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# Advanced production techniques and designing of porous titanium bio implants and scaffolds

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## ABSTRACT

Traditional manufacturing processes such as casting and machining are being largely replaced by the advanced manufacturing techniques such as ALM and MIM in the bio-implant manufacturing sector due to their design flexibility, minimum wastage of raw materials, power efficiency, ability to produce complex porous structures and accuracy. These techniques suffer from drawbacks due to their high market cost and low surface finish of the implant produced. Porous titanium implants/scaffolds are being extensively manufactured by these advanced techniques due to their high strength, high corrosion resistance, better surface characteristics for bio attachments and biocompatibility. By making porous, the density and strength of the bio scaffolds/implants can be matched with the surrounding tissues and bones for greater grip and provisions for bone in-growth. In this paper, the current designing and production methods of porous titanium bio implants and scaffolds are being described in detail. In the designing phase of the implants, topology optimization is playing a crucial role in increasing the flexibility in design by eliminating the need fortrial and error method for improved biocompatibility and mechanical property.

**Keywords:***Biocompatibility; Implants; Scaffolds; Titanium; Porous, Additive Layer Manufacturing, Metal Injection Moulding, Topology Optimization.*

## 1. INTRODUCTION

The bones in our body are complex structured links thatmaintain its healthy mechanical homeostasis condition by discarding mature bone cells and replacing with new ones [1]. Bones generally exhibit a young's modulus in the range of 3-30 GPa and stresses might sometimes exceed its limit resulting in fracture or any other damage to the bone. In such situations, metallic implants and scaffolds need to be attached to the actual bone as supportive links and be intact until the healing is complete [2]. Metals and alloys, that exhibit biocompatibility with the body tissues and bones, are commonly employed materials for the production of the metallic implants and scaffolds which includes titanium and titanium alloys, cobalt based alloys and stainless steel. Titanium and their alloys [56] have a limited usage due to their high production cost but has some of most superior properties such as high resistance to corrosion, high specific strength [3], bio-compatibility and low conductivity which is responsible for retaining a suitable PH value (comparable to human body PH [4]) of the titanium oxides, formed on the surface of the titanium specimen by a process of electrochemical oxidation [5]. Moreover, pure titanium (CP-Ti) is considered the most biocompatible material [6] due to the high resistance to corrosion of its oxide layers [57] and spontaneous formation of the oxides in contact with the oxidizing environment, maintaining a stable and inert environment. The major mechanical limitations of Ti and its alloys include their low wear resistance and high Young's Modulus (ranging around 110 GPa) [7,8,9]. Due to the extreme mismatch in the Young's Modulus of the titanium implant and the bones [10], stress shielding and bone resorption are a common occurrence which needs to be avoided by reducing the elastic modulus [11]. An effective technique in reducing the Young's modulus of the titanium and titanium alloys is the introduction of interconnected pores or adjustable relative density in the material as suggested by [12] for isotropic material. This also facilitates bone in-growth and formation of channels for transportation of nutrients and metabolic waste [13,14]. The mechanical properties of the porous titanium implants can be altered by adjusting the pore size distribution or volume fraction [15] of the pores. Elastic modulus under compressive load has been found to be decreased with an increase in the size of the pores [16]. Porous titanium implants can effectively be produced employing the advanced techniques of manufacturing of biomaterial implants which include the Additive Layer Manufacturing (ALM) and Metal Injection Moulding (MIM). These techniques yield accuracy in the implants, less wastage of material, complex porous structure manufacture and provide flexibility and cost effectiveness in design alterations. In this paper, the design of the porous titanium implant/scaffold, the advanced techniques of ALM including SLS, SLM and EBM and MIM processing techniques, advantages and limitations are described in detail.

## 2. POROUS TITANIUM IMPLANT/ SCAFFOLD DESIGN

In order to match the mechanical properties of the bones and the titanium implants and scaffolds, manufacture of porous material proves to be an effective way of employing the advanced techniques of manufacturing such as ALM and MIM. The production of an appropriate porous structure begins with the design phase which can be implemented using different modelling and analysis methods such as CAD and Finite Element Analysis (FEA), image based design, implicit surface designs and topology optimization.

CAD based designs are generally performed employing various CAD tools. Based on the scaffold libraries, CAD system has been employed to automate the entire design process of optimizing parts for better unification of the properties of the damaged bones, surrounding tissues and the titanium implants/scaffolds and for model topologies [17,18,19]. The libraries are enriched with the introduction of Bio-inspired parts and contributing to improvement in the overall mechanical performance of the scaffold/implant structure [20,21,22]. Image based designs are based on Computed Tomography (CT) scan and Magnetic Resonance Image (MRI) data which are utilized to design the actual structure of the damaged bone in the form of 3D computer models and comparing using Boolean combination of the actual digital image with the architecture image (empirical or Bio inspired shapes) [23,24]. Implicit surface design enables introduction of pore shapes using a single mathematical equation for modelling of porous scaffolds employing flexible systems such as the Tripy periodic minimal surfaces (TPMS) [25,26].

Topological optimization is a mathematical technique to fabricate the scaffolds/implants in its desired properties for optimized biocompatibility and mechanical performance by rearranging the material and satisfying to specific constraints. Thus, minimizing the effort for trial and error method and facilitating complex scaffold/implant designing. It is a computational method that was first developed for structural engineering designs [27]. Currently, this method has been developed far beyond the scope of just the traditional structural engineering design [28].

The design and fabrication parameter selection of the porous titanium scaffolds and implants, influence greatly the properties and qualities of the final structure of the part [29]. Moreover, the processability of the designed part by the methods of the advanced production technique of ALM must be considered during the topology optimization stage of designing so that the production of the final part can be seamlessly executed.

## 3. ADDITIVE LAYER MANUFACTURING (ALM)

ALM technology can be suitably employed for the production of porous titanium implants and scaffolds with complex features and customization. Apart from the flexibility in its production capability, multi phase materials can also be fabricated using ALM technology. ALM is based on a process of depositing layers of the material one over the other having specified area of deposition to form the final product. The data for the specified area and dimension of the part to be fabricated is imported into the ALM device from the CAD design software. Advanced ALM techniques include powder based Selective laser sintering (SLS), Selective laser melting (SLM) and Electron beam melting (EBM) [53, 54,55, 58]. These are described below:

***Electron beam melting (EBM).***

In electron beam melting, electron beam emitted from an electron source is accelerated and concentrated onto the titanium powder by letting it pass through a magnetic field, to melt the metal powder layer upon layer, building the final solid porous structure. The electron beam is directed at a power of upto 3 kW and under vacuum which is a favourable condition for working on titanium at elevated temperature. The major challenge in the production of porous titanium implants/ scaffolds is the surface roughness problem which is difficult to minimize due to involvement of a number of factors like particle size, electron beam current and part orientation. The surface interaction of the titanium bio metal and the biological environment is important as it determines the biocompatibility and mechanical suitability of the implants /scaffolds. The bone ingrowth and bone bonding improve and enhances the load bearing capability of the implants/scaffolds. It has also been shown that the surface roughness having the range within 0.5 μm proves to be possessing the property of ideal biocompatibility [30].

The structure fabricated using the EBM process is of high strength and elasticity of around 1.34 GPa, having the microsructure containing both the phases ( $\alpha + \beta$ ) and are influenced by the high temperature working and lower cooling rate. Due to higher temperature, titanium gets enough time and fluidity to fuse for higher elastic modulus. EBM produces a shallow and a larger diameter weld spot of around 128 μm and due to its lower cooling rate, a dwell period of temperature is maintained within the pool which differentiates the microstructure obtained from all other processes while maintaining the mechanical property intact [31].

***Selective Laser Melting (SLM).***

In selective laser melting, laser light source instead of electron beam can be converted by optical means to a very small diameter spot (less than 100 μm), enhancing the energy density to a small point. Due to such concentration of energy, the accuracy of the operation increases and larger depth can be achieved. Integrating SLM with the CAD system or CT scan, complex porous titanium implants/scaffolds can be fabricated with high precision and biocompatibility, mimicking appropriately with human bone [32]. The major drawback of building parts using SLM process is the low surface finish that is obtained.

An important parameter of the SLM process that influences the strength and the pore characteristics of the porous titanium bio implants and scaffolds arethe scan spacing width. With increase in the width of the scan spacing, the porous material tends to reduce in its Young’s modulus of elasticity. For better interconnections between the pores in the bio-implant, the pore size must be 3 times larger than the particle size and thus the ideal pore size is taken to be ranging between 250 to 450μm [33**].** Young’s modulus of the titanium alloy has been reduced to match with the mechanical strength of the cortical bone by introducing 5-10% of porosity in the material [34]. Pore size and interconnection between the pores influences the bone in-growth and bonding with the implant/scaffold surface and an optimal pore size of 600 μm is taken, for better mechanical strength, fixation and biocompatibility [35]. Fabrication capability of the SLM process has been investigated in terms of dimensional accuracy of the titanium alloy (Ti-6Al-4V) part with the actual CAD model which gives an excellent result [36].

There are two important process parameters of SLM such as laser scan speed and power which need to be optimized for the best quality porous structure of titanium. The ratio of the laser power to the scan speed is generally termed as light energy density (LED), the value of which when increased (or decrease of scan speed) forms micro balling and cracks in the structure. Reducing the LED value or increasing the scan speed, disordered solidification and fusion of powder particles takes place and low strength parts manufactured [37].

***Selective Laser Sintering (SLS)***

SLS system utilizes a low temperature fusion process of powder particles for manufacture of complex porous structure thus facilitating the application of polymers, polymer bio-ceramic composites, NiTi and Titanium silica. The powder particles are heated to its sintering temperature and partially melted to fuse together. SLS was the first powder bed fusion technology to be commercialized. It differs from the other powder bed fusion based techniques in its material usage and low temperature requirement. Metallic composite based SLS system utilizes heat from the laser source to partially melt the metal particles to fuse together with the polymer particles acting as a binder in its melt state. After completion of the solidification, the polymer is removed by the process of de-polymerization to obtain a porous metallic structure. Metallic foams are commonly produced porous structure-based implants and scaffolds using SLS system. Metallic foams have been fabricated to imitate the cellular structure of the cancellous bone and at the same time introducing required porosity, strength, shape, size and biocompatibility [38,39].

The important parameters to be considered for better performance of the SLS process in production of porous structure metallic implants can be given as the scanning speed, laser power, fabrication layer thickness and laser hatch spacing. SLS systems can be used efficiently for the fabrication of bone scaffolds made of a mixture of Titanium and silica in a ratio of 2:1. Titanium implants have been reported to consume a laser power of about 15-16 kHz with a scanning speed of 100mm/s. Later after the fabrication, the implant is taken through the sintered temperature of $900^0$C for 120 minutes to acquire the strength of around 142 MPa [40].

## 4. METAL INJECTION MOULDING (MIM) MATERIALS AND METHODS

Metal injection moulding is a unique powder metallurgy (PM) operation with the incorporation of plastic injection moulding technique, that provides enough flexibility in implant design [41,42,43,44] and is capable of producing both porous and solid titanium implants. MIM can be effectively exploited for the manufacturing of small and medium sized implants with complex dimensions in industries. The attributes of the PM such as the flexibility in selecting the composition of the powder, low cost and simplicity are combined with the characteristics of the plastic injection moulding such as rapid production and complex parts manufacturing ability [42]. Nelles et al. [45] published the first U.S. patent in 2003 in developing a MIM system to produce porous titanium implants using space holders such as KCl or NaCl. Later on, developmental works in improving the MIM process to incorporate space holder as the means to produce porous structure of titanium implants have been performed [46,47,48]. With the help of MIM technique and using hydrate dehydrate (HDH) titanium powder and space holder (NaCl) as raw material, Chen et al. [47] produced a porous titanium implant with 60% porosity. The steps in producing a porous titanium implant using MIM technique [52] have been described in detail below:

***Feedstock Preparation.***

The input material for the MIM technique is first prepared by mixing different Titanium powder particles, space holders and binder together under different thermal condition. Commercially available pure titanium powder (higher than 99.6% purity) that has been gas atomized, KCl micro cube particles as the space holders for porous formation of the final implant and a combination of high density polyethylene (HDPE) of 36% wt, paraffin wax of 61% wt and stearic acid of 3% wt as the binder material have been taken for the preparation of the feedstock. 95% of the titanium powder particles had the size lesser than 45 $\mu m$ while KCl micro cubes for space holder had the size greater than 250 $\mu m$ with the value of the volume ratio of (Ti+KCl) to the binder material in solid loading condition, taken as 69%. This percentage of solid loading was found to be appropriate for the mixing process and the injection moulding process as suggested by previous studies [44].

The Ti powder, KCl space holder and the binders are first mixed thoroughly under the dry condition for about 60 mins which are then taken to a preheated mixer to mix the particles at a temperature of $150^0$ C for 2 hours under an argon atmosphere to avoid oxidation at elevated temperature. The mixture is then cooled to room temperature and further mixed by repeated extrusion through an extruder that has been preheated to $160^0$ C. Finally the extruded material is hand crushed to reduce the size of the particles to less than 3 mm for MIM process.

***Metal Injection Moulding.***

The crushed granulated titanium feedstock with binder in it is then fed into the injection mould where under extreme pressure of the ram and at a temperature lesser than $200^0$ C, the material is injected into cavities that havebeen shaped in the form of the implants /scaffolds. The green part obtained after solidification and cool down is then immersed into a bath of Hexane kept at a temperature of $50^0$ C and for a duration of 20 hours for complete removal of the paraffin wax. This phase is termed as the solvent debinding phase which is then followed by immersion of the part into a water bath kept at $60^0$C for a duration of 24 hours to eliminate the KCl particles (space holder). After the solvent debinding, the next step is the thermal binding where the Ti part is taken to a temperature of about $550^0$C at the rate of $1^0$C/min under an argon flow of around 3L/min and then maintained isothermally at that temperature for about 1 hour. This thermal debinding operation extract out the remaining HDPE material to form a brown part which is subsequently followed by the sintering process under a vacuum condition, slowly raising the temperature at the same rate to a temperature of about 1150,1250 and $1300^0$C (in steps) and then cooled at a relatively higher rate of $4^0$C/min.

The surface finish obtained after the sintered Ti part is cooled to room temperature is not appropriate which is basically influenced by processing parameters such as starting powder particle size and the tool finish of the mould cavity. Requirement of improved design of the furnace to avoid contamination of the titanium at elevated temperature, availability of carbon free binders and quality titanium powder are few other drawbacks of Ti based MIM technique. The microstructure, mechanical compatibility and biocompatibility of a Ti implant manufactured by MIM technique were studied by Sago et al. [49] that was found to have a satisfactory result.

## 5. CHALLENGES AND FUTURE DIRECTIONS

A few challenges associated with implication of advanced manufacturing techniques are the surface roughness (obtained from both the techniques) which can be corrected by applying few chemical and mechanical post processing and coatings. Further development in improving the surface complexities of the implant is needed to enhance the cell and tissue attachment and bone ingrowth.

Due to the mechanical strength and biocompatibility of titanium-based material, it is increasingly expanding its range of usage in bio-medical industries. Advanced manufacturing techniques such as ALM and MIM recently are being used extensively in production of porous titanium bio-implants and arereplacing the traditional casting and machining operations. This is supported by their various advantages in metal implant production such as no wastage cost, flexibility in design, energy efficiency, reduced processing cost and improved functionality. Topological optimization is becoming a powerful tool in generating optimized structures for complex porous implants facilitating improved surface attachments with the surrounding tissues, bone in-growth and desired mechanical properties.

Customized production of bio-implants using advanced manufacturing techniques will be common in future. In 2012, 16.4% of the total AM related revenue was from the biomedical applications [50]. Metal AM industries are competing among themselves to produce AM machines that enable cheap and faster bio-product manufacture. Also, efforts have been made by Desktop Metal [51] to introduce new generation processing techniques in metal AM that is expected to revolutionize the market of biomedical implants and scaffolds.

## 6. CONCLUSIONS

From the above discussions, it is clear that porous titanium implants and scaffolds can be suitably manufactured by employing the advanced manufacturing techniques of ALM and MIM. Before the actual production, a thorough investigation into the design of the implant/ scaffolds is done and analyzed for mechanical strength, sufficiency in porosity, biocompatibility and adequacy in surface roughness using various CAD tools. Topological optimization is another aspect in design phase of porous titanium bio-implants which provides a mathematical tool to optimize for the properties of the material for the best bio-compatibility and strength of the bone. In order to produce customized metallic bio implants with higher accuracy, flexibility and minimum usage of resources and energy, the advanced manufacturing techniques prove to be better contender as compared to all other conventional methods like casting and machining. The drawbacks of the advanced manufacturing process lies in the cost of the equipment and surface roughness of the produced implants which therefore later needs to be followed by other post-processing techniques.

## 7. REFERENCES

1. Currey, J.D. *Bones: Structure and Mechanics*. Princeton University Press, **2002**.
2. Bose, S.; Vahabzadeh, S.; Bandyopadhyay, A. Bone tissue engineering using 3D printing. *Mater. Today***2013**, *16*, 496-504, https://doi.org/10.1016/j.mattod.2013.11.017.
3. Guo, S.; Qu, X.; He, X.; Zhou, T.; Duan, B. Powder injection molding of Ti-6Al-4V alloy. *J. Mater. Process. Technol.* **2006**, *173*, 310–314, https://doi.org/10.1016/j.jmatprotec.2005.12.001.
4. Schiff, N.; Grosgogeat, B.; Lissac, M.; Dalard, F. Influence of fluoride content and pH on the corrosion resistance of titanium and its alloys. *Biomaterials* **2002**, *23*, 1995–2002, https://doi.org/10.1016/S0142-9612(01)00328-3.

Quinn, R.K.; Armstrong, N.R. Electrochemical and surface analytical characterization of titanium and titanium hydride thin-film electrode oxidation. *J. Electrochem. Soc.* **1978**, *125*, 1790–1796

6. Elias, C.N.; Lima, J.H.C.; Valiev, R.; Meyers, M.A. Biomedical applications of titanium and its alloys. *JOM* **2008**, *60*, 46–49, https://doi.org/10.1007/s11837-008-0031-1.
7. Long, M.; Rack, H. Titanium alloys in total joint replacement - a materials science perspective. *Biomaterials***1998**, *19*, 1621-1639, https://doi.org/10.1016/S0142-9612(97)00146-4.
8. Niinomi, M. Recent research and development in titanium alloys for biomedical applications and healthcare goods.*Sci. Tech. Adv. Mater.***2003**, *4*, 445-454, https://doi.org/10.1016/j.stam.2003.09.002.
9. McAfee, P.C.; Farey, I.D.; Sutterlin, C.E.; Gurr, K.R.; Warden, K.E.; Cunningham, B.W. The effect of spinal implant rigidity on vertebral bone density: a canine model.*Spine* **1991**, *16*, S190-S197, https://doi.org/10.1097/00007632-199106001-00003.
10. Zhao, X.; Chen, L.; Xin, L.; Huang, W. Study on microstructure and mechanical properties of laser rapid forming Inconel 718. *Mater. Sci. Eng. A Struct.* **2008**, *478*, 119–124, https://doi.org/10.1016/j.msea.2007.05.079.
11. Bidaux, J.E.; Closuit, C.; Rodriguez-Arbaizar, M.; Zufferey, D.; Carreno-Morelli, E. Metal injection moulding of low modulus Ti-Nb alloys for biomedical applications. *Powder Metall.* **2013**, *56*, 263–266, https://doi.org/10.1179/0032589913Z.000000000118.
12. Gibson, L.J.; Ashby, M.F.*Cellular Solids: Structure and Properties.* Cambridge University Press, 1999; https://doi.org/10.1017/CBO9781139878326.
13. Ponader, S.; Von Wilmowsky, C.; Widenmayer, M.; Lutz, R.; Heinl, P.; Körner, C.; Singer, R.F.; Nkenke, E.; Neukam,

F.W.; Schlegel, K.A. *In vivo* performance of selective electron beam-melted Ti-6Al-4V structures. *J. Bio. Mater. Res. A* **2009**, *92*, 56–62, https://doi.org/10.1002/jbm.a.32337.

14. Tan, X.P.; Tan, Y.J.; Chow, C.S.L.; Tor, S.B.; Yeong, W.Y. Metallic powder-bed based 3D printing of cellular scaffolds for orthopaedic implants: A state-of-the-art review on manufacturing, topological design, mechanical properties and biocompatibility. *Materials Science and Engineering.C***2017**,*76*, 1328–1343, https://doi.org/10.1016/j.msec.2017.02.094.

15. Murr, L.E.; Amato, K.N.; Li, S.J.; Tian, Y.X.; Cheng, X.Y.; Gaytan, S.M.; Martinez, E.; Shindo, P.W.; Medina, F.; Wicker, R.B. Microstructure and mechanical properties of open-cellular biomaterials prototypes for total knee replacement implants fabricated by electron beam melting. *J. Mech. Behav. Biomed. Mater.* **2011**, *4*, 1396–1411, https://doi.org/10.1016/j.jmbbm.2011.05.010.

16. Parthasarathy, J.; Starly, B.; Raman, S.; Christensen, A. Mechanical evaluation of porous titanium (Ti6Al4V) structures with electron beam melting (EBM). *J. Mech. Behav Biomed. Mater.* **2010**, *3*, 249–259, https://doi.org/10.1016/j.jmbbm.2009.10.006.

17. Sudarmadji, N.; Tan, J.Y.; Leong, K.F.; Chua, C.K.; Loh, Y.T. Investigation of the mechanical properties and porosity relationships in selective laser-sintered polyhedral for functionally graded scaffolds.*Acta Biomater*. **2011**, *7*, 530-537, https://doi.org/10.1016/j.actbio.2010.09.024.

18. Naing, M.W.; Chua, C.K.; Leong, K.F.; Wang, Y. Fabrication of customised scaffolds using computer-aided design and rapid prototyping techniques.*Rapid Prototyp. J.***2005**, *11*, 249-259, https://doi.org/10.1108/13552540510612938.

19. Cheah, C.M.; Chua, C.K.; Leong, K.F.; Cheong, C.H.; Naing, M.W. Automatic algorithm for generating complex polyhedral scaffold structures for tissue engineering.*Tissue Eng.***2004**, *10*, 595-610, http://dx.doi.org/10.1089/107632704323061951.

20. Nam, J.; Starly, B.; Darling, A.; Sun, W. Computer aided tissue engineering for modeling and design of novel tissue scaffolds.*Comput. Aided Des. Appl.***2004**, *1*, 633-640, https://doi.org/10.1080/16864360.2004.10738308.

21. Bucklen, B.S.; Wettergreen, W.A.; Yuksel, E.; Liebschner, M.A.K. Bone-derived CAD library for assembly of scaffolds in computer-aided tissue engineering.*Virtual Phys. Prototyp.***2008**, *3*, 13-23, https://doi.org/10.1080/17452750801911352.

22. Sun, W.; Starly, B.; Nam, J.; Darling, A. Bio-CAD modeling and its applications in computer-aided tissue engineering.*Comput. Aided Des.***2005**, *37*, 1097-1114, https://doi.org/10.1016/j.cad.2005.02.002.

23. Hollister, S.J. Porous scaffold design for tissue engineering.*Nat. Mater.***2005**, *4*, 518-524, https://doi.org/10.1038/nmat1421

24. Hollister, S.J.; Levy, R.A.; Chu, T.M.; Halloran, J.W.; Feinberg, S.E. An image-based approach for designing and manufacturing craniofacial scaffolds.*Int. J. Oral Maxillofac. Surg.* **2000**, *29*, 67-71, https://doi.org/10.1034/j.1399-0020.2000.290115.x.

25. Kapfer, S.C.; Hyde, S.T.; Mecke, K.; Arns, C.H.; Schr€oder-Turk, G.E. Minimal surface scaffold designs for tissue engineering.*Biomaterials***2011**, *32*, 6875-6882, https://doi.org/10.1016/j.biomaterials.2011.06.012.

26. Derby, B. Printing and prototyping of tissues and scaffolds.*Science* **2012**, *338*, 921-926, https://doi.org/10.1126/science.1226340.

27. Bendsoe, M.P.; Sigmund, O.*Topology Optimization: Theory, Methods and Applications*. Springer Science & Business Media, 2003; http://dx.doi.org/10.1007/978-3-662-05086-6.

28. Zhou, S.; Li, W.; Sun, G.; Li, Q. A level-set procedure for the design of electromagnetic metamaterials.*Opt. Express***2010**, *18*, 6693-6702, https://doi.org/10.1364/OE.18.006693

29. Wang, D.; Yang, Y.; Liu, R.; Xiao, D.; Sun, J. Study on the designing rules and processability of porous structure based on selective laser melting (SLM).*J. Mater. Process Tech.* **2013**, *213*, 1734-1742, https://doi.org/10.1016/j.jmatprotec.2013.05.001.

30. Springer, J.C.; Harrysson, O.L.A.; Marcellin-Little, D.J.; Bernacki, S.H. In vitro dermal and epidermal cellular response to titanium alloy implants fabricated with electron beam melting. *Medical Engineering & Physics***2014**, *36*, 1367-1372.

31. Galarraga, H.; Lados, D.A.; Dehoff, R.R.; Kirka, M.M.; Nandwana, P. Effects of the microstructure and porosity on properties of Ti-6Al-4V ELI alloy fabricated by electron beam melting (EBM). *Additive Manufacturing***2016**, *10*, 47-57, http://dx.doi.org/10.1016/j.addma.2016.02.003.

32. Habijan, T.; Haberland, C.; Meier, H.; Frenzel, J.; Wittsiepe, J.; Wuwer, C.; Köller, M. The biocompatibility of dense and porous Nickel–Titanium produced by selective laser melting. *Materials Science and Engineering: C***2013**, *33*, 419-426, http://dx.doi.org/10.1016/j.msec.2012.09.008.

33. Zhang, S.; Wei, Q.; Cheng, L.; Li, S.; Shi, Y. Effects of scan line spacing on pore characteristics and mechanical properties of porous Ti6Al4V implants fabricated by selective laser melting. *Materials & Design***2014**, *63*, 185-193, http://dx.doi.org/10.1016/j.matdes.2014.05.021.

34. Yan, C.; Hao, L.; Hussein, A.; Young, P. Ti–6Al–4V triply periodic minimal surface structures for bone implants fabricated via selective laser melting. *Journal of the Mechanical Behavior of Biomedical Materials***2015**, *51*, 61-73,http://dx.doi.org/10.1016/j.jmbbm.2015.06.024.

35. Taniguchi, N.; Fujibayashi, S.; Takemoto, M.; Sasaki, K.; Otsuki, B.; Nakamura, T.; Matsuda, S. Effect of pore size on bone ingrowth into porous titanium implants fabricated by additive manufacturing: An in vivo experiment. *Materials Science & Engineering C-Materials for Biological Applications***2016**, *59*, 690-701, https://doi.org/10.1016/j.msec.2015.10.069.

36. Yan, C.; Hao, L.; Hussein, A.; Young, P. Ti–6Al–4V triply periodic minimal surface structures for bone implants fabricated via selective laser melting. *Journal of the Mechanical Behavior of Biomedical Materials***2015**, *51*, 61-73, http://dx.doi.org/10.1016/j.jmbbm.2015.06.024.

37. Gu, D.D.; Hagedorn, Y.C.; Meiners, W.; Meng, G.B.; Batista, R.J.S.; Wissenbach, K.; Poprawe, R. Densification behavior, microstructure evolution, and wear performance of selective laser melting processed commercially pure titanium. *Acta Materialia***2012**, *60*, 3849-3860,https://doi.org/10.1016/j.actamat.2012.04.006.

38. Guden, M.; Celik, E.; Cetiner, S.; Aydin, A.*Metals foams for biomedical applications: processing and mechanical properties, in: N. Hasirci, V. Hasirci (Eds.), Biomaterials: From Molecules to Engineered Tissue*. Springer US, Boston, MA 2004; pp. 257–266. https://doi.org/10.1007/978-0-306-48584-8_20.

39. Azidin, A.; Taib, Z.; Harun, W.; Ghani, S.C.; Faisae, M.; Omar, M. Investigation of mechanical properties for open cellular structure CoCrMo alloy fabricated by selective laser melting process.*IOP Conference Series: Materials Science and Engineering***2015**, 012033, https://doi.org/10.1088/1757-899X/100/1/012033.

40. Mitsuishi, M.; Bartolo, P.; Liu, F.H.; Lee, R.T.; Lin, W.H.; Liao, Y.S. First CIRP Conference on BioManufacturingSelective Laser Sintering of Bio-Metal Scaffold. *Procedia CIRP***2013**, *5*, 83-87, http://dx.doi.org/10.1016/j.procir.2013.01.017

41. Ebel, T. Advances in the Metal Injection Moulding of Titanium at Euro PM 2014. *PIM Int.***2015**, *9*, 51–61.

42. German, R.M. Progress in Titanium Metal Powder Injection Molding. *Materials* **2013**, *6*, 3641–3662, https://doi.org/10.3390/ma6083641.

43. Qian, M. Metal Injection Moulding (MIM) of titanium and titanium hydride reviewed at PM Titanium 2013. *PIM Int.* **2013**, *8*, 67–74.

44. Dehghan-Manshadi, A.; Bermingham, M.; Dargusch, M.; StJohn, D.; Qian, M. Metal Injection Moulding of Titanium and Titanium Alloys: Challenges and Recent Development. *Powder Technol.***2017**, *319*, 289–301, https://doi.org/10.1016/j.powtec.2017.06.053.

45. Nelles, H.; Bram, M.; Buchkremer, H.P.; Stöver, D. Method for the Production of Near Net-Shaped Metallic and/or Ceramic Parts. *U.S. Patent 7351371***2008**.

46. Carreño-Morelli, E.; Rodríguez-Arbaizar, M.; Amherd, A.; Bidaux, J.E. Porous titanium processed by powder injection moulding of titanium hydride and space holders. *Powder Metall.***2014**, *57*, 93–97, http://dx.doi.org/10.1179/0032589914Z.000000000164.

47. Chen, L.J.; Li, T.; Li, Y.M.; He, H.; Hu, Y.H. Porous titanium implants fabricated by metal injection molding. *Trans. Nonferr. Met. Soc. China* **2009**, *19*, 1174–1179, https://doi.org/10.1016/S1003-6326(08)60424-0.

48. Deing, A.; Luthringer, B.; Laipple, D.; Ebel, T.; Willumeit, R. A porous TiAl6V4 implant material for medical application. *Int. J. Biomater.***2014**, *2014*, 904230, http://dx.doi.org/10.1155/2014/904230.

49. Sago, J.A.; Broadley, M.W.; Eckert, J.K.; Chen, H. Manufacturing of implantable biomedical devices by metal injection moulding. *Adv. Powder Metall. Part Mater.* **2010**, *4*, 89–99.

50. Wohlers, T.; Wohlers Report 2013: *Additive Manufacturing and 3D Printing State of the Industry AnnualWorldwide Progress Report*, Wohlers Associates, Fort Collins, Inc., 2013.

51. Rotman, D. The 3-D Printer That Could Finally Change Manufacturing. **2017**.

52. Dehghan Manshadi, A., Chen, Y., Shi, Z., Bermingham, M., StJohn, D., Dargusch, M., Qian, M., Porous titanium scaffoldsfabricated by Metal injection Moulding for Bio-medical applications. *Materials* **2018**, 11, 1573, https://doi.org/10.3390/ma11091573.

53. Shahali, H., Jaggessar, A., Yarlagadda, P.KDV., Recent advances in Manufacturing and surface modification of titanium orthpaedic applications. *Procedia Engineering* **2017**, 174, 1067-1076. https://doi.org/10.1016/j.proeng.2017.01.259.

54. Harun, W.S.W., Kamariah, M.S.I.N., Muhamad, N., Ghani, S.A.C., Ahmad, F., Mohamed, Z., A review of powder additive manufacturing processes for metallic bio materials. *Powder technology*, **2018,** 327, 128-151. https://doi.org/10.1016/j.powtec.2017.12.058

55. Javaid, M., Haleem, A., Current status and challenges of Additive manufacturing in orthopaedics: An overview. *Journal of Clinical Orthopaedics and Trauma*, 2018, https://doi.org/10.1016/j.jcot.2018.05.008

56. Kaur, M., Singh, K., Review on titanium and titanium based alloys as biomaterials for orthopaedic applications. *Materials Science & Engineering C***, 2019** https://doi.org/10.1016/j.msec.2019.04.064

57. Wang, Q., Btit, F., Wang, R., Corrosion of orthopaedic implants. ElsvierInc**, 2017**, https://doi.org/10.1016/B978-0-12-801238-3.99863-5

58. Alabort, E., Barba, D., Reed, R.C., Design of metallic bone by additive manufacturing. *Scripta Materialia*, **2019**, 164, 110-114. https://doi.org/10.1016/j.scriptamat.2019.01.022.