Additive Manufacturing of Drug Delivery Systems

M. Gieseke¹, V. Senz², M. Vehse³, S. Fiedler³, R. Irsig⁴, M. Hustedt¹, K. Sternberg³, C. Nölke¹, S. Kaierle¹, V. Wesling¹, J. Tigggesbäumker³, K.-H. Meiwes-Broer³, H. Seitz³, K.-P. Schmitz³, H. Haferkamp¹
¹Materials and Processes Department, Laser Zentrum Hannover e.V., Hannover, Germany
²Institute for Biomedical Engineering, University of Rostock, Rostock, Germany
³Chair of Fluid Technology and Microfluidics, University of Rostock, Rostock, Germany
⁴Institute of Physics, University of Rostock, Rostock, Germany

Abstract

New Drug Delivery Devices are produced using Selective Laser Micro Melting (SLµM). In a first approach, hollow micro needles with an inner diameter of 160 µm were manufactured from 316L stainless steel powder. Afterwards, the hollow micro needles were successfully filled with a test liquid. In a second approach, fully dense micro needles with an outer diameter of 200 µm were produced. A femtosecond laser setup was used to create discrete drug depots in fully dense micro needles.

1 Introduction

Nowadays, Additive Manufacturing offers the possibility to create three-dimensional structures from various metal and non-metal materials with less limitation in geometry compared to conventional manufacturing techniques. The Selective Laser Melting Process, as an additive manufacturing technique, is used for building up fully dense metal structures with comparable properties to cast material. In this process, a layer of metallic powder is deposited onto a build platform in a first step. In a second step the powder is melted by a scanner-controlled laser beam (see image 1). Facing long building times through layer-wise build up and expensive powder material on one side, individual parts with complex structures can be built easily with less preparation and changes in the manufacturing process [1].

![Image 1 Sketch of a SLM process](image1)

Since biocompatible materials such as stainless steel and cobalt-chromium-alloys are established in the process, the described technique offers a great possibility to generate complex patient adapted implants [3]. This concept is already realized industrially for manufacturing patient-adapted dental implants [4].

This technology offers new possibilities to create complex surface structures on implants to enable new drug delivery systems as it is done in the REMEDIS project. Currently drugs cannot be applied efficiently during and after implantation because suitable drug delivery systems are missing. In conventional pharmaceutical forms, high concentrations of the drug are delivered into the target and surrounding tissue at the beginning, followed by an exponential decrease. This leads to a very short time period where the required concentration of the drug is available in the tissue. To overcome this problem, new drug delivery systems, having a controlled and constant drug delivery in the target tissue, are invented [5].

In new biomedical approaches, the drug is surrounded by an inert membrane or embedded in a micro-porous or biodegradable polymer matrix or it is chemically bonded onto the base material. Using polymers as a carrier system, special properties regarding biocompatibility, biodegradability, productivity and bonding of the drug must be reached [5].

![Image 2 Drug delivery device for drug injection into the media](image2)
In an European Patent, Momma et al. described another a drug delivery device for injecting a drug into the media of a blood vessel (see image 2). The device consists of a hollow micro needle directly added onto the base implant. The cavity is filled with the drug and sealed by biodegradable polymer layers which control the delivery. The device is manufactured by electro polishing, laser ablation or micro lithography [6]. Based on this idea, investigations on manufacturing new drug delivery systems by Selective Laser Melting are carried out to generate solid drug delivery systems out of the implants’ base material.

As Gieseke et al. reported in 2012, a Selective Laser Micro Melting (SLµM) setup, i.e. a modified SLM process, was established in order to create hollow micro needles. Using this Selective Laser Micro Melting setup equipped with a 25 W fiber laser and a manual powder depositing mechanism, resolutions of less than 50 µm and an aspect ratio of 30:1 could be reached by building up straight walls [7].

A process parameter map for 316 L stainless steel powder was established to figure out parameter sets (laser power and scan speed) in order to produce fully dense micro structures with defined wall heights and without defects. Thus, first hollow micro needles could be produced with an inner diameter of 160 µm. Nevertheless powder particle adhesion caused by the energy input during the process which is necessary to get plain and fully dense structures could not be prevented in this process [7].

2 Methods

Based on the work of Gieseke et al. [7], two strategies for manufacturing micro needles with discrete drug depots have been investigated. First, hollow micro needles were produced using SLµM. Powder particle adhesions were ablated by femtosecond laser pulse treatment subsequently. Second, fully dense micro needles were produced by SLµM and afterwards discrete drug depots were drilled using femtosecond laser pulse processing. Finally, all micro needles were loaded with a test liquid.

The femtosecond laser pulse process was carried out at the Institute of Physics of the University of Rostock. The loading of the drug depots was done at the Chair of Fluid Technology and Microfluidics of the University of Rostock [8, 9].

2.1 Selective Laser Micro Melting (SLµM)

The biocompatible stainless steel alloy 316L (1.4404) was used to fabricate arrays of micro needles with sizes between 80 µm and 320 µm onto a 316L substrate plate in the first step. Therefore, 316L powder material with particle sizes from 5 µm to 25 µm was used to build up the needles having 20 µm thick layers. First the powder was deposited manually using a ceramic cylinder [7]. All investigations were taken out in a shielding gas atmosphere containing less than 300 ppm oxygen. Additionally, first trials using an automated powder depositing mechanism (see image 3) were done.

Image 3 Selective Laser Micro Melting setup

According to the previous investigations, powdered particle adhesion seems not to be preventable [7]. Therefore, investigations on ultrasonic cleaning in acetone were carried out in order to remove such particles subsequent to the SLµM process. Furthermore trials on plasma polishing were done by Plasotec GmbH, Germany for the same purpose.

2.2 Femtosecond laser treatment

For manufacturing the drug depots and ablating the powder particles, the micro needle array was placed on a linear positioning system and adjusted to the laser beam using a CCD camera. Here, a femtosecond laser with a center wavelength of 793 nm was used. The needles were irradiated with an average power of 150 mW, a pulse frequency of 1 kHz and a pulse width of 150 fs – 200 fs [8].

Image 4 Femtosecond laser pulse treatment setup

2.3 Loading method

The discrete drug depots were loaded with a test liquid using a piezoelectric drop-on-demand printhead [9]. The minimal droplet volume is about 100 pl. The drug depot array was placed on a motor driven x-y table to enable automated filling (see image 5).
3 Results

Hollow micro needles with a height of 1,200 µm and a minimum wall thickness of 100 µm were fabricated using 21 W laser power, 225 mm/s scan speed and a manual powder depositing mechanism. For leveling the molten structures, each layer was exposed for five times. In order to get fully dense and plain structures, the energy input was not decreased.

Due to the higher specific energy input caused by the circular microstructure, a larger melt pool was formed compared to straight walls and the maximum resolution of <50 µm could not be reached. The high energy input also led to increased powder adhesion at the lateral surfaces of the needles. Consequently the hollow structures were blocked partially. Due to this the minimum average inner diameter of a fully hollow structure was limited to 160 µm. Image 7 shows the cross section of micro needles of two different sizes with partly hollow (left side) and fully hollow (right side) structures. It is assumed that the decreasing inner diameter results from the changing process conditions during building up thin micro structures with a high aspect ratio. Thus the needle on the left side started to close the structure above a height of 550 µm and the inner diameter of the right structure decreased to 80 µm at the top. In addition, the wall thickness of both needles increases after having melted the first layers because of the decreasing energy dissipation into the base material and the resulting widening of the melt pool caused by the high energy input.

Minimizing the diameter of the scanning circle down to 80 µm led to fully dense micro needles with an outer diameter of 200 µm (image 8). Manufacturing larger needles is possible by adjusting the scanning strategy but was not investigated in this study.

Using the automated powder depositing mechanism, the processing time decreased from more than 90 minutes to 10 minutes. Hollow micro needles were manufactured, having an inner diameter of 120 µm. Since the process parameters were not changed, the powder adhesion was not reduced. Due to agglomeration of the fine powders the automatic deposited layers were not perfectly flat. Thus a modification of the depositing system is necessary.

Removing powder particles on the micro needles by 30 minutes of ultrasonic cleaning at 35 kHz and plasma polishing showed no effect. A mechanical cleaning using a wire brush is successful since the particles have low binding forces to the structure. Nevertheless, the applied forces may damage the micro structure.

3.1 Subsequent fs-laser treatment and loading

Using the femtosecond laser setup, holes with a diameter of 50 µm could be drilled into the fully dense micro needles in order to achieve discrete drug depots (image 9).
Due to the maximum achievable diameter of the present drilling process, this setup could not be used to ablate the adhering particles on the inner side of the hollow micro needles whose diameter is much bigger than 50 µm.

![Image 9](drug depot) Drug depot manufactured by fs-laser treatment

Hollow micro needles manufactured by SLµM were successfully filled by the drug printhead setup [8]. Theoretically, 45 nl – 50 nl of the methanol test liquid are filled into the depots. The really charged amount can only be estimated because of the fast methanol evaporation at room temperature and ambient pressure.

4 Conclusion

The SLµM process offers the possibility to create three dimensional micro structures with a minimum wall thickness below 50 µm and an aspect ratio of 30:1. Using this technique, hollow micro needles with a minimum inner diameter of 160 µm were successfully manufactured using 316L powder material. Fully dense micro needles with an outer diameter of 200 µm were produced by scanning circles with a diameter of 80 µm. Caused by the circular scanning structure and the resulting high energy input into the structures, the wall thickness exceeded 50 µm and powder adhesions on the produced structures could not be minimized. The manufacturing time could be decreased by 83 % using the automated powder depositing mechanism instead of manual powder depositing. Nevertheless the depositing mechanism has to be improved in order to enable a long-term stable powder depositing process.

Removing the adhering powder particles by ultrasonic cleaning and plasma polishing was not successful. The particles were sintered on the structures so that a cleaning with a wire brush is possible but can destroy the micro structures. Using this femtosecond laser setup holes with a diameter of 50 µm could be generated in fully dense needles. Due to the maximum achievable diameter of 50 µm, this setup is not suitable to ablate the powder particles on the inner side of hollow micro needles that have a bigger diameter. Using a piezoelectric drug printhead setup, hollow micro needles manufactured by SLµM could be filled with methanol as test liquid.

Further investigations will be done towards adjusting the SLµM parameters in order to achieve less powder adhesion and reduced wall thicknesses. Parallel trials on removing adhering particles using a subsequent etching process will be carried out. The automated powder depositing mechanism will be modified towards depositing a perfectly flat layer of fine powders.

Further investigations on manufacturing discrete drug depots by femtosecond laser treatment will be carried out at the Institute of Physics at the University of Rostock [8]. The filling of the produced drug depots with other liquids and the corresponding drug release of hollow micro needles manufactured by SLµM will be investigated in collaboration with the Chair of Microfluidics and the Institute for Biomedical Engineering at the University of Rostock [9].

5 References


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