POLITECNICO MILANO 1863

SCUOLA DI INGEGNERIA INDUSTRIALE E DELL'INFORMAZIONE

EXECUTIVE SUMMARY OF THE THESIS

Hydraulic bulge test for the mechanical characterization of uncoated and drug-coated polymeric materials constituting angioplasty balloons

MASTER'S THESIS IN BIOMEDICAL ENGINEERING

AUTHORS: MARTINA FERRARI (968652) – ELENA FOMIATTI (969181)

ADVISOR: PROF. PASQUALE VENA

CO-ADVISORS: ENG. LUCA D'ANDREA, ENG. DEEPTHISHRE GUNASHEKAR

ACADEMIC YEAR: 2021-2022

1. Introduction

Peripheral Artery Disease (PAD) is a pathologic condition that leads to the obstruction of vessels responsible for transporting blood from the heart to the body's extremities. The use of angioplasty balloons is a valuable treatment option for PAD as they allow for vessel dilation without leaving behind foreign material, unlike stenting. However, the pressure exerted on the arterial wall during the procedure can cause scar tissue to form, leading to restenosis of the treated vessel. To avoid that, drug-coated balloons (DCB) could be a solution. DCBs are angioplasty balloons coated with an antiproliferative therapeutic drug and an excipient (drug carrier) [1]. They reduce the complications of in-stent restenosis and late thrombosis associated with stent implantation by providing a high dosage of the drug to the vessel.

Currently, angioplasty balloons are manufactured using polyethylene (PE), polyethylene terephthalate (PET), Nylon (polyamide), and poly(ether-block-amide) (Pebax®). The coating process involves applying a solution of excipient and drug on the polymeric substrate, employing various techniques, including spray-coating and micropipette-coating. The commonly used excipients are polysorbate, poly(ethylene oxide) (PEO), and polyethylene glycol (PEG); while frequently used drugs are Paclitaxel (PTX), Everolimus and Zotarolimus [2].

The major limitation of current DCBs is the lack of effective drug delivery control, which can result in low therapeutic levels and drug loss. To address this issue, it is important to evaluate the multi-axial mechanical response of the balloon material and drug coating. The aim of this study is to investigate the mechanical properties of the polymer substrates and to assess the mechanical integrity of the excipient layer and of the excipient-drug system upon straining the underlying substrates. These purposes are achieved through in-situ mechanical testing, i.e. uniaxial and multiaxial (bulge test) straining. The bulge test and the simultaneous use of confocal laser microscopy allow for the extraction of information about the inflation of the tested samples at different levels of pressure.

Experimental data are complemented with finite element (FE) models of the bulge tests. The FE analysis is created using the mechanical properties obtained from the uniaxial tensile tests. The FE models allow for determining strain distribution over the bulged membranes and for identifying critical strain at which coating failure occurs.

2. Materials and methods

2.1. Material samples

Mechanical tests are conducted on uncoated (polymeric substrate only) and coated samples. Uncoated specimens are of two types, including thin films and unfolded/folded balloons. Commercially available Nybax and polyamide balloons are provided by Boston Scientific and L2Mtech, respectively, while Montpellier University provides the heat-pressed Pebax® thin films. The confocal laser microscope (LEXT OLS4100, Olympus®) is employed to measure the thickness of the samples. Knowing the refractive indices of the different materials (1.51 for Pebax® and 1.53 for Nylon), the laser beam identifies the thickness of the layers of the sample.
Furthermore, Montpellier University provides coated samples, including those with excipient (Pluronic 123) only and those with both excipient and drug (Everolimus), prepared using spray and micropipette techniques.

2.2. Uniaxial tensile test

The uniaxial tensile test is performed using the micro-biaxial machine (μBTM) in a uniaxial configuration, described in details in [3]. The sample is cut into a rectangular shape with a dimension of 7×23 mm and glued on the cantilever for a length of 5 mm on each side. The specimens are subjected to a displacement rate of 0.01 mm/sec and tested along both the circumferential and axial directions to investigate the material's anisotropy.

2.2.1 Experimental data analysis

The force-displacement data obtained from the uniaxial tensile tests are processed by discarding values below a given cut-off threshold (0.1 N), as the samples exhibited wrinkling in the initial configuration. Engineering stresses and strains are then computed and used for theoretical analysis of the material behavior. An error minimization approach is used to match the experimental stress-strain curve with the predicted analytical model, determining values for C_1, C_2, and C_3. Specifically, the Yeoh hyperelastic model ($Eq. 1$) is selected to describe the behavior of the balloons, while the elastoplastic model with von Mises yield function is chosen for the Pebax® films.

$$\Psi = C_1(I-3) + C_2(I-3)^2 + C_3(I-3)^3 \quad (Eq. 1)$$

2.3. Bulge test

The bulge test is an inflation test performed using a pressure delivery system and a bulge test device. In this study, a 5 mm circular-shaped balloon sample is bonded through double-sided tapes to a metal cap, which has a circular window in the center exposing the material to loading. A differential hydraulic pressure is applied from below using a manual pump filled with water. The sample is analyzed using the LEXT to determine the out-of-plane displacement field caused by the inflation of the membrane.
The acquisitions are performed with a 20x lens, characterized by a working distance of 1mm and a field of view (FOV) of 640μm. Since the FOV is insufficient to capture the behavior of the whole material's surface, a stitching procedure is performed. This process consists in acquiring and merging different images with the aim of having one larger single image with the same resolution of the single ones. The stitching is performed on a 4×4 matrix at the first acquisition, while the subsequential acquisitions are made on a 2×2 matrix to focalize on the center of the material and to reduce acquisition time. In conclusion, considering a 10% overlapping of single images, the acquired balloon's surface has a size of 2.35×2.35 mm. The pressure is increased with each acquisition by 1 atm, starting from 1 atm to a maximum of 14 atm. Before each acquisition, a 3 minutes holding time is applied with the purpose to dissipate viscoelastic phenomena. As sample inflation increase, acquisition time increases as well. The result of this process is a 3D profilometry of the material surface at each level of pressure.

2.3.1 Experimental data analysis

The data extracted from the microscope at each pressure level consist of a cloud of points. Each point represents the vertical displacement (z), and it is characterized by its two spatial coordinates (x and y). By the implementation of a proper MATLAB 2022® code, the cloud representing the displacements is fitted with a square grid, defined by 101x101 nodes, using the function `gridfit`.

For each (x,y) point, the 2×2 curvature matrix, containing the second-order derivatives in x and y and the mixed derivatives, is calculated.
Values for the maximum vertical displacement and, at the same point, the principal curvatures are then extrapolated for each pressure level. Since the configuration obtained at 1 atm is considered as the reference, for each pressure value, the vertical displacement is calculated by subtracting from the maximum displacement the one achieved with the first acquisition:

$$\Delta z_{pi} = z_{pi} - z_{p0}$$

where *i* ranges from the first pressure increment to the last one reached.
Regarding the curvatures, the degree of anisotropy (DA) is calculated for each pressure increment [4]:

$$DA_i = \frac{C_{max} - C_{min}}{C_{min}}\Big|_i \qquad \text{(Eq. 2)}$$

where C_{max} and C_{min} are the maximum and minimum eigenvalues of the curvature matrix, respectively. DA turns out to be zero in the case of an isotropic behavior, resulting in a deformed configuration characterized by circular contour lines. On the contrary, the higher DA values denotes an anisotropic response of the membrane.

2.5. Finite element modeling of the bulge test

To realistically reproduce the experiment, a finite element model is implemented in ABAQUS/Standard. The simulation includes two components: the balloon sample and the metal cap of the device. Due to the geometry and isotropic behavior of the examined material, an axisymmetric assumption is made. A circular plate (r=3.5 mm) and a circular bulge window (r=1 mm) are used to recreate the shape. The polymeric sample (r= 2.5mm), which is a deformable solid, is meshed with 3354 quadratic axi-symmetric quadrilateral elements of type CAX8. The material assigned to the metal cap is steel, with a Young Modulus E = 200 GPa and a Poisson's ratio υ = 0.25. To describe Nybax and polyamide balloons, the polymeric sample is characterized by a hyperelastic isotropic material, described by the Yeoh constitutive model (Section 2.2.1). The Pebax® film's stress-strain curve is fitted by an elastoplastic model, setting E=300 MPa, υ=0.45 in the linear region, while σ_y= 27 MPa and perfect plasticity in the plastic region.

A surface-to-surface hard contact is set between the metal cap and the polymeric sample, with finite sliding. The metal plate is fully constrained, preventing vertical translation of the underlying polymeric sample. The specimen inside the bulge window is loaded with a uniform vertical pressure up to 1.4 MPa (i.e. 14 atm).
The simulation takes place in a single step and pressure increments of 0.1 MPa, while the outputs are stored in evenly spaced time intervals, n=14, to correlate every time step to a 0.1 MPa increment of pressure. For each simulation, the coordinates in the plane of the specimen and the vertical displacement U2 of the nodes belonging to the last layer of the mesh on the material sample are extrapolated.
Initially, simulations have been carried out using the average of material parameters obtained from uniaxial tests $(C_1^{ut}, C_2^{ut}, C_3^{ut})$. However, the analytical pressure-deflection curve did not adequately match the experimental one with these parameters. To address this, a range of variability has been defined around the initial guess $(C_1^{ut}, C_2^{ut}, C_3^{ut})$, and around 500 simulations have been performed. Each simulation reproduces a pressure-deflection curve that is then compared with the experimental one. An error minimization criterion is used to find the best combination of $C_1^{fem}, C_2^{fem}, C_3^{fem}$ that can most accurately describe the experimental curve.

3. Results and discussions

3.1. Experimental results of uniaxial tensile test

The uniaxial tensile test is performed on Nybax balloons (8 short and 8 long), and Pebax® films (6 samples) to determine the engineering stress and strain values. For the sake of simplicity and for the lacking of knowledge on the balloon material behavior upon unloading, hyperelastic constitutive modeling is assumed, furthermore, time dependence of the material is also neglected. The experimental σ-ε curve is compared with the analytical one, obtained using stress and strain computed with the Yeoh model (Figure 1).
The results obtained from the uniaxial tests on Pebax® film samples indicate that Pebax® exhibits a non-linear material response with the achievement of the maximum stress at increasing applied strain. Beyond a yield stress of approximately 27 MPa, the material undergoes

plastic deformation, with stress levels remaining relatively constant as the strain increases.

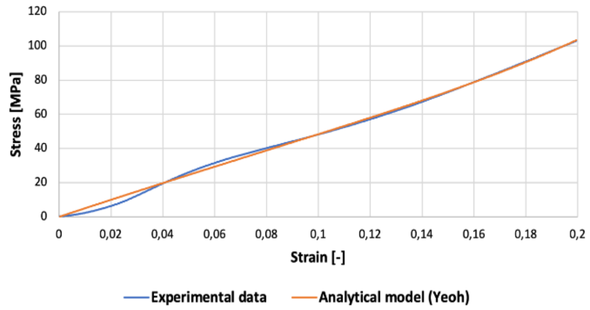

Figure 1: Comparison between the analytical σ-ε curve and the average experimental one of Nybax balloons.

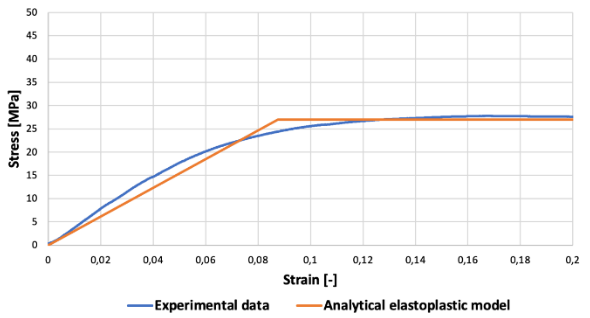

Figure 2: Comparison between the analytical σ-ε curve and the average experimental one of Pebax films.

The experimental curve is divided into two regions: a linear and a plastic region (Figure 2).
The linear part of the curve is used to estimate the Young modulus of the Pebax®. While the plastic region is characterized by a yield stress σ_y and a plastic strain ε_p. In this case, E= 300 MPa, σ_y = 27 MPa; yield stress is kept constant as plastic strain increases (perfect plasticity).
Overall, material parameters found through the uniaxial tensile tests serve as initial values to start performing finite element simulations of the bulge test on ABAQUS/Standard.
Moreover, the σ-ε curves obtained by testing the specimens along the circumferential and axial directions show similar trends, particularly for strains less than 10%, indicating the isotropic behavior of the material.

3.2. Experimental results of bulge test on uncoated samples

The bulge test is performed on 14 samples of Nybax balloons (short and long) from Boston Scientific, 7 samples of polyamide balloons from L2MTech, and 5 samples of Pebax® films from the University of Montpellier (Figure 3).

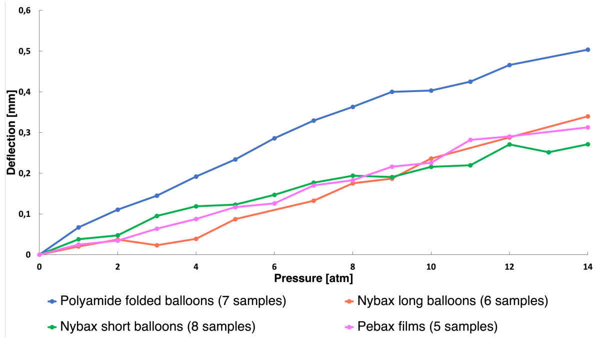

Figure 3: Average of pressure-deflection curves obtained performing the bulge test on Nybax balloons, Pebax® films, and polyamide folded balloons.

The confocal laser microscope measured a thickness of approximately 50 μm for the unfolded balloons and Pebax® films while 20 μm for the folded balloons. The inflation behavior of the Nybax and Pebax® samples are found to be similar, while the polyamide samples exhibit a higher tendency to inflate displaying greater compliance. The observed disparity in behavior could potentially be ascribed to the variation in sample thickness.
Moreover, DA is calculated for all samples at each pressure level ($Eq. 2$). The obtained values, which are less than 0.1, provide further confirmation of the isotropy of the materials.

3.3. Numerical simulation of bulge test

A range of parameters (C_1, C_2, C_3) variation is set to start the finite element simulations referring to the Yeoh analytic parameters calculated by fitting the uniaxial tensile test data for Nybax unfolded balloons. Since polyamide folded balloons are not subjected to uniaxial tensile test because of their small dimensions and stiffness, FE simulations of these samples are carried out assuming the same constitutive parameters as that of the Nybax balloons. Approximately 500 simulations are conducted for each sample type of unfolded balloons using a MATLAB® code that runs Abaqus simulations sequentially after suitable changes of input parameters. A clear correlation between alterations in a single parameter and modifications in the slope of the curve is not observed. The variation in the curve seems to be solely dependent on the joint influence of the three factors.
For each FE pressure-deflection curve and the corresponding experimental curve, the differential deflection function $f(z)$, with respect to the reference state at 1atm, is calculated as:

$$f(z) = z_i - z(1\ atm)$$

Then, error minimization criterion is computed as:

$$e = \sqrt{\frac{\sum_i (f_i^{exp} - f_i^{FEM})^2}{14}}$$

The numerical curve that exhibits the lowest error *(e)* is selected as the most suitable fit. The Yeoh analytical parameters that correspond to this selected curve represent the behavior of the sample during the experimental bulge test. An example of the fitting is shown in Figure 4.

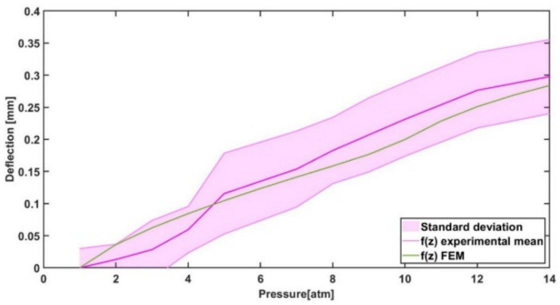

Figure 4: Yeoh analytic parameters of the fitting FE curve for Nybax balloons.

To evaluate the consistency of the findings, the inflation profile of the surfaces obtained through finite element simulations is compared with the surfaces captured by the microscope during the bulge test (Figure 5).

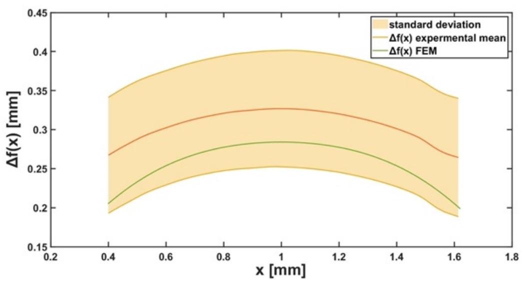

Figure 5: Comparison with FE and experimental inflation profiles for Nybax balloons.

Overall, the results obtained in this study demonstrate that the deflection profiles generated by the Finite Element method are consistent with the experimentally determined mean and standard deviation, falling within an acceptable range of error. This finding is indicative of the reliability of the numerical model in predicting the deflection behavior of the structure under consideration. As Nybax is a composite of Nylon and Pebax®, it is conceivable that the set parameters are not entirely accurate descriptions of Nylon alone. Therefore, further studies are needed for Nybax constitutive parameters identification.

The modeling of Pebax® films differs from that of balloons, as an elastic-plastic model is used. The findings of the numerical simulation fall within the same range of variation as the experimental data, suggesting that the simulation is a reasonable representation of the physical system. Nonetheless, there are certain limitations or inaccuracies in the simulation. The polymeric material reaches plasticity (σ_y = 27 MPa) before the maximum pressure of 14 atm is achieved. Consequently, the simulation is unable to evaluate the behavior of the material up to the maximum pressure. For applied pressure higher than 12 atm, necking and shear band formation occur at the point of contact between the material and the metal plate; this phenomenon cannot be verified experimentally.

In this bulge experiment, the validated FE models can be used to infer the stress and strain occurring in the central region of the patch in which a biaxial loading occurs. In particular, the homogeneity of the strain distribution in this area is relevant for studying the coating behavior.

The nominal strain variation at each pressure increment is evaluated (Figure 6).

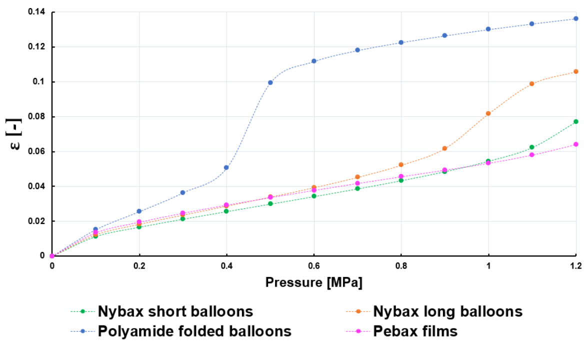

Figure 6: Nominal strain on the center of the material's surface of Nybax balloons (long and short), Pebax® films, and polyamide folded balloons.

3.4 Experimental results of bulge test on coated samples

The results of the bulge test conducted on polymer-spray-coated samples indicate that the coating remains relatively undamaged between pressures of 1 atm and 6 atm, while evidence of cracking appears at 7 atm when the strain of the underlying material reaches 4.17%. Subsequently, a considerable number of fractures becomes evident in the upcoming configurations, particularly in the final stage, where the pressure reaches 11 atm with a strain of 5.8% (Figure 7 (left)).

Polymer-micropipette-coated samples exhibited a non-uniform coating thickness (not shown). Upon subjecting the samples to the bulge test up to

14 atm, it is found that the integrity of the excipient layer remained roughly unaffected.
In the experimental investigation of the drug-polymer-coated specimens, it is observed that cracks initiate at a pressure of 4 atm. Furthermore, at a pressure of 9 atm, corresponding to a strain of the underlying material of 4.9%, the fractures open up (Figure 7 (right)).

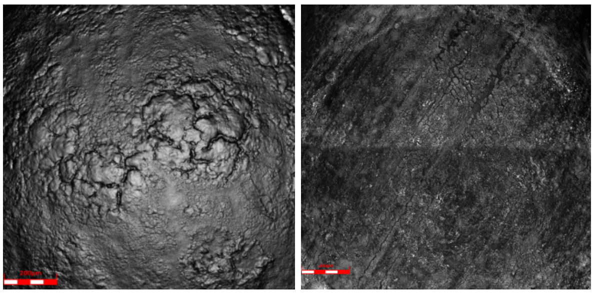

Figure 7: Fractures on polymer-spray-coated Pebax® film at 11 atm (left) and fractures on drug-spray-coated Pebax® film at 9 atm (right).

Finally, the pressure-deflection trends of both coated and uncoated samples are compared (Figure 8). It is observed that all coated samples exhibited similar trends, while the uncoated ones demonstrate lower deflection values. This unexpected result prompts further investigation to identify the possible reasons contributing to the difference. Two potential factors are identified as possible explanations: the influence of the coating on the underlying material, or a difference in the thickness of the samples.

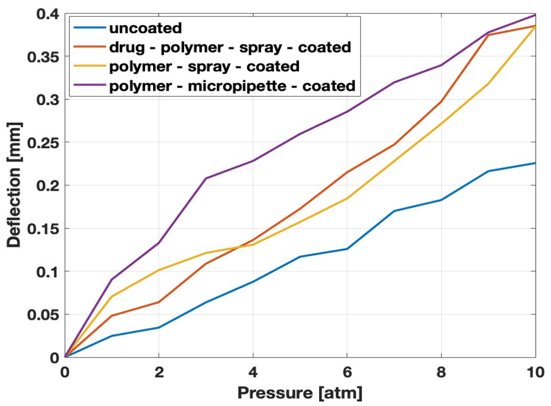

Figure 8: Mean of pressure-deflection curves obtained performing the bulge test on uncoated and coated samples.

4. Conclusions

The aim of this work was the quantitative assessment of the mechanical stability of drug coating on balloons for angioplasty for the treatment of peripheral artery disease. To this purpose, bulge tests were carried out on bare and drug-coated polymeric membranes.
A secondary objective which is needed to achieve the final aim was the mechanical characterization of polymeric membranes. The Yeoh hyperelastic model accurately captures the mechanical characteristics of Nybax and Nylon; although, establishing the relationship between the pressure-deflection curve and the value of the parameters C_1, C_2, and C_3 needs further investigation. Differently from Nybax and Nylon, Pebax® material was modeled by using the elastoplastic constitutive equations.
The nature of the coating in terms of thickness and homogeneity is verified, noting that in the micro-pipette-coated samples, the coating is much less homogeneous than in the spray-coated ones. This proves that the coating method affects its homogeneity.
Moreover, the effect of the coating on the underlying material or a difference in sample thickness can affect the sample response to multiaxial loading. This study highlighted the essential need for a method for an accurate measuring of the coating thickness.
With regard to the mechanical integrity of the coating, the experimental method used in the present study, successfully identified a critical biaxial strain range at which the coating (with and without drug) undergoes fracturing phenomena. However, in the case of micro-pipetting, this does not occur, at least in the range of pressures used in this work.

References

[1] E. Goel *et al.*, "Pre-clinical investigation of keratose as an excipient of drug-coated balloons,", 2020.

[2] G. M. Xiong *et al.*, "Materials technology in drug eluting balloons: Current and future perspectives," 2016.

[3] P. Vena *et al.*, "Design and development of a micro-biaxial stage with in situ microscopy," Politecnico di Milano, 2017.

[4] L. D'Andrea *et al.*, "Anisotropic mechanical response of bovine pericardium membrane through bulge test and in-situ confocal-laser scanning", 2022.