A NOVEL EXPANDABLE BIORESORBABLE ENDOVASCULAR STENT WITH PROTEIN CONTROLLED PRLEASE

Meital Zilberman (1), Robert C Eberhart (2,3)

(1) Department of Biomedical Engineering
Tel Aviv University
Tel Aviv
Israel

(2) Department of Surgery
University of Texas Southwestern
Medical Center at Dallas
Dallas, TX

(3) Joint Biomedical Engineering Program
The University of Texas at Arlington
and the University of Texas Southwestern Medical
Center at Dallas
Dallas, TX

INTRODUCTION

There is an increasing interest in bioresorbable polymeric stents for coronary applications[1]. The rationale for the bioresorbable stent is support of the vascular wall only during vessel healing, delivery of drug and/or gene therapy agents from an internal reservoir and no need for a second surgery to remove the device

We developed a novel multiple lobe expandable bioresorbable stent, made of PLLA fibers, for coronary application [1]. The current research focuses on the stent's mechanical properties. Bioresorbable stents can serve simultaneously to support blood vessels and as drug / protein delivery platforms. Drugs such as steroids can be incorporated in the PLLA fiber during melt processing. However, only small drug quantities (less than 10 wt%) can be incorporated without getting an adverse effect on the fiber and stent mechanical properties. Also, most of the drugs and all of the proteins will be destroyed while exposed to an elevated melt processing temperature. In order to solve this problem, protein loaded bioresorbable microspheres were developed and bound to the PLLA fibers and stents. The protein controlled release from the microsphere loaded stent was studied.

MATERIALS AND METHODS

Fiber Preparation

Bioresorbable fibers were made of relatively high molecular weight Poly(L-lactide) (PLLA), RESOMER L21 (inherent viscosity = 3.6 dL/g in $CHCl_3$ at 30 ^oC), Boehringer Ingelheim, Germany. The fibers (0.15 mm diameter) were melt spun at 190 ^oC in a batch mode (Alex James, Greer, SC) and drawn 8:1 at 80 ^oC. The following tensile properties were acieved: ultimate strength: 974 Mpa, young's modulus: 4.9 GPa, maximal strain: 0.88.

Stent Preparation and Testing

A four lobe stent was designed using a linear, continuous coil array principle, by which four furled lobes convert to a single large lobe upon balloon expansion. This stent design is presented in Fig. 1. The stent preparation is described elsewhere [1]. Stents of 15 mm length, 3.0 mm final (dilated) diameter and 1.8 mm pre-dilated diameter were used in this study. Both, single and double fiber stents were investigated. Each dilated coil stent contained 12 loops, each of them bonded to three longitudinal support fibers, i.e., 36 binding points per each single fiber stent and 72 binding points per each double fiber stent. The radial compression strength of the stents was measured using a special chamber, constructed in our laboratory.

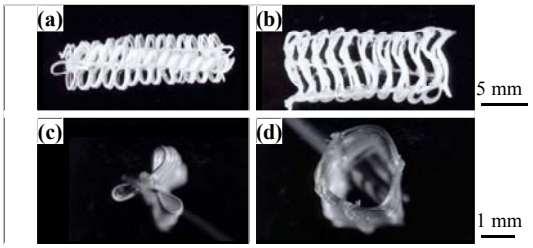


Fig. 1: The design concept of the stent: (a) pre-dilated, (b) dilated, (c) pre-dilated, side look, (d) dilated, side look.

Microsphere Preparation and Albumin Release Study

75/25 poly(DL-lactide – co – glycolide) (PDLGA) microspheres containing Bovine Serum Albumin (BSA) were prepared through the water/oil/water (W/O/W) double emulsion process. Two kinds of 75/25 PDLGA polymer were used: intrinsic viscosity (i.v.) = 0.35 dL/g (~43,000 Daltons) and 0.69 dL/g (~118,000 Daltons). The "oil" phase contained 20 wt% polymer in methylene chloride and the internal water phase contained 20 wt% Albumin. The quantity of the "oil" phase was constant and two different (internal water / oil phase) (W_1/O) ratios were used; 1 (relatively large water volume and Albumin content) and 0.2 (relatively small water volume and Albumin

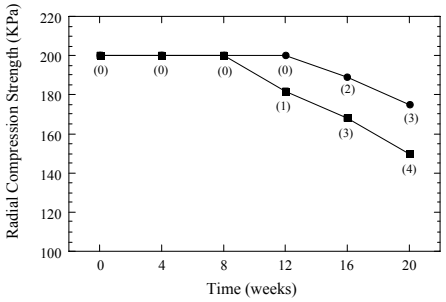
content). Four types of Albumin loaded microspheres were produced. These were bound to the stents.

To determine the release kinetics of Albumin from the microsphere coated stents, they were immersed in phosphate-buffered saline (pH 7.4) at 37 ^{O}C for 6 weeks. Samples of 1.5 ml were collected periodically and their Albumin content was determined via a standard curve by measuring absorbance at 562.0 nm, using Beckman DU-600 Spectrophotometer.

Expandable Stents

The initial radial compression strength of the dilated form of both, single and double fiber stents was higher than 200 KPa. It should be mentioned that the maximal applied pressure using our radial compression chamber is 200 Kpa, therefore, higher strength values could not be measured.

The stents were immersed in phosphate-buffered saline at 37 ^{o}C, for certain periods of time, in order to investigate the effect of their in-vitro degradation on mechanical properties. The mode of failure observed was rupture of binding points, where the longitudinal support fibers were glued to the coil. The radial compression pressure needed in order to create a rupture of at least one binding point, in both types of stents, is presented as a function of immersion time in Fig. 2. The number of ruptures (binding points that failed) is indicated in parenthesis for each immersion time. Both types of stents did not undergo any failure, after applying 200 KPa, throughout the first eight weeks. Then the radial compression pressure required to create a rupture at binding points showed a linear decrease with time and the number of ruptures was increased with time. In general, these stents demonstrated good radial compression endurance. They resisted at least 150 KPa (approximately 75% of the initial strength) and exhibited only several rupture points, while most of the binding points remained intact.



a function of immersion time in PBS at 37 ^{o}C: (■) – single, and (●) – double fiber stents. The number of rupture points is indicated.

Albumin Release from Microsphere Loaded Stents

Albumin loaded microspheres of 10-70 μm with smooth surface and a core/shell (aqueous phase / polymer) structure were prepared. Most of the Albumin (85 wt%) used was encapsulated in the microspheres. Both, surface and shell are non-porous. The (W_1/O)=1 microspheres, containing high water content, exhibited a relatively thin polymer shell, while the (W_1/O)=0.2 ones, containing low water content exhibited a relatively thick water shell.

Microspheres were bound to the fibers and stents. The initial radial compression strength of all types of microsphere loaded stents was higher than 200 KPa. This indicates that the partial dissolution of the surface layers that was done in order to enable microsphere attachment to the fiber practically did not affect the radial compression strength of the stent.

The cumulative Albumin release profiles from the four types of microsphere loaded stents are presented in Fig. 3. In general, a burst effect is accompanied by linear cumulative release profile, as expected for a "reservoir" system, such as these core/shell microspheres. After 6 weeks of incubation, the relatively low molecular weight (i.v.=0.35) microspheres exhibited rough surface features with cracks and ruptures, and a porous shell structure, due to erosion processes. In contrast, the the higher molecular weight microsphere (i.v.=0.69) exhibited only very thin cracks on the surface. Therefore, the release rate from the i.v.=0.35 microsphere stents was higher than that from the i.v.=0.69 ones, and the burst effect of the former is higher than that of the latter. Also, the low (W_1/O) ratio, leading to thick polymer shell, is effective in reducing the burst effect.

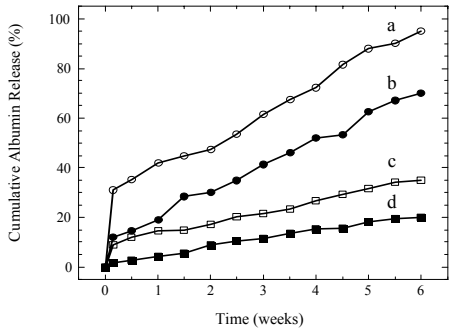


Fig. 3: In-vitro cumulative Albumin release from PDLGA microsphere loaded stents. (o) i.v.=0.35 dL/g, W/O = 1, (●) i.v.=0.35 dL/g, W/O = 0.2, (□) i.v.=0.69 dL/g, W/O = 1, (■)i.v.=0.69 dL/g, W/O = 0.2.

CONCLUSIONS

Novel PLLA expandable stents demonstrated excellent initial radial compression strength and good in-vitro degradation resistivity. Hence, the combination of the suggested design and the relatively high molecular weight PLLA is applicable for supporting blood vessels for at least 20 weeks and was chosen for further studies.

Microspheres bound to these stents enable effective protein loading, without reducing the stent's mechanical properties. The protein release profile from the microsphere loaded stent is determined mainly by the initial molecular weight of the bioresorbable polymer and its erosion rate, and is strongly affected by the microsphere structure.

ACKNOWLEDGEMENT

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REFERENCES

1. Eberhart, R. C., Su, S. H., Nguyen, K. T., Zilberman, M., Tang, L., Nelson, K.D, and Frenkel, P., "Bioresorbable Polymeric Stents: Current Status and Future Promise" J. Biomater. Sci. Polym. Ed., In press.