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Optimization of online particle counting with a 3D-printed bubble trap

Abstract: Particulate evaluation is needed for the approval of cardiovascular devices. Air bubbles lead to higher particle counts when light obscuration method (LOM) is used. The aim of the study was to test a custom made bubble trap that removes air bubbles (2 – 100 µm) from a flow circuit prior to online particle counting. Artificially generated air bubbles were counted with an online particle counter with and without the bubble trap. Air bubbles were reduced by about 71 % to 91 % by using the bubble trap.

Keywords: online particle measurement, particle counting, bubble trap, implant testing

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1 Introduction

Cardiovascular devices such as drug-eluting stents or drug coated balloons are used to treat vascular stenosis caused by atherosclerosis in the coronary or peripheral arteries, respectively [1]. Particulate generation during the implantation process could lead to major events such as emboli, stroke or cardiac infarction [2]. For that reason, implant testing includes the evaluation of particulate generation during a simulated use test procedure. It is required by the authorities during product approval and claimed in standards as ASTM F2394-07(2013) and ISO 25539-2:2012 [3, 4].

According to the USP788, the light obscuration method (LOM) can be used as a method to count and size of particles [5]. In previous studies, we showed the advantages of the usage of an online particle measurement system, because counting the particles directly after the generation avoids agglomeration and dissolution of hydrophilic particles [6].

One remaining challenge was the generation of air bubbles during the simulated implantation process, as they cannot be differentiated from particles by the LOM and lead to higher particle counts [7]. Commercially available bubble traps that are used for example in medical infusion or for High Performance Liquid Chromatography measurements [8] do not work with the required high flow rate needed for the used test setup (75 ml/min).

Within the current study a custom made bubble trap was developed, manufactured and tested within the online particle measurement test setup.

2 Material and methods

2.1 Design and manufacturing of the bubble trap

For the design of the bubble trap, the computer aided design software PTC Creo Parametric 5.0 (Parametric Technology GmbH, Unterschleissheim, Germany) was used.

The bubble trap consists of a hydrophobic membrane (PTFE, D=25 mm, Bohlender GmbH, Waltersberg, Germany) with a pore size of 0.02 µm for bubble capture and a polymeric body that contains the tube fittings and a holder for the membrane.

To keep the setup for degassing as small as possible, an assembly without an external vacuum pump was used. Air bubbles are supposed to leave the liquid through a hydrophobic membrane with small pores so that the water could not leak through [9]. The membrane has to be on top of the bubble trap so that air bubbles that rise upwards will reach the membrane and leave the liquid.

Manufacturing was performed via stereolithography with a 3D-printer Form 2 (Formlabs, Somerville, MA, USA). As

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water and temperature resistance were necessary material properties, the photopolymer resin Tough FLTOTL05 (Formlabs) was chosen. During post processing the parts were UV-hardened and polished. The bubble trap was manufactured in two separate components. The main component contains the inlet and outlet as well as the volume where the fluid passes the hydrophobic membrane. The connectors have an inner diameter of 7 mm (inlet) and 3 mm (outlet), respectively. The cover plate is mounted with screws on the main component. The hydrophobic membrane is clamped and sealed between the two parts. The bubble trap has a total diameter of 45 mm [10]. Figure 1 shows a disassembled schematic image of the custom made bubble trap.

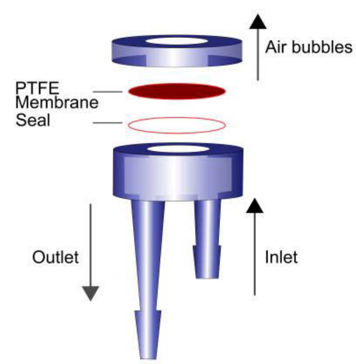

Figure 1: Schematic image of the 3D-printed bubble trap

2.2 Test setup

The test setup for online particle measurements with the additional bubble trap based on previous tests [6] is shown in Figure 2.

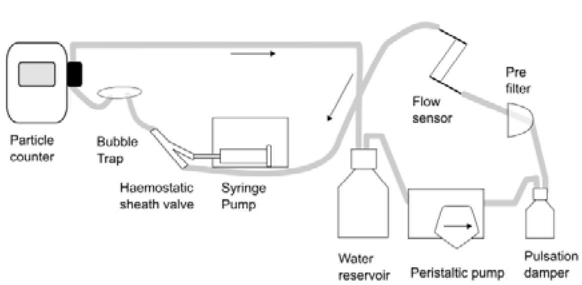

Figure 2: Test setup for the determination of the reduction of air bubbles by the bubble trap

From the reservoir, particle free water (sterile water for irrigation, Fresenius Kabi, Bad Homburg, Deutschland) is circulated with the help of a peristaltic pump (Ismatec IPC, Cole-Parmer GmbH, Wertheim, Germany) with a flow rate of 75 ml/min. The medium passed a pulsation damper and a filter (Sartobran capsule 150, Sartorius, Göttingen, Germany). The flow rate was monitored with an ultrasonic flow sensor (LeviFlow, Levitronix GmbH, Zurich, Switzerland). A haemostatic sheath valve was used to introduce defined air bubbles in a reproducible frequency. Air bubbles were generated by an air-filled syringe with a cannula that led air with a flow rate of 1.67 ml/min into the circuit via the haemostatic sheath valve. The constant air flow rate was generated by a syringe pump (Perfusor S, BBraun, Melsungen, Germany). Air bubbles were counted with an online particle counter (PC3400, Chemtrac Inc., Norcross, GA, USA) based on the LOM. It is assumed that the size determination of air bubbles is the same as with particle size determination.

2.3 Test procedure

As reference measurements the reproducible generation of air bubbles was tested within the test setup without the bubble trap. Results were used as reference value for the amount of introduced air bubbles. Air was pumped into the circuit for 840 s and the particle counts were recorded with a sample period of 5 s continuously. The particle counts of the whole duration were added up to determine the total count value that represents the number of air bubbles introduced into the test setup. The test was repeated five times.

Then, the bubble trap was mounted into the test setup between the haemostatic sheath valve and the particle counter in a second test sequence. The test was performed six times for 840 s. Particle counts were recorded during the whole test duration and the total count value was determined. The bubble trap was not reset between the runs to simulate the long term performance.

In a third test sequence the test was performed as described before, but the bubble trap was removed, emptied from water and mounted again in between each of the six measurements to analyse the effect of the usage of the bubble trap in shorter time periods.

3 Results

The bubble trap could be successfully manufactured by 3D-printing. No leakages were observed. The required flow rate of 75 ml/min could be reached with the bubble trap. The number of counted particles represents the number of generated air bubbles.

The average number of bubble counts for all three test sequences is shown in Table 1. The generation of air bubbles was reproducible during the six repetitions. A total account of 6867±97 air bubbles between 2 and 100 µm was generated. The generation of air bubbles was comparable for all iterations.

Table 1: Generated air bubbles during 840 s

Size class	Reference w/o bubble trap	With bubble trap (without reset)	With bubble trap (with reset)
2-5 µm	3199 ± 71	922 ± 543	84 ± 28
5-10 µm	1048 ± 31	281 ± 167	24 ± 10
10-25 µm	1316 ± 29	267 ± 53	124 ± 36
25-50 µm	885 ± 14	262 ± 48	157 ± 58
50-100 µm	420 ± 33	232 ± 82	208 ± 107
Total (2-100 µm)	6867 ± 97	1962 ± 757	598 ± 211

The test of the long term performance of the bubble trap (without reset) showed a reduction of the particle counts that represent the number of air bubbles. A total amount of 1962±757 air bubbles was detected.

Test results of the single measurements of the test sequence about the long term performance of the bubble trap are presented in Figure 3. The counted particles or bubbles, respectively, increased from one measurement to the next, especially when considering air bubbles smaller than 25 µm.

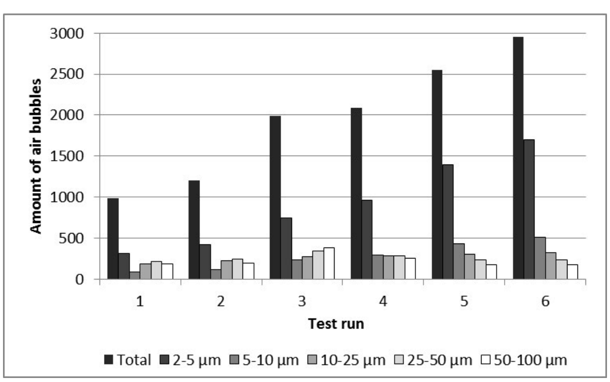

Figure 3: Amount of air bubbles in different size classes, bubble trap stayed in the circuit for all repetitions

The single measurement test results of the third test sequence (short term performance of the bubble trap, with reset) are shown in Figure 4. The counted air bubbles were comparable between each single measurement. On average 598±211 air bubbles were counted in total.

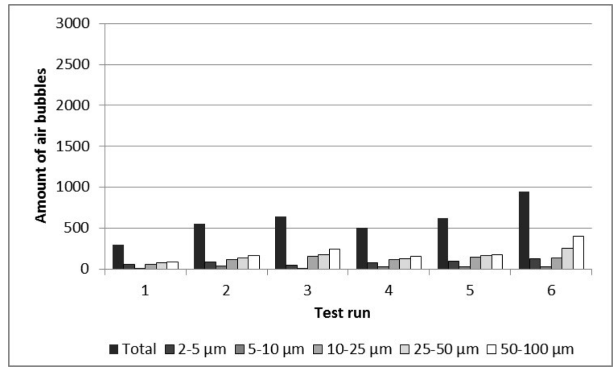

Figure 4: Amount of air bubbles in different size classes, bubble trap was reset between all repetitions

4 Discussion

Within this study a bubble trap was developed and tested in order to reduce the negative influence of air bubbles during online particle measurements.

The test results show, that the developed bubble trap has the potential to effectively reduce air bubbles in the test circuit. Table 2 shows the relative amount of air bubbles that were detected by the online particle counter in long term and short term usage of the bubble trap compared to the reference measurements without bubble trap.

Table 2: Amount of air bubbles with the usage of the bubble trap compared to the reference

Size class	Bubble trap, (without reset)	Bubble trap, (with reset)
2-5 µm	29%	3%
5-10 µm	27%	2%
10-25 µm	20%	9%
25-50 µm	30%	18%
50-100 µm	55%	50%

During long-term usage (without reset) air bubbles could be reduced to 20 - 55 % of the amount compared to the reference measurements. Considering the single measurements an increase of air bubbles was found, caused by an accumulation of air bubbles at the outlet observed visually through the partial transparent body of the bubble trap.

During short-term use (with reset) air bubbles could be further reduced to 2 - 3 % for small particles between 2 and 10 µm when the bubble trap was removed and emptied between the runs. Considering the larger air bubbles with a diameter of 50-100 µm, the amount of air bubbles was comparable when using the bubble trap without reset (50%). The reset of the bubble trap avoided the accumulation of air bubbles and thus, improved the performance of the device.

In Figure 5 the amount of air bubbles is shown in absolute counts for each size class.

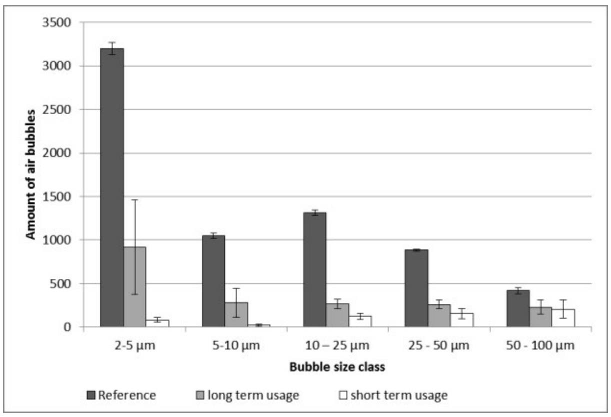

Figure 5: Amount of air bubbles in different size classes, long term and short term usage of the bubble trap in comparision to the reference

The reduction of air bubbles worked better for small air bubbles with a diameter range between of 2 and 25 µm than for air bubbles larger than 50 µm. It is assumed, that smaller air bubbles merged to larger ones within the volume of the bubble trap and then were counted as air bubbles larger than 50 µm. Another interpretation of the data could be that larger air bubbles are not able to pass the pores of the membrane. In previous studies it turned out that air bubbles appear rather in smaller size classes (< 25 µm) [7, 11] Thus, the particular efficacy of the bubble trap appears relevant.

Further investigations with other methods (e.g. dynamic image analysis [12]) allow a distinction between air bubbles and particles. They could be applied additionally in case of the appearance of irregular high amounts of particles, but require additional effort.

5 Conclusion

The developed bubble trap showed a good handling performance. A reduction of air bubbles within the test setup could be reached. Thus, the test setup for online particle measurement could be improved by the usage of the bubble trap. For the long term use of the bubble trap design optimizations are necessary to avoid the accumulation of air bubbles at the outlet of the bubble trap.

Author Statement

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