Activated Adhesives for Delivery of Drug Impregnated Thin Films on Vascular Tissues

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Statement of Purpose: Bioadhesive drug impregnated films attract much attention in drug delivery especially in mucosal and transdermal applications. The bioadhesiveness of the films assures a good retention at the site of injury and thus an enhancement of local drug targeting and a longer drug release as compared to direct drug administration that faces problems like low targeting and systemic elimination by the body. But very few studies were found to apply this concept on vascular tissues.

This study focuses on a novel application using bioadhesives, that is to transfer a drug impregnated thin film on vascular tissue by balloon angioplasty to reduce restenosis. The film that will wrap the angioplasty balloon will be composed of three layers: a releasing layer (that will detach from the balloon at 37°C), a drug impregnated layer (that will release an anti-inflammatory drug to the arterial wall) and a adhesive layer that will fix the entire multi layer film on the arterial wall (Fig. 1).

In this study, films made of different bioadhesive (BA) polymers were evaluated for the application aimed. The multi layer film should remain at least two weeks at the injured site to release the anti-inflammatory drug. To assess the performance of the BAs, the force of adhesion of the films was characterized using a tensile tester. The lowest dissolution rate of bioadhesive could also play an indicator to determine the most suitable bioadhesive. To attain two-week retention, it is indeed important that the bioadhesive does not wash out at an extensive rate. The rate of dissolution of these bioadhesives was assessed using light absorption measurement. The more bioadhesive dissolves, the more the solution becomes opaque and thus light absorption increases.

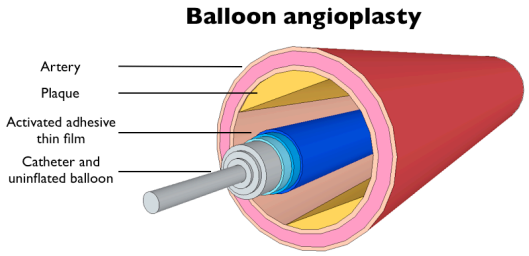

Figure 1. Schema of transfer of adhesive drug impregnated film on the arterial wall by balloon angioplasty.

Methods: BAs (971CP and NO-AA1 from Lubrizol – Ohio USA) were dissolved in distilled water and cast in films at 20 to 30 um thickness. The force required to detach the BA films from synthetic collagen was performed using an *Instron* 5667 tensile tester with a 10N cell load. The square-shape BA films were fixed on the upper movable carriage using cyanoacrylate glue, whereas the substrates were fixed on the lower movable carriage. The upper carriage was lowered down at 0.05 mm/s and a pressure of 5 N was applied between the two surfaces for 1 min. The upper carriage was then lifted up and the force required to detach the two surfaces was measured. For each type of BA, the test was performed ten times at ambient air with 200 l PBS on the synthetic collagen. Fig.2 shows a schema of the protocol experiment to test the transfer of the films. To test the adhesion force of the BAs, the releasing layer was absent.

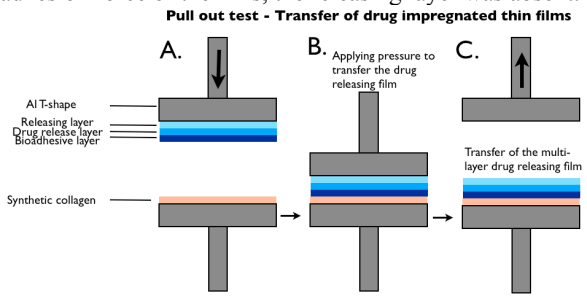

Figure 2 Protocol experiment to test the transfer of the adhesive drug impregnated thin film in vitro using a 5667 *Instron*.

For the dissolution assay, the BAs were cast at the bottom of a 96-well plate and were dried at ambient air for 1 week. 150 ul per well of different concentrations of BA forming the standard curve were placed in the same 96-well plate. The wells with dried BAss were then filled with 150 ul of PBS and the 96-well plate was immediately read at specific time points.

Results*:* The peak detachment force was measured for each BA against synthetic collagen (Fig.3 A). The BAs NO-AA1 and 971CP showed detachment force values at 0.60 and 0.65 N respectively.

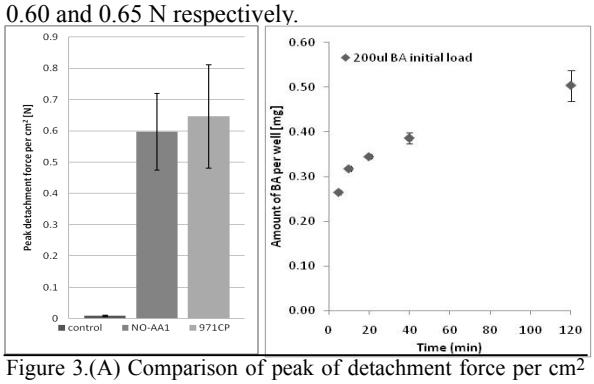

Figure 3.(A) Comparison of peak of detachment force per cm^2 of NO-AA1 and 972CP. (B) 971CP dissolution curve.

Finally, the dissolution rate of the bioadhesive 971 CP was assessed using light absorbance by spectrophotometry. It was possible to quantify the dissolution of the bioadhesive within 120 min.

Conclusions: Two methods were evaluated in order to compare the performance of BAs. By using the pull-out test, NO-AA1 and 971CP BAs showed high detachment force suitable for the aimed of this study. Early attempts to measure the dissolution rate of the BAs were performed using light absorbance. This method showed that it is possible to measure the rate of dissolution of BAs. These two methods will be applied on other BAs and further determine which BA is the most suitable for the application aimed in term of adhesion force and dissolution rate. Future studies will include to perform the pull out test against native substrates (porcine aortas) and under immersed PBS condition. Finally, the bioadhesive will be tested to transfer a drug impregnated film in vitro on an artery by balloon angioplasty to test the feasibility of the concept.