Bioresorbable Implants using Selective Laser Melting

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Abstract

Using bioresorbable materials implants can be manufactured which dissolve in the human body and are replaced by natural bone structure. For large implants an interconnecting porous structure needs to be integrated in the implant for a good vascularisation. Using additive manufacturing technology these internal structures can be directly manufactured. The structure can be designed by consequent following the guidelines of the medical expert. This paper describes the development of Selective Laser Melting to process bioresorbable materials Poly(D,L-lactide) and β-Tricalciumphosphate. The properties of the parts concerning microstructure, mechanical and biological properties after processing are analyzed in laboratory and animal tests. Possible applications are demonstrated and include individual bone substitute implants in cranio-maxillofacial surgery.

Introduction

In medical science rapid prototyping (RP) and rapid manufacturing (RM) are manufacturing technologies with rapidly growing influence and large potential for several applications. Some applications are already industrial standard with growing numbers of applicants. These are for example the manufacturing of teeth restorations out of Cobalt-Chromium-alloy or the manufacturing of complex orthopedic devices. The manufacturing of bone substitute implants using RM technology is another field of interest. Additive Manufacturing like Selective Laser Melting (SLM) (also described as Direct Metal Laser Sintering or LaserCusing) or Electron Beam Melting (EBM) has advantages to conventional manufacturing like milling or casting concerning geometrical freedom, flexible production, material consumption and manufacturing time. The manufacturing with additive technology becomes economical in two cases. The first case is the manufacturing of individual implants in small series. There is no need for the casting or deep drawing. Individual implants based on CAD-data can be directly manufactured without changes in machine set up. Secondly manufacturing becomes economical when new functionalities can be integrated in the implant which would not be possible by conventional manufacturing. When these functionalities result in better quality of life of the patient, higher production costs can be negotiated be better durability and functionality of the implant. These functionalities can be for

example controlled porosity of the implant, adapted mechanical properties or new composite materials.

There have been many investigations on the manufacturing of permanent medical implants out of titanium(alloys), cobalt-chromium-alloys or implant steel [1, 2]. There were already clinical studies and applications of implants in the human body which were manufactured by Rapid Manufacturing technologies [3]. In many cases regenerative methods would be much better suited for the treatment of bone defects. There is taking place a strategical change in implantology from permanent implants to regenerative methods using resorbable materials. The gold standard at the moment is human bone taken e.g. from the iliac crest. This method requires a second surgery with its secondary morbidity. To avoid this, bioresorbable bone substitute materials are developed. There are several products on the market using different materials and different processing technologies. The materials can be used by the surgeon as paste, granules or semi-finished parts like cuboids or wedges. At the moment there is no processing technique to manufacture individual implants out of bioresorbable materials. This is based on two reasons. Conventional manufacturing methods involve a sintering process. This requires a tool to shape the implant. Individual implants would therefore be expensive due to expensive tool production. The second reason is the internal structure of bioresorbable implants. For full vascularisation of large implants an interconnected porous structure needs to be integrated in the implant. By varying the pore size ingrowth of cell tissue into the implant is possible. To realise a full vascularisation the pore size and interconnectivity needs to be well defined. These two problems for manufacturing of individual bioresorbable implants can be solved by rapid manufacturing technologies. The geometrical freedom of additive manufacturing makes the production of individual geometries and the realisation of a defined interconnected porosity possible by integrating the porous structure in the design of the implant.

There are several bioresorbable materials for example polymer-based [4], bioglass [5], resorbable metals or bioceramics [6, 7]. Bioceramics based on calcium phosphate (e.g. β-TCP) have the highest acceptance in medical science since their chemical structure is closest to human bone. In this work the additive manufacturing with Selective Laser Melting (SLM) is applied. For fusion of the powder a melt phase is required. Materials with thermal instability (like β-TCP) cannot be processed with SLM directly. Materials suitable for processing using melting of the material are polymer based materials e.g. polylactide (thermoplastic). During the resorption of polylactides an acidic environment is generated next to the implant due to the lactidic structure of the resorbable polymer. An acidic environment in human tissue results in inflammatory reactions [4].

For optimised properties of manufactured implants a combination of both materials is chosen: polylactide for processing using SLM and β-TCP for optimised biological properties. The approach of combining two materials has other medical advantages. The acidic surrounding can be decreased by using a composite with alcaline materials like calcium phosphate ceramics.

Using a composite of polymer and ceramic material the mechanical properties of the parts can be enhanced to pure polymer [8].

The main challenges for manufacturing bioresorbable implants using SLM are the preparation of the used materials for the SLM process and the processing of the material without damaging or changing its structure and chemical composition.

This work deals with the process adaption of Selective Laser Melting to process the bioresorbable composite poly(D,L-lactide) and β -tricalcium phosphate (PDLLA/ β -TCP). This is a completely new approach using medical approved materials to generate parts by full melting of PDLLA and embedding of β-TCP in a matrix of PDLLA.

Materials and Methods

Reflection of radiation

The processing of the used material with SLM strongly depends on the optical properties of the material. The laser source (wavelength) is then used depending on the measured reflection spectrum. As the material was used as a powder, the reflection of radiation of different wavelengths is analyzed on powder material. For wavelengths ranging from 400-2600 nm an UV/VIS/NIR Spectrometer Lambda 9 from Perkin Elmer is used. For wavelengths from 1900-22000 nm a FT-IR Spectrometer 1725 X from Perkin Elmer is used.

Powder morphology

β-TCP powder (Biovision GmbH Biomaterial, Wiesbaden, Germany) and PDLLA (Boehringer Ingelheim, Ingelheim, Germany) was used to produce the composite powder. Both materials were filled in a polyethylene bottle. Zirconia milling balls were added and the bottle was put on a rolling platform for three weeks. The resulting powder was prepared with a sieve of 90 µm mesh. The prepared composite powder was characterized before and after the milling process. The particles size distribution was measured using a particle size analyzer (Mastersizer 2000, Malvern, Worcestershire, Great Britain). The milled particles were embedded in a resin and a cross-section was prepared and analyzed using scanning electron microscopy (LEO 440i, Carl Zeiss SMT AG, Oberkochen, Germany).

SLM processing

For the processing of the composite material PDLLA and β -TCP using SLM, a process chamber developed at ILT was used together with a CO_2-laser (FEHA 400S, FEHA, Germany). The laser beam was projected on the powder bed using a scanning device (hurryscan 20, Scanlab, Germany) and an F-Theta focusing lens. The CO_2-laser operates in cw-mode at a wavelength of 10600 nm. To adjust the laser power for low intensities (0.2-10 W) a power attenuator (ULO optics, United Kingdom) was used. A schematic of the experimental set up is shown in Fig 1. To achieve a reproducible deposition of powder layers the powder deposition device was adopted.

For qualifying the SLM process for the processing of the composite material an adaption of the process parameters laser power, laser beam diameter, scanning velocity, track distance as well as powder layer thickness was done.

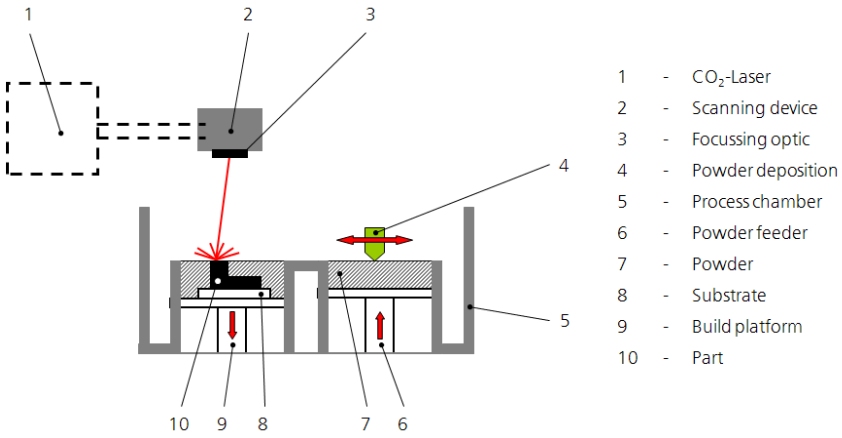


Fig 1: Schematic of the experimental setup

Microstructural analysis

One problem of powder based additive manufacturing is the appearance of pores and defects in the microstructure of the generated parts. This results in poor mechanical properties. Therefore the first aim for qualifying SLM to process the composite material PDLLA/β-TCP is to produce dense parts with a relative density >98%. Analysis of the density is done by optical analysis of cross sections of parts generated with different process parameters. An optical microscope and an analyzing software (Analysis, Olympus, Hamburg, Germany) is used to perform the measurement of the density.

Mechanical properties

The mechanical properties of bioresorbable bone substitute implants are tested with compression tests on porous test samples. This is in correlation to the literature [9, 10]. Cubes with varying pore diameter (500, 600 and 800 µm) and resulting porosity are manufactured using SLM and compressed until fracture of the part.

Biological analysis

The implementation of new manufacturing technologies for the processing of medical approved materials for series production of implants requires biological and medical analysis of manufactured parts. In biological tests (*in vitro* tests) the effect of the generated parts on bone cells (osteoblasts) is analyzed. Bioresorbable test geometries will be manufactured with an interconnecting pore structure to induce the ingrowth of bone into the implant for full resorption of the part. The pore diameter shows significant influence on the growth behavior of the cells. Test parts with different pore diameters are manufactured and the proliferation of the cells on the parts is measured using life / dead staining of the cells and optical analysis. To minimize the geometrical influence of the parts on the results, the same test geometry is used for *in vitro* and

in vivo tests (animal tests). The geometry is a cylinder of 15.6 mm diameter and 5 mm thickness. Pore structure is designed using CAD software according to Fig 2 using multiplied unit cells. The pore diameter is varied between 500-800 µm.

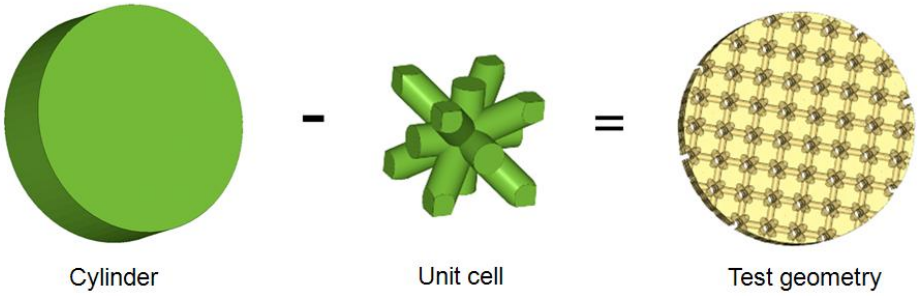


Fig 2: Schematic of the design of porous test geometries using multiple unit cells.

The test geometries are manufactured using process parameters for manufacturing of dense parts without defects to achieve high strength of the parts. The powder remaining in the pore structure is then removed by blasting with alumina particals. The manufactured and blasted test parts are then cleaned in ethanol, γ-sterilized and populated with human osteoblasts (HOB). The analysis of the cultured cells takes place after 1, 3 and 6 weeks. The results are compared to reference material (poylvinylalcohol, PVA) and phase pure medical grade β-TCP. The cells are then counted using optical analysis.

Animal experimental studies

Results concerning degradation and bone ingrowth into porous implants can only be achieved by suitable models of animal studies. To evaluate the properties of SLM implants with inter-connected porous structure *in vivo* 16 implants as described in the previous section with a pore channel diameter of 600 µm are manufactured. The parts are then sand blasted, washed in ethanol and γ-sterilized as described earlier. The animals are 20 rabbits of the race Chinchilla. The bone defect is located in the skull (calvarium) of the animals as shown in Fig 3. Four defects are filled with autologous bone (control), 16 defects are provided with SLM implants.

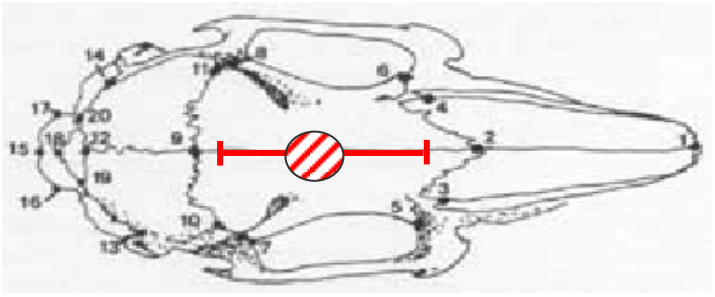


Fig 3: Schematic of the bone defect and the skin incision

Histological analysis is performed on cross sections of the test area after 8 weeks.

Results

Reflection of radiation

Fig 4 shows the measured diffuse reflection coefficient on composite powder out of PDLLA / β-TCP. At λ=10600 nm (CO_2-laser) a reflection of radiation of 4.5 % is measured. No transmission of radiation on powder layers of thickness > 30 µm is observed. Therefore 95.5 % of the radiation is absorbed in the powder layer and is used for the melting of the powder layer. The absorption coefficient at wavelength λ=1064 (Nd:YAG-laser) is between 2-6 %. The process of SLM is therefore expected to be efficient and more stable using CO_2-laser radiation.

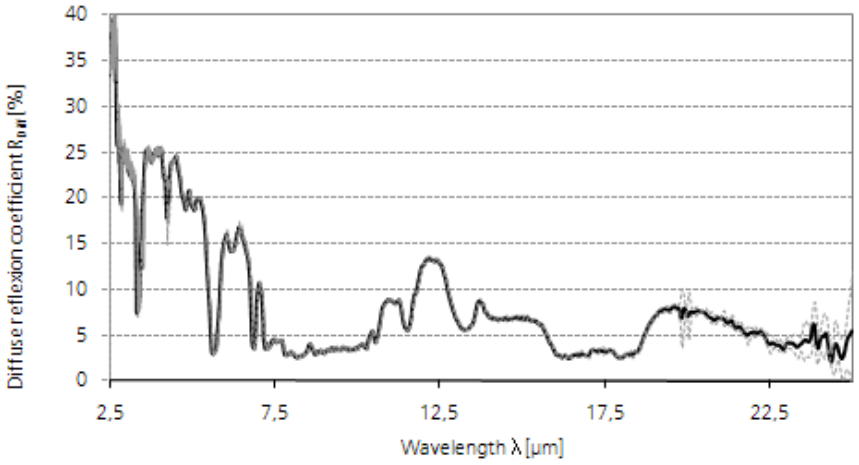


Fig 4: Reflexion of radiation at wavelength λ=2500 – 22500 nm for composite powder material

The results were confirmed using the SLM process chamber with different laser sources (diode pumped Nd:YAG laser (λ=1064 nm) and CO_2-laser (λ=10600 nm)). Much more laser power (tenfold) is needed to melt the polylactide using Nd:YAG-laser radiation. Once the material is molten, absorption increases and the material is burned. No suitable processing window could be identified to generate parts using Nd:YAG-laser radiation.

Powder morphology

Fig 5 shows SEM-pictures of the prepared composite particles out of PDLLA and β-TCP. Particles show a homogenous size distribution and are of cuboidal shape. To ensure a homogenous distribution of the composite materials in the generated part, homogenous distribution of the materials in each particle is aimed for to prevent separation during powder layer deposition. By grinding both materials in one process, the smaller β-TCP particles are ground into the PDLLA particles (Fig 5 b)).

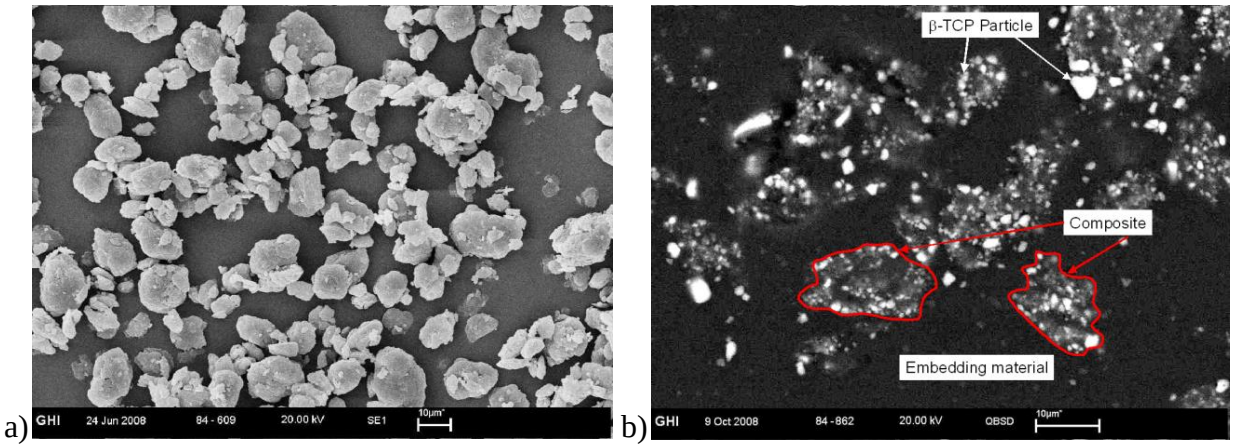


Fig 5: Composite particles out of PDLLA / β-TCP a) SEM picture, b) cross section

The particle size distribution is shown in Fig 6. The first maximum of particle size results of β-TCP particles which are between 1-5 µm of size. The second maximum at 35 µm is given by the PDLLA particles.

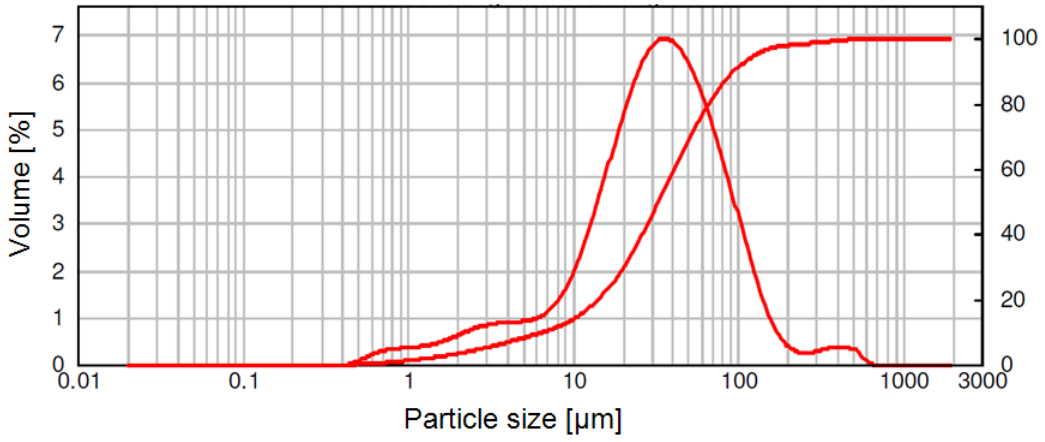


Fig 6: Particle size distribution for composite material out of β-TCP / PDLLA

The particle size distribution is suitable for the SLM process since the particles are smaller than one powder layer (50-100 µm). The flowability of the particles is limited, a suitable powder deposition technique needs to be developed.

Powder deposition

Due to the grinding process the powder particles are not spherical with poor flowability compared to spherical metal particles which have been used for SLM in the past [1]. For a reproducible powder layer deposition the powder deposition device is varied. The powder layer is crucial for the manufacturing of dense parts. Each layer has to be dense and of a defined thickness varied between 30 – 100 µm.

During SLM of metals the powder is deposited using a carbon fibre brush or a metal blade. This works well with spherical particles of high density (e.g. metals). Transferring these results to the deposition of the composite material a new deposition device is essential. The reason is the poor flowability of the particles and the low packing density due to low density of PDLLA (1.2 g/cm³). Therefore a powder deposition with additional compression of the powder layer needs to be developed. One attempt is the use of a bended aluminium plate (see Fig 7 a)). This approach results in a powder layer shown in Fig 8 a). The powder layer is of defined thickness, the compression is very high. Due to inhomogeneous compression of the powder bed powder ripples appear. This technique is not suitable for reproducible powder deposition. Different approaches with different angles of the plate surface to the powder bed resulted in no significant improvement in the appearance of ripples. Another approach is using a counter rotating cylinder. The schematic is shown in Fig 7 c). Using this and after varying the moving and rotating speed of the roller a reproducible and dense powder layer could be deposited (Fig 8 b)).

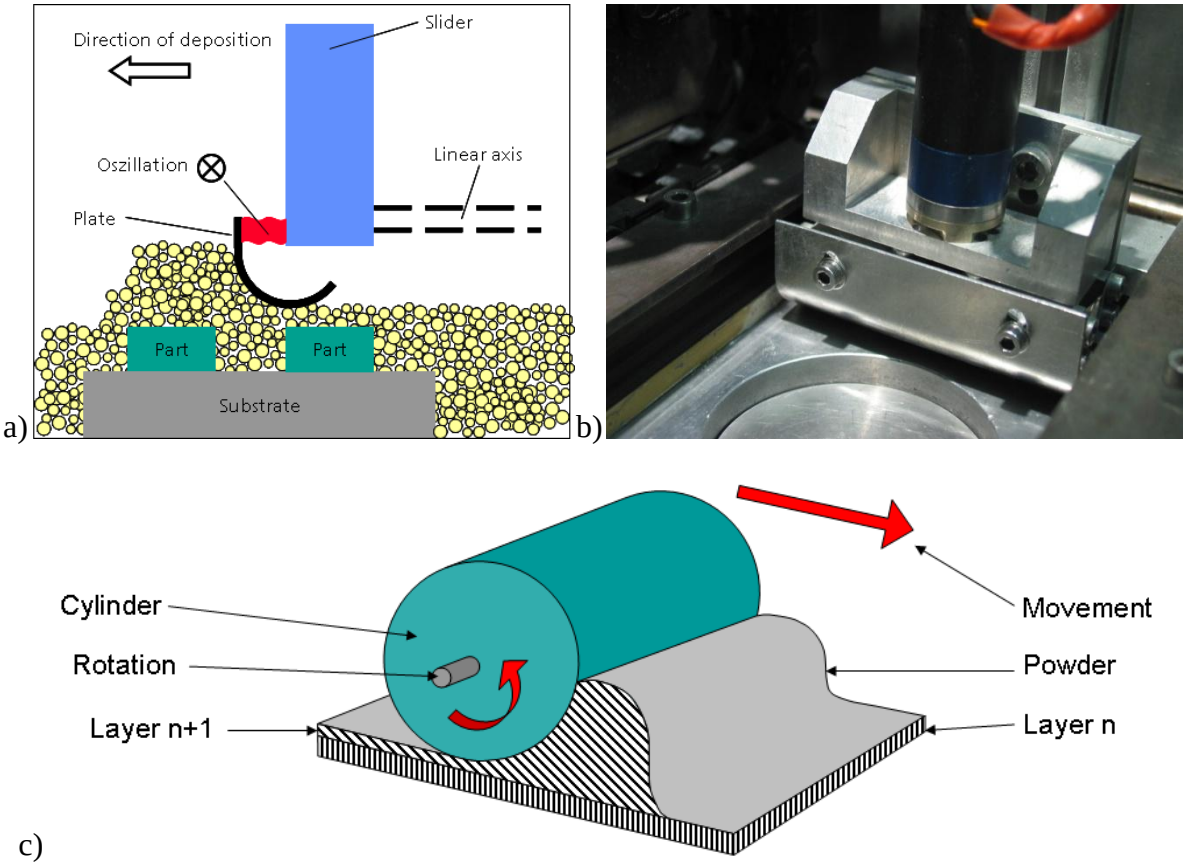
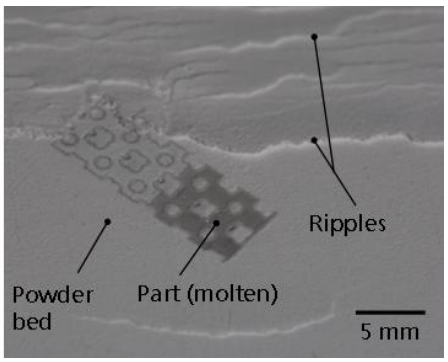


Fig 7: Powder deposition techniques a) schematic of bended plate, b) photo of bended plate, c) schematic of rotating roller

a) 

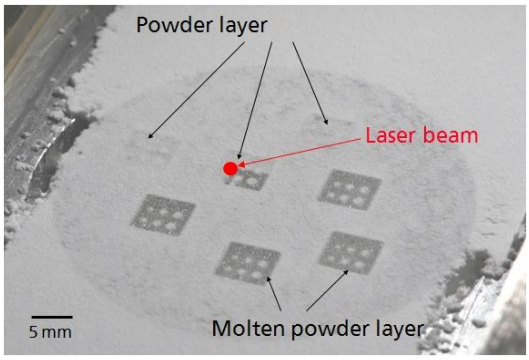
b) 

Fig 8: Resulting powder layer a) bended plate b) rotating roller

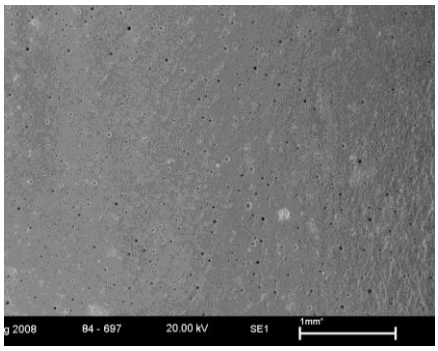
Process parameter variation

The range of variation of process parameters is given in Tab 1. The variation is performed by building test cubes of 6 mm edge length. Cross sections of the cubes are prepared and optical analysis of the density of the parts is performed.

Process parameter	
Laser power P_L [W]	0,2 - 10
Scanning velocity v_{scan} [mm/s]	5 - 500
Track distance Δy_s [µm]	10 – 200
Layer thickness D_s [µm]	20 - 100
Beam diameter d_s [µm]	< 500
PDLLA fraction [Wt. %]	30 - 70

Tab 1: Variation of process parameters

Fig 9 a) shows an SEM image of a cross section of a test part. Single pores can still be observed, the overall density is >98 % in the processed area. This result is the basis for manufacturing of demonstrational implants. One application is an implant for a large bone defect in the skull with individually fitted design to reproduce the original shape of the bone. A demonstrational implant is manufactured using parameters leading to nearly full density of the part (Fig 9 b).

a) 

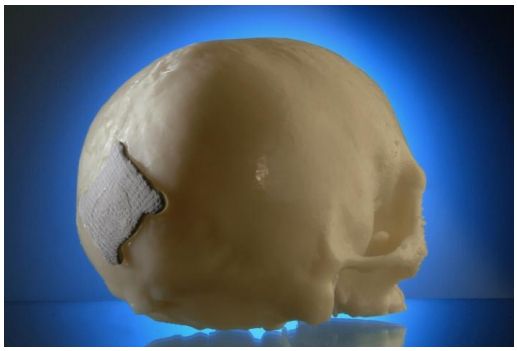
b) 

Fig 9: a) Cross section of test geometry out of PDLLA / β-TCP, b) Individual cranial implant

Mechanical properties

The compression strength of the test geometries is shown in Fig 10. Depending on the porosity of the test parts compression strength between 3.4 – 8.8 MPa were achieved. As supposed, parts with higher porosity (larger pore diameter) show lower strength. The strength of the parts is in the area of medium to high strength of cancellous bone (2-12 MPa [11]).

Pore diameter d_P [µm]	Porosity P [%]	Compression strength σ_{komp} [MPa]
0,5	35	8,80 ± 0,05
0,6	47	4,22 ± 0,51
0,8	53	3,43 ± 0,77

Tab 2: Compression strength of porous test geometries with different pore structure

Since the strength of the parts is comparable to cancellous bone SLM creates the possibility to manufacture bone substitute implants for non load-bearing bone defects which are suited for clinical use.

Biological analysis (*in vitro*)

The test geometries for *in vitro* and *in vivo* analysis manufactured with SLM are shown in Fig 10.

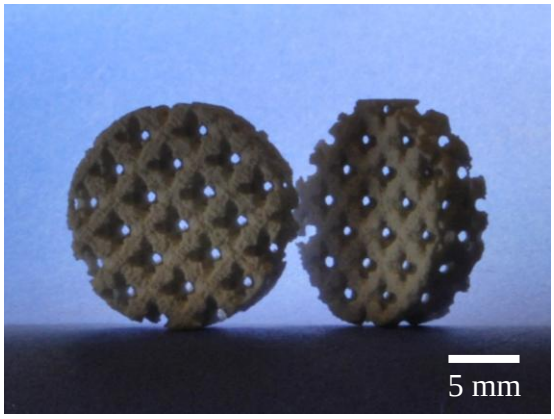


Fig 10: Manufactured parts with interconnecting pore structure for *in vitro* and *in vivo* analysis

The results of the *in vitro* analysis are shown in Fig 11. The graph shows the relative fluorescence of the living cells, greater fluorescence therefore indicates a higher number of living cells. The proliferation of osteoblasts exceeds for SLM-parts with pore size 600 µm and 700 µm the results achieved on the control and phase pure β-TCP. Since no conclusion can be drawn out of this result between 600µm and 700 µm, 600 µm is chosen for animal testing which is in good accordance with the literature [2, 12]). These results show as well that the SLM process has no toxic influence on the proliferation of bone cell.

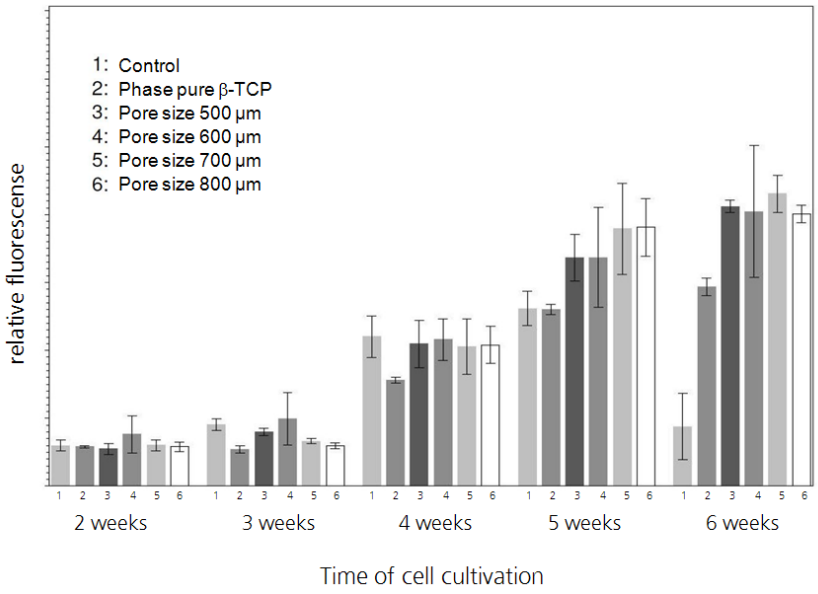


Fig 11: Proliferation of osteoblasts on SLM test geometries for different pore sizes

Animal studies (rabbits)

The removed implants are analyzed on the presence of new bone formation. Histological sections are shown in Fig 12. After 12 weeks natural bone minerals (NBM) can be seen in Fig 12 a). New bone formation can be observed in Fig 13 b) (arrows).

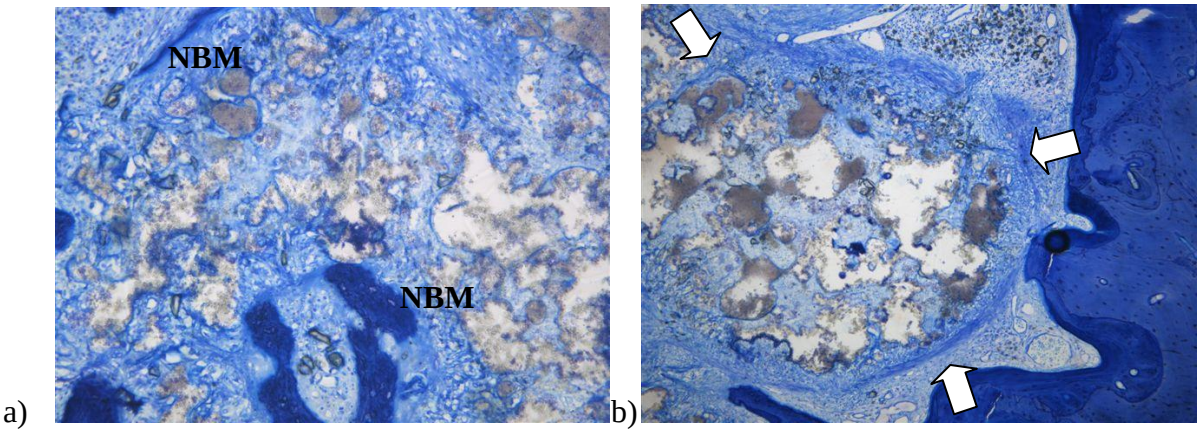


Fig 12: Histological sections (200x) of implants showing natural bone minerals (a) and new bone formation (b)

Histological analysis show, that new bone formation has started after 8 weeks with bone formation in critical size defects, i.e. bone defects that do not heal without scaffold. This demonstrates the potential of future application of SLM implants for healing large bone defects.

Discussion

The presented results show, that bioresorbable bone substitute implants can be manufactured with Selective Laser Melting (SLM). Particles out of a composite material of poly(D,L-lactide) (PDLLA) and β-Tricalciumphosphate (β-TCP) have been prepared by grinding. Particles show homogenous distribution of the composites and are suitable for powder layer deposition during additive manufacturing. SLM process has been developed to generate dense parts with a homogenous distribution of composites without major changes in physical and chemical properties of the materials. For full vascularisation of bioresorbable implants an interconnecting porous structure is necessary. Using additive manufacturing technology SLM, pore structures can be integrated in the design of the implant and are reproduced in the part. To demonstrate the possible application of the manufacturing technology a skull defect is used to manufacture an individually designed implant with interconnecting porous structure shown in Fig 13.

The mechanical properties of fabricated test geometries are in the medium to high range of human cancellous bone and the implants are therefore suitable for application in non load-bearing bone defects. *In vitro* experiments show good proliferation and no cytotoxicity of human osteoblasts on SLM test geometries. This result demonstrates that no changes of the biological material properties occur during the processing of the material. Following these positive results animal studies have been carried out to analyze the new bone formation in the implant *in vivo*. Histological analysis shows that natural bone minerals and new bone formation takes place during 8 weeks in the scull of a chinchilla. Bone ingrowth is observed into the porous structure of the test geometries. These first results show the high potential of porous structures manufactured by SLM for the reconstruction of large bone defects. Still more and large scale studies have to be carried to confirm the potential. Using SLM a high freedom of design of the interconnected porous structure is possible which opens up new approaches for designing pore channels for optimized vascularisation of the implants.

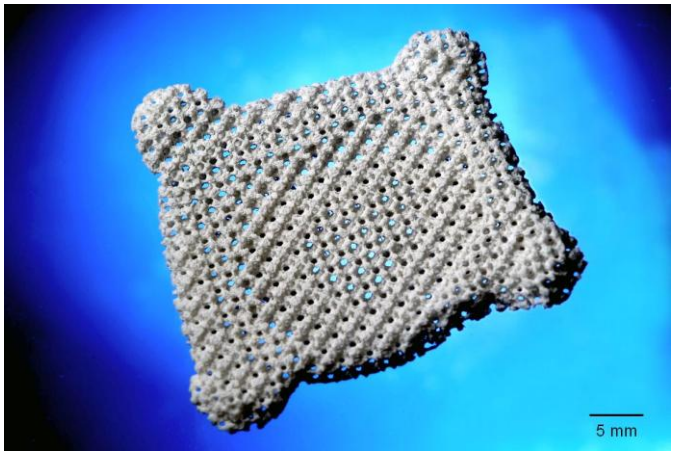


Fig 13: Demonstrational implant with interconnected porous structure

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