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РАЗРАБОТВАНЕ НА ПОЛИМЕРНИ ОПЛЕТЕНИ СТЕНТОВЕ

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DEVELOPMENT OF POLYMERIC BRAIDED STENTS

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Metallic stents have been largely used over the last decades to treat vascular diseases like coronary artery or peripheral vessel stenosis. Although they remain the gold standard for vascular treatment, they are subjected to in-vivo complications such as corrosion, structural failure, fractures, and re-stenosis due especially to the material which is used. Polymeric stents were developed as an alternative to replace commercial metallic ones presenting several failures caused especially by the used metals. Among those materials, the polyethylene terephthalate (PET) have been used to develop stents since PET is suitable for several biomedical uses such as vascular prosthesis. Braiding technique was used since it provides flexible structures. In this paper methods and materials for the development and characterization of PET braided stents were given and the main results were highlighted. Results bring out that PET braided stents show very promising structural and mechanical performances comparing to metallic stents. They guarantee in particular a good flexibility and stability to cyclic loadings predicting their long term behavior. As a conclusion, PET-braided vascular stents show a huge potential to replace commercial stents but their manufacturing parameters should be carefully chosen.

Keywords: Polymeric stents, non-biodegradable, PET, braiding.

Introduction

Despite advances in cardiovascular stent materials and designs to decrease post-deployment complications, starting from the "Wallstent" implanted in 1986 (1) until today, problems such as corrosion, structural failure and fractures causing inflammation, early thrombosis and in-stent re-stenosis are still existing '(2),(3),(4),(5),(6),(7).

These complications are mainly due to the metallic material used as well as to the structure itself, more precisely, to a poor tolerance of the organism to their long-term presence, to an excessive rigidity causing a high mechanical stress on the vessel wall, to a lack of flexibility especially in tortuous arteries or to a low resistance to fatigue caused by in-vivo cyclic displacements due to the blood flow, etc. For this, stents are classified by the European authorities as the most implantable medical devices showing important risks of local and general complications after implantation.

Research is advancing on all fronts, especially towards the use of other materials. Among the solutions that could be promising in reducing complications related to commercial stents, several research groups developed and characterized polymeric vascular stents, braided or knitted, using non-biodegradable polymers such as polyethylene terephthalate (PET), polypropylene (PP), polyurethane (PUR), polyamide (PA), etc. (6) (8) (9) (10) (11) (12). From the results, PET-braided stents are found to be the best candidates to replace metallic stents.

This study gives a review about polymeric non-biodegradable stents, and then summarizes and discusses the main findings about PET-braided vascular stents.

Materials and Methods

A literature review was performed in order to compare between findings of the different studies held about non-biodegradable polymeric stents. First of all, we should point on the main problems encountered with commercial stents.

Weaknesses of commercial stents

Bare metallic stents (BMS) have been largely used over the last decades to treat successfully vascular diseases like stenosis. Generally, 316L stainless steel and Nitinol Ni-Ti alloy stents are the most common commercial ones. 316L stainless steel is used because it is cheap and easily processed (13) and Nitinol is well known for its shape memory effect and flexibility which is 10 to 20 times greater than stainless steel '(2).

Although metallic stents remain the gold standard for vascular treatment, they are subjected to chemical and mechanical fatigue inducing in-vivo complications after a certain time of implantation. Studies have proved the possibility of immunologic reactions of the host tissues to the significant release of metallic ions (5) (14) . Corrosion, fretting wear and fracture have been also found in metallic stents (14). In fact, due to in vivo cyclic displacements, some Nitinol self expanding stents showed fracture occurrences of up to 50% after one year especially on the superficial femoral artery (4). Moreover, deformations have been observed in stainless steel stents due to the lack of flexibility '(2).

Metallic Drug Eluting Stents (DES) were then developed in order to reduce early in-stent restenosis rates found in BMS. However, they have shown increased stent thrombosis and endothelial dysfunction when compared with BMS (15). Also, they could delay healing of the vascular wall, which have raised concerns about the long-term safety (16).

Currently, bioresorbable stents are under development to reduce complications of previous stents. Bioresorbable polymeric stents (BRS) (15) and biodegradable

magnesium alloy stents (BMgS) were developed, with the idea that they would gradually disappear after providing healing of the arterial wall. Multiple clinical trials confirmed an increased rate of thrombosis and myocardial infarctions with BRS (17) (18). Observations report that BRS problems may be partially explained by relatively weak bioresorbable polymer material, low radial strength leading to strut disruption (17), asymmetric material degradation from local stress concentration and microstructural damage from stent crimping and implantation. Magnesium alloys offer superior mechanical properties and uniform degradation behavior to polymeric materials. However, they are prone to the same asymmetric strains and degradation introduced by crimp(18).

Towards non-biodegradable polymeric stents

Several research studies have been carried out with the aim of avoiding the complications encountered with commercial vascular stents in use today. According to the literature, the development of non-biodegradable polymeric stents is one of the most promising avenues. Indeed, synthetic non-biodegradable polymers used for medical purposes have proven their effectiveness in various medical applications (vascular prosthesis, sutures, artificial ligaments, etc.) thanks to their interesting properties, namely good biocompatibility, the possibility of modifying their composition and their physical and mechanical properties, their low friction coefficients, the possibility of modifying their surface chemically or physically, etc. Furthermore, they do not cause carcinogenicity, immunogenicity, teratogenicity or toxicity. In addition, polymers are less rigid than metallic materials, which would limit the long-term stress exerted on the vessel wall, and consequently reduce the risk of restenosis.

In this axis, several research groups have studied the potential of non-biodegradable polymeric stents, braided or knitted, in polyethylene terephthalate (PET) (6) (8) (9) (10) (19), in polypropylene (PP) (6) (11), polyurethane (PUR)(12) "(20) and polyamide PA (6). These studies are summarized in Table 1.

Table 1. Studies reporting the development of non-biodegradable polymeric vascular stents.

Authors	Year	Material and technique used
Van der Giessen et al. (8)	1992	PET- braided stent for coronary arteries.
Irsale and Adanur (9)	2006	PET- braided stents, tubular for the coronary arteries and bifurcated for the aneurysm.
Yuksekkaya and Adanur (10)	2009	PET- braided stents.
Schreiber et al. (12)	2010	PUR-braided stent.
Freitas et al. (11)	2010	PP braided and knitted stents for coronary arteries.
Singh and Wang **(20)**	2015	Knitted stent composed of elastic parts in PUR and rigid parts in PET.
Rebelo et al. (6)	2015	PET, PA and PP braided stents for coronary arteries.
Jaziri et al. (19)	2019	PET-braided stents for peripheral arteries.

After the analysis of results described by these studies, we can conclude that braiding technique and PET polymer are the most suitable to develop non-biodegradable vascular stents. In fact, braided stents had the best results in terms of dimensional stability, lateral strength and recovery of the original shape than knitted stents (11). In addition, the most significant disadvantage of knitted stents is the difficulty of their removal from the human body. When placed in an organ, it is difficult to bend and remove the dilated knitted stent (21). Singh and Wang "(20) also developed a knitted stent composed of elastic parts in PUR and rigid parts in PET in order to improve their mechanical behavior. However, the problem detected when using PUR is that it has shown phenomena that should be minimized, namely relaxation and creep stresses. Also, because of its mechanical properties much lower than those of Nitinol, PUR must be used with thicker fibers (6). Rebelo et al. (6) demonstrated that PET braided stent showed better mechanical performances than PA and PP stents, comparable to those of commercial Nitinol stents.

For all these reasons, we will focus on the materials and methods used to develop and characterize PET-braided stents.

Development of PET-braided vascular stents

The objective is to develop PET braided vascular stents able to replace metallic stents in use today and able to maintain the integrity of their structure and physical and mechanical properties in short and long term.

Braided stents were manufactured using a vertical or horizontal braiding machine. The possible braiding parameters to vary in order to obtain the ideal stent design are the wire (monofilament) diameter, the stent internal diameter (or more precisely the mandrel diameter which is a cylindrical support for the produced braid), the braiding angle, the braiding pattern and the number of wires in the braid. After braiding, PET stents should be stabilized in a heat-setting machine in order to fix the filament helical geometry in the stent.

In this work, PET monofilaments (TROFIL®, MONOFIL-TECHNIK GmbH, Germany) were used to develop polymeric braided stents. Stents were braided with a 24-carriers horizontal braiding machine (Steeger HS100/24, Steeger GmbH, Wuppertal, Germany) using cylindrical mandrels as a support for the braided structures. In order to obtain stable structures, the stents were stabilized in a dry-heat stenter (Heraeus UT6120, Geminibv, Netherlands) at 180C during 75 min. All the braided stents are open loop stents (Figure 1(A)). 2.1.2.

Various parameters were considered in the design of the stents for comparison and optimization purpose: (1) braiding angle: defined as the angle α between the braid axis and the monofilament axis (Figure 1(B)) (2) filament crossing pattern, (3) stent diameter, and (4) filament diameter. Two braiding angle ranges were taken into account: low (between 30 and 40) and high (between 50 and 60). These ranges are not defined more precisely here because the final braiding angle after the relaxation of the braid varies. In fact, open braided structures (with very low cover factor) can have a wide range of stable relaxed states, represented as pairs of diameter and braiding angle.

Any axial force leads to change of the angle in the structure.25 During the manufacturing, the braiding angle is adjusted by the control of the relation between the mandrel diameter, the rotation speed of the horn gears and the braiding velocity. In the current case, the take-off velocity was set between 0.8 mm/s and 1 mm/s in order to obtain angle values between 45 and 65, which are standard values in the field of stents.

However, this limitation did not prevent the interpretation of the results as the differences regarding the stent behavior were significant between the two angle ranges.

Regarding the braiding pattern, two interlacements were compared: a more rigid one (diamond [1:1–2]) and a more flexible one (regular [2:2–1]), both represented in (Figure 1(B), (C)). Actually, the overall rigidity of a stent influences the movement between neighbor filaments and is expected to affect the fatigue and friction properties in the structure. Plain pattern (1:1–1) (simple 1/1 wire crossing) was excluded from the study because its production, for the same number of filaments as the other samples, would require double larger braiding machine with 48 carriers, arranged in 1 full – 3 empty arrangement (partial occupation). Such machine was not available in the laboratory. The preliminary tests with 12 wires in plain pattern led to too loose braids if the same mandrel diameter was used. In order to take various anatomic con- figurations into account, three mandrel diameters (stent's internal diameters) were considered (6, 10, and 14 mm).

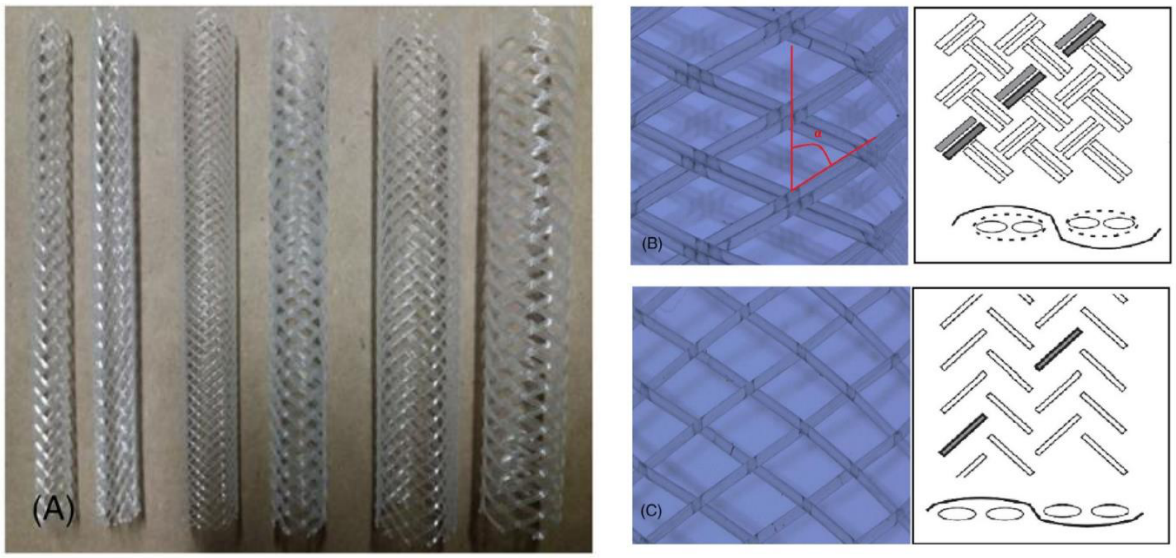

Figure 1. (A) Some developed stents (B) “Diamond 1: 1-2” braiding pattern (C) “Regular 2: 2-1” braiding pattern

Evaluation of stents key performances

In order to compete with commercial stents, PET-braided stents should meet certain criteria. They should have the capacity to support the arterial wall while avoiding all the risks and complications encountered with commercial stents. In fact they have to be enough flexible, elastic, resistant to radial and longitudinal compression and fairly stable structurally and mechanically over the whole period of its implantation. Table 2 summarizes the key performances to be assessed.

Table 2. Stents main performances and their in-vitro assessment methods.

Studied performance	Measurement method	Measured characteristic
Ability to adapt to the anatomy of the implantation site and uniformity of the stent	Cover factor calculation (6)	Cover factor
Flexibility	3 points bending test, (*ASTM F2606-08*)	Bending force Bending stiffness
	Measurement of the bending diameter (6)	Percentage of unchanged bending diameter
Crush resistance	Compression between parallel plates test (*ISO 25539-2:2012)*	Lateral compression force
Resistance to longitudinal compression	Longitudinal compression test (22)	Longitudinal compression force
Elongation	Longitudinal elongation test (22)	Elongation Longitudinal rigidity
Resistance to radial compression	Static and dynamic radial compression tests *(ASTM F3067 – 14)*	Static and dynamic maximal radial forces Percentage of radial force change after dynamic compression Percentage of the diameter's elastic recovery
Fatigue resistance	Accelerated fatigue test	Percentage of radial force loss after fatigue Percentage of the diameter's elastic recovery after fatigue

The cover factor $CF_{\%}$ of a vascular stent is defined as the ratio between the stent area covered by the material used and the total stent area (6) (23). In other words, it is the amount of fibrous material deposited on the surface of the mandrel during the braiding operation. Vascular stents should have a cover factor between 20 and 30 % (i.e., porosity of approximately 70-80 %) (24) (25) to minimize surface thrombosis (26). The $CF_{\%}$ is calculated as follows:

$$\mathbf{CF\%} = [\,\mathbf{1} - \left(\mathbf{1} - \frac{\mathbf{\emptyset_f\ N}}{\mathbf{2\pi\ \emptyset_s\ cos\alpha}}\right)^{\mathbf{2}}\,] \times \mathbf{100} \qquad \textbf{Eq.1}$$

With:

$Ø_f$: Monofilament diameter (mm) ; N : Number of wires ; α : Braiding angle (°) : It represents the angle between the wires and the longitudinal axis of the braided structure (6) and measured by image processing (*Fig.2*).

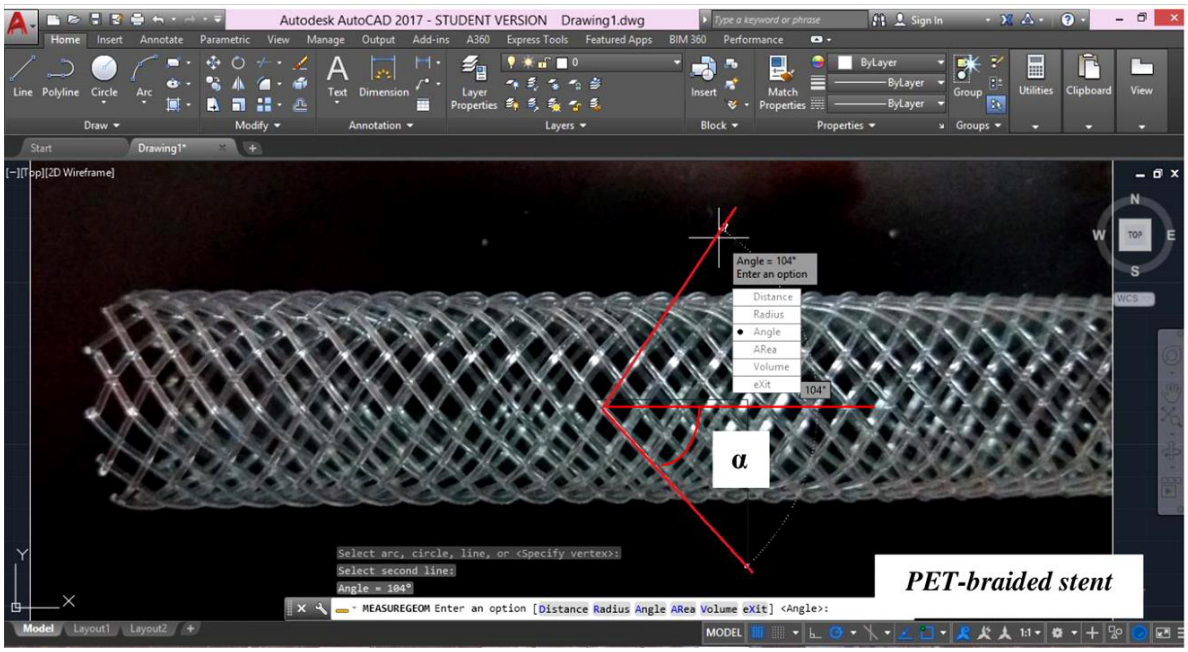

Fig. 2. PET-braided stent showing the braiding angle α.

Flexibility is one of the main performances for vascular stents since they could be subjected to bending actions, especially when implanted in the peripheral arteries (27) (28) (29). For this, they must show a minimum bending stiffness which is measured via a three-point bending test (*ASTM F2606-08*) (*Fig.3.A)*, and they must have the ability to maintain at least 75% of the original diameter when flexed (6) (30). For that, the percentage of the unchanged bending diameter is calculated as the ratio between the diameter at the midpoint of the bent section (*Fig.3.B)* and the initial stent diameter.

The lateral compression strength should be sufficient to prevent the stent crush after implantation, so in order to measure it, a lateral compression between plates test is performed (*ISO 25539-2:2012)* (*Fig.3.C)*. In addition, stents should be resistant to longitudinal compression otherwise they will be easily compressed at their ends and should be elastic enough. For purpose, longitudinal compression and extension tests were performed according to recommendations of *"GoreMedical®"(22)* (*Fig.3.D.E)*.

Additionally, the radial compression behavior should be assessed in particular the radial force and the diameter's elastic recovery. In fact, the radial force is the load the stent can sustain before permanent deformation occurs or the stent is completely destroyed (13). Furthermore, every stent should recover 100% of its initial diameter after radial loading. For those reasons, a radial compression test using a dedicated radial compression machine is performed *(ASTM F3067 – 14)* (*Fig.3.F)*. The long term behavior of PET-braided stents could be predicted by performing a dynamic radial compression test and an in-vitro axial fatigue test (*Fig.3.F.G)*.

Fig. 3. Characterization methods: (A) Three points bending test (B) Unchanged bending diameter measurement (C) Parallel plates compression test (D) longitudinal compression test (E) Elongation test (F) radial compression test (G) Accelerated fatigue test.

Results and Discussion

All studies about PET-braided stents have demonstrated the huge influence of the braiding parameters on the stents performances(6)(9)(10)(19)"(31). The cover factor of PET-braided stents is an important parameter that must be taken into account when designing the stent (10) and could be in the same range as the metallic braided stents if the braiding parameters were chosen correctly(6)(19). Jaziri et al. (19), developed a PET stent having a cover factor of 35 %, larger than what is obtained for a metallic braid (20%) used as reference in order to have similar radial strength. Actually, polymer material being less stiff than Nitinol, it is necessary to increase the quantity of material involved in the braid to obtain a similar radial strength. For that purpose it is necessary to increase either the diameter of the filaments involved in the braid or the number or filaments over the circumference, or the braid angle which all contribute to increasing the cover factor.

Regarding the bending behavior of PET-braided stents, bending stiffness can be between 10 and 20 times less stiff than Nitinol braided metallic stents. With respect to the

bending diameters, different PET-braided stents were characterized by values around 95% of the nominal diameter (above the 75% minimum expected for commercial peripheral stents)(19).

Lateral and longitudinal compression forces are highly dependent on manufacturing parameters. Furthermore, the braiding angle has been found to be the braiding parameter which directly influences the mechanical properties of the developed braids (6) (9) "(31). Stents with a higher braiding angle are more resistant to lateral compression. For higher braiding angles, the wires are deposited more and more towards the transverse axis, resulting in greater resistance to transverse forces acting during lateral compression "(31). In addition, a higher braiding angle also improved the cover factor and compactness of the stent resulting in a higher resistance to lateral forces (6). In addition, stents with larger monofilament diameter have a higher longitudinal compression force due to their high flexural rigidity, as in longitudinal compression stents are also subjected to flexion and buckling (6). Also, stents with higher elongation showed lower longitudinal rigidity "(31).

Comparing with commercial Nitinol stents (22), developed PET stent show lateral and longitudinal compression forces and percentage of elongation in the same range of commercial stents and even higher in some cases "(31).

All of the previously mentioned studies have investigated the structural and mechanical properties of developed PET stents only in a static state, which can predict their behavior only in the short term (during and immediately after implantation). However, the investigation of the PET-braided stents behavior under cyclic loadings, in particular their behavior to dynamic radial compression and to in-vitro fatigue, have been reported only with Jaziri et al. (19) (32). Results of cyclic radial compression tests showed that the PET-braided stents present a 100% elastic recovery after 20 % diameter compression over 2000 repetitive loading cycles despite the friction that occurs in the braid. Regarding the radial force, it is highly influenced by the stent design and the braiding angle in particular. Furthermore, it came out that radial strength remains stable after long term repeated fatigue stress up to 100.000 cycles with no wire breakage. Compared to metallic braided stents, it was observed that polymeric stents are more flexible and less subjected to inter-wire wear due to friction(32).

Conclusion

This study demonstrates that PET braided stents have the potential to mimic the mechanical performance of commercial metallic stents, if all of their design and manufacturing parameters are carefully chosen. In fact, the combination between PET and braiding could guarantee flexibility and radial strength at the same time. PET admits a low stiffness compared to metals (elastic modulus of PET of 2500 MPa against 80 GPa for Nitinol), and it is widely used in medical applications because of its interesting characteristics. Braiding technique can increase the flexibility of stents, especially in mobile environments such as the superficial femoral artery (SFA) and could limit the crushing of stents in a tortuous implantation environment, or what is called as the "kinking phenomenon". This could be a promising solution especially in the stenting of peripheral arteries which remains a challenging surgical procedure. Further work is now necessary to determine the most suitable stent design and further animal tests are important in the next step in order to assess in-vivo long term behavior of these devices.

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