sterilization procedure was evaluated regarding the effect on mechanical properties and inherent viscosity:

During ethylene oxide sterilization the polymer is exposed to temperatures up to 50°C and humid atmosphere to enhance the penetration of ethyleneoxide. To evaluate the effect of the gas-sterilization on the fiber-reinforced materials 10 mm x 3 mm samples were sterilized. Sterilization without the usual prehumidification was compared with a normal gas sterilization process, where the samples are prehumidified.

Test Methods: The in vitro testing consisted" of short term 4 point bending, torsion and shear test, relaxation (bending and torsion), cyclical loading and a simulation test (bending and torsion). Testing methods are specified in table 1. Except otherwise stated mechanical tests have been performed at 37°C in water bath or wetted continuously by water of 37°C, In simulation tests a cyclical loading has been applied until break down of the samples.

Table 1: In vitro test methods

Test Method	International Standards
Inherent viscosity	ISO 1628 (1); 25°C; 0.174 chloroform; Ubbelohde 0c
Gas Chromatography	ISO/DIS 13741-1 & -2; 1995-12 (Head Space - GC)
Bending Test (4-point)	ASTM D 790 M-82, II,B (related)
Torsional Test	ISO 458-1 (related)
Shear Test	DIN 50141 (related) 21°C, dry
Bending Stress Relaxation	No standard, design ace. ASTM D 790 M-82, II,B displacement 1,4 mm in 0,4 see; relaxation time 15h
Torsional relaxation	No standard available, design ace. ISO 458-1 torsion 0,3" in 0,4 see; relaxation time 15h
Degradation Test	ISO-DIS 13781-1995, pH 7.4, 37°C

For the determination of mass loss the samples were washed 3 times in destined water and then dried in vacuum until constant weight. Each single sample was weighted separately before and after the degradation process.

Explanted plates have been tested in 3-point bending test because of their short length. The results were compared with original samples tested by 3-point bending as well.

Animal Test

Many publications are made on the tissue compatibility and the degradation rate of polylactides. But since both of them are depending on processing conditions and physical properties like crystallinity, at first information is necessary on tissue compatibility, chronic toxicity and 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 cause adverse tissue reaction independently from the implant material.

Eighteen (18) mature New Zealand rabbits were used with body weight ranged between 3-4,5 kg.

On the tibia of each of 18 rabbits one plate (5 x 1,5 x 40 mm³) respectively was implanted. The skin was incised laterally through intramuscular septum down to the bone. The periosteum left intact in place. The polylactide plate was applied and fixed to the bone using 2 AO screws with washer (1,5 mm core of the screw) which were inserted outside the plate pressing it firmly to the bone. In this way a "stable mechanical environment" was achieved avoiding mechanical loading. Right tibia was used as 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 1, 6 and 12 months and analysed by histology, inherent viscosity and mechanics, where appropriate.

A second group included 3 animals to show the relationship between soft tissues-plate-bone in one picture for the early stages. These animals S1, S3, S6 were sacrificed in 1, 3 and 6 months post-op and only undecalcified sections were done.

Results

Sterilization

Inherent viscosity and bending modulus were almost unaffected by the EtO sterilization (figure 1), The strength was decreased by about 8% not depending significantly on the sterilization method used.

Therefore the usual sterilization process was chosen for the future samples.

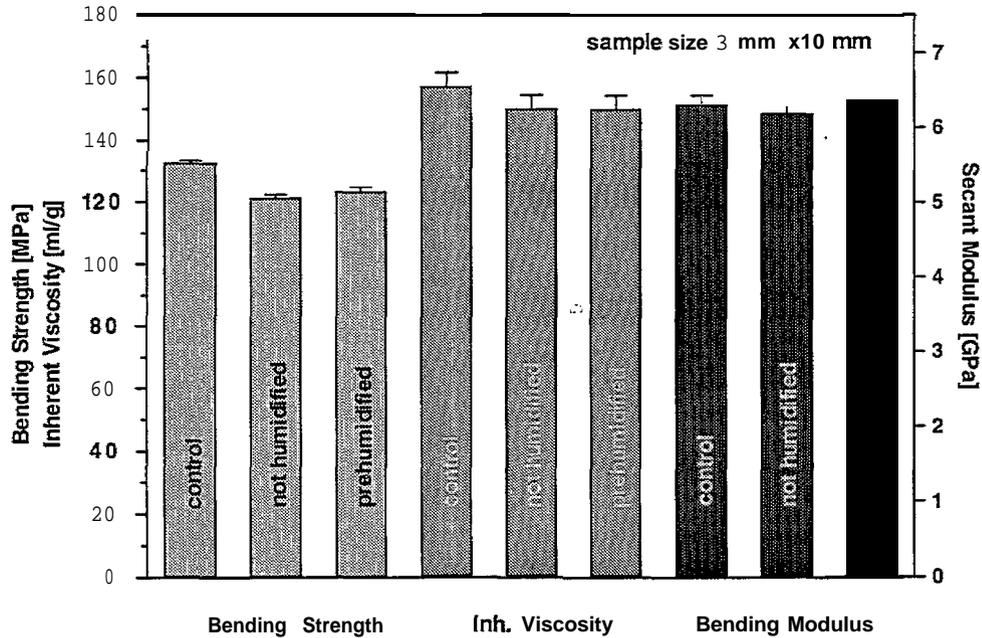


Figure 1: Effect of sterilization method on material properties
 P-L-LA fiber reinforced P-L/DL-LA 70:30; sample 3mm x 10mm x 60mm
 (4-point bending test at 37°C in water, 1h preconditioned)

In vitro Degradation

Static 4-point bending, degradation

Figure 2 describes the results of 4-point bending test up to 2 mm deflection over a degradation period up to 26 weeks of both, in vitro and in vivo degradation. Bending stress and bending modulus remain stable up to 8 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, may be due to the explanation. After 52 week all samples had started to disintegrate.

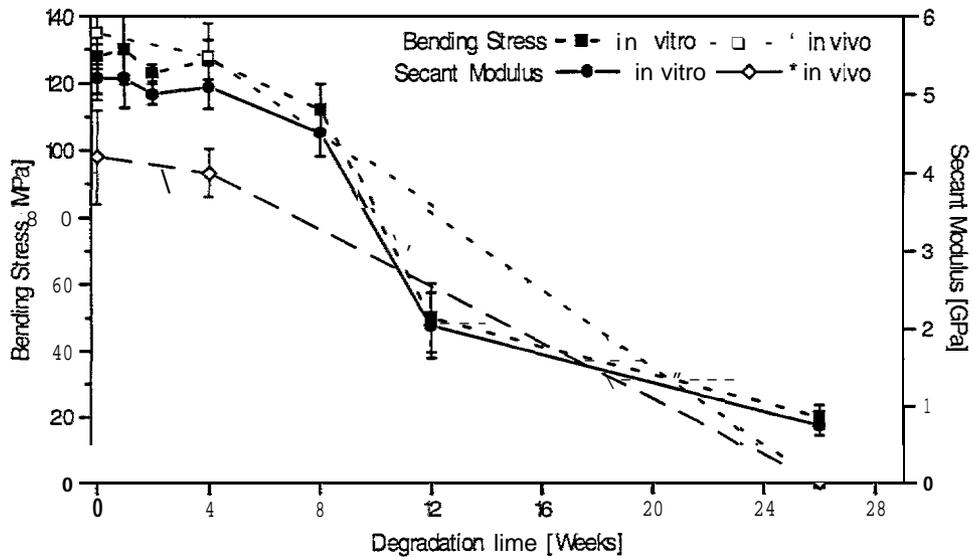


Figure 2: Bending stress and secant modulus at 2 mm deflection of sterile P-L-LA/P-L-DL-LA 70:30; sample: 1,5 mm x 5 mm x 48 mm conditioned with buffer solution, pH 7.4, 37°C

Static torsion, degradation

Figure 3 shows the change in both the applied torque (N.mm) and the secant stiffness in torsion (T) (GPa*10) at 10 degrees of torsion respectively with the degradation time at the prescribed periods of time.

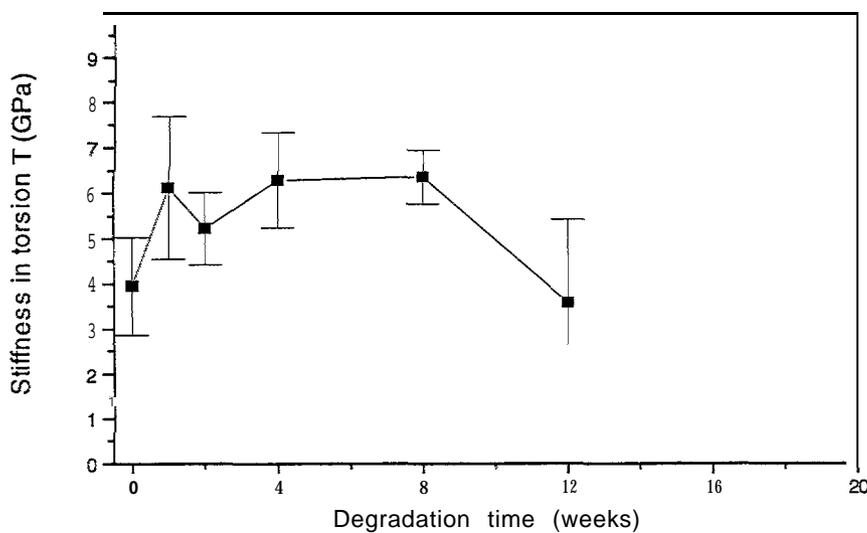


Figure 3: Applied torque and the secant stiffness in torsion T at 10 degrees of torsion; change with the degradation time. Tested in buffer solution, pH 7.4, 37°C

Both torsion modulus and torque of the \varnothing 3 mm pins are heavily increased after 1 week immersion in buffer solution. They remain constant up to 8 week followed by a decrease to the original value after 12 week. At 26 weeks the material could not be measured because it was mechanically degraded.

Relaxation test

Figure 4 shows the stress (% of initial stress S_0) of 1.5x5 mm and 3x10 mm plates against time under relaxation loading in 4-point bending test. The displacement of 1,4 mm was in between the linear portion of the stress-strain curve.

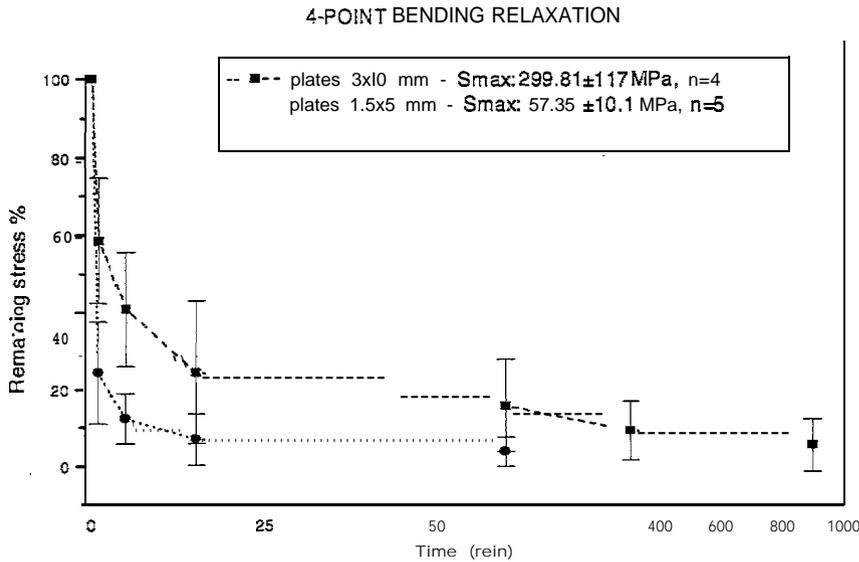


Figure 4: Remaining load during 4-point bending relaxation test with time (buffer solution, pH 7.4, 37°C)

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

Shear Test

3 mm pins were tested regarding shear force at room temperature after conditioning at 37°C in water for one hour. A shear strength of 104 ± 4 MPa was obtained. Comparing an injection moulded, not reinforced PLA-pin, this result confirms earlier observation that the fiber-reinforcement increases the shear strength by about factor 2.5.

Inherent viscosity

The inherent viscosity as a measure of the molecular mass is decreased very fast at the beginning, but that decrease is rehardened at the 8 week period (see figure 5). This can be explained by a decrease of the molecular mass of the matrix which has reached a low level after 8 weeks, but still remained in mass. After 26 weeks the matrix starts to resorb. The fibers remain in place, their contribution to the mixed

inherent viscosity increases by the resorption of the matrix. It is not possible to measure the reinforcement fibers and the matrix separated as they are solved in the same solvents.

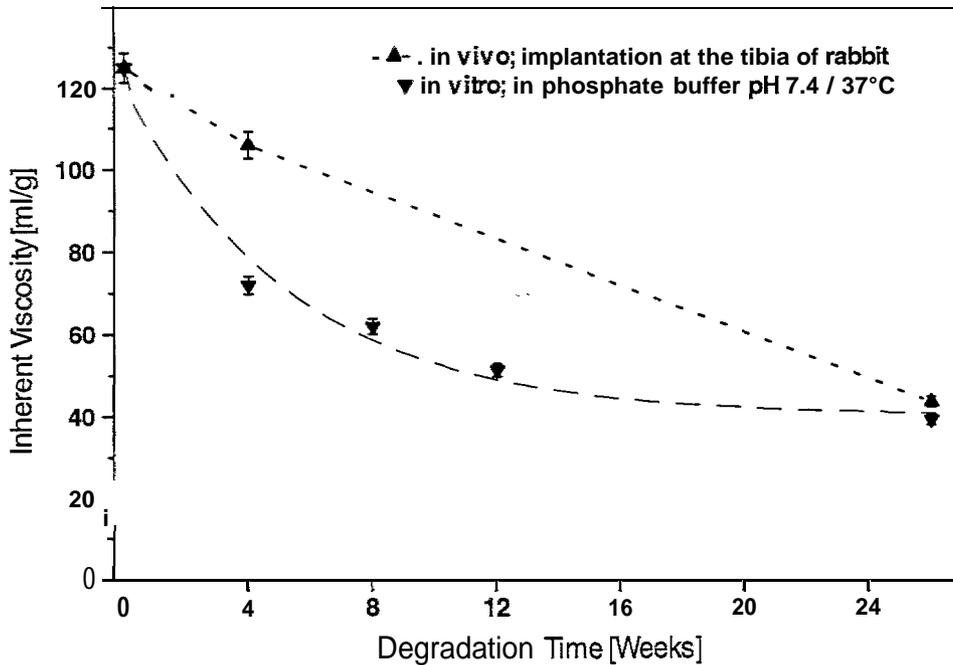


Figure 5: inherent viscosity of sterile P-L-LA/ P-L-DL-LA 70:30 after in vitro and in vivo tests

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 4 weeks is not confirmed at the half years values, which are almost identical for degradation in vitro and in vivo respectively.

Resorption: loss of mass

Figure 6 shows the remaining mass, as percentage of the initial mass after each degradation period. The measured weights of the samples were in the range of **200** to **900** mg, while the resolution of the weighting scale was ± 1 mg.

The loss of mass started even at 4 up to 8 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.

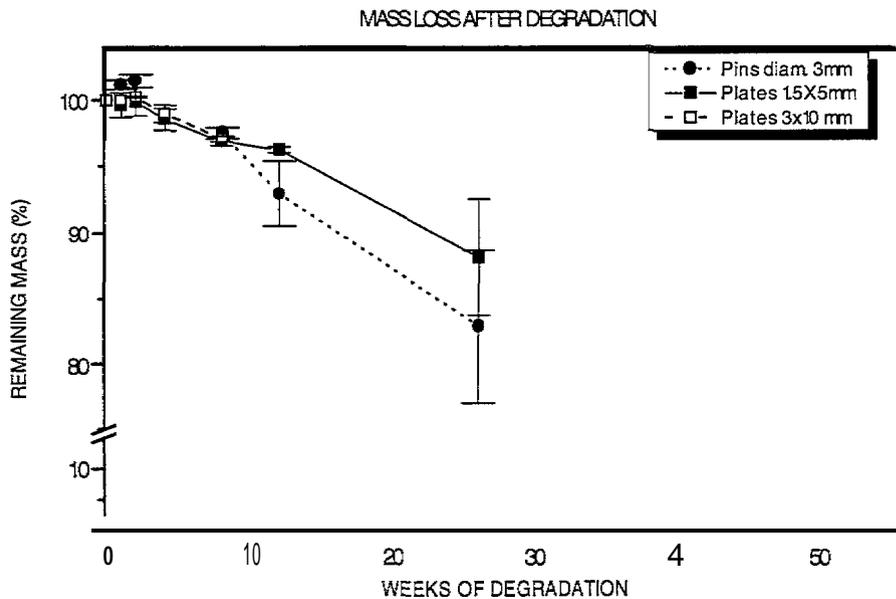


Figure 6: Loss of mass at in vitro degradation

[n vivo results

Three of the animals died during general anaesthesia (IV Ketalar) and the remaining 15 were divided in three groups of 5 each. Unfortunately 2 more died during the post-op period and one became infected, not related to the implants respectively. Hence at the end 4 animal on each group were studied.

Histology

A) Around the Plate:

1 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 birefringent particles in only one specimen were identified using polarized light. This was probably due to mechanical damage of the plate during implantation process.

Undecalcified: Fibrous and loose connective tissue (about 1,5-2,0 mm wide

3 months: Undecalcified: Hypertrophy and hyper-cellularity of the periosteum below the tested material.

6 months: Conventional histology performed to 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.

12 months: Undecalcified sections were examined under conventional and polarized microscope using GOLDNER and TOLOWDINE 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.

S1 , S3, S6: • Undecalcified sections showing loose connective tissue encapsulation of the plate

B) Femoral condyles (undecalcified sections)

1 month: • Fibrous and loose connective tissue around pins.

- New bone formation around the pins within the osseous tunnel.

6 months: • Fibrous connective tissue with a few macrophages and giant cells.

- Approximately 30 % of the pin broken down to fibers and macrophages started phagocytosis of the particles. Almost all matrix has been replaced by fibrous hypercellular connective tissue.
- On the bone tunnel mixed areas of woven and mature bone was found.

12 months: • Same as at 6 months, but almost 90 % of the pin was broken down to fibers.

- Many macrophages and giant cell found around the particles in phagocytosis process.
- In the tunnel mixed areas of woven and mature bone. Areas of the tunnel started to fill up with newly formed bone.

Resorption in vivo

Plates

- 1 month: • No resorption
- 6 months: • Just started in both ends (sealing defector mechanical damage)
- 12 months: • 30% - 40% of the plate. No autocatalytic effect but surface degradation

Pins

- 1 month: • No resorption
- 6 months: • 30 % resorbed
- 12 months: • Almost 90 % resorbed

Conclusions

Mechanical properties

The MODULI (bending, torsion) of the devices are satisfying already, but will be increased by higher Youngs modulus of the reinforcement fibers.

The 2.5 times higher values of the SHEAR STRENGTH of the reinforced materials compared with not reinforced materials support the importance of fiber reinforcement,

Regarding RELAXATION behaviour of polylactides, only few literature /16,17/ was 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 at nonwovens showing high shrinkage when exposed to water at 37°C /18/.

DEGRADATION tests: The increase of modulus and strength after 4 weeks degradation at the 3 mm pins, the embrittlement after 8 weeks, and the fast decrease of the inherent viscosity in the beginning is considered to be due to the monomer content:

Even the original material has a (relative) high monomer content (1,0 -3,0 %). Together with water diffusion into the bulk an acidic environment is caused showing the so called autocatalytic effect with high degradation rate/19-21/. This degradation takes place in the center of the samples. At the border monomer can migrate to the surrounding, a quasi neutral pH in the material results, if the immersion solution is buffered. Similiar 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 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.

The early changes in the sample mass can be measuring artefacts, for example residual crystals from the buffer solution will increase the measured weight. The decrease up to 3% of some samples 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 the unhomogeneous degradation from the center, significant mass loss could be measured even when some strength is retained.

MECHANICAL PERFORMANCE after in vivo tests was feasible to be tested only after 1 month, whereas after 6 months 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 which almost immediately dissolved to the reinforcement fibers alone.

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

On the other hand in pins bioresorption starts after the first three months and the breakdown of the pin is rather uniform (+ autocatalytic effect?),

As far as BIOCOMPATIBILITY is concerned it can be concluded that the used polymer is biocompatible since no acute or chronic inflammatory reaction was detected. Encapsulation was done by loose connective tissue and no bone resorption was found to the cortical diaphysis. The hypertrophy and hyper-cellularity 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 twelve months post-op is of no clinical significance.

The only problem was that soft tissues were not firmly attached to the plate but this should be due to 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 difference of the produced samples. Due to the operation method and the required histology, mass loss could not be quantified with the few samples accordingly.

Future Work

The already satisfying bending modulus of about 7 GPa shall be further increased by improvement of the spinning processes and by increasing the fiber content. The initial monomers will be avoided in order to have a 50% strength retention up to 6 months. The high advantage of the process technology to orient the fibers in the main load direction will be exploited in prototype implants first.

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

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

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