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Fabrication of 316L Stainless Steel Cardiovascular Stent by Laser Welding Process and Paclitaxel-Loaded PLGA Coating

Mahyar Fazeli[1*] **and Faegheh Fazeli**[2]

[1]*Department of Materials Science and Engineering, Federal University of Rio de Janeiro, Brazil*

[2]*Department of Periodontology, School of Dentistry, Isfahan University of Medical Sciences, Isfahan, Iran*

[*]**Corresponding author:** Mahyar Fazeli, Department of Materials Science and Engineering, Federal University of Rio de Janeiro, Brazil, Tel: +988733664645; E-mail: m.fazeli@metalmat.ufrj.br

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Abstract

This paper covers the fabrication method of 316L stainless steel cardiovascular stent and it studies and also compares the mechanical and physical properties of the fabricated stent with the commercial stent. The main purpose of this research is to make the cardiovascular stent in an inexpensive and new way to reduce the final cost of the product for patients. According to the diligence and meticulousness, the way of laser welding of 316L stainless steel thin wires is chosen. The type and general shape of the stent are chosen according to the removed stent from patient's body. Furthermore, the polymer frame is designed by means of graphic software and constructed by the laser-cut machine to deform the 316L stainless steel thin wires. The micro hardness test indicates that the welded wires joints are 90 Vickers harder than commercial stent wires joints. Scanning electron microscopy (SEM) of laser welded parts of the fabricated stent shows a uniform connection without any cracks. The ultimate tensile stress (UTS) of laser welded spots are compared with the commercial stent by tensile test and it reveals that the UTS of the fabricated stent is about 41 MPa more than the commercial stent. The metallographic images show that there is not any change in steel structure due to laser welding process and the time and temperature of the process should be optimized to obtain the appropriate strength. Paclitaxel-loaded PLGA is coated by the spraying method. Ultraviolet-visible spectrophotometry (UV-Vis) is used to measure the *in vitro* drug release. Characteristics of the coating are studied by Fourier transform Infrared spectroscopy (FTIR) and atomic force microscopy (AFM).

Keywords: Cardiovascular stent; Drug-eluting stent; Heart attack; Restenosis

Introduction

Over the past century, heart disease has accounted for more deaths than any other major cause of death in the world [1]. While a heart artery becomes narrow by aggregation of fatty deposits called plaque, the blood flow decreases and the heart attack occurs. Angioplasty surgery which is used instead of open heart surgery is a new route to dilate arteries [2]. There are several ways in angioplasty such as putting balloon and using the laser to dilate the blocked arteries [3]. Due to the potential of stenosis returning of arteries after using the balloon, the heart surgeon may choose stenting treatment [4]. The stent is an artificial mesh-like tube made of different materials which are placed in a natural passage of the body, especially inside the arteries to prevent the topical contraction of flow. Hence, the potential of stenosis returning notably reduces [5]. Cardiovascular illnesses lead to 40% of annual catastrophes of death in the European Union and result in an evaluated cost of 196 billion Euros [6]. Atherosclerosis of coronary arteries is one of the most ordinary cardiovascular diseases [7]. This type of illness can be treated either by drugs or by surgical procedures. Cardiovascular stents are utilized in the surgical procedure called "angioplasty" and have tubular and reticular structures. They are interpolated into the blood vessels to hold the vessels open and to reestablish the normal blood flow. As implantable medical devices, stents should possess mechanical strength, radiopacity, longitudinal flexibility, high radial expansion, corrosion resistance, biocompatibility and easy handling [6,8]. Stents can be built from different materials such as metal or polymer but metallic stents, especially stainless steel, are the most popular commercial stents according to their good mechanical characteristics [9]. Restenosis occurs in almost 30% of the patients after the surgical procedure of stenting and is associated with a high fatality rate as well as high cost of health care [10]. One of the main problems caused by restenosis is the damage of arteries by stent's metallic structure, resulting in the inflammatory response by the human body [11]. In order to minimize the problems caused by the metallic stents, various kinds of drug-loaded polymer coatings are used such as paclitaxel [12], dexamethasone [13], sirolimus [14], everolimus [15] and so on as the drugs and poly(lactic-co-glycolic acid) [16], poly(glycolic acid) [17], polycaprolactone [18], polyhydroxybutyrate-valerate [19], Poly (ortho esters) [20], Polyethylene glycol [21], Polyurethane [22] and so on as the polymers.

The objective of this paper is to introduce a new method of fabricating stent in an easier and more accurate way to achieve better mechanical properties than other fabricating methods for the bare metal stent. Laser welding process is chosen because of the accuracy of the method and high tensile strength of the fabricated stent. Also, the paclitaxel is selected as the drug in stent coating because of two reasons. The first and the most important reason is that the restenosis will not return after the surgical procedure [23]. The second reason is that the damaged inner wall of arteries after stenting procedure will cure rapidly [24]. Paclitaxel helps to cure the damaged inner wall of arteries after stenting procedure. PLGA is selected as the drug carrier because the paclitaxel releasing from PLGA is easy according to the physical reaction between their molecules [25].

Materials and Methods

316L Stainless steel thin wires with 0.3 mm diameter are selected as the stent body structure. Poly (methyl methacrylate) (PMMA) sheets in 2 mm thickness are utilized to build a frame for shaping the stent wires. The sheets are cut with the laser and connected together to fabricate a jaw frame and the procedure is demonstrated in frame building section. The stent pattern is taken from a cardiovascular stent AmozoniaPax (Minvasys Company, France).

Laser welding method is selected to fabricate the stent because of its accuracy. The method is explained. Then, the mechanical properties of the fabricated stent are studied and compared with commercial stent by using the micro hardness test and tensile test. Also, the microstructure of the stent is studied by using scanning electron microscopy and metallography method. In another hand, the fabricated stent is coated by paclitaxel-loaded PLGA coating by spraying method and the characteristics of the coating are studied by atomic force microscopy (AFM) and Fourier transform Infrared spectroscopy (FTIR). Finally, the drug release rate of stent coating is obtained by using Ultraviolet-visible spectrophotometry (UV-Vis). Vial of paclitaxel 6 mg/ml and poly(lactic-co-glycolic acid) (PLGA) are prepared by Pharmashield and Merck.

Frame building

The jaw like frames which are made of Poly (methyl methacrylate) (PMMA) is cut by accurate laser cutting machine (Acrylic laser cutting machine TR-1080). The thickness of the sheets is 2 mm. Then, five polymer sheets are stuck together to build a proper lower frame. In another hand, this process is repeated for upper frame and thickness of both upper and lower frames are 10 mm. Hence, the upper frame and lower frame can enter to each other easily. Design of stent is drawn by Corel Graphic Program exactly like the model Figure 1a and the dimensions are shown in Figure 2. Hence, by locating the wires between the upper frame and lower frame and putting those between jaws of the vise and by using a little force, the shape of the straight wires are changed to the shape of Figure 1c which is proper to use as one ring of the stent. To fabricate a stent, this project needs eight shaped wire like Figure 1c.

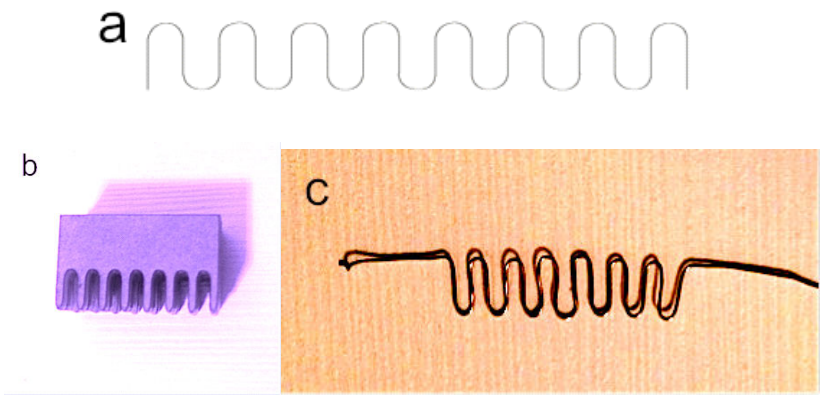

Figure 1: (a) Drawn picture of stent through Corel graphic program, (b) stent frame made from five polymer sheets with 2 mm thickness, (c) formed stainless steel wires.

Table 1 indicates dimensions of the fabricated stent. Actually, Figure 2 demonstrates the dimensions and final product of stent by the schematic figure. Hence, the number of rings, stent diameter, width and length of each ring and stent length are obvious in Table 1 and Figure 2.

Stent wire diameter	0.3 mm
Stent length	33.2 mm
Length of each ring **Width of each ring**	41.5 mm 4.15 mm
Stent diameter	66 mm
Number of rings	8

Table 1: Dimension of stent exited from patient body.

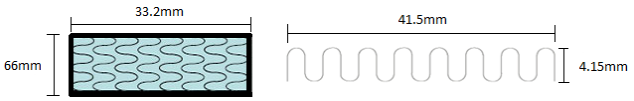

Figure 2: Schematic image of fabricated stent.

Laser welding

Laser spot welding is used to connect each of two preformed wires. Subsequently, tensile test (3382 Floor Model Universal Testing System, Instron Company), metallography of welded locations and scanning electron microscopy (SEM) are performed on welded wires. Table 2 shows the characteristics of laser welding machine.

Laser type	ND: YAG
Wavelength	1064 nm

Maximum exited power	30 W/60 W
Highest energy pulse	30 J/6 ms
Pulse Length	0.5-10 ms
Repetition Speed	0.5-8 Hz
Cooling method	Air cooling
Electrical source	220 V/50 Hz (60 Hz)/15A
Power consumption	2.5 KW

Table 2: Laser welding machine's characteristics.

Figure 3 shows the welded locations of the stent by red points. These locations are welded by laser welding machine with high accuracy. Hence, the primary structure is like a mesh. Then, this mesh should be carefully bent. Then, the first point of each ring should be welded to the last point of that. Therefore, this procedure leads to a cylinder mesh-like. Figure 4 shows the fabricated stent in this project by 316L stainless steel wires.

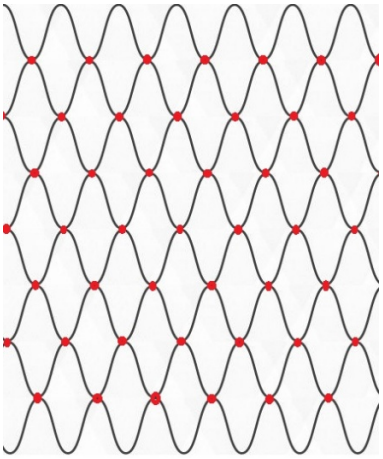

Figure 3: Schematic image of welded locations in stent structure.

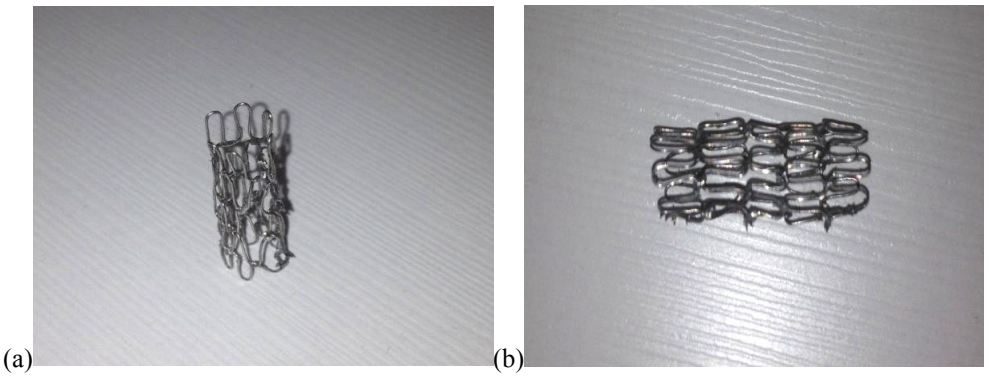

Figure 4: Stents made by 316L stainless steel wires.

Welded point characteristic tests

Micro hardness testing: Two transverse and longitudinal samples are provided from welded points of wires. Micro hardness testing is carried out on three points of the samples after mounting and the average of obtained results are compared with the average of hardness testing results of the commercial stent.

Tensile test

The tensile test is executed to compare the strength of welded spots created by laser welding machine with the strength of welded spots of the commercial stent. In order to place stress concentration on one point of welded points, its connection points are separated in a way which is demonstrated in Figure 5b. In this way, stress concentration in the tensile test will be in red point in Figure 5b. Hence, the results of the tensile test show the strength of every single welded point in stent structure. The tensile strength of all welded points and complete stent are defined using Universal Testing Machine QC-503A1, with 500 N load cell and 1 mm/sec.

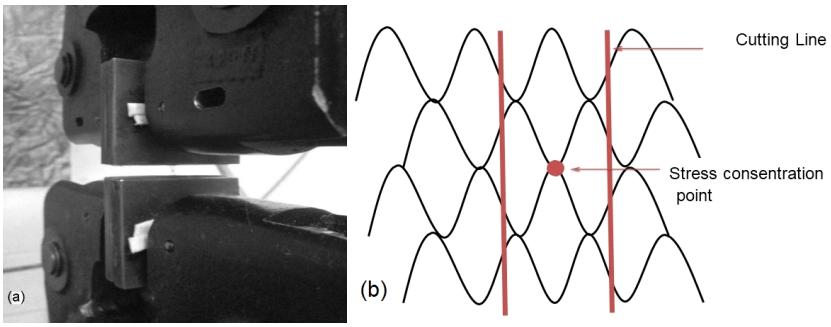

Figure 5: (a) The way to placing tensile load on the laser welding spot to create stress concentration in one connection point of stent, (b) way of cutting stent to place stress concentration in one welding point in tensile testing.

Microscopic observations

Scanning electron microscopy: The microstructure of the welded points is investigated by a VEGA3 SB- Tescan scanning electron microscopy (TESCAN, Czech Republic) at an accelerating voltage of 25 kV and magnification of 100x to 2000x. Scanning electron microscopy is executed in order to consider the existence of crack and uniformity in the connection points of the wires.

Metallographic observation

The process of metallography is carried on analyzing the difference between welded parts of the commercial stent and fabricated stent. Samples of welded parts of fabricated and commercial stents are cut and mounted subsequently. A solution of hydrochloric acid 50 wt% is used as an etch solution for 45 seconds. Then, the surfaces of mounted samples are washed with distilled water and ethanol and are dried by cool air flow. The microscopic observation is performed using MOTIC BA310 (Ted Pella, Inc.) optical microscope.

Characteristics of coating

Fabrication of paclitaxel-eluting PLGA stent: The fabricated stent is carefully polished using the electrochemical method and then cleaned successively with acetone, ethyl alcohol and distilled water under the condition of ultrasound. To evaporate the residual water, the stent is kept under vacuum chamber for 1 hour. The spray solution is provided by dissolving paclitaxel and PLGA in tetrahydrofuran and sprayed onto the stent surface. Figure 6 shows the schematic of the spraying system. The stent is located on a mandrel which is connected to the rotary drive. Hence, the mandrel rotates and moves in a direction which is obvious in Figure 6. The solution is sprayed by the high pressure of the equipment on the surface of the stent. All the surface of thin wires can be coated in this way.

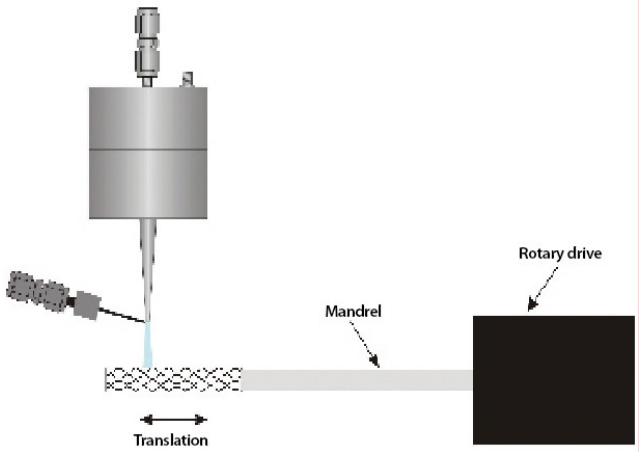

Figure 6: Schematic of spraying system.

Fourier Transform Infrared (FTIR) of coating

The chemical structure of PLGA, paclitaxel and paclitaxel-loaded PLGA coatings is analyzed by Fourier Transform Infrared spectroscopy (FTIR), VERTEX 80, BRUKER, Germany. The scanning wavenumber range is from 4000 cm^{-1} to 500 cm^{-1}. The PLGA coating is prepared via casting method. The casting solution is gained by dissolving PLGA in tetrahydrofuran. Then, the solution is slowly decanted into clean glass Petri dishes to obtain the coating. The solvent in the coating is slowly evaporated in 48 h and then kept in vacuum for evaporating the residual solvent. Paclitaxel-loaded PLGA coating was prepared in the same way by 30% (w/w) Paclitaxel with PLGA in tetrahydrofuran. These coatings are prepared to analyze by FTIR.

***In vitro* drug release:** The paclitaxel release behavior is studied *in vitro* by incubating the paclitaxel-loaded PLGA coating in a 50 mL centrifuge tube consisting 100 mL phosphate buffer saline (PBS) at 37°C, pH 7.4. Ultraviolet-Visible spectrophotometer (Shimadzu UV-3100) is used to determine the concentration of released paclitaxel in PBS solution. The coated stent is located on PBS. Each three days, 5 mL of the remained solution is taken out for analysis. This process lasts 30 days. The absorbance value of the controlled release of paclitaxel is determined accurately. By analyzing the obtained results of UV-Vis in

30 days for released paclitaxel in PBS solution, the drug release rate is calculated.

Atomic Force Microscopy (AFM) of loaded coating

Topology and characteristics of the surface of the coated stent are studied by atomic force microscopy (BRUKER ICON AFM). Stents samples are fixed on glass slides by using melted Polyethylene glycol (Mw - 20,000). Stent surface topography is obtained by lightly tapping the surface with the oscillating Si probe (RTESP probe, Bruker, Germany) at f=300 kHz. The surface of the coated stent before drug releasing is analyzed to compare with the surface of the coated stent after drug release.

Results and Discussion

Micro hardness testing

Table 3 shows results of micro hardness test on cut transverse and longitudinal welded part of fabricated and commercial stents. As can be seen in Table 3, the calculated values of transverse are 71 Vickers and 29 Vickers greater than longitudinal for fabricated and commercial stent because of anisotropy in the welded zone which is very important in welded point of the stent. From obtained results of the test, mean hardness of the prepared welded point of the fabricated stent was about 30% more than the commercial.

	Transverse micro hardness (Vickers) (HV0.1)	Longitudinal micro hardness (Vickers) (HV0.1)
Fabricated stent	292 ± 12	221 ± 10
Commercial stent	198 ± 5	169 ± 5

Table 3: Results of micro hardness test on fabricated and commercial stents.

Tensile testing

Figure 7 indicates that the tensile strength of the laser welded connection points of the fabricated stent is 65% more than welded connection points of the commercial stent. The reason of that can be attributed to the homogeneity of the welded dots microstructure in laser welded samples compared with these welded points in the commercial stent. This homogeneity of composition in laser welded dots leads to finer welding points compared with commercial stents. Tensile test of the whole fabricated stent is shown in Figure 8. The tensile test is carried out on the sample which is shown in Figure 2 because there are many welded points on this fabricated mesh. Hence, the tensile strength of the whole stent which depends on the weakest welded point is calculated. By increasing the stress. In the first stage, the stent undergoes an elastic deformation with 0.02% elongation. By increasing the stress more than an ultimate strength (65.3 MPa) the welded points start to detach which accompanies with a sudden decrease in the stress-strain curve. By applying more stress to the stent, the welded points start to fail till all of them detach and the sample completely breaks. There are 5 steps in the stress-strain curve in Figure 8 which the first one is attributed to the weakest welded point and the value of tensile strength for this first step is 65.3 MPa. After breaking the weakest welded point, stress concentration on other welded point increase. Then, other welded points start to break.

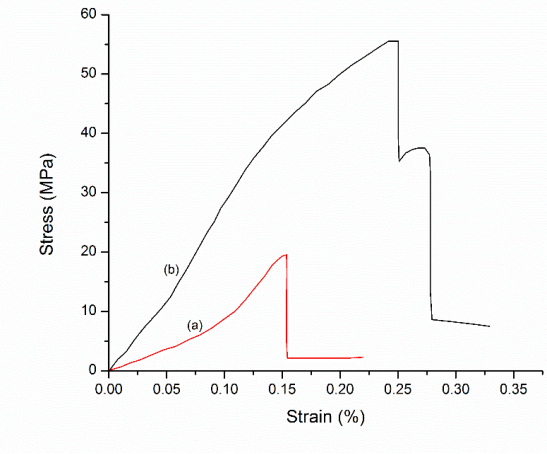

Figure 7: (a) Stress- strain curve of commercial stent, and (b) fabricated stent.

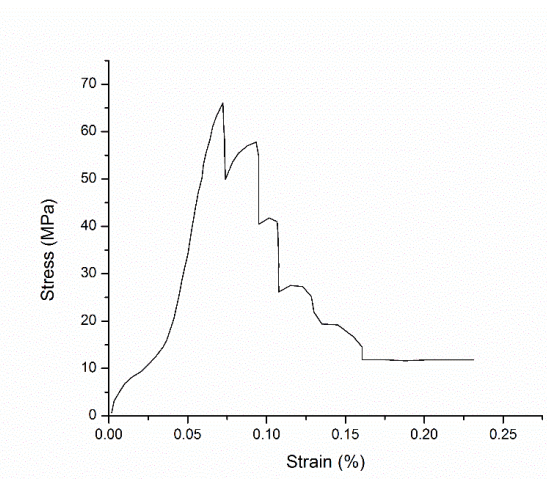

Figure 8: Stress-strain curve of fabricated stent.

Scanning electron microscopy

Figure 9 indicates the scanning electron microscopy of the welded connections of 316L stainless steel used in the structure of the fabricated stent. As can be seen in SEM 100x, two 316L stainless steel thin wires connected to each other perfectly and other images show the welded point without any crack and defect. The whole microstructure of wires remains without any unnecessary deformation and just the welding process is carried out to the connection point of the wires. Because of this perfect welded point, the tensile strength of the whole fabricated stent was greater than the tensile strength of the commercial stent.

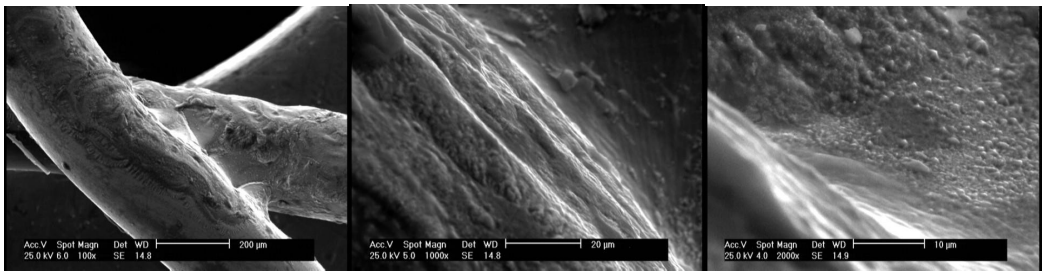

Figure 9: SEM scanning electron microscopy of laser welded 316L stainless steel wires.

Metallography

Figure 10 shows the metallography images of the laser welded points and not-welded parts. The structure of welded and not-welded part is similar. Hence, the laser welding process does not change the microstructure of 316L stainless steel and there is not any defect or deformation in the welded zone. Although the 316L stainless steel wires are so fine and thin, welding process does not change their microstructure because laser welding process time is so short and concentration of high-temperature occurs in the very small part of the wire. Hence, this high temperature can decrease rapidly according to the conductivity of stainless steel. In another hand, some black lines can be seen in taken pictures that these are tracks which are created during mechanical polishing.

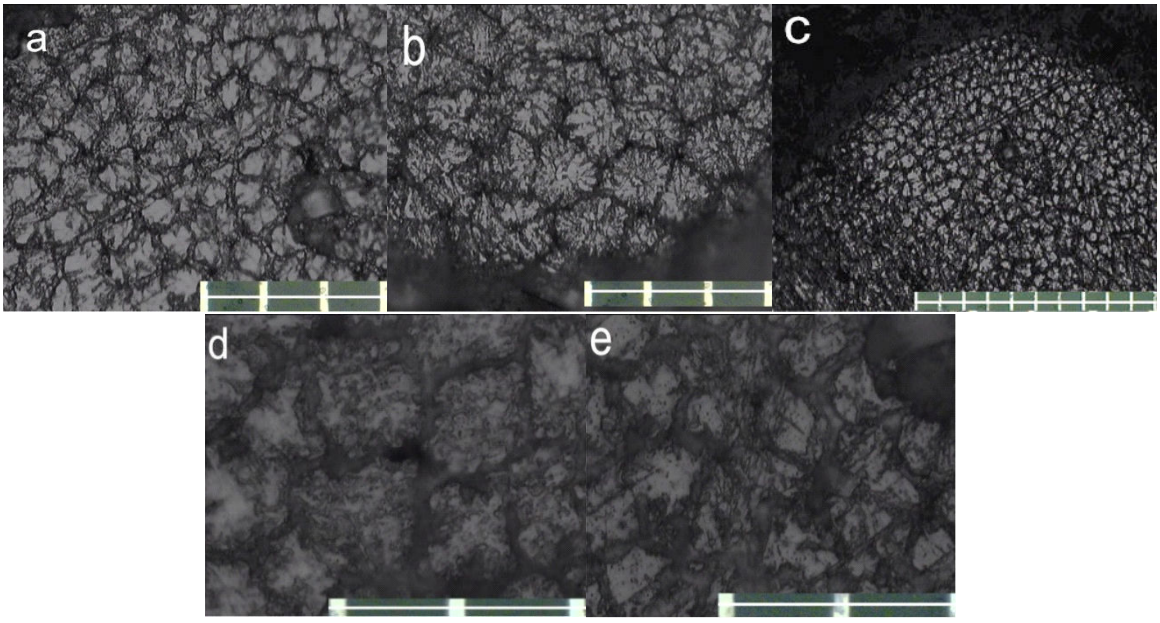

Figure 10: Images of (a) welded point with magnification 500x, (b) not-welded part of wire with magnification 500x, (c) welded point with magnification 200x, (d) welded point with magnification 200x, (e) welded part of wire with magnification 1000x.

Analysis of drug release by Ultraviolet-Visual Spectrum (UV-Vis) spectrophotometer

Figure 11 shows UV-Vis of paclitaxel, PLGA, and paclitaxel-PLGA. As can be seen, there is a peak in UV-Vis of PLGA in wave length range of 220 to 240 nm and there is a peak with same range in UV-Vis of paclitaxel too. Hence, this range of wave length can not be used for absorbance measurements of drug release from coated stent. In spite of that, there is another peak in the wavelength of 280 nm in UV-Vis of paclitaxel curve. According to the UV-Vis of paclitaxel-PLGA curve, the peak of 280 nm can be used for absorbance measurements of drug release because of this specific peak that exists just in paclitaxel curve. Hence, the absorbance intensity of this peak (280 nm) represents the amount of drug release in solution.

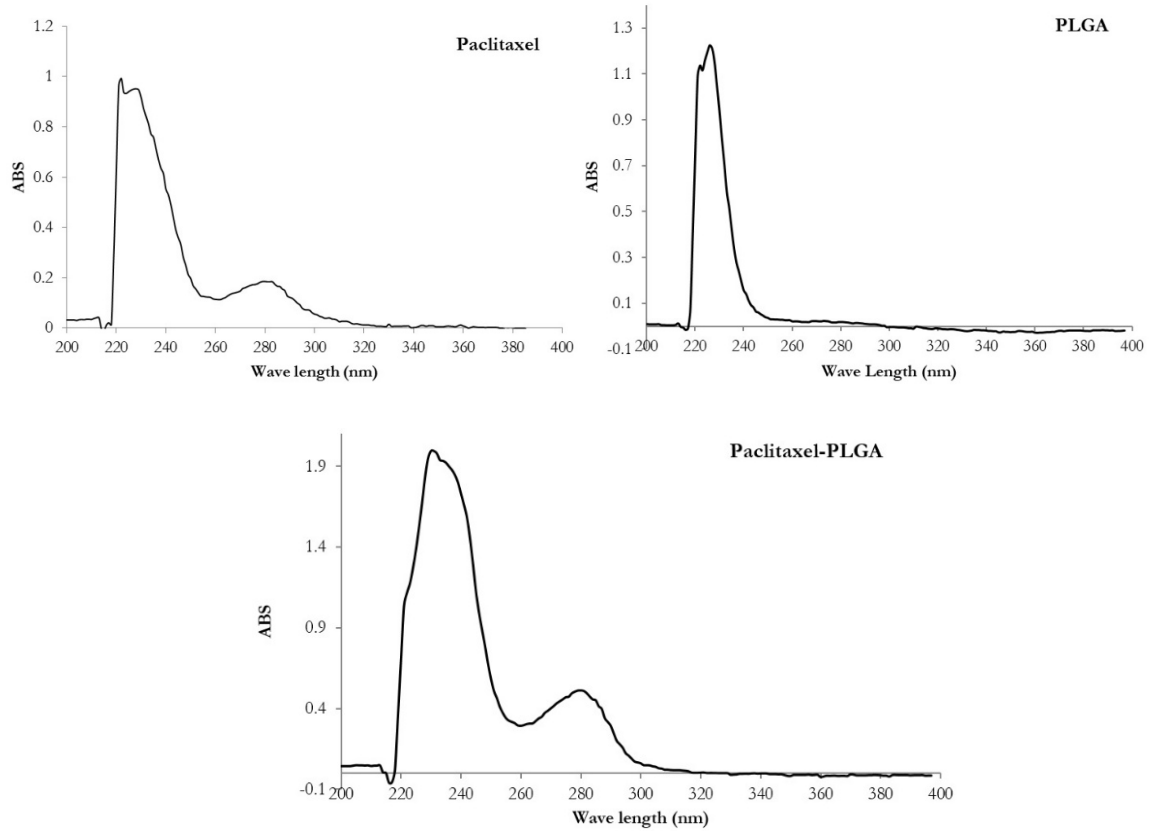

Figure 11: UV-Vis of paclitaxel, PLGA and Paclitaxel-PLGA.

Figure 12 shows the results of drug release by ultraviolet-visual spectrum (UV-Vis) spectrophotometer. The absorbance of paclitaxel released in PBS solution is measured in Figure 12 regularly. Each curve in Figure 12 belongs to a specific time. The rate of drug release is obtained by using the apexes of UV-Vis curve in the wave length of 280 nm. The obtained results of absorbance are used in Figure 13 to calculate the drug release behavior. It is obvious in Figures 12 and 13 that in early days the rate of release is high because of high concentration of paclitaxel in the coating. Then, the rate of release decreases. Actually, after day 30 the results of UV-Vis for paclitaxel don't change anymore. Hence, the test is finished in day 30 practically.

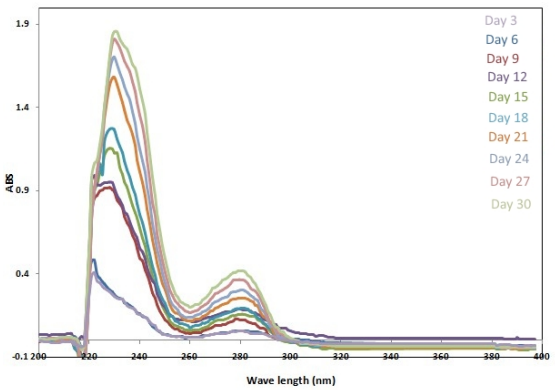

Figure 12: UV-Vis of drug release.

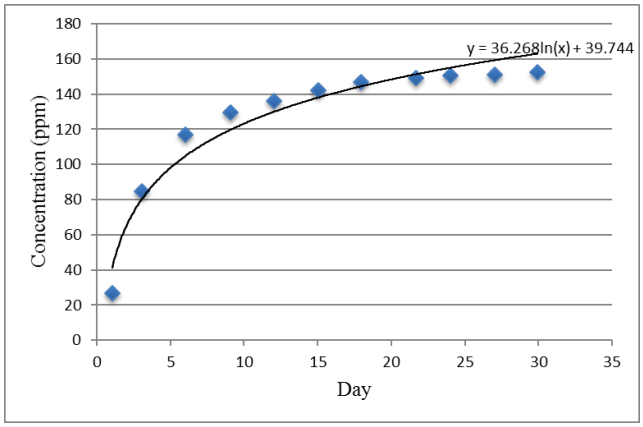

Figure 13: Drug release curve.

Fourier Transform Infrared (FTIR)

The chemical structure of paclitaxel-loaded PLGA coatings is studied by FTIR. Figure 14 shows the spectra of PLGA and the peaks around 3503 cm^{-1} (O-H), 2974 cm^{-1} (C-H) and 1756 cm^{-1} (C=O) are detected. In FTIR spectra of paclitaxel it can be seen that the absorption peaks of 3470 cm^{-1}, 2940 cm^{-1}, 1650 cm^{-1} and 1060 cm^{-1} are attributed to hydroxyl stretch vibration, methyl stretch vibration, carbon-carbon double bonding stretch vibration and fluorocarbon bonding vibration, respectively. After the loading of paclitaxel into the PLGA polymer, the coating preserves all of the peaks of paclitaxel and PLGA. These results indicate that blended paclitaxel in the PLGA polymer still keeps its chemical stability. Indeed, no chemical reactions are observed between PLGA and paclitaxel.

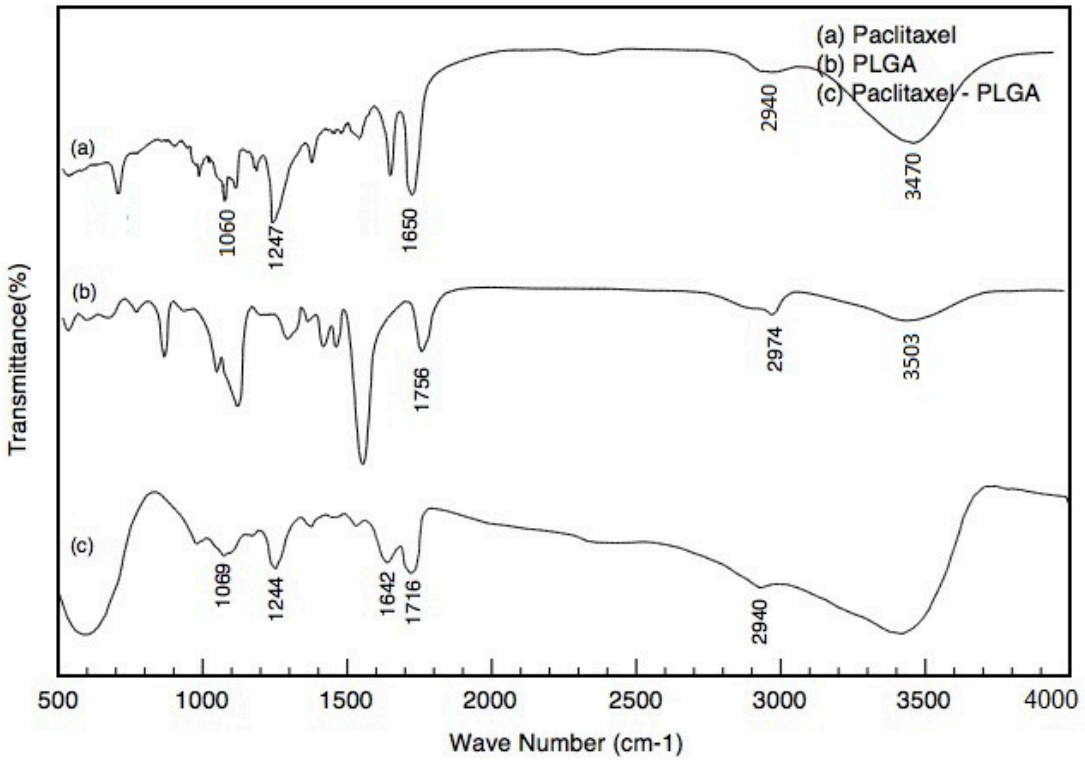

Figure 14: FTIR of (a) paclitaxel, (b) PLGA and (c) paclitaxel-PLGA.

Atomic Force Microscopy (AFM) of coated stent

Topography analysis of surface is very imperative in implanted devices, especially in cardiovascular stents. Figure 15a shows the topography of stent surface before putting the coated stent on phosphate buffer saline solution. As can be seen, the surface of the coated stent is very soft and smooth and the height of the highest point is 500 μm. As a result, the topography of the coated stent surface after releasing the drug (after 30 days) is very different. Indeed, the surface after release is very rough. The height of the highest point in the analyzed area is 800 μm and physical structure of the surface is totally changed.

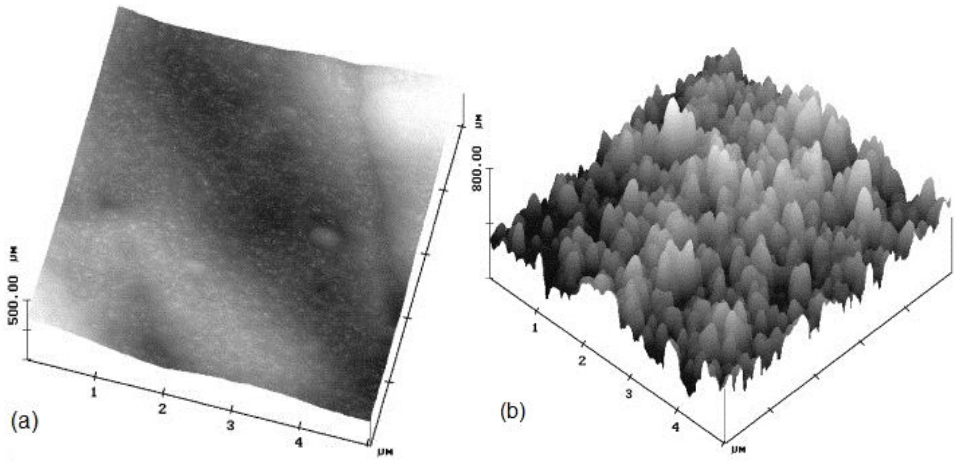

Figure 15: Surface topography of the coated stent (a) before and (b) after drug release.

Conclusion

A new method of stent fabrication is introduced and is well done by laser welding in this paper. Accuracy and high production rate are two advantages of this method. Scanning electron microscopy and metallography of bare stent proved the perfect welded joints in stent structure and showed a relative uniform welding with no crack and no exfoliation. Furthermore, tensile and microhardness tests showed the high quality of mechanical properties of fabricated welded points compared to the commercial stent. Also, atomic force microscopy demonstrated the alteration of the surface micro structure after drug release. In addition, AFM showed beyond doubt the result of paclitaxel release from the surface of the paclitaxel-PLGA coated stent. In another hand, the behavior of drug released obtained by using the UV-Vis method. Additionally, FTIR used to prove that there is not any chemical reaction between PLGA and paclitaxel.

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