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Automated manufacturing of drug-coated balloons for coronary artery disease

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Abstract

Drug-coated balloons were established as an improvement for coronary angioplasty in recent years. However, due to the balloons' high manufacturing variance, coating them evenly is challenging. Therefore, production is still carried out at least partially manually. Within the framework of the presented research project, a four-axis machine kinematics has been developed, enabling even coating of balloon catheters of various sizes in a controlled climate. High-precision measurement using a confocal sensor allows for compensation for the manufacturing variance of the balloon catheter by means of surface mapping. The average coating thickness as well as its distribution can be determined similarly. Thus, in case of insufficient coating, local reapplication can be carried out.
With the developed machine system, it is therefore possible to produce coating area densities in the range of 4 µg mm^{-2} < a < 20µg mm^{-2} with minimal inhomogeneities.

Keywords: Drug coated balloons, coating, machine development

1. Introduction

For many years cardiovascular diseases are the leading cause of death globally [1]. Coronary angioplasty is a minimal invasive treatment for coronary heart disease, a common type of cardiovascular disease where coronary vessels locally narrow and sufficient blood flow to the heart is no longer sustained. To locally expand the blood vessel a guiding wire carrying a deflated balloon catheter is inserted in a large easily accessible blood vessel and then pushed to the narrow segment of the vessel. Then the balloon is inflated for a short duration to widen the vessel without disrupting blood flow for a prolonged period. In addition, a metal stent can be permanently inserted to stabilise the expansion and reduce the risk of restenosis significantly [2]. The use of drug-eluting stents further reduces risk of restenosis from 10.3% to 5.3% [3]. Drug-coated balloons present another opportunity to prevent restenosis without the insertion of foreign material in the body [4], but high manufacturing variance prevented a full automatization of production so far.
The goal of the presented project was to develop a reliable, fast and fully automated coating process for balloon catheters of various sizes with inline quality assessment of the drug distribution.

2. Methodology

2.1 Machine setup

A four-axis machine setup (Figure 1) was built with three linear axes reserved for the positioning of the confocal sensor and the coating tool. A fourth rotary axis was used to tension and rotate the catheter. The setup was housed in an enclosure with ventilation and a heating/cooling system for environmental control. For dosing of the coating solution, a Cetoni NEMESYS syringe pump, CETONI GmbH Automatisierung und Microsysteme, Korbussen, was used.

Coating tool and confocal sensor are mounted to an adapter plate and are therefore easily interchangeable. If necessary, an additional tool for preconditioning the balloon surface can be mounted. Mechanical transmission on both ends of the balloon catheter allows for torsion-free rotation of the balloon catheter.

2.2 Measurement technology

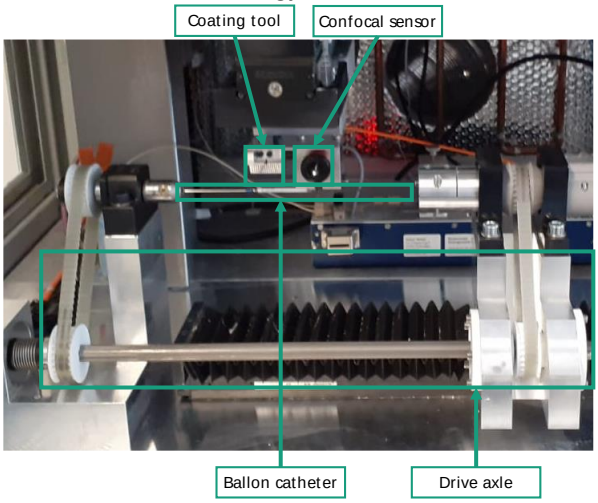

Figure 1: Machine setup with coating head near the catheter

For inline balloon surface mapping and evaluation of the coating distribution, a confocal sensor (IFS-2405-1), Micro-Epsilon Messtechnik GmbH & Co. KG, Ortenburg is used. Microscope images were obtained using a Leica M205 C microscope with a Flexacam C1 and Leica Application Suite X, Leica Microsystems GmbH, Wetzlar, Germany.

2.3 Coating strategy

The coating process starts by scanning the catheter axis to detect the balloon position. If this process fails a different angle is used for scanning. After balloon detection the coating tool is positioned at the left balloon edge and the coating

process is started (Figure 2). To achieve an evenly distributed coating, the balloon surface is evenly wetted with coating solution by pulling a droplet over the balloon surface with the coating tool which also supplies fresh solution to the droplet (Figure 3).It is essential to use a movement speed and volume flow which allows for the droplet to travel without tearing but doesn't oversaturate the balloon surface with fluid, since gravitational effects would lead to an uneven drug distribution around the balloon. After wetting the surface, the solvent is evaporated while the balloon is rotated to reduce gravitational effects and the drug crystalizes. After application of the desired dose and a final drying step the balloon is scanned once more to evaluate drug distribution.

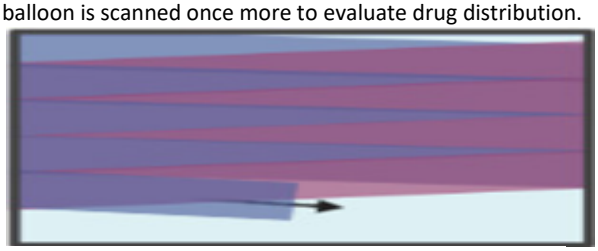

Figure 2: Movement pattern

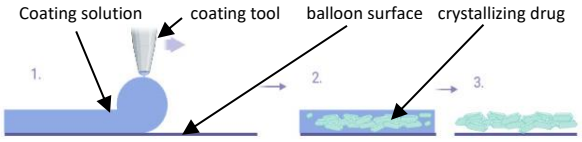

Figure 3: Coating strategy

2.4 Concept for the balloon compensation

To compensate for the manufacturing variance of the balloon a series of scans along the balloon from different angles are performed. Based on the theoretical balloon geometry and distance data a warped and tilted cylinder is simulated and deviations from the balloon middle axis to the real axis of rotation are calculated. The coating movement is adjusted in real-time based on the balloon simulation.

3. Results

3.1 Coated balloons

On a macroscopic level the coating appears to be evenly distributed across the balloon (Figure 4). Deviations only occur at the edges of the balloon, where it tapers and connects to the shaft.

Figure 4: Drug-coated balloon

3.2 Crystal structure of the drug coating

Under a reflected-light microscope the crystal structure of the coating can be observed (data now shown). The degree of crystallinity was later verified by differential scanning calorimetry (Figure 5).

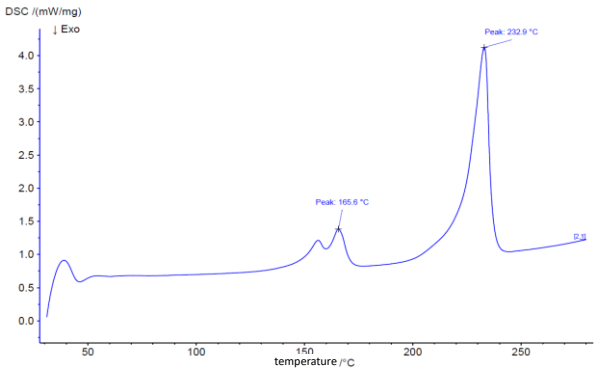

Figure 5: DSC analysis of scraped balloon coating. First peak: sublimation. Second peak: melting peak

3.3 Drug distribution

Despite large local fluctuations in coating thickness due to the crystalline surface structure, overall an even drug distribution was achieved. The medium coating thickness was d = 19.41 µm with a standard deviation of σ = 2.28 µm between four different angles. For a coating area density of a = 4 µg mm^{-2} a medium coating thickness of d = 21,64 µm with a standard deviation of σ = 1.66 µm was achieved (N=3).

4. Discussion

The resulting balloons were visually indistinguishable from the state-of-the-art balloons. The crystallinity was sufficient to ensure high potency of the drug coating. The coating thickness gradient showed no signs of uneven drug distribution on a macroscopic level, despite strong fluctuations on a microscopic level due to the coating's crystalline structure. Therefore, a consistent drug elution across the balloon surface is to be expected. To ensure effectiveness, dissolution tests as well as tests on pigs will be carried out in the near future.

5. Conclusion

For the first time a fully automated process for drug--coating balloon catheters has been implemented. The resulting balloons were of good quality, but tests of in vivo effectiveness are pending. By reducing labour cost and increasing process stability without increasing coating times automation of the coating process as demonstrated here should reduce the cost of drug-coated balloons significantly and could enable the use of drug-coated balloons in a wider range of application in the future.

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