ISSN: 2977-0041

Research Article

Journal of Material Sciences and Engineering Technology

Solid-Phase Orientation (Die Drawing) of Polymer Tubes to Enhance Mechanical Properties of Bioresorbable Vascular Scaffolds

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Received: March 18, 2024; **Accepted:** March 22, 2024; **Published:** March 29, 2024

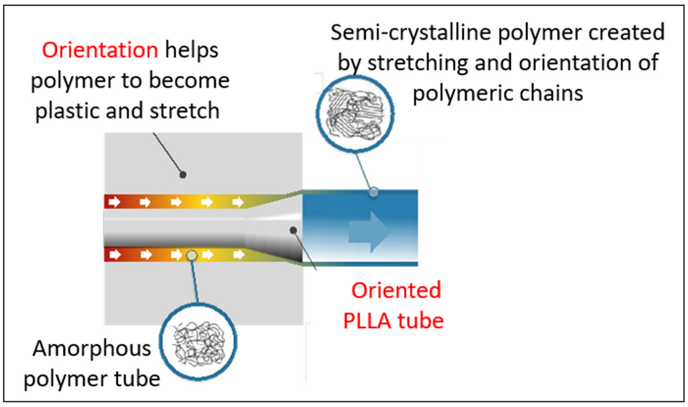
ABSTRACT

Die-drawing, also known as solid phase orientation, is a technique used to enhance the mechanical properties of polymers for non-medical applications [1]. Arterius has adapted and optimised this technology to manufacture state-of-the-art bioresorbable polymeric scaffolds (stents) based on polylactic acid (PLA) for vascular and non-vascular applications. The mechanical properties of the polymer are improved by orientating the polymer chains and introducing crystallinity to the polymer. As the PLA polymer is drawn over a mandrel and through a die, close to the glass transition temperature ($T_g > 55$ °C), the polymer chains align, gradually increasing orientation with the bi-axial draw, thus promoting significantly improved mechanical properties. In-house testing of the die-drawn tubing compared to the extruded tubing showed an increase in tensile modulus up to 79.7%, yield strength increases of up to 121.5%, ultimate tensile strength increases of up to 267.9% and elongation at break increase of up to 1,022.8%. The die-drawing process also introduces crystallinity into the PLLA tubing, initially the amorphous extruded tube has a crystallinity of around 1.3% which increased to around 40% crystallinity after the die-drawn process. Another attribute of the orientated polymer tubing is the radial strength it provides to the scaffold once it has been laser cut into an innovative closed-cell design, which is comparable to market-leading metallic stents.

Keywords: Die Drawing, Solid Phase Orientation, Bioresorbable Polymers, Polylactic Acid, Vascular Scaffolds (Stents), Tensile Properties, Radial Strength

Introduction

Die drawing is a form of solid-phase orientation - a process in which molecular alignment of a polymeric material is achieved by heating the polymer to a temperature between its glass transition (T_g) and melting temperature (T_m) then drawing over a mandrel and through a die to change its cross-sectional area and orientate the polymer chains, as depicted in the image below.



A process of producing high modulus filaments of polyethylene by die drawing was first patented by Ian Ward in March 1981 (Patent number US 4,254,072), he followed this by filing a further patent in 1989 (Patent number US 5,096,654) where he describes methods of solid phase deformation of orientable, semi-crystalline polymers.

Initial work on die drawing concentrated on monoaxial orientation in polymers which was achieved by aligning the chains in one direction only. However, the enhanced strength and stiffness in this direction were at the expense of properties which are at right angles to the stretching plane, which weakened rapidly with the increased deformation. This issue was overcome by introducing biaxial orientation, in this process, the material is stretched in two directions, either simultaneously or sequentially, and the molecules line up in a plane parallel to the stretch plane. Extensive research into these two models has been described in the book titled “Solid Phase Processing of Polymers” by I.M. Ward and P.D. Coates [1,2].

With the biaxial orientation, deformation of the material aligns polymer molecules in both radial and axial directions, improving tensile strength and stiffness of the polymer. Blow moulding is a technique used to radially orientate and expand polymer tubes,

Citation: Naveed Ahmed, Nial Bullett, Will Balmer, Kadem Al-Lamee. Solid-Phase Orientation (Die Drawing) of Polymer Tubes to Enhance Mechanical Properties of Bioresorbable Vascular Scaffolds. J Mat Sci Eng Technol. 2024. 2(1): 1-6. DOI: doi.org/10.61440/JMSET.2024.v2.22

first used by Abbott to produce bioabsorbable cardiovascular stents as described in a patent (US 7740791 B2) filed in 2006. Advantages of the die drawing method over blow moulding are the superior mechanical properties and the fact that you can continuously produce tubing as the process requires fixing of the tube only at one end whereas blow moulding requires the tubing to be fixed at each end.

In 2010, Arterius initiated development of a biaxial die drawing process to manufacture bioresorbable tubes which would be used in the production of bioresorbable scaffolds. Arterius collaborated with the team at the University of Bradford, who at that time utilised the technology to manufacture large industrial pipes. The feasibility and early-stage development of bioresorbable polymer tubing resulted in a joint patent being filed in September 2013 (Patent number: WO/2014/045068), in which it describes methods of simultaneous bi-axial orientation of Polylactic acid (PLA) tubes by drawing the tube over a mandrel and through a die. Arterius then designed and built an innovative die-drawing system which allowed Arterius to further develop in-house the process of biaxial die-drawing, resulting in the ability to produce tubing that had significantly improved mechanical properties, high radial strength and a wall thickness of bioresorbable polymeric tube as low as 80 µm, it also gave the ability to manufacture die-drawn tubing in-house using a validated process and in a cleanroom environment.

The idea of bioresorbable scaffolds (stents) (BRS) for treating coronary artery disease was introduced in the 1980s by Igaki Medical Planning Company, Kyoto, Japan, who were the first to implant the 170 µm Igaki-Tamai stent made of monofilament Poly-L-lactic acid (PLLA) [molecular mass 183KDa, with a zigzag helical design] in a human trial [3]. The BRS was developed to overcome late stent thrombosis, in-stent restenosis associated with the metallic stent and to a “leave nothing behind” approach. While the first generation of BRS is novel and interesting, the initial experience with BRS was hampered by the increased rate of thrombosis compared with metallic Drug-Eluting Stent (DES). Another first-generation bioresorbable scaffold developed by Abbott Vascular was manufactured by blow-moulding of poly-L-lactic acid (PLLA) resulting in a scaffold that had a high wall thickness (167µm) to improve the radial strength of the scaffold, but this increased the likelihood of narrowing (restenosis) and thrombosis of the coronary arteries after implantation. This was due to the scaffold protruding into the bloodstream and increasing the potential for blood clots. In 2016, Patrick Serruys presented 3-year data on the ABSORB II trial, the outcome of the trial was that it did not meet its co-primary endpoints of superior vasomotor reactivity and non-inferior late luminal loss for the Absorb bioresorbable scaffold with respect to the metallic stent [4]. It was further reported in 2017, in the ABSORB III trial, that 3-year adverse event rates were higher with bioresorbable vascular scaffold (BVS) than with metallic stent, particularly target vessel myocardial infarction (TVMI) and device thrombosis. TVMI through 3 years was increased with BVS (8.6% vs. 5.9%; $p = 0.03$), as was device thrombosis (2.3% vs. 0.7%; $p = 0.01$) [5].

A further study performed By Nicolas Foin demonstrated there was a higher disruption to the blood flow as the wall thickness of the scaffold increased, it was concluded that perturbed flow patterns around large, protruding struts are associated with increased platelet adhesion, inflammatory responses, and reduced re-endothelialisation [6]. This meant there was a need for thinner-walled scaffolds that had good radial strength and were manufactured cost-effectively.

With this, Arterius’ journey began to produce thin-walled scaffolds for the treatment of coronary artery disease (CAD) and peripheral artery disease (PAD), it would be the first time die drawing would be utilised to produce tubes for scaffolds with a wall thickness of less than 100 µm.

Materials and Methods

Materials

Medical grade extruded PLLA tubes were purchased by Zeus Corporate Research (USA) the product name of the extruded tube is Absorv™ PLLA., and the PLLA material is manufactured by Corbion Purac (Netherlands).

Methods

Die Drawing

The extruded PLLA tubes were die-drawn by Arterius's novel method as described above.

Mechanical properties of the extruded and the oriented tubes were measured using uniaxial tensile testing of Mecmesin Multitest 1-i tensometer.

Crystallinity

Crystallinity testing was performed using a Modulated TA Instruments Q2000 Differential Scanning Calorimeter (DSC).

Laser Cutting

The die drawn PLLA tubes have been laser cut at MeKo (Germany) to produce Arterius novel design scaffolds (Patent number: US 9,707,109).

Dog-bone samples laser cut at MeKo (Germany) using die drawn tubing produced at Arterius. Dog bone samples from both the radial direction and axial direction were produced from each tube. These samples were loaded onto a Mecmesin tensometer following the same procedure used to test tube samples.

Radial Strength Testing

Radial strength testing of scaffolds was performed using a Blockwise TTR2 Radial Strength Testing Machine to measure radial strength during the development stages. The test method follows in-housework instructions which conform to BS EN ISO 25539-2 Endovascular Devices Part 2 - Vascular Stents, Section D.5.3.4.

Radial strength is the amount of force needed to compress a scaffold device, the radial force applied by a radial compression mechanism (or a “crimping head”) to the scaffold is usually measured by a linear force transducer that senses the force applied by an actuator. This generates a Force vs Diameter trace using Blockwise software, from this trace the following data can be interpreted:

- Radial Force at Inflection Point by Unity of Length (N/mm)
- Max Radial Strength by Unity of Length (N/mm)
- Stiffness until Inflection Point by Unity of Length (N/mm^2)

Results and Discussion

Tube Tensile Testing

Tensile testing is a destructive test process that generates information regarding the tensile strength, yield strength, and ductility of the test material. It measures the force required to break a plastic specimen and the level to which the specimen elongates to the breaking point. A typical trace generated after the test is shown in Figure 1.

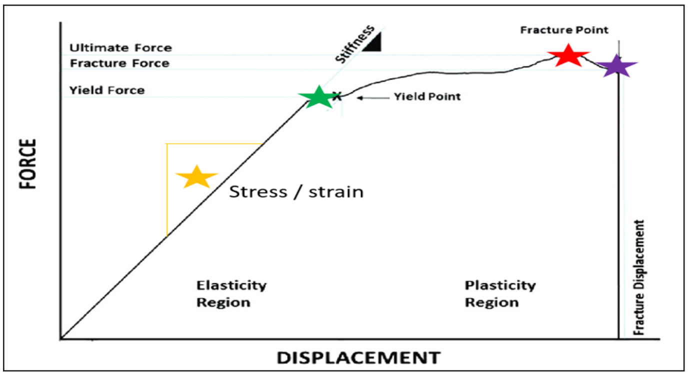


Figure 1: Tensile test stress-strain curve

Comparing in-house tube tensile testing results of a typical orientated PLLA tube versus an extruded PLLA tube, as displayed in Figure 2, results show a significant difference in the stress-strain curves of the two tubes.

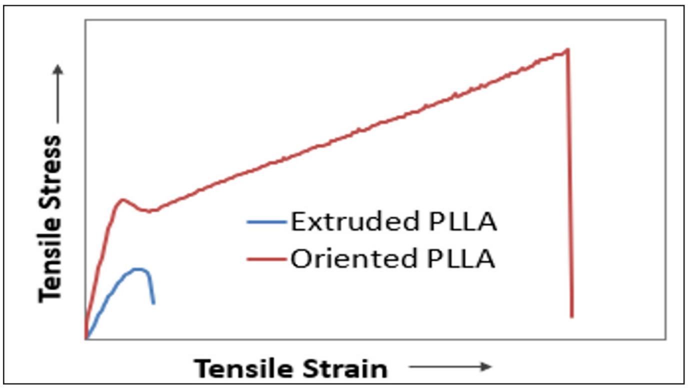


Figure 2: Comparing behaviour of extruded versus orientated PLLA tubes

All the mechanical properties have improved substantially. The die drawn material exhibited higher modulus (gradient) values in the elastic region with an increase of nearly 80%, representing increased stiffness of the material. The tube then deforms elastically to a peak tensile stress, with the die-drawn tube exhibiting a 122% increase over the extruded tube. Shortly after the elastic deformation, a strain-hardening resonance effect occurs at which the Ultimate (maximum) Tensile Strength is measured resulting in an increase of around 268% over the value of the extruded tube. Finally, the tube fails and an Elongation at break value is recorded resulting in an increase of up to 1,022% after die-drawing, polymers with a higher elongation at break percentage have higher ductility. High ductility indicates that a material will be more likely to deform and not break.

Data exhibited in Table 1, compares the tensile properties of orientated PLLA tubing with that of extruded PLLA and Magnesium alloy which is used to manufacture bioresorbable metallic stents.

Table 1: Mechanical property comparison between extruded PLLA, die-draw 2.89x95µm PLLA and Magnesium alloy

Material	PLLA	Orientated PLLA	Magnesium Alloy
Ultimate Tensile Strength (MPa)	69.9	257.2	280
Tensile Modulus (GPa)	1.98	3.56	45
Elongation (%)	5.7	64	23

The die drawing process has been fully validated to produce 95µm PLLA tubes. Figure 3 shows stress-strain curves for the first, middle and last tubes of a batch that were produced following the validated procedure.

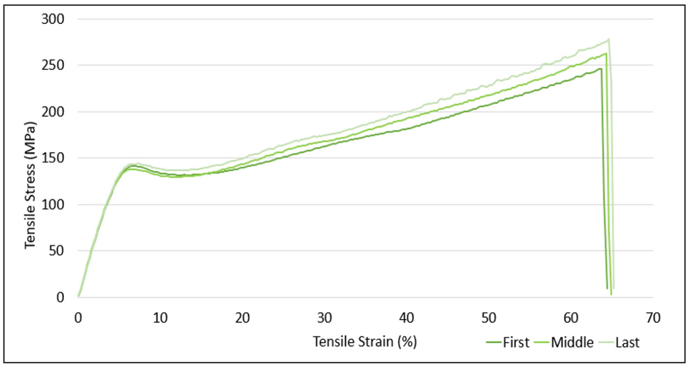


Figure 3: Tube tensile data showing reproducibility of tube production

Results show excellent reproducibility within the batch, with all three runs virtually identical and showing the typical characteristic of a stress-strain curve.

Dog Bone Tensile Testing

With this next example, two sets of extruded PLLA tubing, each with different outer diameters were die-drawn to achieve a wall thickness of 95µm, which meant both tubes would receive a varying degree of orientation in each direction, both axial and radial. To measure the mechanical properties of both tubes a biaxially tensile test of the die-drawn tubing was performed.

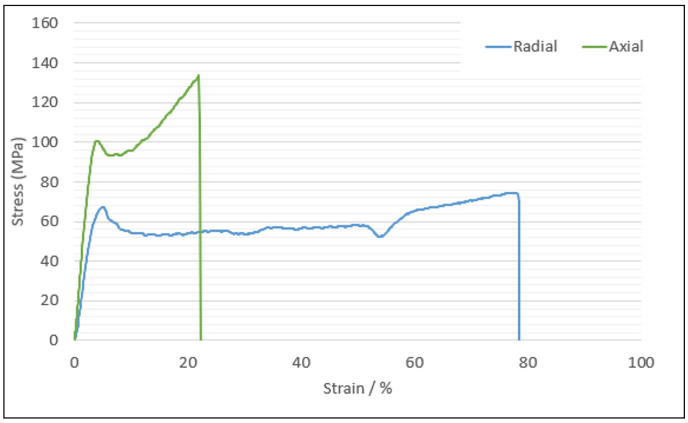


Figure 4: Typical stress-strain curves for dog bone tensile testing

Results obtained from the biaxial tensile testing of the dog bone samples are summarised in Figure 4. The axial dog bone samples exhibit a higher degree of orientation shown by the higher stress values but this in turn has reduced the plastic deformation, whereas the radial dog bone samples show the opposite, slightly lower stress values but with greater plastic deformation region. This means the tube is more ductile and has a greater ability to expand in the radial direction a property which is more favourable when it comes to designing a scaffold.

- Blue line represents mechanical properties of the radial dog bones.
- Green represents mechanical properties of the axial dog bones

Data extrapolated from the traces in Figure 4 support the finding of there being a high degree of orientation of polymer chains in the axial direction compared to the radial direction for both tube sizes, shown by the yield strength (Figure 5) where the axial samples have values of 125 MPa compared to 67 MPa for the radial samples, and the ultimate tensile strength (Figure 6) values again are higher for the axial samples with values of 180 MPa compared to 75 MPa for the radial samples.

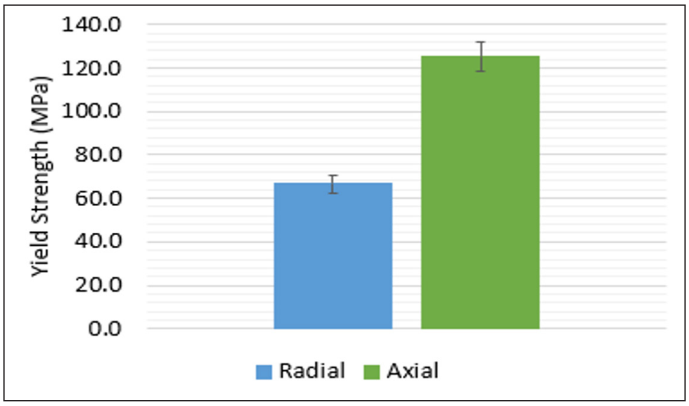


Figure 5: Yield strength of dog bone samples

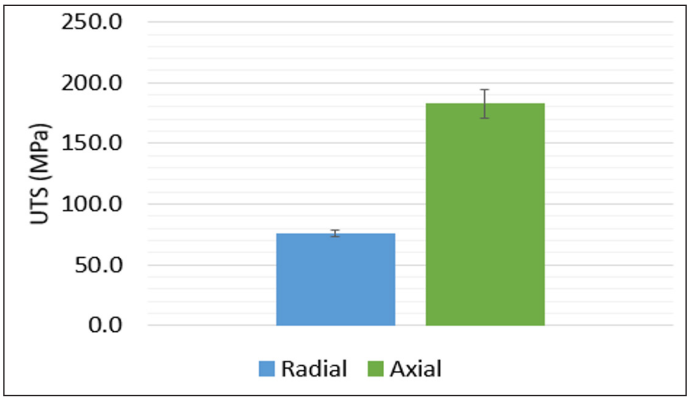


Figure 6: UTS of dog bone samples

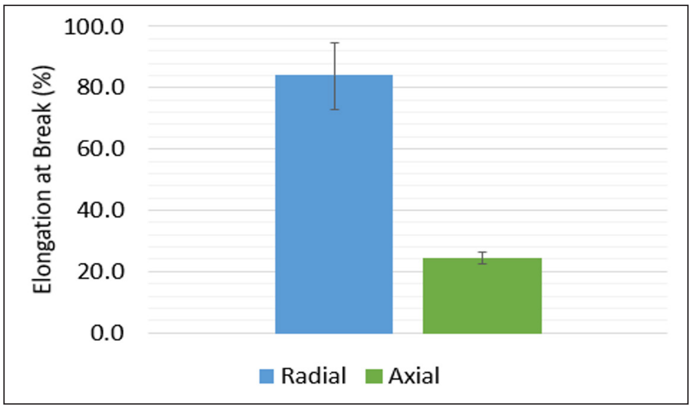


Figure 7: Elongation at Break dog bone samples

The increase in orientation in the axial direction has meant that the elongation to break has decreased to around 23%, as shown in Figure 7, a low elongation to break means the polymer is less ductile and therefore higher tendency to fracture when the scaffold is expanded in the axial direction. As there is no significant expansion in the axial direction, this is not a major concern when it comes to the scaffolds, as the majority of the expansion occurs in the radial direction, and this is where the elongation to break is the highest. This means the polymer is more ductile in the radial direction and less likely to fracture when the scaffold is expanded, this is shown by the ability of the Arterius scaffold to expand 1mm above nominal without any fractures.

It is crucial when optimising parameters for die drawing that all these factors are considered so that the optimum material is produced.

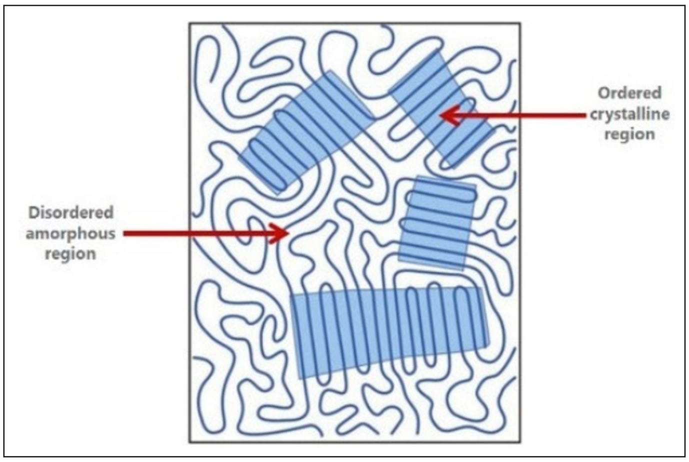


Figure 8: Regions of order crystalline polymer chains

The crystallinity of a polymer can be measured using thermal analysis techniques such as Differential Scanning Calorimetry (DSC) which regulates the temperature and heat flow associated with material transitions as a function of time and temperature.

From the modulated DSC experiments, a typical heat flow chart is generated, as shown in Figure 9, from which the degree of crystallinity is calculated.

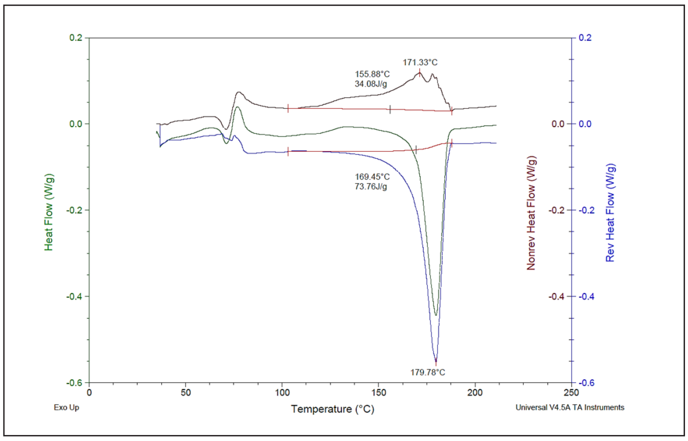


Figure 9: Typical analysis of thermal data using Discovery DSC

The crystallinity for extruded PLLA tubes was measured to be 0.1 - 1.3%, during the die-drawn process, crystallinity is introduced, and this value increases to 40.94 ± 4.83% (mean ± standard deviation). This significant increase in crystallinity is likely a result of the raised temperature to which the tube is exposed to strain-induced crystallisation during the die-orientation process. Parameters can be adjusted to give optimal crystallinity; too high crystallinity will render the polymer too brittle and not be a suitable material for scaffold production as it would be prone to fractures as the scaffolds are expanded, too little crystallinity would mean the scaffold would have poor radial strength.

Radial Strength

For scaffolds to function effectively, they must have a radial strength capable of withstanding the radial compressive forces exerted by the luminal wall of a blood vessel. Arterius measured the radial strength of the manufactured scaffolds against a market-leading metallic stent which has been proven to be a success in the stenting market.

Due to the enhanced mechanical properties gained from the die-drawing process, Arterius gained an advantage over competitor products by having the ability to manufacture scaffolds that had similar mechanical properties to that of the metallic stent.

Results exhibited in Figure 10 show the Arterius scaffolds manufactured from die-drawn tubes have a similar radial strength to the market-leading vascular metallic drug-eluting Xience stent when expanded to nominal diameter. Therefore, the Arterius scaffolds will have the radial strength to hold open diseased artery walls, as successfully demonstrated by the Xience stent.

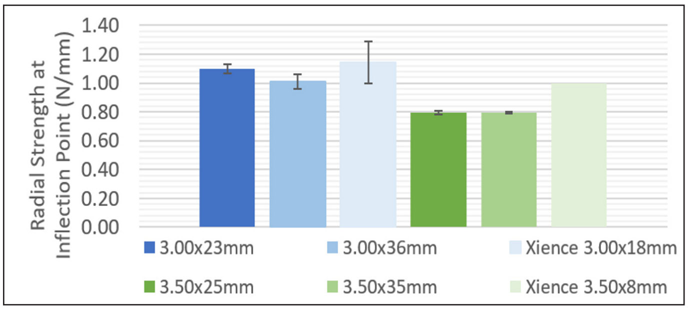


Figure 10: Radial strength results of Arterius scaffolds versus Xience

Figure 11 shows results for the radial stiffness of Arterius scaffolds compared to Xience metallic stents, again very similar values were recorded, by having a similar level of stiffness to the metallic stents, resisting the compressive forces applied by the pulsatile flow.

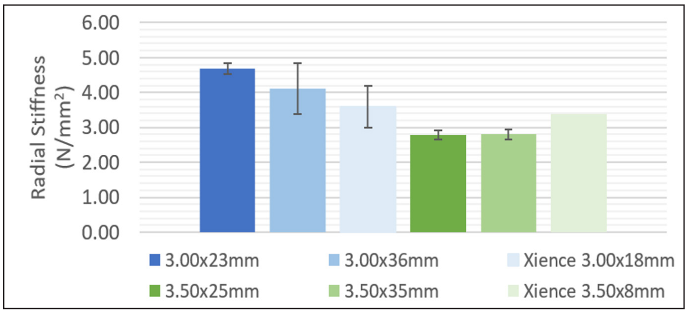


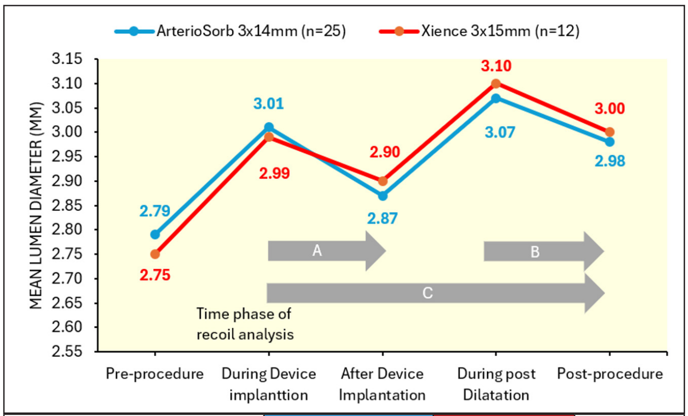
Figure 11: Radial stiffness results of Arterius scaffolds versus Xience

In-Vivo Performance of Arterius Scaffold

Arterius developed a second-generation BRS, ArterioSorb™ using a patented die-drawing processing technique of poly-L-lactic acid (PLLA) that results in improved radial strength, allowing reduced strut thickness (95µm). This resulted in a low crossing profile and is likely to reduce the occurrence of in-device thrombosis caused by bulky struts disrupting the arterial blood flow.

An in-vivo study was performed to evaluate ArterioSorb™ scaffolds compared to clinically approved metallic Xience stent (manufactured by Abbott Vascular) implantation in the coronary arteries of Yucatan mini pigs, assessing angiographic and optical coherence tomography (OCT) results.

Quantitative Coronary Angiography (QCA) results show serial changes in mean lumen and balloon diameter during the procedure absolute and recoil after device deployment and the one after post-dilatation were comparable between ArterioSorb™ (3.0 x 14mm) and XIENCE (3.0x15mm) as shown in Figure 12.



	ArterioScorb	XIENCE	p-value
Immediately affer device deployment (A)	N=25	N=15	
Absolute recoil (mm)	0.14±0.22	0.09±0.15	0.388
Relative recoil (%)	4.69±7.38	2.70±4.52	0.367
From PD to post-procedure (B)	N=25	N=12	
Absolute recoil (mm)	0.09±0.17	0.10±0.16	0.931
Relative recoil (%)	2.81±5.52	3.03±5.21	0.907
Global recoil (C)	N=25	N=12	
Absolute recoil (mm)	0.03±0.27	-0.01±0.18	0.636
Relative recoil (%)	0.55±8.27	-0.46±5.64	0.705

Figure 12: Recoil assessment by QCA during procedure. The graph lines show serial changes in mean lumen diameter in device segments. PD: post-dilatation.

OCT imaging (Figure 13) showed that the lumen area 180-day decreased in comparison to the post-implant value for the Arterius device and the metallic Xience stent, not significant difference was recorded between the Arterius scaffold and metallic Xience stent.

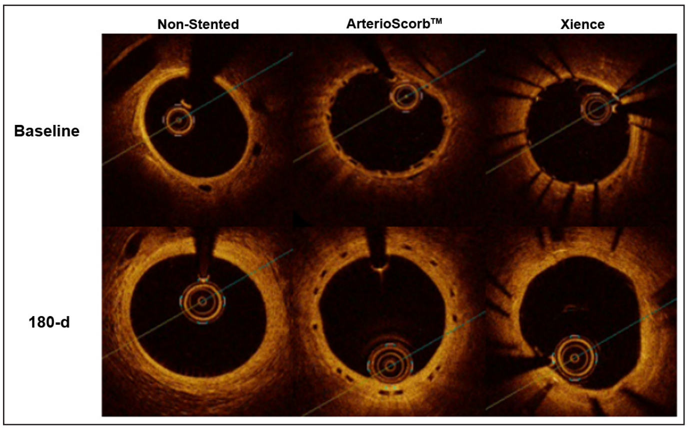


Figure 13: Optical Coherence Tomography Imaging in porcine model comparing non-stented vessel with ArterioSorb and Xience stent over 180 days.

Micro CT was performed at the end of the study to evaluate the structural integrity of the scaffolds.

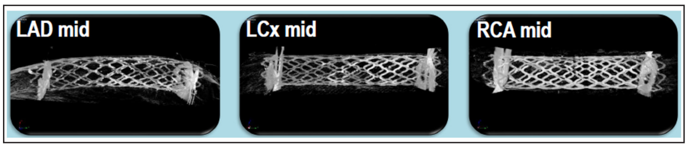


Figure 14: Micro CT at 180-day implantation of Arterius scaffold in porcine model

The micro-CT Image analysed (Figure 14) shows the Arterius scaffold present at the 180-day timepoint. Despite the onset of the degradation process and strut discontinuities, the scaffolding property remained intact, and the scaffolds were well deployed with an open and straight structure allowing good vessel patency.

Conclusion

In this study, the effects of Arterius' novel Solid-Phase orientation (die-drawing) of PLLA tubes to produce bioresorbable scaffolds (stents) that have similar attributes to market-leading metallic stents were investigated. The following conclusions were drawn:

(1). Solid-phase orientation (Die-Drawing) significantly enhances the mechanical properties of die-drawn PLLA polymer.
(2). Compared to the extruded tube, tensile modulus increased by a maximum of 79.7%, the yield strength increased by a maximum of 121.5%, the ultimate tensile strength increased by a maximum of 267.9% and elongation at break increased by a maximum of 1022.8%.
(3). Compared to the extruded tube, the level of crystallinity increased from around 0.1-1.3% to approximately 40%.
(4). Enhanced mechanical properties of the die-drawn tube have contributed to the successful manufacture of scaffolds that have similar radial strength to market-leading metallic stents.
(5). In-vitro and In-vivo data have shown that the redial strength of Arterius' scaffolds is comparable to best-in-class metallic drug-eluting stents. This oriented polylactide polymer rendered the manufacture of thinner struts possible without loss of radial force and without an increase in recoil.

Conflict of Interest

Kadem Al-Lamee, PhD is a co-founder and CTO of Arterius Ltd. Nial Bullett, PhD is an employee of Arterius Ltd. Naveed Ahmed, PhD is an employee of Arterius Ltd. Will Balmer, MEng is an employee of Arterius Ltd.

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