University of Cincinnati

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I, Tarannum R Tiasha, hereby submit this original work as part of the requirements for the degree of Master of Science in Materials Science.

It is entitled:
Biodegradable Magnesium Implants for Medical Applications

Student's name:  Tarannum R Tiasha

This work and its defense approved by:

Committee chair: Vesselin Shanov, Ph.D.

Committee member: Rodney Roseman, Ph.D.

Committee member: Mark Schulz, Ph.D.
BIODEGRADABLE MAGNESIUM IMPLANTS FOR MEDICAL APPLICATIONS

A thesis submitted to the
Graduate School
of the University of Cincinnati
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Master of Science
in the Department of Mechanical and Materials Engineering
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by

TARANNUM RAHMAN TIASHA

B.S (Physics) University of Dhaka, Bangladesh, 2008
M.S (Physics) University of Cincinnati, 2013

University of Cincinnati
24 March, 2017

Committee Chair: Dr. Vesselin Shanov
Committee members: Dr. Mark Schulz and Dr. Rodney Roseman
ABSTRACT

A number of biodegradable devices with various applications has been fabricated; mostly by a novel photochemical etching (PE) technique. A diverse array of biodegradable magnesium (Mg) AZ31 stents of different dimensions and textures has been fabricated by this technique. Results of stent expandability tests and stent expansion simulations led to multiple design modifications; which include elimination of end rings, reduction in stent length as well as elimination of the welding bar. These design modifications resulted in uniform expandability of the stents. The PE technique has also been employed to fabricate helical flow inducing devices; namely the Mg AZ31 helical stent; which exhibited an expansion mode different from that of the cylindrical stent. Preliminary in vivo studies with such a device in porcine models demonstrated promising characteristics of a helical flow pattern. Corrosion studies of photochemically etched cylindrical Mg AZ31 stents were performed. A flow induced shear stress (FISS) based corrosion study revealed localized corrosion of small amount under static conditions and uniform corrosion under dynamic conditions. Another corrosion study was carried out with Mg AZ31 stents with different polymer coatings; in which poly(carbonate urethane) urea i.e. PCUU-coated stents showed improved corrosion resistance as well as reduced thrombotic deposition in comparison with uncoated or poly(lactic-co-glycolic acid) i.e. PLGA-coated stents. A corrosion study on photochemically etched helical Mg AZ31 stents in three different environments (static immersion, in vitro and ex vivo) revealed a high dynamic degradation rate as well as production of intermediate corrosion products. Another helical stent made of a Mg single crystal has been fabricated; which is expected to show higher ductility and fracture toughness in comparison with polycrystalline Mg. In addition, fabrication of biodegradable Mg AZ31 staples for soft tissue
application has been attempted by employing the PE method. However, the bending of the staple strip to the target shape remains a challenge; due to the required small radius of curvature of the current staple design.
ACKNOWLEDGEMENTS

First of all, I would like to thank the Almighty for blessing me with the gift of life, good health and the privilege to pursue the path of my interest. I would then like to thank my advisor Dr. Vesselin Shanov for giving me the opportunity to work on this project regarding biodegradable magnesium implants and also for his continuous guidance, encouragement and support throughout the period of research. I am grateful to Dr. Mark Schulz and Dr. Rodney Roseman for consenting to be a part of my MS thesis defense committee. I would also like to express my heartiest gratitude to all the members in my research group including Pravahan, Guangqi, Jibao, Madhura, Pavan and Dr. Vibhor for their active involvement, advice and cooperation at various stages of my research. I am thankful to our research collaborators at North Carolina Agricultural and Technical State University and at University of Pittsburgh for their efforts, suggestions and assistance. I am extremely grateful to my family for their eternal affection, care and support; because of which I have become a stronger and better human being. Finally, I would like to thank my friends Nabila, Lima, Soumendu, Sumeet, Vineeta and Deeptha for their endless support and encouragement which kept me going through the difficult phases.
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CHAPTER 1: INTRODUCTION

1.1 Rationale of biodegradable stent

Stents are tubular implants having a mesh like structure and are used in treatment of narrow or blocked arteries. Plaque deposition over time causes narrowing of arteries; which leads to disruption of normal blood flow. In order to restore normal blood flow, stents are placed inside arteries by surgery and are expanded either via self-expansion or by balloon catheters. In this process, the plaque is crushed as stents are pushed up against the artery wall. Stents thus keep arteries open by remaining fixed in position; as shown in figure 1.1. Although prominently used in coronary arteries for treatment of cardiovascular disease (CVD), stents are used in other blood vessels as well.

Figure 1.1: (A) A blood vessel with plaque accumulation; (B) Insertion of a stent in the blood vessel via a balloon catheter and (C) Expansion of the stent via balloon inflation.[1] [Parts (A), (B) and (C) of this figure has been adapted from Carver, L. Understanding Drug-Eluting stents at Boston Scientific, Comsol Blog; comsol.com. (2014) © 2014 Comsol.]

The major limitations of balloon angioplasty with enabling scaffolding, prevention of early recoil and late vascular remodeling led to the introduction of intravascular stents in the 1980s.[2] However, late-stage thrombosis (blood clotting) and restenosis (re-narrowing of arteries) still remain the major challenges in arterial stenting. Placement of stents in arteries may lead to vessel wall injury, which triggers proliferation of smooth muscle cells in the vessel wall i.e. neointimal hyperplasia; which is the prime cause of restenosis.[3]
To address this limitation, stents capable of releasing antiproliferative drugs i.e. drug eluting stents (DES) have been developed. Such stents have been able to significantly reduce restenosis, but also have been associated with a small but increased risk of late-stage thrombosis;[4-6] which requires prolonged antiplatelet therapy for at least 12 months.

Other disadvantages of bare metallic stents (BMS) include prevention of lumen expansion associated with late favorable remodeling,[7,8] impairing of vessel geometry, delayed re-endothelialization (regrowth of endothelial cells) as well as obstruction of side branches. Moreover, BMS are incompatible with imaging techniques such as magnetic resonance imaging (MRI) and multislice computerized tomography (MSCT).

The requirement of mechanical support for the healing artery is temporary (6-12 months) and once arterial remodeling and healing is achieved, BMS lead to complications rather than beneficial effects.[9] Since biodegradable stents disappear after a certain period, late-stage thrombosis is unlikely and hence, prolonged antiplatelet therapy is not required. Biodegradable stents are compatible with MRI and MSCT imaging and hence, provide improved lesion imaging.[9] Other advantages of biodegradable stents include facilitation of repeat treatments (surgical or percutaneous) and prevention of side-branch obstruction by struts as well as of restenosis induced by strut fracture. Such stents are potential candidates for pediatric applications; since they allow vessel growth and do not require eventual surgical removal.

Requirements of the stent material for biodegradable stents are as follows:

- Biocompatibility of the stent material as well as of its degradation products
- Sufficient mechanical strength for a certain period (of arterial healing)
- Controllable degradation rate
- Facilitation of endothelialization (growth of endothelial cells)
1.2 Rationale of biodegradable metallic stent

Biodegradable stents may be polymeric or metallic. Drug or gene delivery can be accomplished by loading biodegradable polymers on metallic stents and such polymers completely erode by the time the drug has been released, whereas the stent remains fixed in the vessel wall.

However, the relatively slow bioabsorption rate of biodegradable polymeric stents may lead to restenosis. There remains possibility of early recoil after implantation because of low strength of such stents in comparison with metallic stents. Table 1.1 shows general design constraints and criteria for a biodegradable metallic stent and table 1.2 shows mechanical properties and in vitro degradation rate for commonly used stent materials. It is obvious from table 1.1 that a consensus regarding some of the properties has not been reached yet.

Table 1.1: General design Constraints and criteria for a biodegradable metallic stent [10]

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Constraints</th>
</tr>
</thead>
</table>
| Bioabsorption              | Mechanical Integrity for 3-6 months  
Mechanical Integrity for 4 months  
Mechanical Integrity for 6-12 months  
Full absorption in 12-24 months |
| Biocompatibility           | Non-toxic, non-inflammatory, hypoallergenic  
No harmful release/retention of particles  
No Al/Zr content |
| Mechanical Properties      | Yield Strength > 200 MPa  
Tensile Strength > 300 MPa  
Elongation to failure > 15-18%  
Elastic recoil on expansion < 4% |
| Microstructure             | Maximum grain size = 30 µm  
Maximum grain size of 10-12.5 µm |
| Hydrogen evolution         | Evolution < 10µL H2 cm-2 day-1 |
| Corrosion rate             | Penetration rate < 20 µm year-1 |
Table 1.2: Mechanical properties and in vitro degradation rate for stent materials [8], [11], [12]

<table>
<thead>
<tr>
<th>Material</th>
<th>Elastic Modulus (GPa)</th>
<th>Yield Strength (MPa)</th>
<th>Tensile Strength (MPa)</th>
<th>Elongation (%)</th>
<th>Density (g/cm³)</th>
<th>In vitro degradation rate (mm y⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>316L stainless steel (ASTM F138 and F139; annealed)</td>
<td>190</td>
<td>331</td>
<td>586</td>
<td>40</td>
<td>7.9</td>
<td>-</td>
</tr>
<tr>
<td>Nitinol (Austenite phase)</td>
<td>83</td>
<td>195-690</td>
<td>895</td>
<td>-</td>
<td>6.7</td>
<td>-</td>
</tr>
<tr>
<td>Nitinol (Martensite phase)</td>
<td>28-41</td>
<td>70-140</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cobalt-chromium (ASTM F90)</td>
<td>210</td>
<td>448-648</td>
<td>951-1220</td>
<td>-</td>
<td>9.2</td>
<td>-</td>
</tr>
<tr>
<td>Pure iron</td>
<td>211.4</td>
<td>120-150</td>
<td>180-210</td>
<td>-</td>
<td>7.87</td>
<td>-</td>
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<tr>
<td>Pure magnesium (as cast)</td>
<td>-</td>
<td>20</td>
<td>86</td>
<td>13</td>
<td>-</td>
<td>407</td>
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<tr>
<td>Magnesium WE43 alloy</td>
<td>44</td>
<td>162</td>
<td>250</td>
<td>-</td>
<td>1.84</td>
<td>-</td>
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<td>Magnesium AM60B-F (die cast)</td>
<td>-</td>
<td>-</td>
<td>220</td>
<td>6-8</td>
<td>-</td>
<td>8.97</td>
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<tr>
<td>Magnesium ZW21 (extruded)</td>
<td>-</td>
<td>200</td>
<td>270</td>
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<td>Magnesium WZ21 (extruded)</td>
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<td>140</td>
<td>250</td>
<td>20</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Magnesium AZ 31 (extruded)</td>
<td>-</td>
<td>165-200</td>
<td>241-260</td>
<td>12-16</td>
<td>-</td>
<td>-</td>
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Biodegradable metallic stents have attracted interest because of their capability to perform similarly to stents of stainless steel (SS); which is the most widely used material for stent fabrication. Till date, biodegradable metallic stents have been developed from alloys of iron and magnesium. Iron is an essential element for the human body. Due to a high elastic modulus (211.4 GPa), iron is capable of providing high radial strength; which facilitates fabrication of stents with thinner struts. The high ductility of iron provides an advantage if the stent undergoes plastic deformation during implantation. The proximity in the values of the yield strength (120-150 MPa) and the tensile strength (180-210 MPa) of pure iron may lead to stent fracture during deployment.[11] However, the slow in-vivo degradation rate of iron remains a major challenge
yet to be overcome. Moreover, degradation of iron results into a large volume of potentially hazardous iron oxide products; the degradation of which may not take place in the human body.[13]

1.3 Rationale of biodegradable magnesium (Mg) stent

The biocompatibility, biodegradability and non-toxicity of magnesium made it a suitable candidate for biodegradable stent fabrication. Magnesium is an essential trace element and a structural constituent of the tissue. It is not only a substantial intercellular cation involved in more than 300 biological reactions of a cell, but also is regarded as a non-carcinogenic element.[14] The amount of magnesium in blood plasma can be tolerated up to a relatively high level of 85-121 mg L\(^{-1}\)[15] and is countered by the efficient excretion of magnesium in the urine.[16] The recommended daily dosage is 310 mg day\(^{-1}\) and 400 mg day\(^{-1}\) for adult males and females respectively.

In terms of mechanical properties such as yield stress and retainment of inflated stent shape without excessive recoiling, magnesium is better than biodegradable polymers. However, the low ductility of magnesium may lead to difficulty in tubular precursor fabrication in the required dimension range for stents.[17] The rapid in-vivo degradation rate of magnesium may lead to smooth muscle cell proliferation (neointimal hyperplasia) due to tissue overload with degradation products as well as to loss of mechanical integrity over a short period of time.

The usage of magnesium alloys as stent materials results in a decrease of the degradation rate. Witte et al. [18] briefly summarized the pathophysiological and toxicological characteristics of the usually considered alloying elements in human body; some of which are presented in table 1.3. Hence, only a few metals which are tolerable to the human body are capable of being used as alloying elements in biodegradable implants. Aluminum, manganese, zinc and rare earth (RE) elements are the most commonly used alloying elements.
Table 1.3: A brief summary of the pathophysiology and toxicology of some of the alloying elements [11]

<table>
<thead>
<tr>
<th>Element</th>
<th>Pathophysiological/toxicological effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magnesium</td>
<td>Influences growth factor effectiveness; co-regulator of energy metabolism, cell proliferation, protein synthesis, onset of DNA synthesis; long term influence on cellular reactions.</td>
</tr>
<tr>
<td>Calcium</td>
<td>Most abundant mineral in the human body (1-1.1 kg); mainly stored in bone, teeth.</td>
</tr>
<tr>
<td>Aluminum</td>
<td>Risk factor in generation of Alzheimer’s disease; can cause muscle fiber damage; decreases osteoclast viability.</td>
</tr>
<tr>
<td>Zinc</td>
<td>Essential for the immune system; co-regulator for specific enzymes in bone and cartilage; neurotoxic at higher concentrations.</td>
</tr>
<tr>
<td>Manganese</td>
<td>Important role in metabolic cycle of lipids, amino acids and carbohydrates; influences the function of the immune system, bone growth, blood clotting, cellular energy regulation and neurotransmitter synthesis; neurotoxic at higher concentrations.</td>
</tr>
<tr>
<td>Lithium</td>
<td>Compound of drugs for treatment of psychiatric disorders; over dosage causes nephrological or lung dysfunctions; possible teratogenic effects.</td>
</tr>
<tr>
<td>Rare earth elements</td>
<td>Many rare earth elements exhibit anticarcinogenic properties.</td>
</tr>
</tbody>
</table>

The magnesium alloys AE21 [2% aluminum, 1% rare earth elements (cerium, praseodymium, neodymium), 97% magnesium], WE43 [zirconium (<5%), yttrium (<5%), rare earth elements (<5%) and magnesium (<85%)] and AZ31 (3% aluminum, 1% zinc, 96% magnesium) have been used for stent fabrication till date. The magnesium alloy AZ31 strikes a balance between the mechanical properties and corrosion behavior. Since this alloy shows good deformability, it can
be extruded to small precursors, which can later be laser machined to obtain the stent. Another advantage of this alloy is its commercial availability in the form of extruded bars.

1.4 Rationale of magnesium (Mg) single crystal helical stent

Salunke et al. reported that magnesium single crystal specimens exhibited a remarkable tendency for higher ductility (50%-60%) in comparison to that of polycrystalline magnesium (~10%); despite having low yield strength (60-70 MPa).[19] This high ductility is indicative of potential superplastic behavior. The test results also revealed the overall toughness and energy absorption in magnesium single crystal to be much higher than in polycrystalline magnesium. This aspect makes magnesium single crystal a potential candidate for biomedical implants.[19]

Polycrystalline magnesium or magnesium alloys consist of small crystals with random orientations i.e. grains separated by grain boundaries. Since these boundaries are regions of orientation mismatch, they exhibit characteristics different from the grain interior. There is a tendency for impurity segregation and minority phase precipitation along the grain boundaries; thus facilitating corrosion and stress corrosion cracking of the boundaries.[18] A higher corrosion rate at the grain boundaries often leads to enhanced evolution of hydrogen; which is responsible for creation of local gas cavities in vivo.[20,21] Differences in microstructural phases in polycrystalline magnesium alloys can give rise to galvanic corrosion. Literature suggests that pitting corrosion, hydrogen evolution or local alkalinity cannot be fully prevented by coating and chemical treatments like anodization.[21-24] Mechanical treatment, although promising; remains unproven in a biological environment.[25] Hence, elimination of grain boundaries will result into reduction of defects as well as reduction in corrosion. The usage of a single crystal can be useful in this regard. The corrosion rates of magnesium single crystal are dependent on crystallographic orientations and hence are anisotropic.[26,27] The magnesium
(0001) surface exhibits pitting corrosion; whereas the (1010) and (1120) are more corrosion resistant.[26] Thus specific orientations of magnesium single crystal implant will enable acceleration or retardation of the corrosion rate as per requirements.
CHAPTER 2: LITERATURE REVIEW

2.1 Progress in biodegradable Mg stent research

2.1.1 Mg AZ31 alloy stent

Demir et al. reported a biodegradable Mg stent design of AZ31 alloy, which consisted of 5 rings connected by curved links with 6 peak-to-valley struts in the circular direction.[17] Advantages of selecting AZ31 alloy as the stent material include a good compromise between mechanical properties and corrosion behavior, good deformability for material extrusion to small precursors and commercial availability of the alloy in the form of extruded bars. However, reduction in biocompatibility due to inclusion of aluminum in the alloy remains a drawback. [17]

Figure 2.1(A) shows a micrograph of extruded D4d3 AZ31 tube (Outer diameter: 4 mm, Inner diameter: 3 mm), which has been generated from the mid-thickness of the longitudinal sections of AZ31 samples. The micrograph depicts a relatively more refined microstructure with equiaxed grains after extrusion; due to the initial facilitation of recrystallization by the concurrent action of temperature and strain during extrusion. Figure 2.1(B) shows the orientation maps generated by electron backscatter diffraction (EBSD) in which a preferred orientation of the AZ31 extruded alloy is revealed. The predominant red grains feature their (0001) planes aligned parallel to the sample surface i.e. longitudinal axial sections.

The inverse pole figure of the starting bar [Figure 2.2(A)] shows a weak texture given by the prismatic planes \(\{10\overline{1}0\}\) and \(\{2\overline{1}0\}\) aligned along the longitudinal axis of the bars. A change in texture is obvious in the inverse pole figure of the extruded bar [Figure 2.2(B)]; which shows a typical (0001) extrusion texture; in which the basal plane is aligned along the extrusion direction.
Figure 2.1: Microstructure of extruded D4d3 AZ31 tube on longitudinal section: (A) Optical micrograph; (B) Orientation map from EBSD.[17] [This figure has been adapted from Demir et al. Int. J. Comput. Integr. Manuf. (2013) 1-10 © 2013 Taylor & Francis.]

Figure 2.2: Inverse pole figures taken from longitudinal sections of (A) the starting bar; (B) the extruded tube and (C) Tensile (T) and compressive (C) stress-strain curves for starting bars and for hot- extruded D6d3 AZ31 tubes.[17] [Parts (A), (B) and (C) of this figure has been adapted from Demir et al. Int. J. Comput. Integr. Manuf. (2013) 1-10 © 2013 Taylor & Francis.]

The initial part of the tensile and compressive stress-strain curves for the AZ31 alloy for both starting bars and extruded bars has been shown in figure 2.2(C). In both cases, the tensile yield strength is significantly higher than the compressive yield strength. Extrusion resulted in a more pronounced decrease in compressive yield strength. The reported 0.2% offset compressive yield
stress of as-received bars and extruded D6d3 tubes were 109.6 MPa and 91.8 MPa respectively; whereas 0.2% offset tensile yield stress of those were 149.7 MPa and 166.5 MPa respectively. Loss of yield strength (compression vs. tension) in as-received bars was reported as 26.8% whereas that in extruded D6d3 tubes was reported as 44.9%. [17]

The authors attributed the anomalous behavior of the compressive stress-strain curve to {10-12} deformation twinning; which was activated during the compressive mode along the extrusion direction. The texture in extruded tubes did not permit activation of such twinning under tensile loading. Finite element analysis showed that the loading modes lead to external compression and internal tension into the U-shaped structure of the stent during expansion and vice versa during scaffolding. Since tensile yield strength is much higher than compressive yield strength; material at exterior of the stent U-shaped structure will be easily deformed during expansion and will lead to an inhomogeneous stress distribution as well as deformation; which is likely to facilitate stress corrosion cracking.[17]

2.1.2 Mg AE21 alloy stent: in vivo results

Heublein et al.[28] first implanted Mg AE21 alloy stents into the coronary artery of eleven domestic pigs. Angiographic studies at 10, 35 and 56 days after implantation; and intravascular ultrasound (IVUS) studies at 35 and 56 days after implantation were performed. Quantitative coronary angiography (QCA) data suggests that a lumen loss due to induced plaque formation between days 10 and 35 was later balanced by positive arterial remodeling between days 35 and 56. IVUS studies revealed an insignificant increase in plaque thickness and a significant increase of perfused lumen area after day 35; which indicates loss of mechanical integrity of the stent between 35 and 56 days. This observation led to two important conclusions: (1) The degradation
rate has to be reduced to ensure mechanical integrity over a longer period and (2) The loss of stent integrity facilitates positive remodeling of the local vessel tissue.[28]

No platelet deposition or thrombosis was observed at endothelial sites. The inflammatory response at each strut was not significant. Figure 2.3 shows the stent segment at days 10, 35 and 56 post-implantation.

Figure 2.3: (A) Unequal extension of the stents and minimal corrosion and neointimal proliferation after 10 days; (B) Advanced and irregular corrosion and neointimal proliferation after 35 days; (C) and (D) : Advanced and irregular corrosion and neointimal proliferation after 56 days.[28] [This figure has been adapted from Heublein et al. Heart, 89 (2003) 651 -656 © 2003 BMJ.]

Although this extensive study was the first of its kind; the mechanical properties of the AE21 alloy stent have not been reported. Also, stent design plays a crucial role in terms of expandability; which directly impacts vessel wall injury and hence, neointimal growth. However, no image or description of the stent has been provided in terms of the design aspect. Very little information is provided about the stent fabrication technique. The reported IVUS and QCA data have been recorded from different individual pigs of same groups that were harvested at different periods. Serial intraindividual QCA and IVUS studies would have increased the degree of
accuracy of the observations. The impact of degradation on inflammation and neointimal growth could not be separated from that induced by vessel wall injury due to unequal stent expansion.

2.1.3 Mg WE43 alloy stent: in vivo results

The Mg WE43 alloy was used to fabricate the Lekton Magic coronary stent; which was implanted in 20 patients of critical lower limb ischemia. As reported by Peeters et al.[29], no toxic or allergic response was observed. A biodegradable magnesium stent (diameter 3 mm, length 10 mm) was successfully implanted in the left pulmonary artery of a preterm baby by Zartner et al.[30]; which completely degraded with no symptoms of in-stent obstruction or neointimal hypertrophy over a period of 5 months. In 2007, 71 WE43 stents were implanted in coronary arteries of 63 patients and an increased diameter stenosis of 17% was observed via angiography at 4 months.[31] Serial IVUS examinations suggested safe degradation of these stents after 4 months.

A 3-month long safety and efficacy study of WE43 alloy stents (Lekton Magic) in porcine coronary arteries was conducted by Waksman et al.[32] by random deployment of magnesium WE43 alloy stents as well as SS stents (Lekton Motion) coated with amorphous silicon carbide. Follow-up studies were performed at 3 days, 28 days and 3 months after implantation. At 3 days, the WE43 alloy stents were found to be completely expanded as well as intact; with no signs of immediate recoil. The WE43 alloy stent is shown in unexpanded condition in figure 2.4(A), and in implanted condition in figure 2.4(B).

At 28 days and 3 months, neointimal area in WE43 alloy stent segments was significantly less (2.44 ± 0.88 mm² and 1.16 ± 0.19 mm²) in comparison to those of SS (5.03 ± 1.5 mm² and 1.72 ± 0.68 mm²); which was attributed to overall low injury and inflammation as well as to alloy degradation. Also, the early degradation rate and local interaction with absorbed magnesium did
not lead to an increased inflammation in comparison with SS stents. Micrographs exhibiting corrosion behavior as well as neointimal growth of WE43 alloy stents and SS stents are shown in figures 2.4(C) and 2.4(D).

Figure 2.4: (A) Unexpanded magnesium WE43 alloy stent and (B) Dehydrated and defatified porcine coronary arteries showing the magnesium WE43 alloy stent. Representative photomicrographs of hematoxylin-eosin stained sections of porcine coronary arteries 28 days after stent implantation (C) with stainless steel stent (40×) and (D) with magnesium WE43 alloy stents (40×). [32] [Parts (A) – (D) of this figure has been adapted from Waksman et al. Catheterization and Cardiovascular Interventions, 68 (2006) 607 -617 © 2006 Wiley Online Library.]

However, the less neointima formation did not lead to a larger lumen; probably due to underexpansion of the stent at deployment, or early/late recoil or both. Intravascular images of SS and WE43 alloy stents depicting the lumen area at 28 days are shown in figures 2.5(A) and 2.5(B) respectively. Figures 2.5(C) and 2.5(D) are X-ray photographs of SS and WE43 alloy stents at 28 days post-implantation; in which the poor radiopacity and loss of continuity of the WE43 alloy stent struts is obvious.
Figure 2.5: Intravascular images of porcine coronary arteries 28 days after stent implantation: (A) with stainless steel stent and (B) with magnesium WE43 alloy stent. X-ray photographs 28 days after stent implantation: (C) with magnesium WE43 alloy stent and (D) with stainless steel stent. [32] [Parts (A) – (D) of this figure has been adapted from Waksman et al. Catheterization and Cardiovascular Interventions, 68 (2006) 607 -617 © 2006 Wiley Online Library.]

2.2 Laser beam machining (LBM): The traditional approach for stent fabrication

The fabrication of stents includes an expanding range of diverse processes; such as laser machining, electroforming, microelectrodischarge machining and photochemical etching.[2] LBM is based on material removal via sublimation, melting or oxygen reaction and has been the most widely used process till date. Advantages of sublimation include minimization of dross adherence as well as thermal effects on microstructure and mechanical properties.[2] The drawback of sublimation is low cutting speed. Despite being high speed processes, melting and oxygen reaction techniques often facilitate burr formation, surface deposition of removed material and oxidation at the cuts. Additional finishing steps such as microblasting with aluminum oxide powder, pickling, electrochemical polishing or soft etching may be required for the purpose of dross removal.[2] Depending on the stent material type, the laser-cut stent may be
heat treated and/or surface coated. The various steps in a generic production cycle of a stent by LBM are shown below in figure 2.6.[17]

![Generic production cycle of a stent by LBM][17]

Extrusion of magnesium alloys in the dimensions required for stents is a difficult task. The microstructure of material, which is a manifest of the in-vivo stent degradation rate, is determined by the extrusion process.

In case of AE21 alloy stents, extruded AE21 rods were drilled into tubes having wall thickness between 150-200 µm, length 10 mm and outer diameter 2 mm.[28] A femtosecond laser (Laser Zentrum, Hanover, Germany) was used to cut stents of mass 4 mg out of the tubes; after which the surface was left in its original condition. The laser cut stents were sterilized and stored in an alcoholic solution. LBM was also used for fabrication of WE43 alloy stents from single tubes of magnesium alloys (3×15 mm²).[32]

Fabrication of AZ31 alloy stents by Demir et al. included usage of an active fiber nanosecond laser with 50W maximum average power (IPG-YLP-1/100/50/50 Q-switched laser).[17] Microcutting with small kerf widths was accomplished by a beam spot of 23 µm, which was obtained by coupling of the laser source with a cutting head (LaserMech Fine Kerf; Novi, MI,
USA). Other reported parameters include a laser wavelength of 1064 nm, maximum pulse energy of 1 mJ, minimum pulse duration (FWHM) of 100 ns and a beam quality factor ($M^2$) of 1.7. Successful removal of dross and cleaning of kerf were achieved by chemical etching by an acidic etchant (10 ml HNO$_3$ of purity 65% and 90 ml ethanol).[17]

Although femtosecond lasers are capable of machining objects on the nanometer scale; cost remains a drawback. Excimer lasers cause ablation by disruption of molecular bonds; which leads to the absence of adverse heat effects. However, the beam quality is not as good as other laser systems; whereas lateral resolution is about 10 µm.[2] Among laser parameters, pulse length is important; since longer pulses (>10 ns) are able to impact material properties in the vicinity of the pulse beam; because of heat diffusion and conduction.[2] On the other hand, shorter pulses (e.g. in the fs range) and higher pulse repetition rates have capability of reducing the heat affected zone (HAZ).

Figure 2.7: Holes drilled on thin steel films by (A) femtosecond laser pulses and (B) nanosecond laser pulses.[33] [Parts (A) and (B) of this figure has been adapted from Chichkov et al. Appl. Phys., A 63 (1996) 109 - 115 © 1996 Springer - Verlag.]
The effect of laser pulse length on material is evident in figure 2.7.[33] Figure 2.7(A) shows an SEM image of a hole drilled in a 100 µm thickness steel foil femtosecond laser pulses (200fs, 120 µJ, F=0.5 J/cm²) at 780 nm. No accumulation of molten material is evident. On the other hand, the SEM image of a hole drilled on steel of the same thickness by nanosecond laser pulses (3.3 ns, 1 mJ, F=4.2 J/cm²) at 780 nm show substantial and non-uniform accumulation of molten material; as shown in figure 2.7(B).[2]

There are also some drawbacks regarding the post fabrication treatments such as chemical etching. Once the stent is laser cut, it is chemically etched in order to remove the dross and recast areas around the cutting zone. However, there remains possibility of the stent body to be significantly etched; resulting in reduction of body weight as well as thickness.[34] The reduction in thickness during chemical etching of laser cut Mg AZ31 stents was observed in the study of Demir et al. The duration under which thickness reduction was no more than 10% of the 200 µm thickness of the stent (i.e. 20 µm) was defined as the limiting etching duration and was reported to be 10 seconds. However, the thickness reduction of the laser cut stent was found to be 25 µm after 10 seconds of chemical etching; which was slightly higher than the limiting condition of 20 µm.

The effect of chemical etching on removal of oxidized zones is evident in figure 2.8. The dark areas in the images represent oxidized zones near the cut kerf. Although laser microcutting was performed with the inert gas Ar, the high reactivity of Mg gave rise to surface oxidation, which is evident in figure 2.8(A). Chemical etching enabled substantial reduction of the oxidized zones; which is obvious in figure 2.8(B). [34]
Figure 2.8: SEM images of the laser cut Mg AZ31 stent showing the effect of chemical etching on oxidized zone removal: (A) Before chemical etching and (B) after chemical etching. [34] [Parts (A) and (B) of this figure has been adapted from Demir et al. Advances in Materials Science and Engineering, Vol. 2013 (2013) 692635 © 2013 Hindawi.]

Figure 2.9: SEM images of the laser cut Mg AZ31 stent showing the effect of chemical etching on surface roughness: (A) Before chemical etching and (B) after chemical etching.[34] [Parts (A) and (B) of this figure has been adapted from Demir et al. Advances in Materials Science and Engineering, Vol. 2013 (2013) 692635 © 2013 Hindawi.]
Chemical etching also affects the surface roughness profile of the laser cut Mg AZ31 stent; as shown in figure 2.9. Figure 2.9(A) shows the surface roughness of the stent after laser microcutting under inert gas (Ar) conditions. Material spatter around the stent wall was clearly visible.

The surface roughness condition after chemical etching is depicted in figure 2.9(B). Not only was the spatter around the stent wall significantly reduced, the edges were also rounded because of the polishing effect of the chemical etching. Before chemical etching, the surface roughness was found to be 1.42 µm; whereas the post etching surface roughness was found to be 1.26 µm; suggesting a clear improvement in surface roughness due to chemical etching.[34]

2.3 Photochemical Etching (PE): What is known in the public domain to date

Photochemical etching (PE) enables successful removal of selected (unmasked) material areas via the application of a wet chemical etchant through apertures fabricated in a photoresist stencil; without any changes in physical as well as chemical properties.[35] Allen et al. have demonstrated that PE is economically more favorable over rival machining processes such as LBM and electro-discharge machining (EDM) because of capability of manufacturing complex designs within a thin metal part with high resolution.[36] Although non-conventional, PE is a burr-free process; and hence, no post fabrication treatments such as chemical etching or thermal annealing are required; as required in the conventional LBM process. Also, PE prevents sputtering of Mg as well as re-deposition on the stent surface; as observed in conventional LBM processes. The method allows large-scale manufacturing of stents of any size and of any feature. The PE process is thus scalable, cost effective, affordable in practice, and attractive for
commercialization in case of stent production. Figure 2.10 shows steps involved in the PE process.[37]

![Diagram of the PE technique][1]

**Figure 2.10:** A schematic diagram of the PE technique.[37]

Literature suggests that PE of Mg has been achieved by far only by the usage of powderless etching techniques. The most common industrial etchant is ferric chloride; which causes a coarse, insoluble, black deposit on the surface of magnesium. The presence of insoluble byproducts implies that the standard etchant ferric chloride cannot be used in PE of Mg. As a result, fabrication of Mg stents has not been attempted by the PE method to date; although stents of AISI316 SS as well as nitinol have been fabricated by this method.[35]

However, Allen et al. reported the successful fabrication of a 2D thin Mg component i.e. micro air vehicle (MAV) wing with thin intricate line widths via a modified PE method. [35] The set of
processing steps employed during the course of fabrication were completely different from those employed in the conventional powderless etching methods used in industrial fabrication of printing plates or dies.

Figure 2.11: Processing steps in PE of a 2D Mg micro air vehicle (MAV) (Counterclockwise): (A) Cicada wings, (B) CAD forewing model, (C) Developed hydro-solve photoresist image and (D) The 2D Mg component. [Parts (A) – (D) of this figure has been adapted from Allen et al. J. Micromech. Microeng. 20 (2010) 105101 © 2010 IOP Publishing.]

In this optimized PE method, the desired component i.e. a Cicada wing was reproduced in the form of a CAD file via the AutoCAD® software; as shown in figures 2.11(A) and 2.11(B). 10% v/v nitric acid was used as the etchant and hydro-solve was used as the photoresist. The developed photoresist image is shown in figure 2.11(C). The initial temperature of the etchant was $27.5 \pm 2.5 ^\circ C$. Thus, minimum feature widths of 0.15 mm were achieved within a 2D, 0.25 mm thick Mg foil; as shown in figure 2.11 (D). The use of a simplified, uniform linewidth phototool design was recommended for achieving smaller line widths.
2.4 Helical stents: devices to induce helical flow in arteries

The cellular activity within an arterial wall is significantly influenced by the local hemodynamics i.e. local blood flow pattern. Regions of disturbed flow and of low wall shear stress (WSS) are preferential development sites for atherosclerosis.[3] An understanding of the blood circulation dynamics may therefore be beneficial in reducing in-stent restenosis.

The natural blood flow in the arterial system has been reported to be spiral laminar in nature; in the sense that there is a rotational component or secondary motion to laminar blood flow. This spiral or helical flow is induced by non-planar arterial curvatures as well as by twisting of the heart i.e. left ventricle during contraction.[38] The helical flow becomes more pronounced after entering the aortic arch.[39,40]

In a study of indicator dispersion in arterial models, Caro showed that large secondary flows were induced at bends in the models.[41] These secondary flows caused mixing of flow as well as reduction in variation of velocities over the cross section of the models. Prevention of formation of stagnation zones and hence, prevention of flow separation at arterial branches were listed as possible advantages of such secondary flows.

Decades later, fibre-optic angioscopic studies of blood flow patterns in the right common and distal superficial femoral and the left common femoral arteries by Stonebridge et al. revealed the presence of a secondary rotational motion;[42] which gives rise to an overall spiral (helical) flow; which was detected by Doppler ultrasound visualization technique [figure 2.12(A)].[43] The authors proposed several spiral flow-induced beneficial effects; which include rotationally-induced stability, reduced turbulence as well as favorable effects on mechanisms of endothelial damage. These aforementioned effects; as well as other potential beneficial effects available in literature are presented in table 2.1.
Figure 2.12: (A) The Doppler ultrasound set up for detection of spiral flow;[43] and (B) The characteristic red-blue split depicting the helical flow; as observed in vivo.[44] [Part (A) of the figure is adapted from Stonebridge and Brophy. Clinical Science 91, 17 - 21 (1996) © 1996 Portland Press and part (b) of the figure is adapted from Stonebridge, et al. Methodist DeBakey cardiovascular journal, 7 (2011) 21-26 (2011) © 2011 Houston Methodist.]

A comparative study by Stonebridge et al. on helical and non-helical flow patterns through a stenosis via magnetic resonance imaging (MRI) in vitro and computational fluid dynamics (CFD) modeling revealed a 700% reduction in turbulence energy for helical flow beyond the stenosis.[45]

Table 2.1: Potential beneficial properties of spiral laminar flow[44]

<table>
<thead>
<tr>
<th>Property</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laminar stability</td>
</tr>
<tr>
<td>Reduced laterally directed forces</td>
</tr>
<tr>
<td>Reduced near-wall turbulence</td>
</tr>
<tr>
<td>Suppresses acute thrombus formation with no increase in platelet activation</td>
</tr>
<tr>
<td>Enhances oxygen flux to the arterial wall</td>
</tr>
<tr>
<td>Reduces luminal surface low-density lipoproteins concentration</td>
</tr>
<tr>
<td>Dampens wall stress temporal gradients</td>
</tr>
<tr>
<td>Lowers oscillatory shear stress index</td>
</tr>
</tbody>
</table>
In order to establish hemodynamics that mimics that natural blood flow and inhibits in-stent restenosis, Veryan Medical Limited developed a bare-metal, nitinol, self-expanding stent with 3D helical-centreline geometry; called BioMimics 3D helical stent. Apart from the capability of generating a spiral flow; the stent possesses design features such as tapered radial stiffness and collinear stent ends. These features enable the stent to provide a more gradual change in the wall stress as well as in the luminal area between the stented and unstented region of the artery; since a dramatic change is prone to forming stagnation zones; which in turn may facilitate thrombus and neointimal formation. [3]

![Figure 2.13: Biomimics 3D helical stent.][3] [This figure has been adapted from Murphy et al. Cardiovascular Engineering and Technology, 3 (2012) 353-373 © 2012 Springer.]

In a study of intimal hyperplasia (IH) in porcine common carotid arteries, Caro et al. reported that the helical BioMimics 3D stent led to helical deformation of the artery; as shown in figure 2.14(A). [46] Not only did the helical stent generate swirling flow; less IH was reported in the helical-centreline stented vessel, as compared to the straight-centreline stented vessels. This observation was in agreement with theory. A CFD study demonstrated intraluminal swirling and
substantial in plane mixing in a helical conduit; as shown in figure 2.14(B). The numerical study further revealed that in a straight tube downstream of the helical conduit, the in plane mixing can continue; despite the fact that it diminishes progressively.

Figure 2.14: (A) Angiogram showing porcine carotid arteries with straight stent (left) and helical stent (right);[46] and (B) CFD study demonstrating swirling and mixing in a helical conduit.[46] [Parts (A) and (B) of this figure has been adapted from Caro et al. J. R. Soc. Interface, 10 (2013) 20130578 © 2013 The Royal Society Publishing.]

2.5 Conclusions from literature

Biodegradable metallic stents have been fabricated from various iron and Mg alloys. In vivo studies conducted with AE21[28] and WE43[32] Mg alloy stents revealed that such stents are safe and are associated with less neointimal growth. However, improvements in corrosion resistance as well as mechanical stability are necessary.

Biodegradable Mg stents have been fabricated by the conventional as well as expensive LBM technique, which is expensive and requires high capital investment for femtosecond lasers,
optics, the dross extraction system and temperature control. In addition, secondary treatment of the fabricated stent is needed to mitigate the effect of laser material removal. The novel PCE technique is not only cost-effective, but also capable of fabricating intricate designs with extreme precision. Moreover, it is a burr-free process and does not affect the structural and magnetic properties of the metal. Although certain challenges exist in case of photochemically etching Mg, a 2D Mg component (MAV) of high geometric complexity has been fabricated by this method. Hence, the PE method can be attempted as an alternative approach in case of Mg stent fabrication.

It has been shown in literature that helical flows in arteries possess beneficial hemodynamic characteristics. These include increased rotationally-induced stability, greater mixing of particle trajectories as well as reduction in turbulence, stagnation zones, recirculation zone length and near wall particle residence times. Moreover, helical flow has the capability of reducing both the range and extent of WSS regions and also of increasing the oxygen flux through the arterial walls; which may lead to reduction in NIH and eventually to reduction in in-stent restenosis rates. Thus helical flow inducing devices are promising and have been developed. A biodegradable Mg AZ31 stent would be the first of its kind and would be able to inhibit in-stent restenosis by developing a helical flow.

Although stents are primarily used for coronary arteries, their usage can be extended to other fields; e.g. in the case of an AVF (an artificial connection between an artery and a vein). An AVF is surgically created to achieve a dialysis access that is capable of being cannulated repeatedly and also of providing adequate blood flow for dialysis in treatment of kidney failure. Accordingly, veins become larger and vein walls thicken; a process termed maturation. However, the maturation failure rate of the fistulae due to venous neointimal growth is
significantly high (28 - 53\%).[47] It is proposed that helical Mg AZ31 stents will be capable of preventing maturation failure by reducing venous neointimal hyperplasia and hence, venous stenosis.

The prerequisite to successful stent performance is an extensive investigation on stent material, stent design and stent fabrication technique. All of these aspects are interconnected; and there should be a good trade-off between mechanical properties, corrosion properties and biocompatibility of the stent material. The aim of the proposed study is to fabricate novel biodegradable devices; mainly stents for various applications; by the PE technique by overcoming the existing challenges in photochemical etching of Mg; as well as to evaluate the performance of these stents in an integrated as well as multidisciplinary approach; in which stent properties will be tested by both in vivo and in vitro methods.
CHAPTER 3: EXPERIMENTAL WORK

3.1 Design and fabrication of stents by PE

3.1.1 Method

3.1.1.1 Mg AZ31 stents

The Mg AZ31 stents were fabricated by photochemical etching. The starting material was a Mg AZ31 sheet of 250 µm thickness. At first the desired pattern was transferred to stencils called photomasks. The surface of the Mg AZ31 sheet was cleaned to ensure proper adherence of the photosensitive resist; namely photoresist. The Mg AZ31 sheet was then coated with the photoresist on both sides. This coating is sensitive to UV light; but is resistant to the etchant (acid). The photoresist-coated Mg AZ31 sheet was then sandwiched between the two photomasks and was exposed to UV light. Upon exposure, the resist in unmasked areas of the sheet became hardened; whereas the resist in the masked areas remain soft. The sheet was then passed through a developer, in which the soft resist was washed away; keeping the areas with hardened resist unaltered. The next step was exposure of the sheet to a wet chemical etchant, which removed Mg-based material in the areas without resist; thus giving rise to the desired pattern on the Mg AZ31 sheet. The desired pattern was thus transferred from the photomask to the Mg AZ31 sheet. The final step was removal of the photoresist mask from the Mg based sheet using appropriate solvent.

The photochemically etched Mg AZ31 sheet was then rolled into a cylinder; which was joined via spot welding. The fabrication process was thus complete; the steps of which are shown in figure 3.1.
Figure 3.1: Steps in fabrication of a stent via photochemical etching.

3.1.1.2 Mg single crystal stents

For this stent, Mg single crystals were grown in a 2-zone vertical crystal maker furnace J5409 by First Nano CVD Equipment Corporation under ultra-high purity Ar atmosphere. After being loaded in a graphite crucible, the raw materials were melted in an evacuated quartz tube surrounded by the crystal growing furnace. Upon soaking for 8 or 14 hours in liquid state, the melt was subject to rotation for homogenization. The melt was thus solidified into single crystal rods by controlled withdrawal of the furnace chamber under a suitable thermal gradient according to the Bridgman-Stockbarger method. The grown Mg single crystal rods had a diameter of 20 mm and length of 150 mm.

3.1.2 Materials

For the Mg AZ31 stents, the Mg AZ31 sheet (Mg 96%, Al 3%, Zn 1%) of 250 µm thickness was purchased from Goodfellow and was used as the starting material in the PCE process. In case of the Mg single crystal helical stent, the raw material for single crystal growth was poly-crystalline Mg of purity 99.99%; which was purchased from Alfa Aesar.
3.1.3 Characterization Techniques

3.1.3.1 Expandability tests

The expandability of the stents of length 5 cm and of diameter $\frac{3}{4}$ mm were tested by a Dorado PTA Dilatation Catheter (9mm × 2cm). For expandability tests of stents of other designs and dimensions, a Dorado PTA Balloon Dilatation Catheter (8mm × 4cm) was used. Stents were mounted on the balloon catheters and pressure was applied via a syringe; which caused the balloon; and ultimately the stents to expand. Videos of the stent expansions were recorded by a Keyence VHX 2000 digital microscope. Images of the stents before and after expansion were also taken using the microscope.

3.1.3.2 Tensile tests

Mg AZ31 ribbons of 2 different widths (3 mm and 5 mm) were cut into pieces of length 2 cm. Three specimens of each width of these small length Mg AZ31 ribbons were tested using an Instron tensile tester (Model 5948); during which a 100N cell was used.

3.1.3.3 Corrosion tests

3.1.3.3.1 Flow induced corrosion behavior of Mg AZ31 stents [48]

The Mg AZ31 stents of length 33 mm and of diameter of 4.5 mm were incubated for 7 days in a vascular bioreactor, which consisted of a test channel, a corrosion medium, a variable-flow chemical transfer pump, a reservoir and an incubator. Silicone tubing with a diameter of 6.3 mm was used as the test channel. The pseudo-physiological corrosive solution was chosen to be Dulbecco’s modified Eagle’s medium (DMEM) with 10% fetal bovine serum (FBS) and 1% penicillin-streptomycin; the volume of which was kept at 300 ml. The stents were mounted on an
angioplasty balloon in the test channel and was inflated from 4.5 mm to 6.3 mm; leading to the adhesion of the stent struts to the inner wall of the tubing.

3.1.3.3.2 Corrosion behavior of polymer coated Mg AZ31 stents [49]
Poly(carbonate urethane) urea (PCUU) and poly(ester urethane) urea (PEUU) coated Mg AZ31 stents of length 13 mm and of diameter 4 mm were expanded to 6 mm in diameter using an Abbott Vascular Viatrac® 14 plus peripheral dilation catheter; whereas the control group consisted of photochemically etched Mg AZ31 stents with poly(lactic-co-glycolic acid) (PLGA) coating and bare stents. Stents before and after expansion were coated by gold palladium via sputtering and were then subject to scanning electron microscopy (SEM; JSM – 6330F, JEOL, USA). Dulbecco’s modified Eagle’s medium (DMEM) with 10% fetal bovine serum (FBS), 1% penicillin-streptomycin and 100 U/ml lipase solution were used as the corrosion medium; the volume of which was kept at 300 ml. Dynamic degradation testing of stents of length 10 mm and of diameter 3 mm was performed for 3 days in a vascular bioreactor; which consisted of a reservoir, pump and flow channel of silicone tubing of inner diameter of 3.2 mm. Corrosion morphologies before and after dynamic degradation were obtained from 3D images of the metallic samples by micro-CT (Phoenix Nanotom-M™, GE sensing and Inspection Technologies, GmbH, Germany).

3.1.3.3.3 Corrosion behavior of helical Mg AZ31 stents [50]
Mg AZ31 helical stents of two different dimensions were used in corrosion studies of static immersion, in vitro luminal flow and ex vivo intraluminal flow. For the in vitro test, the experimental set up consisted of a reactor, a flow transfer pump, a reservoir and a flow controller. Mg AZ31 helical stents of length 25 mm and diameter 2 mm with three different expansion rates (0%, ~58.8% and ~98.5%) were inserted in silicone tubing (EW-95802-04, EW-95802-07, Cole Parmer, IL, USA) of 10 cm length via a balloon catheter for dynamic in vitro
tests. For the ex vivo test, Mg AZ31 helical stents of length 30 mm and diameter 4 mm were inserted in porcine abdominal aortas. The humidified incubator was maintained at 37 °C in 5% CO₂. Same environmental conditions were maintained for the static immersion test; which was simultaneously conducted.

3.2 Evolution in Mg AZ31 stent design based on expandability tests and simulations

Since the low mechanical properties of Mg are not significantly improved by alloying; material properties alone are not sufficient to ensure successful stent performance. It is the stent design that is of substantial importance in terms of influencing stent performance. Balloon expandable stents are manufactured in the crimped state and are expanded to the vessel diameter; as mentioned previously. The balloon inflation thus plastically deforms the stent; which accordingly resists the inflation process. Strut shape, dimensions and thickness play important roles in stent expansion. All these design parameters contribute to a uniform stent expansion ~ 50%; although a small amount of recoil is present. The stent design contributes to increase in diameter without reaching the ultimate tensile strength (UTS). The general design requirements for stents are as follows:

1. Sufficient mechanical strength to bear blood vessel loads and retain overall shape during expansion by preventing bending and twisting
2. Flexibility for uniform expansion of the balloon

A variety of biodegradable stents of Mg AZ31 alloy was designed and later fabricated by the novel photochemical etching technology.[51] These balloon expandable stents were of cylindrical geometries and varied in length, diameter and texture. Stent expansion tests
performed by balloons i.e. expandability tests have been carried out to determine a qualitative measure of radial stiffness of the stents. Radial stiffness is an important property in case of stent implantation; since higher radial stiffness is beneficial in reducing stent failures such as recoil.[52] Based on the expandability tests, the design of stents has evolved a lot over time. The design modifications are presented in a sequential manner below.

Figure 3.2: (A) The first generation of photochemically etched Mg AZ31 stents and (B) A close up view of one stent.

Figure 3.3: (A) A Generation 2 photochemically etched Mg AZ31 stent after balloon expansion and (B) A Generation 3 photochemically etched Mg AZ31 stent.

The first generation of photochemically etched Mg AZ31 stents i.e. generation 1 stents consisted of a simple square mesh texture with end rings; as shown in figures 3.2(A) and 3.2(B). The design of generation 1 stents fulfilled the criterion of radial strength owing to the property of the
material and behaved as a rigid structure. As a result, it hardly provided flexibility; which was evident in its poor expandability.

The design of generation 1 stents was replaced with a design consisting of 4 concentric circumferential rings; each of which consisted of a zig zag like pattern. These rings were interconnected by zig zag shaped connectors. This design was adapted in order to ensure greater flexibility as well as expansion. The fabricated stents of this design were labeled as ‘Generation 2’ stents. The connectors allowed large expansion as well as plastic deformation while the circumferential rings maintained the general shape and integrity of the stent by inhibiting unequal bending or torsion of the stent. The limitation in material properties was thus overcome by selection of the design. However, the end rings prevented the uniform expansion of the stent via balloon expansion; as shown in figure 3.3(A).

Systematic optimization in stent design led to improvement in laser welding and elimination of end rings; as shown in figure 3.3(B). These design modifications ensured sufficient radial strength for balloon expansion. Stents fabricated without end rings were labeled as ‘Generation 3’ stents.

Photochemically etched Mg AZ31 sheets of 5 different textures were designed and fabricated; as shown in figure 3.4. These sheets were of 2 different thicknesses i.e. 250 µm and 500 µm. Design 1 [figures 3.4(A) and 3.5(A)] consisted of an array of parallel diagonal strips with wave shaped connections. Design 2 [figures 3.4(B) and 3.5(A)] had rows of interconnected diamond shaped structures as the repetitive unit; with zig zag shaped connections between the rows. Design 3 was complex with a repetitive unit of interconnected peak to valley struts. The repetitive units were connected by S-shaped connections; as shown in figures 3.4(C) and 3.5(A). Design 4 [figures 3.4(D) and 3.5(A)] consisted of rows of bow-shaped structures; the rows being connected by
simple connecting rods. Design 5 consisted of a simple diamond mesh texture; as shown in figures 3.4(E) and 3.5(A). Stents of a length of 5 cm of both thicknesses were successfully manufactured out of these photochemically etched sheets; as shown in figure 3.5(B).

Figure 3.4: Photochemically etched Mg AZ31 sheets of 5 different textures: (A) Design 1, (B) Design 2, (C) Design 3, (D) Design 4 and (E) Design 5.
Figure 3.5: (A) Close up on the texture of the photochemically etched magnesium AZ31 sheets and (B) Stents made out of these sheets.

The expandability of these stents of 5 different designs was tested. It was observed that the stents which were highly interconnected by struts i.e. the stents with more dense texture provided high strength but did not expand much (design no. 2, 4 and 5); whereas stents with relatively less interconnections i.e. stents with less dense texture led to more expansion of the balloon; as shown in figure 3.6. However, stents of designs 1 and 3 showed more expansion in the middle region; as compared to the ends; leading to deformation in the middle region.

Figure 3.6(A - E): Expanded as well as unexpanded stents of 250 µm thickness of 5 different designs
The expandability tests carried out with stents of the same design but of a 500 µm thickness did not lead to promising results. It was extremely difficult to insert the balloon into the stents of such thickness and the stents hardly expanded. Moreover, these stents were extremely difficult to deform. Since easy deformability and expandability are requirements during stent implantation; it was concluded that stents of such thickness may not be a suitable option for practical purposes.

Figure 3.7: (A) Original stent design, Simulation result of stent being subjected to (B) a radial displacement of 2 mm and (C) a radial displacement of 4 mm. The color bar represents residual strain in mm.

Figure 3.8: (A) Modified stent design, Simulation result of stent being subjected to (B) a radial displacement of 2 mm and (C) a radial displacement of 4 mm. The color bar represents residual strain in mm.

Expansions of photochemically etched Mg AZ31 stents of design 3 were simulated by Solidworks. The stents were subsequently subject to radial displacements of 2 mm and 4 mm. The complex design of the stent resulted into non uniform stent expansion; as shown in figures
As a result, the stent design was further modified to a shorter length; as shown in figure 3.8(A).

Figure 3.9: (A) New stent design i.e. design 6, Simulation result of stent being subjected to (B) a radial displacement of 2 mm and (C) a radial displacement of 4 mm.

However, despite the reduction in stent length; the stent underwent a non-uniform expansion; as revealed by the expansion simulation and shown in figures 3.8(B) and 3.8(C). This led to adaptation of a new as well as simpler stent design i.e. design 6; as shown in figure 3.9(A). This stent consisted of 5 circumferential rings; each of which consisted of peak to valley struts. Consecutive rings were connected by peak to peak or valley to valley connections. The simulation of this simple design demonstrated the desired uniform expansion; as shown in figures 3.9(B) and 3.9(C).

Based on this promising simulation result, Mg AZ31 stents of length 2.3 cm, diameter 4 mm, and thickness 250 micron were fabricated according to the simple design mentioned above. The expandability of 2 such stents was then tested. When expanded via the balloon, the stent showed a uniform expansion; which was in agreement with the simulation result and is shown in figure 3.10.
Figure 3.10: (A) The unexpanded stent vs. the expanded stent, (B) The expanded struts opposite to the laser welded joint and (C) The expanded struts close to the laser welded joint.

Figure 3.11: (A) The unexpanded stent mounted on the High-Accuracy CMOS micrometer (Keyence, LS-9006MR), (B) Close view of the unexpanded stent mounted on the micrometer and (C) Close view of the expanded stent mounted on the micrometer.

In order to measure the stent expansion in terms of outer diameter in real time (at regular time intervals), the stent of the same dimensions (Length: 2.3 cm, Diameter: 4 mm, Thickness: 250 micron) was mounted on the High-Accuracy CMOS micrometer (Keyence, LS-9006MR) and was expanded via a Dorado PTA Balloon Dilatation Catheter (8mm × 4cm). The stent in unexpanded as well as expanded conditions is shown in figure 3.11. The final outer diameter was 6 mm; as recorded by the device. The stent thus exhibited 40% (approx.) expandability.

The promising results of the stent expansion simulation as well as the expandability test led to fabrication of another generation of stents with a slightly different design i.e. design 7; as shown in figure 3.12. The fabricated stents were of two different diameters i.e. 3mm and 4mm and of
three different lengths i.e. 26.3mm, 21.8mm and 12.9mm. Design 7 differed from design 6 in that it had multiple welding bars to provide sufficient radial strength; as compared to peak to peak and valley to valley connections in design 6.

Figure 3.12: Mg AZ31 stents of design 7 with (A) a diameter of 3 mm, (B) a diameter of 4 mm, (C)-(D): A closer look at the texture of the shortest stent.

Figure 3.13: The unexpanded stent (Length 12.9 mm) vs. the expanded stent in air and water (A) stent of OD 3 mm (B) stent of OD 4 mm.

In case of stents of 3 mm diameter, expandability tests revealed that expansion was obvious only at the stent ends when expanded via air; whereas the stent ruptured at one end despite showing better expansion when expanded via water. The stent of 4 mm diameter showed a better expansion than its 3 mm diameter counterpart in case of expansion by air. In case of water
expansion, the 4 mm diameter stent showed a uniform as well as better expansion compared to the 3 mm diameter stent.

Figure 3.14: (A) The unexpanded stent (Length 21.8 mm) vs. the expanded stent in air and water (A) stent of OD 3 mm (B) stent of OD 4 mm.

When expanded via air, the stent of 21.8 mm length and 3 mm diameter hardly showed any expansion except at the ends. It showed a slightly better and uniform expansion; but ruptured at both of the ends in case of expansion by water. The 4 mm diameter stent showed a better expansion than that of the 3 mm diameter stent; with more expansion at the ends; when expanded via air. In case of expansion by air, the stent showed a somewhat uniform expansion.

Figure 3.15: The unexpanded stent (Length 26.3 mm) vs. the expanded stent in air and water.
The stent with a 3 mm diameter and 26.3 mm length showed little expansion except at the ends in case of expansion via air. Although it showed slightly better and uniform expansion in case of expansion via water; it ruptured at the ends. In summary, the 3 mm diameter stents showed less expansion compared to those of 4 mm diameter. Except for the 4 mm diameter stents of lengths of 12.9 mm and 21.8 mm, the stents ruptured during expansion via water although they expanded more compared to that via air.

Figure 3.16: The 3 mm diameter stent with welding bar: (A) The unexpanded stent of vs. the expanded stent, (B) Cross-sectional view of the same stents; 3 mm diameter stent without welding bar (Generation 4 stent): (C) The unexpanded stent of vs. the expanded stent and (D) Cross-sectional view of the same stents.

Based on the expandability test results, two diameters (3 mm and 4 mm) and a particular length of 2.5 cm were chosen for designing the next generation of the stents. As another design modification; the welding bar was eliminated for better expansion. The fabricated stents without welding bars were labeled as ‘Generation 4’ stents. For each diameter, the fabricated batch of stents consisted of both types i.e. with and without the welding bar. During expansion testing by
a balloon, the stents without welding bars exhibited a uniform expansion similar to that of the stents with welding bars; as shown in figures 3.16 and 3.17. This observation led to the conclusion that a Mg AZ31 stent of this particular design (design 7) and dimensions can be equally effective in terms of expandability despite the absence of a welding bar.

Figure 3.17: The 4 mm diameter stent with welding bar: (A) The unexpanded stent of vs. the expanded stent, (B) Cross-sectional view of the same stents; 4 mm diameter stent without welding bar (Generation 4 stent): (C) The unexpanded stent of vs. the expanded stent and (D) Cross-sectional view of the same stents.

The evolution of stent design from generation 1 to generation 4 is shown in the schematic diagrams in figures 3.18 – 3.21. In case of fabrication of a generation 3 stent (without end rings), the frame of the photochemically etched Mg AZ31 sheet is partially removed before laser welding; as shown in figure 3.20. The fabrication of a generation 4 stent (without laser welded bar) involves complete removal of the frame of the photochemically etched Mg AZ31 sheet followed by spot welding; as shown in figure 3.21.
Figure 3.18: Steps in fabrication of a generation 1 stent via photochemical etching.*

Figure 3.19: Steps in fabrication of a generation 2 stent via photochemical etching.*

Figure 3.20: Steps in fabrication of a generation 3 stent via photochemical etching.*

Figure 3.21: Steps in fabrication of a generation 4 stent via photochemical etching.*

* Schematic diagrams are not to scale
3.3 Design and fabrication of Mg AZ31 helical stents

Figure 3.22: (A) Photochemically etched Mg AZ31 ribbons of 2 different designs, (B) Helical stents made out of the ribbons and (C) One helical stent placed in an arteriovenous fistula (AVF) of the porcine model.

The novel photochemical etching technique has also been applied to the fabrication of a flexible stent with spiral geometry; namely the ‘helical stent’. The starting material was a 2D Mg AZ31 ribbon that was photochemically etched with desired features. The ribbon length, width and thickness were 220 mm, 5 mm and 250 µm respectively. Two such ribbons of different designs i.e. design1 and design 2 are shown in figure 3.22(A). These ribbons were transformed into spiral structures by winding on a guiding rod; as shown in figure 3.22(B). One characteristic feature of the helical stent is that no welding is required. Moreover, the helical stent can be shaped easily by hands before or after delivery. Other advantages of this device fabrication process are that the device dimensions i.e. diameter and length can be widely varied and any design is achievable.

The helical stents shown in figure 3.18(B) were fabricated for placement in the arteriovenous fistula (AVF) of a porcine model; as shown in figure 3.22(C).

It is expected that the spiral texture of the helical stent will be imprinted on the inner wall of the blood vessel via implantation. The blood vessel wall with spiral texture is then expected to
facilitate the flowing of blood in a spiral manner; despite the fact that the fabricated helical stent consists of a straight centerline.

Expandability tests were conducted on Mg AZ31 helical stents fabricated out of ribbons of design 2; which were of 2 different widths i.e. 5 mm and 3 mm. Such a test on a Mg AZ31 helical stent fabricated out of a 5 mm width ribbon (stent OD 4 mm and length 2 cm) revealed a uniform expansion of the stent; as shown in figure 3.23(A).

![Mg AZ31 helical stent](image)

Figure 3.23: (A) The Mg AZ31 helical stent fabricated out of a ribbon of 5 mm width mounted on a balloon, and (B) The unexpanded and expanded Mg AZ31 helical stent.

![Mg AZ31 helical stent](image)

Figure 3.24: The Mg AZ31 helical stent fabricated out of a ribbon of 3 mm width mounted on an inflated balloon: (A) 3 mm OD stent and (B) 4 mm OD stent.
In case of Mg AZ31 helical stents fabricated out of a 3 mm width ribbon, 2 stents of the same length i.e. 2.5 cm but of different diameters i.e. 3 mm and 4 mm were tested. As shown in figure 3.24, both the stents prevented the middle part of the balloon from expanding. As a result, the stents did not show expansion in the middle region. This behavior may be due to the fact that helical stents fabricated out of a 3 mm wide ribbon consist of a greater number of full windings; as compared to helical stents fabricated out of a 5 mm wide ribbon. A greater number of windings lead to greater stiffness of the device in the middle portion. However, both the stents showed a little expansion at the ends; probably due to uncoiling of the loose ends. Therefore, it may be concluded that although stent fabrication from a Mg AZ31 ribbon of 3 mm width is easier in terms of coiling around a guiding rod, stents fabricated from a Mg AZ31 ribbon of 5 mm width show a better and uniform expansion.

In vivo studies have been conducted with such photo-chemically etched Mg AZ31 helical stents in porcine models. The Mg AZ31 helical stents were implanted into the porcine AVF; as shown in figures 3.25(A) and 3.25(B).

Figure 3.25: In vivo studies with Mg AZ31 helical stent: (A) Helical stent being placed in porcine AVF, (B) Helical stent after being implanted in porcine AVF and (C) The characteristic Doppler red-blue shift; indicative of helical flow.
The blood flow visualized by the Doppler ultrasound technique demonstrated a spiral laminar flow pattern; as indicated by the characteristic red-blue split in the obtained color flow image [figure 3.25(C)]. This result shows that the helical stent geometry was capable of generating a swirling motion of intraluminal blood flow, as suggested in literature. Although this preliminary data was promising, further in vivo testing of Mg AZ31 helical stents of different dimensions is required for validation of the results.

3.4 Characterization of Mg AZ31 stent

3.4.1 Tensile test results

![Stress-strain curve for a Mg AZ31 ribbon of 5 mm width. The red curve represents specimen 1; the brown curve represents specimen 2 and the green curve represents specimen 3.](image)

Figure 3.26: Stress-strain curve for a Mg AZ31 ribbon of 5 mm width. The red curve represents specimen 1; the brown curve represents specimen 2 and the green curve represents specimen 3.
As per the stress strain curve shown in figure 3.26, the ultimate tensile stress of all 3 specimens was between 90 MPa to 100 MPa; the average being approximately 93 MPa. The yield strength for all 3 specimens ranged between 65– 70 MPa. From the area under the curve, the mean toughness was found out to be 9.15 MPa. However, in case of all 3 specimens, the curves deviate from ideal behavior as the specimens continued to be expanded after one side of the ribbon frame failed. That is, one side of the ribbon frame fails in the tensile stress range of 40 – 55 MPa; after which the other ribbon frame continues to expand until final failure occurs; as shown in figure 3.27(A). Figure 3.27(B) shows the fractured surface of a part of one of the failed specimens.

Figure 3.27: (A) A failed Mg AZ31 ribbon specimen of 5 mm width and (B) An optical micrograph of the fractured surface of a part of one specimen.
Figure 3.28: Stress-strain curve for a Mg AZ31 ribbon of 3 mm width. The red curve represents specimen 1; the brown curve represents specimen 2 and the green curve represents specimen 3.

For Mg AZ31 ribbons of 3 mm width, specimens 1 and 3 did not show the ideal behavior; because of failure of the specimens in two steps; as described in the case of ribbons of 5 mm width. As shown in figure 3.28; the first ribbon frame failed in the tensile stress range of 50- 55 MPa; followed by failure of the second ribbon frame.

Fluctuations were observed in the stress strain curve of specimen 1, probably due to slipping. However, the three tested specimens exhibited an ultimate tensile stress between 95 MPa to 102 MPa; the average being approximately 100 MPa. Specimens 2 and 3 exhibited yield strength of approximately 80 MPa. From the area under the curve, the mean toughness was found out to be 5.32 MPa.
3.4.2 Corrosion behavior

3.4.2.1 Flow induced corrosion behavior of Mg AZ31 stents [48]

Figure 3.29: (a) A photochemically etched Mg AZ31 stent (b) X-ray micro-CT 3D renderings of a dimensioned repeating unit of the stent geometry. [This figure has been adapted from Wang et al. Acta Biomaterialia 10 (2014) 5213 - 5223 © 2014 Elsevier.]

Corrosion morphologies of the Mg AZ31 stents (figure 3.29) in a vascular bioreactor under static (0 Pa) and dynamic (0.056 Pa) FISS values are shown in figure 3.26. In the static case, a relatively smooth surface was observed on the majority of the stents (figures 3.30a and 3.30b). Some shell-shaped corrosion products were observed in the localized corrosion regions (figures 3.30c and 3.30d, green frame); whereas needle-like morphologies were observed around the shell-like corrosion products.[48]

On the other hand, in the dynamic case, a corrosion product layer was formed due to severe and homogeneous corrosion of the stent surface (figure 3.30e). This corrosion product layer consisted of a network of 100 µm scaled cracks and covered the stent surface (figure 3.30g). In the direction of flow, some stent pieces were detached. CT investigation in ethanol solution also revealed similar observations about detached regions (figure 3.30f, yellow frame). This implies that the drying process required for the SEM imaging was not the cause of the strut detachment (figure 3.30g, yellow frame). In addition, the dynamic flow condition caused a thick strut fracture in the flow direction (figure 3.30e, blue circle). All of the above observations imply that the static flow condition corresponds to a small amount of localized corrosion; whereas the dynamic flow condition corresponds to a uniform corrosion model.[48]
Figure 3.30: Corrosion morphologies of Mg AZ31 stents under static and dynamic conditions by X-ray CT analysis: (a,e) Reconstructions of X-ray micro-CT 3-D, (b,f) Reconstructions of X-ray micro-CT with representative 2-D slices, (c) SEM image indicating localized corrosion under static condition, (d) SEM image showing corrosion products under static condition, (g) SEM image showing cracks and detached regions under dynamic condition and (h) SEM image with an enlarged view of the crack under dynamic condition. [This figure has been adapted from Wang et al. Acta Biomaterialia 10 (2014) 5213 - 5223 © 2014 Elsevier.]

Under both static and dynamic conditions, the elements O, Ca, P and Al were observed in significant amounts and a distinct chemical distribution was observed in the corrosion product layer by means of EDX line analysis; as shown in figure 3.31. The formation of a calcium phosphate complex layer on the surface is indicated by the distribution of O, Ca and P. The dynamic condition led to some detached regions on the stent. EDX point analysis also determined detached pieces around the stent on the bioreactor wall to be corrosion products.
There were no significant changes in volume loss of stents during the static and dynamic degradation. Since the grain diameter of AZ31 is less than 30 µm, no significant second phase segregation is observed at the grain boundary. Localized corrosion is therefore less feasible, due to lack of the driving force required to facilitate micro-galvanic corrosion. This is probably the reason why a uniform corrosion model was observed in case of corrosion under the dynamic condition.[48]

3.4.2.2 In vitro corrosion behavior of polymer coated Mg AZ31 stents [49]

Upon being subject to a wall shear stress of 0.07 Pa for 3 days in a perfusion bioreactor; morphological alterations of the stents were observed; as shown in figure 3.32. Focal regions of marked mass loss and general coverage with a corrosion product layer were observed on the stents under strong flow conditions. Distortion of some stent struts occurred; probably due to the decreased mechanical strength after degradation and mass loss. Hydrogen gas release during the course of stent corrosion may have been the possible cause of the observed blebbing across the PLGA-coated stents. The coated surfaces exhibited wrinkles and cracks. A network of 100 µm-
scale cracks covered the surface of the PEUU coating layer, thereby exposing small areas of Mg AZ31 in some cases. The PCUU coating layer exhibited a smooth and intact surface structure in general; with the exception of one crack on the edge of a stent strut.[49]

![Image of corrosion regions](image)

Figure 3.32: SEM images of corrosion regions on Mg AZ31 stents under the FISS value of 0.07 Pa for 3 days in DMEM (10% FBS, 1% P/S) + 100 U/ml lipase solution at 37°C. Enlarged images of the white dashed boxes in top row images are presented in the bottom row. Scale bar: 1 mm top row, 200 µm bottom row. [This figure has been adapted from Gu et al. Colloids and Surfaces B: Biointerfaces 144 (2016) 170-179 © 2016 Elsevier.]

The corrosion morphology of the Mg AZ31 stents beneath the polymer coating layers was analyzed by micro-CT; as shown in figure 3.33. The uncoated stent struts indicated substantial material removal during perfusion tests, as they were noticeably thinner compared those of the other three coated groups. The uncoated sample showed presence of some large and deep corrosion pits. The PLGA and PEUU coating layers consisted of some corrosion pits; whereas a smooth and homogeneous surface was observed in case of the PCUU coating layer.[49]
3.4.2.3 Corrosion behavior of helical Mg AZ31 stents [50]

Micro-CT images in figure 3.34 show the corrosion behavior of the helical Mg AZ31 stents in case of both static and dynamic fluid flow (wall shear stress 0.68 Pa). The 2D cross-sectional images represent the stents before the corrosion test; whereas the 3D images show the stents after the test. Under the condition of static fluid flow, the relatively smooth helical stent surface indicated a lower degradation rate. The corrosion test for dynamic fluid flow was carried out with stents of different expansion rates i.e. 0%, ~58.8% and ~98.5%. Under the condition of
dynamic fluid flow, a higher degradation rate was indicated by more coverage of the stent surface with a degradation product layer. In case of the 98.5% expanded stent, a broken strut was observed (yellow arrow).

Figure 3.34: Top row: Cross-sectional 2D images of helical stents before the test; Middle row: Reconstructions of X-ray micro-CT 3D images of stents in DMEM (10% FBS, 1% P/S) at 37°C, 5% CO₂ and Bottom row: Enlarged images of the red dashed boxes in middle row images. [This figure has been adapted from Koo et al. Scientific Reports (Accepted) (2017) © 2017 Nature.]
Figure 3.35: SEM images of degradation regions on helical Mg AZ31 stents under the FISS value of 0.68 Pa for 3 days in DMEM (10% FBS, 1% P/S) at 37°C, 5% CO₂. (A)-(C) represents the helical stent with an expansion rate of ~58.8% and (D)-(F) represents the helical stent with an expansion rate of ~98.5%. The table shows the detected elements (at. %) at the two marked positions by EDX. [This figure has been adapted from Koo et al. Scientific Reports (Accepted) (2017) © 2017 Nature.]

<table>
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<th>Position</th>
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<th>Ca</th>
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<td>0.8</td>
<td>2.27</td>
<td>-</td>
<td>-</td>
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<tr>
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<td>12.10</td>
<td>64.91</td>
<td>0.24</td>
<td>3.58</td>
<td>10.31</td>
<td>8.87</td>
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</tbody>
</table>

The degradation products and morphologies of stents with two different expansion rates (~58.8% and 98.5%) were analyzed by SEM and EDX and are shown in figure 3.35. Degradation product layers were observed on stent surfaces in both the cases. In case of the stent with an expansion rate of ~58.8% [figures 3.35(A) – 3.35(C)], the chemical composition is shown at two positions in figure 3.35(C). Mg and O were the predominant elements of the inner side (position 1). Al and
were detected on the surface. A significant amount of P and Ca along with the aforementioned elements were detected in position 2. On the other hand, a broken strut and a corroded strut surrounded by degradation products were observed in the case of the stent with an expansion rate of ~98.5% [figures 3.35(D) – 3.35(F)]. The degradation product layer thickness was found to be 25 µm in a flat surface and was found to be 40 µm in an edge region of the strut.

Figure 3.36: Reconstructions of X-ray micro-CT 3D images of the expanded helical Mg AZ31 stent scaffold implanted in the porcine artery. Left: Cross-sectional side view and Right: Cross-sectional front view. [This figure has been adapted from Koo et al. Scientific Reports (Accepted) (2017) © 2017 Nature.]

As shown in figure 3.36, the helical Mg AZ31 stent in the ex vivo test exhibited substantial expansion (100%) and was in contact with the vessel wall. The front-view image provides a depiction of the spiral stent structure extending in the plane of the image.

The chemical composition of the degradation products of the deployed helical stent in the ex vivo test were analyzed by the SEM and EDX and are shown in figure 3.37. Residual stent pieces were observed in the arterial tissue; as shown in figure 3.37(A). The primary elements
observed in the tissue (position 1) and the lumen (position 5) were found to be C and O (>88% and >6%); the origin of which is probably the embedding resin material.

![Figure 3.37: SEM images of degradation products on helical Mg AZ31 stents under the FISS value of 0.154 Pa for 3 days in DMEM (10% FBS, 1% P/S) at 37°C, 5% CO₂. The table shows the detected elements (at. %) at the five marked positions by EDX. [This figure has been adapted from Koo et al. Scientific Reports (Accepted) (2017) © 2017 Nature.]

Although both C and O were observed in position 3; they were ignored because of lower peak intensity in comparison with the signal-to-noise ratio. C, O, P, Ca, Mg; were the main elements present adjacent to both the tissue and the lumen; along with trace amounts of Mg alloying elements i.e. Al and Zn.
3.5 Mg single crystal helical stents

3.5.1 Fabrication process

Figure 3.38: (A) Mg single crystal grower at UC, (B) A grown Mg single crystal and (C) Hollow Mg single crystal cylinder extracted by EDM.

The fabrication of a Mg single crystal consisted of several steps. First, a Mg single crystal was grown in the single crystal grower; as shown in figure 3.38(A). The grown single crystal had a diameter of 20 mm and a length of 150 mm [figure 3.38(B)]. A hollow Mg cylinder was extracted from the Mg single crystal by EDM; as shown in figure 3.38(C). The approximate diameter of this cylinder was 4 mm. A single crystal plate was cut of this cylinder by EDM; the thickness of which was reduced to 650 µm by polishing; as shown in figure 3.39(A).

The single crystal plate was subject to laser machining (Oxford Scientific Laser Micromachining system) and transformed into a Mg single crystal ribbon; as shown in figure 3.39(B). A simple design was chosen for the Mg single crystal ribbon; which consisted of slant as well as parallel straight strips within its rectangular frame. The final step in fabrication was winding the Mg single crystal ribbon around a rod of diameter 5mm; thus giving rise to a Mg single crystal helical stent of diameter 5 mm and of a length of approximately 2.5 cm; as shown in figures
3.39(C) and 3.39(D). To my knowledge, this is the first helical stent that has been fabricated out of a Mg single crystal.

Figure 3.39: Steps in fabrication of Mg single crystal helical stent: (A) Polished Mg single crystal plate, (B) Laser machined Mg single crystal ribbon, (C) and (D): Two different views of a Mg single crystal helical stent.

The fabricated Mg single crystal helical stent consisted of thicker struts in comparison with stents fabricated by the PE or LBM method. This was because of the high thickness of the polished Mg single crystal plate (650 µm). The struts can be made thinner by usage of a thinner Mg single crystal plate and also by modifying the Mg single crystal ribbon design with strips of less width.

3.5.2 Properties (Mechanical/Corrosion)

The microhardness of a Mg single crystal plate was tested by the Knoop method. The test was performed 4 times under a load of 200 N and loading time of 15s. The average hardness was found to be 39 kgf/mm². The tested specimen is shown in figure 3.40.
3.6 Design and fabrication of biodegradable Mg surgical staples for soft tissue

Biodegradable Mg staples have the capability to degrade in vivo within 3-4 weeks and hence, possess potential benefits over conventionally used stainless steel and Ti-based non-resorbable staples for soft tissue applications. If coated with anti-fibrotic, anti-infective and pro-healing (drug delivery, including antibiotics) coatings, biodegradable Mg staples can reduce the risk of infection. Moreover, due to small surface area of such staples, they have a potential advantage over resorbable suture in lowering the risk of infection. Further, the manipulation to remove the degradable Mg staples used for skin applications may not require medical environment because it is expected that the non-resorbed part of the staple will remain on top of the skin and will fall off easily in a “self-removal mode”. The Mg surgical staple will also enable less residual scarring.

The fabrication of biodegradable Mg staples has been attempted by the PE method. For reasons discussed previously, the chosen alloy was Mg AZ31 and the initial material was a Mg AZ31
sheet with a thickness of 250 microns. A schematic diagram of the manufacturing method of the Mg AZ31 staple array is shown in figure 3.41.

![Schematic diagram of the manufacturing method of the Mg AZ31 staple array.](image)

Figure 3.41: Steps of fabrication of biodegradable Mg staples by the PE method.

However, after fabrication of the Mg AZ31 staple array (figure 3.41), a problem was encountered during the attempt to bend it into the desired shape; as shown in figure 3.42(A). Cracking and fracturing of parts were observed during the bending attempts. This behavior was attributed to the bend radius of the Mg strips being smaller than the minimum bend radius of Mg. Theoretically, the minimum bend radius should be 5.5 times of the material thickness i.e. 1375 microns; whereas the bend radius for the parts was 250 microns. Increasing the part bend radius resulted in the change of the dimensions of the part design; as shown in figure 3.42(B).

![Comparison of original and modified design.](image)

Figure 3.42: The Mg AZ31 staple design: (A) The original design and (B) The modified design with increased radius of bend.
Figure 3.43: Simulation of stress distribution in bending Mg staples made by photo-chemical etching. The color bar represents effective stress in MPa.

Figure 3.44: (A) 3D printed polymer mold for bending of photochemically etched Mg AZ31 staple, (B) Mg AZ31 staple being bent on 3D printed polymer mold and (C) Stainless steel and bent Mg AZ 31 staples using a 3D printed polymer mold.

In order to overcome the limitation of staple bending with small radius of the curvature as well as to optimize the staple design; a simulation of the photochemically etched Mg staple
deformation was generated by Ansys Workbench software; as shown in figure 3.43. Figure 3.43(A) shows a single Mg AZ31 staple strip prior to bending; whereas figure 3.43(B) shows the stress distribution on the staple strip after it has been bent into the desired shape. As expected, maximum stress is imposed upon the points of minimum radius of bend and minimum (zero) stress is imposed upon the points not in contact with the stress imposing mold (on the top).

The simulation result was then translated to reality by bending the Mg AZ31 staple strip into the desired shape by means of a 3D printed polymer mold; as shown in figures 3.44(A) and 3.44(B). A fabricated Mg AZ31 staple is shown and compared with a stainless steel staple in figure 3.44(C). Another limitation was the shape of the staple legs. The legs of the staples fabricated by the PE method consisted of flat and square cross sections; instead of the tapered legs of the SS staple. Sharpening of the legs by further etching could be a feasible option.
CHAPTER 4: SUMMARY AND CONCLUSION

The PE technique has successfully been applied to Mg by fabrication of a diverse array of Mg AZ31 stents of different dimensions and textures. The ability to fabricate stents of high geometric complexity by means of producing thin and uniform metal wire widths proved that the PE technique is a robust approach for fabrication of biodegradable Mg stents. The advantages provided by this technology are capable of promoting further large scale production; which can dramatically lower the price of these devices.

Based on results of stent expandability tests, the Mg AZ31 stent design went through a number of modifications. The material thickness of 500 µm was discarded; as stents fabricated out of material of such thickness exhibited poor expandability and flexibility. In case of stents of 250 µm thickness, initial modifications included elimination of end rings and reduction of the initial stent length of 5 cm to 2.5 cm. Simulations of stent expansion enabled selection of an appropriate design; which later exhibited uniform as well as good expandability. As a further design modification, the laser welding bar was eliminated. Stents without welding bars exhibited expandability as good as stents with welding bars.

The PE technique has also been exploited to manufacture helical flow inducing devices i.e. helical stents. The Mg AZ31 helical stents revealed a different mode of expansion compared to the Mg AZ31 cylindrical stents. Preliminary in vivo studies in porcine models showed that such a device was capable of generating the desired swirling flow. However, further in vivo studies are required to validate this result.
Under the influence of FISS, photochemically etched Mg AZ31 stents exhibited a small amount of localized corrosion under static conditions and uniform corrosion under dynamic conditions. Higher FISS led to increased corrosion due to localized, uniform, pitting and erosion mechanisms. Also, the regions of high shear stress i.e. strut areas facing the flow direction led to corrosion product detachment, which in turn, resulted into strut fracture. EDX line analysis revealed the existence of Al, Ca, P and O in significant amounts in the corrosion layer.

In case of the polymer coated Mg AZ31 stents, PCUU-coated stents showed improved corrosion resistance as well as reduced thrombotic deposition in comparison with uncoated or PLGA-coated stents. The biodegradable PCUU may therefore be considered as a promising drug-eluting coating for biodegradable Mg AZ31 stents.

The study of corrosion behavior of Mg AZ31 helical stents in three different environments revealed a 100% expandability of the stent. The degradation rate was higher under dynamic flow conditions in comparison with the static condition; as expected. The intermediate corrosion products were identified as MgO/Mg(OH)$_2$ and Ca/P. In case of the porcine ex vivo model, the performance of Mg AZ31 helical stent employed as a scaffold was satisfactory, with a high expansion rate (>100%).

Mg single crystals show higher ductility and fracture toughness in comparison with polycrystalline Mg. Hence, the Mg single crystal is a potential candidate to be used for fabrication of coronary cylindrical and helical stents. The first Mg single crystal helical stent of length 2.5 cm (approx.) and diameter 5 mm has been fabricated by laser cutting a Mg single
crystal ribbon out of a Mg single crystal plate; followed by winding of the ribbon around a guide wire. However, mechanical and corrosion properties of this newly fabricated device need to be tested. In addition, thin wall stents (250 micron) are needed and such a study is in progress.

Fabrication of biodegradable Mg AZ31 staples for soft tissue application has been attempted by the PE method. Although the Mg AZ31 staple array was successfully fabricated by this method; the bending of the staple strip remains a challenge; due to the required small radius of curvature of the current staple design. Simulations of the staple strip bending exhibited the stress distribution on the bent staple strip. The Mg AZ31 staple strip was later bent by a 3D printed polymer mold. Although the result was promising, further efforts are required to reproduce the staple as per the current design. The success in achieving the current staple design will lead to the prospect of mass production of biodegradable staples at a low price in future.
FUTURE WORK

1. A benchtop flow visualization system will be set up in order to evaluate the performance of photochemically etched helical stents in terms of generating spiral flow; with water as the working fluid. A helical stent will be inserted into the arterial model of inner diameter 3.876 mm. Flow conditions will be maintained such that a laminar flow is established and dye will be injected into the flow via a syringe pump. A swirling flow is expected to be generated by the stent. In order to mimic conditions of the blood vessel, the experiment will also be repeated with a working fluid whose viscosity is close to that of blood. In this case, a peristaltic pump will be used to generate a pulsatile flow.

2. As a complementary study to the ongoing research, the PE technique will be employed to fabricate stents of non-degradable metals i.e. Nitinol, Co-Cr alloys and stainless steel.

3. Attempts will be taken to fabricate a Mg single crystal helical stent with thinner struts. This task will require cutting of a Mg single crystal plate of less thickness; as compared to that of the Mg single crystal plate (650 µm thickness) used in the fabrication of the reported Mg single crystal helical stent.

4. To overcome the limitation of bending in case of the Mg staple, the staple array of the M-like shape will be attempted to be grown as a Mg single crystal in a specially designed crucible. The M-shaped staple array will then be mechanically cut into Mg staples.
REFERRED JOURNAL PUBLICATIONS RELATED TO THIS WORK


INVITED PRESENTATIONS RELATED TO THIS WORK

REFERENCES


