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RESPONSE
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Adjusting inkjet printhead parameters to deposit drugs into micro-sized reservoirs

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Introduction

Drug delivery systems (DDS) ensure that therapeutically effective drug concentrations are delivered locally to the target site. For that reason, it is common to coat implants with a degradable polymer which contains drugs. However, the use of polymers as a drug carrier has been associated with adverse side effects [1]. For that reason, several technologies have been developed to design polymer-free DDS. In literature it has been shown that micro-sized reservoirs can be applied as drug reservoirs and inkjet techniques are capable of depositing drugs into these reservoirs [2]. In this study, laser-drilled micro-sized reservoirs (circular, diameter of 100 µm) have been laden with a drug (ASA) using a drop-on-demand inkjet printhead. The presented research work identifies the crucial factors of influence while realizing a drug deposition in micro-sized reservoirs using a drop-on-demand inkjet printhead.

Methods

Printhead parameters: In order to deposit drugs in micro-sized reservoirs on implant surfaces a micro-dispensing device (Nanoplotter 2.1, GeSiM Gesellschaft für Silizium-Mikrosysteme mbH, Großerkmannsdorf, Germany) is used. The printhead (PicoTip J, GeSiM, Fig. 1) follows the piezoelectric drop-on-demand principle (DoD). A major requirement is a reproducible droplet formation, with a suitable volume and trajectory of the droplet. The major parameters to control the droplet formation of piezo driven printheads are the voltage, pulse width and frequency as well as the nozzle diameter of the printhead. In this study, the printhead is driven with a voltage of 40 V up to 80 V (in 5V steps). The pulse width (20 µs) and frequency (100 Hz) are set to fix standard values. The nozzle diameter of the printhead is d=25 µm. In order to provide a test substance ASA was dissolved in EtOH (≥99,8 %, Carl Roth GmbH + Co. KG, Karlsruhe, Germany) by 40 mg/ml. The droplet formation is monitored by a stroboscope camera. The results will be compared to the printing process of pure EtOH.

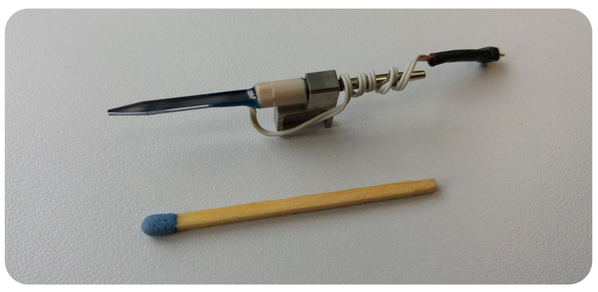

Fig. 1: Drop-on-demand inkjet printhead PicoTip J by GeSiM

Drug depositing: In this work drug depositing (Fig. 2) is applied to two variants of laser-drilled reservoirs. Variant one has a diameter of ~100 µm and a depth of ~20 µm (R100-20); variant two has a higher depth of ~50 µm (R100-50). It is assumed that after being printed, the solvent will vaporize and there will be a deposit of drug in the reservoir. The volume of a reservoir is limited (R100-20: V~120 pl; R100-50: V~270 pl). In order to achieve a fill grade of ~50 %, 42 droplets (~50 pl/droplet) have to be printed in a 100-20 reservoir (calculated with ρASA=1,35 g/cm³). Overfilling should be avoided and such small amounts of fluid are subject to effects like wettability. So there is the need to split the depositing process into steps as follows (there is a delay of ~5 seconds between each step):

- 1st test setup - 14 steps and 3 droplets/step
- 2nd test setup - 21 steps and 2 droplets/step
- 3rd test setup - 42 steps and 1 droplet/step

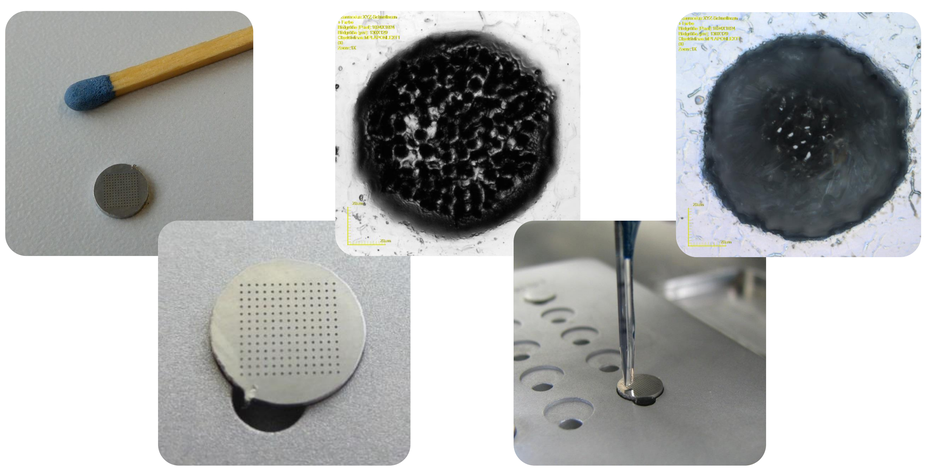

Fig. 2: Process of drug depositing in micro-sized reservoirs

[1] Chen, W. et al. Polymer-Free Drug Eluting Stents: An Overview of Coating Strategies and Comparison with Polymer-Coated Drug-Eluting Stents. Bioconjugate Chem. 2015; 26: 1277−1288

[2] Vehse, M et al. Loading method for discrete drug depots on implant surfaces. Biomed. Tech. 2012; 57(1): 1089-1092

Results

Printhead parameters: As expected the droplet formation depends on the applied voltage pulses of the piezo. Increasing the voltage decreases the angle failure and increases the droplet volume (see Fig. 3). From a driving voltage of 50V to 60V the main droplet is followed by a single satellite droplet (Figure 4 (B)). Increasing the voltage increases the number of satellite droplets as well. If the piezo is driven with a voltage of about 75 up to 80 V, the reproducibility of the droplet formation decreases and a sort of spattering can be observed (Figure 4 (C)). A piezo driving voltage of 60 V was determined for the drug deposition in micro-sized reservoirs. In comparison to inkjet printing of pure ethanol, ASA seemed to have no significant influence on the droplet formation.

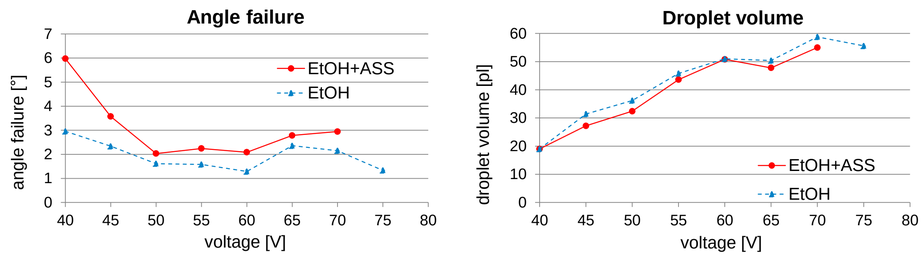

Fig. 3: Angle failure (left) and droplet volume (right) over driving voltage

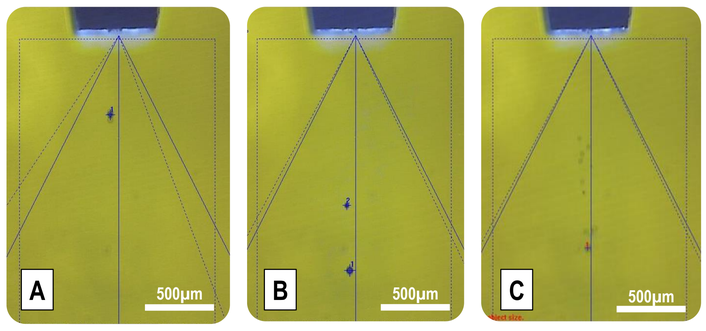

Fig. 4: Droplet formation of EtOH+ASS under different driving voltages (A) 40 V (B) 60 V (C) 80 V

Drug depositing: Figure 5 (A) shows the results of drug depositing in R100-20 by the first test setup. The drug is deposited around the reservoir, instead of inside the reservoir. For test setups no. 2 and 3, the effect decreases significantly. However, drug sedimentations around the reservoir cannot be eliminated (Figure 5 (B)) for this reservoir size. The reason for this could be a wetting of the surface around the reservoir, possibly caused by an overfilling or missing of the reservoirs. In comparison to these results, filling deeper reservoirs (R100-50) results in deposits of the drug inside the reservoir (Figure 5 (C)). This is an indication for valid droplet positioning. However, it can be seen that the deposit of ASA is concentrated at the walls of the reservoir.

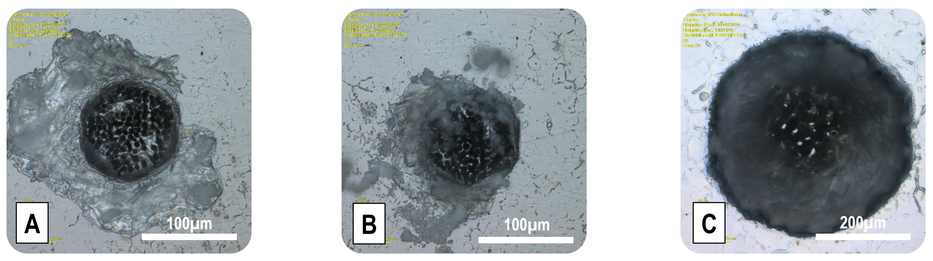

Fig. 5: Drug-laden reservoirs (A) R100-20 filled in 14 steps (3 drop./step); (B) R100-20 filled in 42 steps (1 drop./step); (C) R100-50 filled in 42 steps (1 drop./step)

Conclusion

This study demonstrates drug deposition into micro-sized reservoirs according to the characteristics of the drug solution, operating parameters of the printhead and geometric parameters of the reservoir. In the shown setup of drug deposition, effects such as wettability may have an important influence, especially when the used solvent shows a high wettability of metal surfaces, as is the case for EtOH. It is indicated that there is the need to figure out an optimal ratio between droplet volume and the volume of the reservoir to be loaded. In further investigations the deposition process will be tested using more variations of reservoirs and solvents.

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