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Automation of online particle measurement during the simulated use of catheters and stent systems

Abstract: The assessment of the coating integrity of cardiovascular implants such as catheters and stent systems is of crucial importance for device approval. Released particles may represent a potential health risk for the patients. Thus, an analysis of the particles released at simulated *in-vivo* conditions depending on their size and number is required by international standards (ISO, ASTM) as well as national authorities. In this study, an automated test bench for online particle measurement is presented. For software controlled automation, sensor data transmission and solenoid valves were implemented. A user interface was created for setting test parameters and data recording. The setup was validated by investigating standard particles as well as those released during the simulated application of non-industrial coated balloons. The measurement data were compared with results generated using the previous manual test routine. The results show an improvement in the reproducibility of the measurements, which can be attributed to the simplified handling for the user.

Keywords: Automation, Particle measurements, drug coated balloons (DCB), coating integrity, in-vitro testing, continuous online measurements

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1. Introduction

As part of the approval process for cardiovascular implants, it must be verified that implants comply with international

standards (ISO, ASTM) [1,2] and the requirements of national authorities such as the U.S. food and drug administration (FDA) [3,4]. During percutaneous transluminal angioplasty particles of the implant materials or coatings may be released in addition to the body's own fragments (i.e. calcified plaques). Depending on their number and size, coating fragments pose a potential health risk to the patient. The risks of particle contamination include, above all, the mechanical occlusion of vessels, increased thrombogenicity, and the provocation of inflammatory reactions. The smallest capillary blood vessels have a diameter of 7 μm [5]. If particles $\geq 7 \mu\text{m}$ penetrate into these vessels, obstruction may occur. Any obstruction can result in an oxygen deficiency, leading to local tissue infarction.

An automated controlled bench has to enable online particle measurement in the simulated application of cardiovascular implants. Commercial setups are available but are not well documented for scientific use [6].

The concept of the test bench requires the hardware implementation of all sensors and components needed for particle measurement as well as the software implementation of the developed test routine. Compared to manual testing, an automated testing process should reduce the effort for the user and increase the reproducibility of the results. This paper describes the automation solution for a test bench, as well as its advantages in terms of measurement accuracy and handling compared to a manual test routine.

2. Material and methods

2.1. Setup and automation

For the evaluation of particulate generation of drug coated balloons a coronary artery model with a tortuous path according to ASTM F2394-07 (2013) [7] is used for the simulation of the implantation process. Particles should be recorded by light obscuration method (LOM) which offers a single particle counting. A constant water flow at a defined flow rate (75 ml/min $\pm$ 10 %) is required to lead the released particles through the LOM sensor. To ease handling and reduce the error-proneness the flow circuit should work automatically.

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Figure 1 shows the simplified block diagram of the test bench for automated online particle measurement in the simulated application of cardiovascular implants. The simulated use procedure was conducted within a specifically developed flow loop, containing a guiding catheter, a tortuous path [7], a flow sensor (LEVIFLOW[®] LFS-008, Levitronix, Zurich, Switzerland), a pressure sensor (PCE-910, PCE Instruments, Meschede, Germany) and an online particle counter (Liquid Particle Counter PC3400, Chemtrac Inc., Atlanta, USA). The test routine provides that the

Figure 1: Block diagram of the automated test setup for continuous particle measurements.

implant to be examined is inserted into the vessel model with the test track closed. During use, the bypass keeps the volume flow constant at 75 ml/min. Electronically controllable valves were integrated into the system for automated control.

After completion of the simulated application, the test track is to be opened and the bypass closed so that the released particles can be transported to the particle counter. Due to the hydrodynamic behaviour of the fluid, a certain pressure is required for opening the test track so that the particles arrive at the particle counter after opening with a continuous volume flow of 75 ml/min. In previous tests, a trigger pressure of 370 mbar was determined for the opening of the test track valves with regard to the resulting volume flow as a function of the pressure. During the pressure build-up, all valves are closed. A central processing unit (Raspberry Pi 4 Model B) controls the switching of these valves via a relay module (see **Figure 2**).

All other peripheral devices (the pressure sensor, the flow sensor and the particle counter) were connected to the

Figure 2: Wiring diagram for connecting the valves to the Raspberry Pi.

Raspberry Pi via serial interfaces like Modbus RTU or RS232. Using the graphical programming interface Node-RED, sensor data communication, particle counting, valves and the central processing unit were implemented. A function has been implemented which ensures that after closing all valves in the system, the test track valves only open as soon as a defined pressure is present. The implementation ensures that the introduced particles arrive at the particle counter with the volume flow required for correct particle detection (75 ml/min $\pm 10\%$). Additionally, a user interface was created which enables the user to start a measurement and to monitor and record the measurement data regarding the volume flow and the particle numbers in real time.

2.2. Counting of standard particles

With the automated test routine, measurements of standard particles were identified in the first step. Three suspensions each with particle counting standards with a diameter of 10 μm , 25 μm and 50 μm (CountCal, Thermo Fisher Scientific, Waltham, Massachusetts, USA) were evaluated. The suspensions were created so that each aliquot contained 75.000 particles of the appropriate size standard. The test suspensions were stored in a reservoir that replaced the test path in this step (see **Figure 3**)

Figure 3: Cut-out view of the reduced test bench setup for the measurement of standard particles. Filter, pulsation damper, pump, reservoir and online particle counter are not shown.

2.3. Online particle measurement in the simulated application of drug coated balloons

The particle measurement in the simulated application of catheters and stent systems was carried out using five non-industrially coated balloon catheters. The balloons (size: 3 mm x 35 mm) were coated with a carrier matrix based on the ionic liquid cetylpyridinium salicylate (cetpyrsal) [8]. Since the aim of the online particle measurement in the simulated application of drug-coated balloons (DCB) was to demonstrate the functionality of the automated test routine and not to investigate the drug release by DCBs in detail, coating with embedding of the toxic paclitaxel (PTX) was not performed. Following the conventional PTX concentrations, the balloons were coated with 3 $\mu\text{g}/\text{mm}^2$ cetpyrsal. For this purpose, the ionic liquid was dissolved in methanol. The balloons were inserted into the tortuous path [7] (see **Figure 4**) and expanded and dilated three times at a defined target zone until the balloon was withdrawn again.

Figure 4: Tortuous path (blue) for testing cardiovascular implants in simulated use [7].

3. Results

The automated test bench simplifies user handling. With automated valve control, the volume flow range required for correct particle detection can be maintained at 75 ml/min $\pm 10\%$ with every measurement. **Table 1** lists the particle count data generated during the measurement of standard particles. Due to a random significant deviation with respect to the particle count data in one measurement of the 10 μm standard particles, this measurement was excluded from further evaluation. The recovery rate of the number of particles with a diameter of 25 μm and 50 μm was $98.3 \pm 0.9\%$ and $97 \pm 2.2\%$ which corresponds to the

requirements of the FDA [4]. The recovery rate of the 10 μm particles was $85.7 \pm 1.6\%$ and is thus 4.3 % below the requested recovery rate of 90 %.

Table 1: Results of particle counting of standard particle dilutions

Particle size	Measured value	Deviation from nominal value
10 μm	64301 ± 1201	14,3 %
25 μm	73733 ± 745	1,7 %
50 μm	72814 ± 1652	2,9 %

However, a comparison with the test results generated using the manual test routine (see **Figure 5**) shows that automation decreases the scattering of the data between individual measurements.

Figure 5: Comparison of particle count data of standard particles generated with the manual and the automated test routine.

The standard deviations while using the manual test routine were $\pm 3.7\%$ (10 μm), $\pm 10.2\%$ (25 μm) and $\pm 17.2\%$ (50 μm). Using the automated test routine, the standard deviations from the mean particle number were $\pm 1.9\%$ (10 μm), $\pm 1\%$ (25 μm) and $\pm 2.3\%$ (50 μm).

During the individual measurements of particles emitted by drug coated balloons, counting data were divided in four different size ranges from $\geq 5 \mu\text{m}$ to $\geq 50 \mu\text{m}$. The number of particles detected decreased with increasing size. Within each single measurement a reduction of the particle concentration over time could be observed. The results of particle detection in the simulated application of drug-coated balloons are summarized in Table 2. The standard deviation from the mean particle number is highest in two size ranges $\geq 25 \mu\text{m}$ and $\geq 50 \mu\text{m}$ with 78 % and 138 %, respectively.

Table 2: Results of particle counting in the context of simulated application of drug coated balloons

Particle size	Actual particle counts	Deviation from the mean value
$\geq 5 \mu\text{m}$	62203 $\pm$ 9699	16 %
$\geq 10 \mu\text{m}$	23619 $\pm$ 4895	21 %
$\geq 25 \mu\text{m}$	2914 $\pm$ 2286	78 %
$\geq 50 \mu\text{m}$	738 $\pm$ 1015	138 %

4. Discussion

Within the scope of this work, an automated test setup for online particle measurement in the simulated application of cardiovascular implants was successfully realized. After inserting the implant to be examined, the user operates the test with a custom-made user interface. The test setup monitors volume flow and particle counting data in real time. As the integrated valves open and close automatically after starting the measurement, the reproducibility of the test process could be significantly improved compared to a manual test bench control. The effort for the user was minimized.

Improvement reproducibility of the results was confirmed with standard particle testing. The results show that with the automated test routine, particles in three size classes ($\geq 10 \mu\text{m}$, $\geq 25 \mu\text{m}$ and $\geq 50 \mu\text{m}$) as required by the FDA were detected and classified. The comparatively lower standard deviations in the automated test routine can be attributed to the reduced operator influence.

Particle counting as part of the simulated application of drug coated balloons could be easily implemented with the automated test bench. The results showed that the coating of the balloons was detached by pushing them back and forth within the test section and by expanding them. Particles in the size classes $\geq 5 \mu\text{m}$, $\geq 10 \mu\text{m}$, $\geq 25 \mu\text{m}$, and $\geq 50 \mu\text{m}$ were detected. During testing, the number of particles detected decreased with increasing size. The highest numbers of particles were observed in the first 30 seconds after opening the test section followed by a reduction over time. The standard deviations calculated after simulated application of the coated balloons, see **Table 2**, can probably be attributed to the custom made and thus not identically coated balloons. A different concentration of the ionic liquid (cetpyrsal) resulted in widely varying particle count data during the individual measurements. It is particularly noticeable that the standard deviations in size classes $\geq 25 \mu\text{m}$ and $\geq 50 \mu\text{m}$ are high. It is conceivable that clumping of smaller particles

occurred within the test section during individual measurements while the pressure for automatic opening of the test section valves was building up. These were subsequently detected by the particle counter as large particles.

5. Conclusion

The automated test bench for online particle measurement has led to a significant improvement in handling and has ensured better reproducibility of the results. However, in the simulated application of coated balloon catheters it is still uncertain at which specific step the particles are released because the test track valves only open as soon as a defined system pressure is present. For this reason, there is a need for further optimization of the automation with regards to a fully automatic flow control.

Author Statement

Authors state no conflict of interest. Informed consent: is not applicable.

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