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Mechanical properties and *in vitro* degradation of bioabsorbable self-expanding braided stents

JUHA-PEKKA NUUTINEN[1,2,*], CLAUDE CLERC[2], RAIJA REINIKAINEN[1] and PERTTI TÖRMÄLÄ[1]

[1] *Institute of Biomaterials, Tampere University of Technology, P.O. Box 589, FIN-33101 Tampere, Finland*
[2] *Bionx Implants, Inc., 1777 Sentry Parkway West, Gwynedd Hall, Suite 400, Blue Bell, PA 19422, USA*

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Abstract—The aim of this study was to characterize the mechanical and self-expansion properties of braided bioabsorbable stents. In total four different stents were manufactured from PLLA fibres using a braiding technique. The changes in radial pressure stiffness and diameter recovery of the stents were determined initially, and after insertion and release from a delivery device. The braided stents were compared to three commercially available metallic braided stents. The changes in physical and mechanical properties of the PLLA fibres and stents during *in vitro* degradation were investigated. After release from the delivery device, the PLLA stents did not fully recover to their original diameter. The radial pressure stiffness of the bioabsorbable stents was similar to that of the metallic stents. The *in vitro* degradation study showed that the stents would keep at least half of their initial radial pressure stiffness for more than 22 weeks.

Key words: Bioabsorbable; stent; braiding; PLLA; self-expansion; fibres; *in vitro*.

INTRODUCTION

Metal self-expanding and balloon expandable stents have been used for about 2 decades to treat stenosis or constrictions of the human body ducts and vessels. Metallic stents provide good radial force, X-ray visibility (radiopacity) and fairly good biocompatibility. The main drawbacks of metallic stents are that they tend to elicit hyperplasia, that may eventually lead to vessel occlusion especially at stent extremities, they are difficult or virtually impossible to remove, they may hinder further surgery and they are subject to imaging artifact with magnetic resonance imaging (MRI). For most applications, a stent is deemed to be useful only the

*To whom correspondence should be addressed at Bionx Implants.

first few months after implantation when it provides support during the remodeling process. Therefore, polymeric and especially polymeric bioabsorbable stents may prove to be advantageous over metallic stents.

In 1995, Labinaz *et al.* [1], published a paper reporting the development of a poly-L-lactide (PLLA) stent at Duke University. Ten self-expanding braided stents were implanted in the femoral arteries of dogs. All stents were sterilized and soaked in heparin prior to deployment. The follow-up was performed from 2 h to 18 months. All segments were patent at the follow-up except two (both were traumatic implants). Angiography revealed 50% stenosis in one artery and insignificant narrowing in the others. Neointima appeared by 2 weeks and the stents were fully endothelialized at 12 weeks. At 18 months, the polymer had undergone complete degradation with no inflammatory response. The Cleveland Clinic Group compared the inflammatory response of metal stents, PLLA-coated stents and PLLA-coated stents with dexamethasone. No histological difference was noted between the groups at 28 days. In addition, the tissue response to PLLA was similar to the control (metal stent), consisting of uniform smooth muscle cells in a homogenous extracellular matrix. No foreign tissue response was noted [2]. Bionx Implants was the first company to develop and sell a bioabsorbable spiral stent for use after a minimally invasive (MI) treatment for benign prostatic hyperplasia (BPH) [3, 4]. These MI treatments such as interstitial laser coagulation or microwave therapy often induce a swelling of the prostate gland that may create temporary urine retention. The stent is used to maintain the prostatic urethra open during the weeks following the treatment. In 1997, Schellammer *et al.* [5] found that PLA revealed a good histologic biocompatibility in an arteriovenous fistula in a canine model. In 2000, Tamai *et al.* [6] published the initial results of the clinical study investigating the Igaki-Tamai PLLA bioabsorbable stent. The stent was a self-expanding coil and was delivered with a balloon-expandable, sheath-covered system with heated dye (80◦C) using a 30-s pressure inflation. The stent continued to expand after implantation. A feasibility study was carried out with 84 stents that were successfully deployed in 63 lesions of 50 patients. The restenosis rate was 19.4% at 6 months and 20.7% at 12 months. The target lesion revascularization was 12.1% at 6 months and 16.7% at 12 months. In a 2000 editorial in Circulation, Colombo and Karvouni [7] discussed a bioabsorbable coronary stent saying that the 2 main functions of a stent are the treatment of dissection and the prevention of restenosis. Since both occur within 6 months, a permanent prosthesis has no clear function after this time. A permanent stent freezes recoil, but also freezes remodeling and prevents further lumen expansion associated with late remodeling. In addition, the use of long stents and full lesion coverage may prevent surgical revascularization at a later time. They also noted that a bioabsorbable stent is the ideal vehicle for drug delivery. In 2001, Freeman [8] described the use of a bioabsorbable PLA self-expanding braided stent having a geometry similar to a Wallstent stent in a feasibility clinical study carried out in the US and in Canada in 51 patients for the palliation of malignant biliary strictures. The results were

encouraging with some stents remaining patent in excess of 9 months. Since these bioabsorbable stents had a radial force that was somewhat lower than that of their metallic counterpart, it was necessary to expand them immediately post-deployment with a balloon. Ginsberg *et al.* [9] describe a braided bioabsorbable stent developed by Bionx Implants that is reinforced with an elastomeric axial runner designed to increase the stent radial force and diameter recovery after implantation and make it comparable to a braided metallic stent in terms of mechanical properties. These stents have been implanted up to 10 months in swine bile ducts without eliciting stent-induced inflammation. The stents remained patent at 6 months with some filling defects. Saito *et al.* [10] studied knitted stents in a rabbit trachea model. The stents, knitted from a PLLA fibre with a diameter of 0.17 mm, had a diameter of 6 mm and length of 12 mm. Silicone tubes with similar diameter and length were used as controls. The stents were implanted intratracheally into the cervical trachea and fixed with a polypropylene suture. In the silicone control group, 3 animals died within 4 weeks from airway obstruction by secretions. The remaining 5 animals developed a stridor within 8 weeks and were killed. In the knitted PLLA stent group, one animal died at 3 weeks, because of anorexia and another one at 8 weeks, because of incomplete stent expansion. At 40 weeks of follow-up, the bronchial lumen of the remaining 13 rabbits remained fully open, the stents were absorbed and only the non-absorbable suture was observed. Korpela *et al.* [11] studied the biocompatibility of PLLA stent in a pig bronchus. The PLLA stents were helical spirals made of 1.1 mm self-reinforced wire and they were 9.5 mm in outer diameter and 15 mm in length. The stents were fixed with an absorbable PDS suture. At 2 and 6 weeks postoperatively the stents were seen at the implantation site in the left main bronchus and no evidence of granulation tissue was observed. At 6 months postoperatively, five of six stents and the PDS suture had disappeared. Bronchial stenosis or macroscopical tissue reactions were not observed. These results show that PLLA is biocompatible in bronchial indications and that the degradation of the small PLLA wires occurs within 40 weeks *in vivo*.

In order to be sure that a bioabsorbable stent will not lose its radial strength before healing has occurred, it is important to determine how the degradation process affects the stent mechanical properties. The degradation mechanism for polylactide polymers is mainly hydrolytic and several authors have found no differences between *in vitro* and *in vivo* degradation. However, several authors have reported faster degradation *in vivo* than *in vitro*. These findings have been explained by cellular and enzymatic activity of the body and dynamic loads affecting implanted devices [12–16]. While it remains unclear how would *in vitro* degradation correlate with *in vivo* degradation of bioresorbable stents in various indications, *in vitro* results are a useful guideline for planning *in vivo* studies. In a previous study, it was found that tibres made out of PLLA can provide good mechanical properties and strength retention *in vitro* of about 6 months [17].

The aim of this study was to examine the initial mechanical properties and stent diameter recovery after delivery of braided stents made out of self-reinforced

bioabsorbable polylactide fibres. The changes in mechanical properties, molecular weight and mass during *in vitro* degradation were also studied.

MATERIALS AND METHODS

Materials and stent manufacturing

Purac Biochem b.v. (The Netherlands) supplied the polylactide (PLLA) used in this study. Prior to processing the viscosity-average molecular weight was 647 600 g/mol and the percent crystallinity was 86%, as measured by the material supplier.

The fibre manufacturing process consisted of an extrusion immediately followed by a drawing process to create a self-reinforced structure. In the drawing process, the isotropic polymer is transformed into a highly anisotropic self-reinforced structure. The self-reinforced fibre has a high degree of molecular orientation in the direction of the long axis of the fibre [18, 19]. The vacuum dried material was extruded with an Axon extruder (Sweden), having a 1.0 mm monofilament die. In the drawing process, the PLLA was oriented with draw ratios of 6.2, 6.8, 6.4 and 6.0, corresponding to final diameters of 0.31 mm, 0.33 mm, 0.36 mm and 0.40 mm, respectively.

The self-reinforced fibres were braided into a tubular form onto 10 or 12 mm PVC rods using two vertically operating braiding machines. The stents with a fibre diameter of 0.36 mm were braided using a 24-spindle braider ($24 \times 0{\cdot}36$) and the stents with fibre diameters of 0.31 mm, 0.33 mm and 0.41 mm were braided using a 32-spindle braider ($32 \times 0{\cdot}31$, $32 \times 0{\cdot}33$ and $32 \times 0{\cdot}41$). After braiding, the stents were transferred on a 10-mm stainless steel mandrel and heat-treated at 120°C for 10 min with their ends fixed to stabilize the structure. After heat treatment the average braid angle of the stents was 82°. Figure 1 is a photograph of the ($32 \times 0{\cdot}31$) braided PLLA stent.

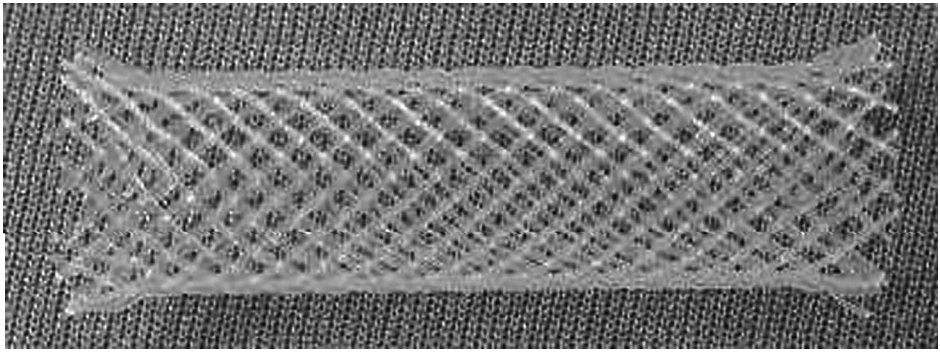

Figure 1. Braided PLLA stent ($32 \times 0{\cdot}31$), length 40 mm and diameter 11 mm.

Fibre and stent characterization

The diameter recovery of the stents was determined by placing the stents for 15 min in air at room temperature into plastic tubes having an inner diameter of 3.0, 3.4, 4.0 or 5.0 mm to simulate a delivery device. The stents were then released from the tube with a pusher in air at room temperature. The diameter of each stent was measured using a calliper before insertion and immediately after release from the tube. Three samples each were tested for radial pressure and diameter recovery per data point.

An MTS material testing machine (MTS Systems, USA) was used for the mechanical testing of the samples. The elastic modulus and ultimate tensile strength of the fibres were measured as follows. The diameter of each fibre was measured with a calliper before testing. Both ends of the fibres were placed in hydraulic grips, the grip distance being 100 mm and the crosshead speed 50 mm/min.

The mechanical properties of the stents were measured as described earlier by Agrawal and Clark [20]. Each stent was placed inside a 10-mm wide plastic collar. The two extremities of the collar were placed in the grips of the material testing machine and pulled with a crosshead speed of 50 mm/min. The initial radial pressure stiffness (K) of the stent was determined from the load/displacement curve as described by Nuutinen *et al.* [21]:

$$K = \frac{\mathrm{d}P}{\mathrm{d}D} = \frac{2\pi}{bD} \times \frac{\mathrm{d}N}{\mathrm{d}c},$$

where P is the pressure, D the stent diameter, b the collar width, N the load and c the stent circumference.

In vitro *degradation study*

The 0.31 mm PLLA fibres and the 32×0.31 stents were used in the *in vitro* degradation study. The fibres and stents used for the *in vitro* degradation study were gamma sterilized at Willie Rüsch (Germany) using a minimum dose of 27 kGy. After sterilization, the stents were placed into a delivery device having inner diameter of 3.4 mm. The stents were kept inside the device for 10 minutes, then released in phosphate buffer solution (PBS, Na_2HPO_4 24·3 mmol/l, $NaH_2PO_4 \cdot H_2O$ 5.5 mmol/l and NaCl 101.0 mmol/l). The stents were tested before sterilization, and after sterilization and release from the delivery device. The fibres were tested before and after sterilization. The fibres and stents were then placed in test tubes, six fibres or one stent in each, and the tubes were filled with PBS solution. The stent were in their unconstrained state when inside the tubes. The solution was kept at $37 \pm 1^{\circ}$C and was changed periodically, at least every other week, to maintain a pH of $7{\cdot}4 \pm 0{\cdot}2$. Six fibres and four stents were tested for each data point during *in vitro* degradation up to 36 weeks.

A gel permeation chromatograph (GPC, Waters, USA) was used to measure the viscosity-average and number-average molecular weight of the stents. Chloroform was used as solvent and as eluant. One specimen was tested for each data point

during *in vitro* degradation. The intrinsic viscosity of the raw material was converted into a viscosity-average molecular weight using the Mark-Houwink equation with $k = 5.4 \times 10^{-4}$ dl/g and $\alpha = 0.73$ [22].

The crystallinity of the vacuum dried samples was measured using a differential scanning calorimeter (DSC, Perkin Elmer DSC7, USA) with indium calibration and heating speed of 20°C/min. The heat of fusion was measured and the percent crystallinity was calculated using the value of 93.7 J/g for a perfectly crystalline PLLA material [23].

The mass loss of the stents was measured by weighing each stent after sterilization and during *in vitro* degradation up to 104 weeks. Each data point is the average of three stents.

Statistical analysis

Statistical comparisons of the change in mechanical properties of the fibres and stents before and after sterilization were done using a two-sided Student's t-test with unequal variances. The level of significance was set to $P = 0.05$.

RESULTS AND DISCUSSION

Self-expanding stents are generally delivered to the obstructed lumen inside a delivery device, the diameter of which is substantially smaller than the expanded

Table 1.
Stent diameter recovery for braided PLLA stents before and after insertion and release from delivery device

Stent	Delivery device inner diameter (mm)	Initial stent diameter (mm)	Stent diameter after self-expansion (mm)	Stent diameter recovery (%)
24 × 0.36 mm	3.0	12.1 ± 0.3	9.6 ± 0.8*	79
	3.4	12.1 ± 0.2	10.2 ± 0.2*	84
	4.0	10.7 ± 0.2	9.7 ± 0.2*	91
	5.0	10.5 ± 0.3	10.1 ± 0.2	96
32 × 0.31 mm[a]	3.4	11.0 ± 0.1	9.6 ± 0.2*	87
32 × 0.33 mm	3.0	10.8 ± 0.1	5.7 ± 0.7*	53
	3.4	11.0 ± 0.1	7.5 ± 0.3*	68
	4.0	11.2 ± 0.2	9.0 ± 0.2*	80
	5.0	11.3 ± 0.2	9.6 ± 0.3*	85
32 × 0.40 mm	4.0	11.5 ± 0.1	6.6 ± 0.2*	57
	5.0	11.5 ± 0.1	9.1 ± 0.1*	79

* Statistically significant difference.
[a] Gamma sterilized.

stent diameter. It is therefore important that the stent does not take a set in the delivery device and expands to a diameter close to its original or unconstrained diameter upon release from the delivery device. The polymeric stents are prone to taking a set during sterilization and/or storage, if kept in the delivery device. Therefore, we anticipate that a self-expanding polymer stent would likely need to be mounted on the delivery device immediately prior to surgery. To determine the effects of stent delivery, we measured the stent diameter and the radial pressure stiffness prior to inserting the stent in the delivery device and immediately after release. The stent diameter recovery is presented in Table 1 and the change in radial pressure stiffness in Table 2. The data in Table 1 show that the stent diameter recovery improves when the inner diameter of the delivery device increases, or the fibre diameter decreases or the number of fibres decreases. This shows that the amount of set taken by the braided bioabsorbable stents inside the delivery device depends on the amount of free space available for the stent inside the delivery device. All the changes in stent diameter during insertion were statistically significant, except for the 24 $\times$ 0.36 mm stent when delivered through a 5 mm delivery device. The 32 $\times$ 0·40 mm stent could not be fitted into 3.0 and 3.4 mm delivery device.

Most of the changes in radial pressure stiffness are statistically significant, despite the fact that the standard deviations are quite high for the measurements made after releasing the stents from the delivery device. The highest decrease was observed with the 24 $\times$ 0.36 mm stent when it was released from the delivery device having an

Table 2.
Change in radial pressure stiffness of braided PLLA stents before and after insertion and release from delivery device

Stent	Delivery device inner diameter (mm)	Initial radial pressure stiffness (MPa/m)	Radial pressure stiffness after diameter recovery (MPa/m)	Change in radial pressure stiffness (%)
24 $\times$ 0·36 mm	3.0	2·4 $\pm$ 0·2	1·9 $\pm$ 0·0	–21
	3.4	2·4 $\pm$ 0·2	2·5 $\pm$ 0·5	4.2
	4.0	2·7 $\pm$ 0·2	2·0 $\pm$ 0·4	–26
	5.0	2·8 $\pm$ 0·2	1·7 $\pm$ 0·4*	–39
32 $\times$ 0·31 mm[a]	3.4	3·2 $\pm$ 0·2	2·0 $\pm$ 0·2*	–38
32 $\times$ 0·33 mm	3.0	4·7 $\pm$ 0·1	6·6 $\pm$ 2·3	40
	3.4	4·6 $\pm$ 0·0	5·5 $\pm$ 0·3*	20
	4.0	4·5 $\pm$ 0·1	4·8 $\pm$ 0·7	6.7
	5.0	4·5 $\pm$ 0·1	3·9 $\pm$ 0·4	–13
32 $\times$ 0·40 mm	4.0	9·3 $\pm$ 0·4	12·1 $\pm$ 0·5*	30
	5.0	9·3 $\pm$ 0·5	8·6 $\pm$ 1·2	–7.5

* Statistically significant difference.
[a] Gamma sterilized.

inner diameter of 3.0 mm. Contrary to what was observed with diameter recovery, we could not see any trend for the radial pressure stiffness. According to the stent model presented by Jedwab and Clerc [24], the compressive radial pressure of a braided stent increases with an increase in fibre diameter, braid angle or number of fibres. The radial pressure stiffness data presented below for the metallic stents with various diameters also show that there is a general tendency for the radial pressure stiffness to increase with decreasing stent size. Therefore, the decrease in radial force expected from a decrease in braid angle is competing with an increase in radial force owing to a decrease in stent diameter. In addition, the mechanical properties of the fibres may have been altered when the stents were inserted in the delivery device.

To determine if the braided stents provide a sufficient amount of compressive radial pressure after release from the delivery device, we compared them to three commercially available braided metallic stents: a stent with a outer diameter of 6 mm and a length of 40 mm (Wallstent model SCH-64002, Schneider), a stent with a outer diameter of 8 mm and a length of 50 mm (6 Fr Easy Wallstent, model SCH-64326, Boston Scientific) and a stent with an outer diameter of 10 mm and a length of 60 mm (Wallstent Endoprosthesis model 43050, Endoscopic Biliary Unistep Plus delivery system, Boston Scientific). The radial pressure stiffness of the 6, 8 and 10 mm metallic stents was 13.7, 3.5 and 4.4 MPa/m, respectively. After the insertion test was done using 4.0 and 5.0 mm delivery devices, the $32 \times 0{\cdot}40$ mm braided PLLA stents had radial pressure stiffness comparable to the 6 mm Wallstent stent. The $32 \times 0{\cdot}33$ mm braided PLLA stents after delivery through 3.0, 3.4, 4.0 and 5.0 mm instruments had a slightly lower radial pressure stiffness than the 10 mm Wallstent stent, but higher than the 8 mm Wallstent stent. The radial pressure stiffness of the $24 \times 0{\cdot}36$ mm braided PLLA stents after the insertion tests was lower than that of any of the Wallstent stents.

The stents with 32 fibres and a fibre diameter of 0.31 mm ($32 \times 0{\cdot}31$) were chosen for the *in vitro* degradation study, because they provide a high radial force and an acceptable diameter recovery. As seen from Tables 1 and 2, the stent diameter and radial pressure stiffness before sterilization were 11.0 mm and 3.2 MPa/m, respectively. After sterilization and release from the delivery device, the stent diameter and radial pressure stiffness decreased to 9.6 mm ($P = 0{\cdot}00$) and 2.0 MPa/m ($P = 0{\cdot}00$), respectively. The fibre elastic modulus and fibre ultimate tensile strength were 4.6 GPa and 205 MPa before sterilization, and 6.6 GPa ($P = 0{\cdot}01$) and 184 MPa ($P = 0{\cdot}05$) immediately after sterilization. Figure 2 presents the retained percentage of stent radial pressure stiffness, fibre elastic modulus and fibre ultimate tensile strength during *in vitro* degradation for the $32 \times 0{\cdot}31$ PLLA stents. The values after sterilization and stent release from the delivery device are taken as the reference values (100%) for the *in vitro* degradation study. The stents lost 50% of their initial radial stiffness pressure within 30 weeks and totally lost their structural integrity within 36 weeks. The elastic modulus and ultimate tensile strength of the 0.31 mm PLLA fibres decreased to 50% of their initial value after

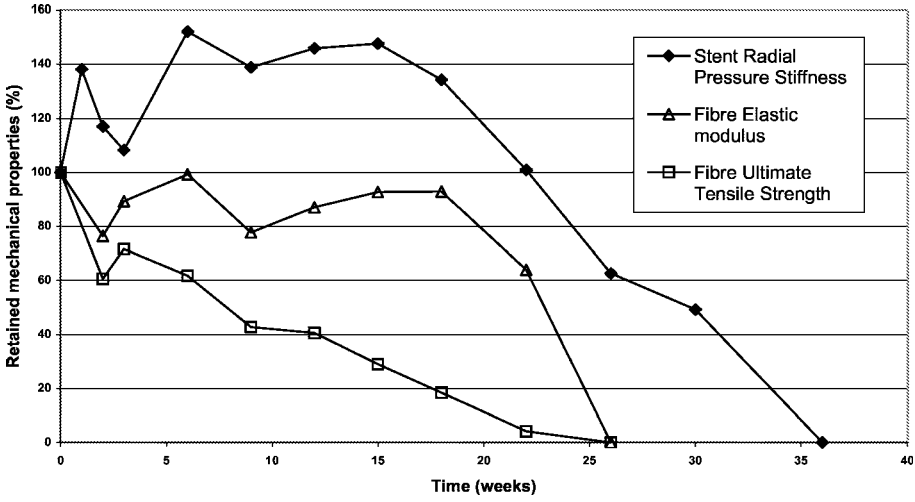

Figure 2. Retained percentage of stent radial pressure stiffness, fibre elastic modulus and fibre ultimate tensile strength during *in vitro* degradation.

23 and 8 weeks, respectively. This is consistent with the stent model [21] that predicts that the stent radial pressure stiffness is proportional to the elastic modulus for practical purposes. The strength retention of the braided PLLA stents during *in vitro* degradation was consistent to what was reported earlier for knitted PLLA stents [17].

The viscosity-average molecular weight was 218 000 g/mol after extrusion and drawing processes and it further decreased to 48 400 g/mol after gamma sterilization. The viscosity-average molecular weight decreased to half of its initial value after sterilization in 18 weeks. At 36 weeks when the stents lost their structural integrity, the viscosity-average molecular weight had decreased to 9200 g/mol. Figure 3 presents the change in number-average molecular weight in a semi-logarithmic scale during *in vitro* degradation up to 78 weeks. The number-average molecular weight was 30 600 g/mol after gamma sterilization. The linear behaviour observed up to 36 weeks is consistent with Pitt's model of autocatalyzed hydrolytic degradation kinetics [25]. This model states that the semilog plot of the number-average molecular weight *versus* the degradation time should be linear until the mass of the specimen starts to decrease. The retained mass of the PLLA stents during *in vitro* degradation up to 104 weeks is presented in Fig. 4. The mass reduction of the stents started after 26 weeks. Between 52 and 78 weeks, the retained mass decreased from 90 to 78%, while the molecular weight remained unchanged, which could indicate a diffusion of the low molecular weight fragments out of the polymer. The percent crystallinity of the stents was 47% prior to sterilization and 62% after sterilization. During the degradation period the percent crystallinity increased steadily up to 52 weeks reaching 82% and then remained constant up to 78 weeks. That indicates that most of the amorphous regions of the polymer had degraded or crystallinized at 52 weeks. Suuronen *et al.* [14] studied multilayer structures of PLLA plates

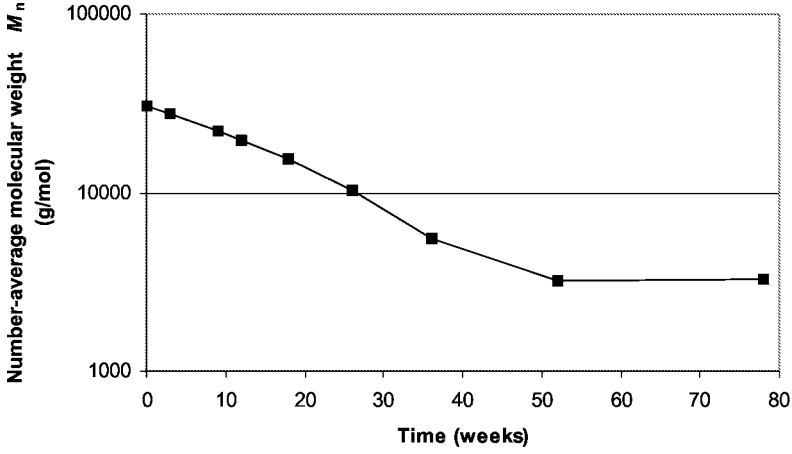

Figure 3. Change in the number-average molecular weight of PLLA during *in vitro* degradation. Semilogarithmic scale.

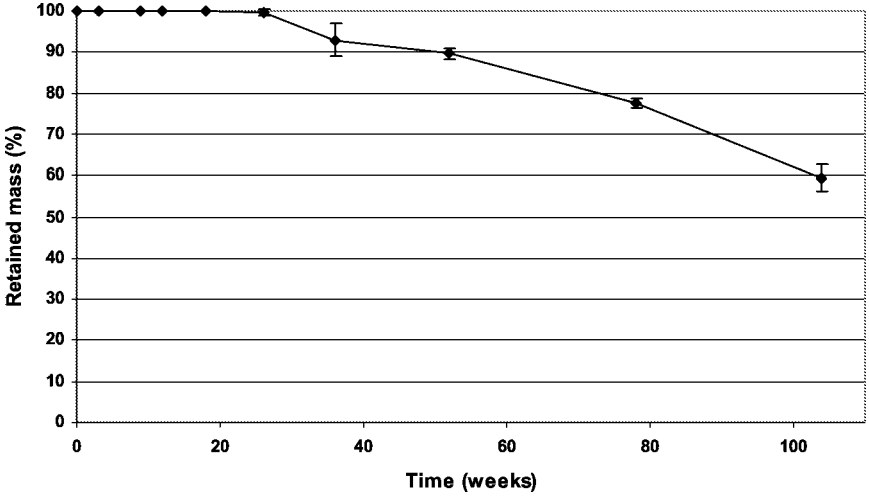

Figure 4. Retained mass of PLLA stents during *in vitro* degradation.

in vitro up to 5 years. They reported a similar type of increase in the crystallinity and decrease in the intrinsic viscosity of the plates up to 78 weeks. After that and up to 5 years, the crystallinity and intrinsic viscosity remained almost unchanged and they concluded that the PLLA crystals were extremely resistant to degradation due to hydrolysis only. The effect of these long lasting crystalline residues is a concern and L- and D-lactide that have a smaller degree of crystallinity may provide a useful alternative to poly(L-lactides). For instance, Hietala *et al.* [26] reported that stent were made out of a copolymer of 96% L-lactide and 4% D-lactide were totally eliminated in 24 months with minimal tissue reaction when implanted in a rabbit aorta.

CONCLUSIONS

The braided PLLA stents can be inserted into a delivery device having an inner diameter as small as 3.0 mm. However, diameter recovery decreased with decreasing delivery device size. The radial pressure stiffness of the braided PLLA stents was slightly lower than that of the commercially available metallic braided stents initially. It took about 30 weeks for the radial pressure stiffness to decrease to 50% of its initial value.

The stents lost their structural integrity within 36 weeks during *in vitro* degradation. During those 36 weeks, the intrinsic viscosity had decreased to about half of its initial value after sterilization and the mass of the stent about to 93% of its initial value.

According to these preliminary *in vitro* results, these bioabsorbable braided stents could be targeted to indications where the required stent size varies from 5 to 10 mm and which can be accessed with a delivery device having a diameter of about 3.5 mm. Accordingly, these stents are mostly targeted for urology, gastrointestinal and airway indications where the stenting site can be reached through a natural channel and the size of the delivery device is not of critical importance.

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