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Additive Manufacturing of Microreservoir Devices for Oral Drug Delivery Using an Acculas BA-30 Micro-Stereolithography Instrument: A Feasibility Study

Lukas Vaut, Kristian E. Jensen, Guido Tosello, Ajit Khosla, Hidemitsu Furukawa, and Anja Boisen

Within the research and the development of protective carrier platforms intended for oral drug delivery, polymeric microreservoir devices with sizes around 300 μm have been proposed as a delivery system capable of unidirectional drug release. So far, microreservoir devices have been fabricated with simple shapes by means of high-throughput fabrication methods. In this feasibility study, state-of-the-art micro-stereolithography 3D printing is used for the fabrication of various microreservoir geometries. Scanning electron microscopy characterization and conducted resolution tests demonstrated the capability of the used technology and unveils challenges and opportunities associated with the proposed fabrication process.

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In the course of this work, the applicability of microstereolithography (µSLA) 3D printing for the fabrication of micro-containers for oral drug delivery was investigated. In this way, the technology was confronted with designs of varying complexity and also with different design dimensions in order to push the technology to its limit and to determine at which dimensions the smallest features can be obtained with the highest level of detail. The first section in this paper describes the fabrication of a complex microcontainer geometry which resulted after employing a topology-optimization algorithm.

Results and Discussion

In the previous section the 3D printing of complex and simple microcontainer designs have been described, respectively. As the printing outcome was neither satisfying in case of the complex model nor in the case of the simple model, a short test on the influence of laser power on the print quality was performed. The 3D printing instrument uses two different laser parameters. One laser power value for the outline of the printed structure and one laser power value for the infill of the printed structure. In the first test (Figures 3a, 3b), the laser power was decreased by 66% for the outline, reaching a power value of 1 mW, and by 20% for the infill, thus reaching a power value of 4 mW, when compared to the previous laser settings (outline: 3 mW; infill: 5 mW). The exemplary SEM-image reveals that the structures were not fully printed as the bottoms of the microcontainers were missing and no micro-pillars could be observed. The gained findings suggest that the dimensions used in this design, especially the minimum feature sizes were too small to obtain acceptable results with the used instrument.

Fabrication of complex three-dimensional micro-structures.—

A microcontainer design with evert ing micro-pillars from which even smaller pillars are branching out was created using a topology-optimization algorithm which solved a heat conduction problem subject to a volume constraint (Figures 1a, 1b, 1g, 1i). This design represented the ideal and ultimately desired geometry in this work and apart from technical limitations it should be fabricated within a size range of 300 to 500 µm in diameter. However, in this size range the smallest feature size would be around 6 µm. Since in the design the pillars are directed outwards from the object, the pillars, up to a diameter of approximately 80 µm, were fabricated. Since the complex microcontainer design presented in the previous paper describes the fabrication of a complex microcontainer geometry which resulted after employing a topology-optimization algorithm.

Influence of laser power on print quality.—In the previous sections the 3D printing of complex and simple microcontainer designs have been described, respectively. As the printing outcome was neither satisfying in case of the complex model nor in the case of the simple model, a short test on the influence of laser power on the print quality was performed. The 3D printing instrument uses two different laser parameters. One laser power value for the outline of the printed structure and one laser power value for the infill of the printed structure. In the first test (Figures 3a, 3b), the laser power was decreased by 66% for the outline, reaching a power value of 1 mW, and by 20% for the infill, thus reaching a power value of 4 mW, when compared to the previous laser settings (outline: 3 mW; infill: 5 mW). The exemplary SEM-image reveals that the structures were not fully printed as the bottoms of the microcontainers were missing and no micro-pillars could be observed.
In conclusion, these results suggest that in the first test the laser power was too low. As a consequence of this fact, the print resin was not fully cured and ultimately the structures of the object did not emerge. Contrary to this, in the second test the laser power was obviously increased by 33% for the outline (4 mW) and by 60% for the infill (8 mW). In this case, the obtained microcontainers exhibited correct cylindrical shape, however, the structures had a rather bulky appearance. The reservoir of the microcontainer was not visible and shapes of micro-pillars could only be detected in a very rudimentary way.

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In summary, the described samples showed that the dimensions of small features, micro-pillars in this case, highly deviated from the appearance of samples (b) was similar to that of (a) and the change in the micro-pillars’ height showed no noticeable effect. In contrast to (a), only the outline of the cavity was more defined for (b) samples. For both types of samples, no single lithographic layers could be detected as it was the case with the two previously presented experiments.

In summary, the described samples showed that the dimensions of small features, micro-pillars in this case, highly deviated from the
overhang. Excluding the pillars, all microcontainers had a height of 500 μm including and from 1000 to 700 μm excluding overhang. As a consequence, the computer algorithm to generate the CAD models placed fewer micro-pillars on top of the containers and increased the space between those. The samples illustrated in (a) and (b) were covered with leftover of uncured resin as it was the case in the previous described experiments. However, in contrast to prior observations, samples (a) and (b) seemed to be covered with less resin, as the uncured material was only connecting the pillars forming a star shape and leaving surface of the microcontainer exposed. In case of the other samples (c-f) even less leftover resin could be observed. Despite the presence of leftover resin on the pillars, the shape of the top diameter could be seen as the pillars displayed a rather shiny surface in the center as compared to the edges. This could be observed best when considering the SEM images taken from an angled perspective. In accordance with prior experiments, the size deviation of the pillars followed the trend of deviating stronger at smaller dimensions, since the pillars were 5.8 (a), 2.6 (b), 3.5 (c), 3.1 (d), 2.6 (e) and 2.5 (f) times larger than given in the CAD drawing. Single lithographic layers were not detected as well. In comparison with the CAD drawings, the cavities were smaller. In case of the sample displayed in (d), the cavity was measured to be 229 μm wide while the CAD-model specified a width of 400 μm. The samples shown in (c) and (e) showed similar print defects as described earlier.

In summary, it can be concluded that the change of container overall size did not deteriorate the general print outcome. In contrast, the placement of fewer pillars on top of the microcontainers facilitated a better separation of the pillars and as a consequence the post-print cleaning process probably removed more resin residue than in the other cases.

In the next experiment, the general container height was decreased from 500 to 350 μm and the height of the pillars was decreased down to 200 μm, because the change of pillar height did not show a noticeable

Specifications that were given by the design parameters, while larger features (e.g., outer diameter of container) deviated less.

Resolution assays.—Proceeding from the previous experiments, more systematic resolution testing was conducted. A microcontainer base structure with fixed dimensions was defined and then arrays of microcontainers with differently sized micro-pillars were additively manufactured (Figure 5). It has to be stressed that these experiments were mainly focused on the print outcome of the micro-pillars as an indication for print resolution. The basic structure consisted of a microcontainer with an outer diameter of 1300 μm including and 1000 μm excluding overhang, an inner diameter of 600 μm, a height of 500 μm and a micro-pillar height of 200 μm. The micro-pillar diameters varied from (a) to (f), starting with a top diameter of 30 μm and a bottom diameter of 80 μm for (a) and changing to values of 60/100, 80/130, 100–170, 120/200, 90/200 μm for the other iterations.

The SEM images of printed microcontainers showed structures that appear to be very different than the CAD models. The cavities of the microcontainers seemed to be at least partly filled and the pillars were not clearly separated. In this way, the print outcome of the first experiment reveals a very poor efficiency of the post-print cleaning process, since all containers and especially all micro-pillars and cavities were obviously covered with leftover of uncured resin material. Despite the blurry and undefined appearance, some indications on the shape of the micro-pillars could be observed. When taking these indications into account and comparing the dimensions of the probable pillar diameters with the dimensions from the CAD model, it becomes apparent that, in accordance with all previous experiments, there is a strong deviation between these dimensions, because the printed pillars were larger in all cases. Though, the extent of size deviation was dependent on the pillar size, as from smaller to larger pillars, the print outcome was 6.3 (a), 3.4 (b), 2.6 (c), 2.4 (d), 2.2 (e) and 2.1 (f) times larger. When comparing the CAD drawings with the SEM images of the printed samples it also becomes apparent that there was much less space in between the pillars and that the different samples generally looked much more similar than the CAD-drawings did. Additionally, some samples (a, e and f) show flat structures protruding out of the container base, suggesting that the print shifted in the XY-plane during the print, causing a print defect. In accordance with the previously described experiments, no single lithographic layers were visible.

In the following experiments, the influence of other single parameters on the print outcome was investigated. At first, the pillar height was increased from 200 μm to 300 μm (Figure 6). Also, in this case, the pillars and container cavities were covered with leftover resin. The overall morphologies were similar to those of the previous experiment and no effect of the increased pillar height could be noticed. The size deviation of the pillars followed the same trend as reported before, since the pillars were 6.7 (a), 3.5 (b), 2.9 (c), 2.4 (d), 2.3 (e) and 1.9 (f) times larger than the dimensions given in the CAD-model.

In the next step, the overall container diameter was decreased from 1300 to 1000 μm including and from 1000 to 700 μm excluding overhang (Figure 7). As a consequence, the computer algorithm to generate the CAD models placed fewer micro-pillars on top of the containers and increased the space between those. The samples illustrated in (a) and (b) were covered with leftover of uncured resin as it was the case in the previous described experiments. However, in contrast to prior observations, samples (a) and (b) seemed to be covered with less resin, as the uncured material was only connecting the pillars forming a star shape and leaving surface of the microcontainer exposed. In case of the other samples (c-f) even less leftover resin could be observed. Despite the presence of leftover resin on the pillars, the shape of the top diameter could be seen as the pillars displayed a rather shiny surface in the center as compared to the edges. This could be observed best when considering the SEM images taken from an angled perspective. In accordance with prior experiments, the size deviation of the pillars followed the trend of deviating stronger at smaller dimensions, since the pillars were 5.8 (a), 2.6 (b), 3.5 (c), 3.1 (d), 2.6 (e) and 2.5 (f) times larger than given in the CAD drawing. Single lithographic layers were not detected as well. In comparison with the CAD drawings, the cavities were smaller. In case of the sample displayed in (d), the cavity was measured to be 229 μm wide while the CAD-model specified a width of 400 μm. The samples shown in (c) and (e) showed similar print defects as described earlier.

In summary, it can be concluded that the change of container overall size did not deteriorate the general print outcome. In contrast, the placement of fewer pillars on top of the microcontainers facilitated a better separation of the pillars and as a consequence the post-print cleaning process probably removed more resin residue than in the other cases.

In the next experiment, the general container height was decreased from 500 to 350 μm and the height of the pillars was decreased down to 200 μm, because the change of pillar height did not show a noticeable
STL-file models (a1-f1) and SEM images (a2-f2, a3-f3) of microcontainers with differently sized micro-pillars placed on overhang. All STL-models featured an overall diameter of 1000 μm in the bottom and 1300 μm including overhang. Excluding the pillars, all microcontainers had a height of 500 μm. The dimensions of the micro-pillar top- and bottom diameters were as follows: (a1) 30 μm-80 μm, (b1) 60 μm-100 μm, (c1) 80 μm-130 μm, (d1) 100 μm-170 μm, (e1) 120 μm-200 μm and (f1) 90 μm-200 μm. The height of the micro-pillars was set to be 300 μm. SEM images (a3-f3) were recorded from a 35° tilted angle.

In (a) and (b), the leftover resin connected the micro-pillars to form a star shape. However, in these cases the cavities of the containers did not seem to be filled with resin residue while they were still smaller as defined in the CAD models. For example, in (a) the cavity was measured to be 257 μm wide instead of 400 μm as given in the design.

The morphologies were not similar with respect to the varying shine of the pillar surfaces that was mentioned earlier. For the samples at hand, no differences were visible. Therefore, close inspection revealed that single lithographic layers were visible at the sides of the micro-pillars in the case of samples (c) to (f). This can be seen best from a tilted angle. With increasing size, the pillars were 6.4 (a), 3.3 (b), 2.9 (c), 2.6 (d), 2.6 (e) and 2.3 (f) times larger than the dimensions given by the design. The differences in morphology, when comparing with previously described results, could not be considered to be associated with the reduction in container and pillar height, since they were probably related to variations in the presence of resin residue.

As a last experiment, the overall diameter of the microcontainers was increased from 1000 μm including and 700 μm excluding overhang to 2000 μm including and 1500 μm excluding overhang (Figure 9). As a consequence of this change, more pillars could be arranged on top of the microcontainer surfaces. The micro-pillars of the samples that are depicted in (a) to (d) were not separated and shared a uniform surface. However, patterns that indicated the shape of the top diameter of the pillars could be found in all cases. Apart
Figure 8. Resolution assay 4: effect of microcontainer height on print outcome. STL-file models (a1-f1) and SEM images (a2-f2, a3-f3) of microcontainers with differently sized micro-pillars placed on overhang. All STL-models featured an overall diameter of 700 μm in the bottom and 1000 μm including overhang. The dimensions of the micro-pillar top- and bottom diameters were: (a1) 30 μm-80 μm, (b1) 60 μm-100 μm, (c1) 80 μm-130 μm, (d1) 100 μm-170 μm, (e1) 120 μm-200 μm and (f1) 90 μm-200 μm. The height of the microcontainers excluding micro-pillars (height = 200 μm) was set to be 350 μm. SEM images (a3-f3) were recorded from a 35° tilted angle.

Figure 9. Resolution assay 5: increasing microcontainer overall size. STL-file models (a1-f1) and SEM images (a2-f2, a3-f3) of microcontainers with differently sized micro-pillars placed on overhang. In contrast to the other figures, all STL-models featured an overall diameter of 1500 μm in the bottom and 2000 μm including overhang. Excluding the pillars, all microcontainers had a height of 600 μm. The dimensions of the micro-pillar top- and bottom diameters were: (a1) 30 μm-80 μm, (b1) 60 μm-100 μm, (c1) 80 μm-130 μm, (d1) 100 μm-170 μm, (e1) 120 μm-200 μm and (f1) 90 μm-200 μm. The height of the micro-pillars was set to be 200 μm. SEM images (A-F3) were recorded from a 35° tilted angle.

from that, the pillars could be recognized when considering the images taken from an angle. These findings suggest that in coherence with the other results, resin residue was covering the pillar structures of the microcontainers. Upon further inspection from the tilted perspective, single lithographic layers could be recognized, not only for the pillars, but also for the container structure. Except from the pillar surfaces which were covered with resin residue, the surfaces of the microcontainers were smooth and the cavities were sharply defined. The measured dimensions of the pillar diameters which are displayed in the SEM images deviated from the dimensions that were defined in the CAD drawings. Beginning from small pillars to large pillars, they were 7.8 (a), 3.9 (b), 3.2 (c), 2.9 (d), 2.6 (e) and 2.1 (f) times larger than specified nominal dimensions. Although the size deviation of the micro-pillars could not be considered to differ a lot from the previous results, the overall print quality of the microcontainers as a whole was improved in this experiment. Additionally, less resin residue could be found.

Conclusions

In this work, challenges and opportunities of using μSLA 3D printing for the manufacturing of various microcontainer geometries were investigated. The reported results showed an obvious deviation between dimensions of the printed structures and the ones given by the CAD models. In general, it could be observed that structures with smaller dimensions deviated more from the defined target values than...
structures with larger dimensions, thus showing the technical limitations of the employed 3D printing system.

Moreover, it was noticeable that in all experiments, the outcome of the 3D printing was substantially affected by the presence of leftover uncured print resin. The resin filled the reservoirs of the microcontainers and the interspaces between the micro-pillars placed on the edges. While the problem of 3D printing “cups” in stereolithography is a known issue, the post processing of 3D printed structures should accommodate for the removal of excess uncured print resin. Under the premise that the post-treatment/cleaning protocol will necessarily need to be the subject of a thorough optimization work, this research demonstrates the feasibility of using μSLA 3D printing to fabricate microcontainers for oral drug delivery since millimeter-sized devices could be realized with this micro manufacturing technology.

From an application point of view a further problem remains. All microcontainers were additively manufactured on a likewise 3D printed grid which irreversibly connected them. However, the working principle of microcontainers for oral drug delivery relies on individually acting containers that attach to the intestinal mucosa. With the current 3D printing method, the release of individual microcontainers is not possible. Therefore, the implementation of 3D printing on a sacrificial release layer as done in micromachining is suggested.

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