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3D-printed PEGDA structure with multiple depots for advanced drug delivery systems

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Abstract: Additive manufacturing technologies have the potential to make an important contribution to the field of personalized medicine. Besides customized implants, drug delivery systems (DDS) should be tailored to the patient's specific needs. We developed a hybrid additive manufacturing system based on stereolithography and inkjet printing to generate DDS with selectively incorporated depots of active pharmaceutical ingredients (API) to tailor the release kinetics of the API. In this work we report on the successful proof-of-principle of 3D printing of PEGDA specimens containing depots with two different inks.

I. Introduction

Additive manufacturing (AM) offers a great potential in personalized medicine to generate a custom-made solution for every individual patient [1]. In addition to orthopedic implants the focus is also on drug delivery systems (DDS). Additive manufactured DDS offer the advantage that the amount of active pharmaceutical ingredients (API) and the release period can be tailored to the respective patient. A milestone of AM of DDS was the approval of the first 3D-printed drug by the FDA in the year 2015 [2]. Among the numerous AM processes on the market, stereolithography (SLA) has come into particular focus because it offers advantages such as high printing resolution, low process heat and the capability of controlling the material properties and the associated release kinetics via photo-polymerization parameters [3][4]. However, a disadvantage of SLA is the inability to generate local drug gradients due to the fact that the API have to be homogeneously dissolved in the resin [1]. To overcome this limitation, we combined SLA with inkjet printing to create a hybrid additive manufacturing process which makes it possible to selectively incorporate a second material into depots inside of the polymer matrix. For this purpose, an SL-apparatus developed in-house (and previously published [5]) was adapted. We integrated inkjet pipettes into the system and adjusted the process flow accordingly. To build the base structure from the resin, the procedure is similar to a classical SLA process. In our case, the curing of the layer is done line-by-line as given by the corresponding bitmap-file of the layer. After a layer is finished, the platform is lowered and raised again to the original position minus the layer thickness of the new layer. After this step the inkjet modules filled with API-fluids are placed over a sheet of water sensitive paper and dispense 5 drops each. This is to check if the inkjet pipettes are reliably dispensing and to prevent drying at the tip and associated clogging of the fluid channel. To place an API-depot in a layer, the previously built structure is lowered and re-coated with resin. The inkjet pipette is placed over the desired depot position and ejects the corresponding number of drops. Immediately after dosing, the optical unit is placed over the spotted area and the laser is switched on for a short time period to fix the API-fluid in its position. This step is repeated for each individual depot in the layer. After all spots for the depots have been placed the line-by-line curing of the whole layer starts. A schematic illustration of the process flow is depicted in Fig. 1.

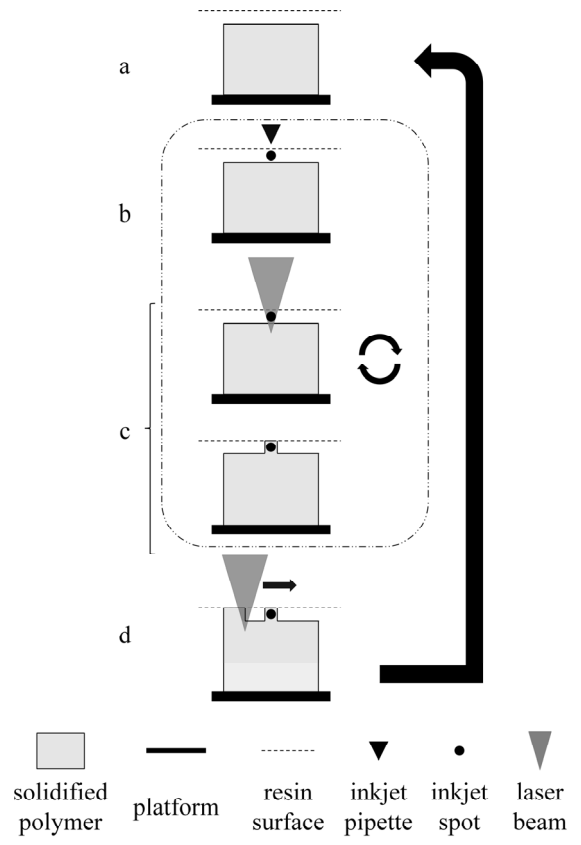

Figure 1: Schematic process flow a) initial state b) spotting with inkjet pipette on desired location c) curing and fixation of spotted area d) line-by-line curing of base structure

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II. Material and methods

An experimental SL-apparatus [6] with two additionally integrated inkjet pipettes type Nano-Tip J (GeSiM mbH, Germany) was used for this study.

A mixture of poly(ethylene glycol) diacrylate (PEGDA, M_n = 700 g/mol, Sigma-Aldrich, USA) and ultrapure water (Water/PEGDA = 1/1) was used as the basic resin for the hybrid manufacturing process. As photoinitiator lithium phenyl-2,4,6-trimethylbenzoylphosphinate (LAP) was used. The resin contained 0.07% LAP based on the mass fraction of PEGDA.

In order to demonstrate the proof-of-principle, test liquid mixtures of ultrapure water and ink were used for inkjet printing of the depots. A blue ink (4001 Tp/6 Königsblau, Pelikan, Switzerland) and a pink ink (4001 Tp/6 Pink, Pelikan, Switzerland) were used. For the test liquids the volume of one ink cartridge each was filtered with a syringe filter (ACRODISC PSF Versapor 0.8 µm, PALL, USA) and then dissolved with 16 ml of ultrapure water.

To show the possibilities of the process, cubic samples with two depots each containing a different test liquid were generated. The edge length of the specimen was s_{xyz} = 4 mm with a layer thickness of z = 0.1 mm. The depots were built over 5 layers each in one spot per layer. In each spot 5 droplets are dispensed, which corresponds to a volume of about 10 nl for each test liquid. The travel speed of the laser in x-direction was v = 30 mm/s. A schematic illustration of the designed specimen with two different incorporated ink depots is depicted in Fig. 2.

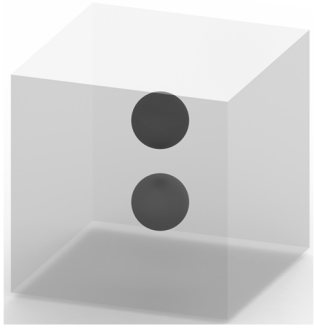

Figure 2: Schematic illustration of the designed specimen with two depots. The upper depot contains blue ink and the lower one pink ink

III. Results and discussion

The specimen was successfully built and is depicted in Fig. 3. The outer shape basically corresponds to the designed cubic structure. The two depots are clearly visible but differ in size. The lower depot containing the pink ink looks larger than the upper blue ink depot. The test sheet of water sensitive paper indicates no failure in dispensing of the inkjet pipettes. However, the depots appear blurred in the horizontal dimension. This leads to the assumption that the alignment of the inkjet pipettes and the laser has to be optimized, since less than the whole spotted volume was fixed by the laser, causing a spreading of the ink in the layer during the subsequent curing process. It may be necessary to enlarge the laser spot for fixation purposes to cure the complete spotted area. Nevertheless, the 3D-printing of PEGDA structures with two incorporated ink depots could be successfully demonstrated.

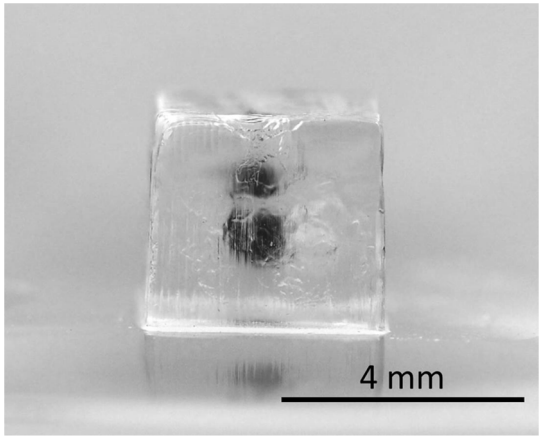

Figure 3: Generated cubic specimen with edge length of s = 4 mm with two ink depots. The upper depot contains blue ink and the lower depot contains pink ink

IV. Conclusions

With the successful realization of PEGDA structures with two incorporated depots another step towards personalized DDS has been taken. The results are promising since it is now possible to incorporate up to two different API into a polymeric structure generated by SLA. This is a further advance over classical stereolithography, as it is now possible to create independent gradients of two API in one DDS. However, much research still has to be done to optimize the process to reach the goal of a DDS that is tailored towards the needs of a specific patient.

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AUTHOR'S STATEMENT

Conflict of interest: Authors state no conflict of interest. Informed consent: Informed consent has been obtained from all individuals included in this study. Ethical approval: The research related to human use complies with all the relevant national regulations, institutional policies and was performed in accordance with the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee.

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