Additive manufacturing of multi-functional biomaterials for bioimplants: a review

Shubhadip Paul1, Ananya Nath1 and Shibendu Shekhar Roy1

1National Institute of Technology Durgapur, India.
E-mail: shibendu.roy@me.nitdgp.ac.in

Abstract. Additive manufacturing (AM) has been emerged recently as a promising technique to manufacture biomaterials for bioimplants creating a high impact in the field of medical science and research. AM technologies facilitate fabrication of the micro- as well as macro-architectural framework of orthopaedic bioimplants both internally and externally with higher precision and flexibility. The topological as well as geometrical porous nature of metallic biomaterials by means of controlled AM processes for fabrication of bioimplants can be adapted with high precision, leading to the upgradation of mechanical properties for bone-mimicking with improved biodegradation features. The increasing demand for the application of multi-functional biomaterials to manufacture metallic bioimplant as substitute of bonefronts the current additive manufacturing technologies. In this paper, recent technological advancement in the manufacturing of Ti-, Mg- and Fe-based biomaterials utilizing multi-material AM technologies is being reviewed for identifying the knowledge gaps and come up with the directions of further researches leading to the progress of multi-material based additive manufacturing technologies to fabricate metallic bioimplants by virtue of multi-functional biomaterials.

Keywords: Additive manufacturing, bioimplants, multi functional bio material

1. Introduction
In the past three decades, Additive Manufacturing (AM) has shown great impact in biomedical applications. Since the following mechanisms like solidification process with architectural blue-print followed by post-treatment activities and its effective implementations are fully material dependent, it can be said that Additive Manufacturing is a materials-based manufacturing technology. Bioimplants are implants that are used for medical therapeutic applications as prosthetics, wearable biosensors, porous bone implants and drug delivery systems. In the present scenario, the market requirement for bioimplants has shown accelerated growth because of aging population [1] and also due to the scarcity of donor organs for the treatment of patients [2]. Advanced level of researches and experimental study in the field of biomaterials [3] has paved the way for the development of several implants, such as implants used in dentistry [4], bioimplants employed in cartilage and bone repairing [5], brain implants [6] and so on. But the major challenging issues related with bioimplants are: Right selection of biomaterials [7], Strategies of manufacturing [7], surface-treating [8] as well as biological assessments [4–7]. Thus, AM technologies, that involve mechanisms of materials addition against substrate without any materials removal as performed in conventional manufacturing processes[2],
shows more opportunities for the manufacturing of highly efficient implants with custom stipulations by virtue of complex geometry.

2. Biomaterials and fabrication technologies

Over the last few decades, the emergence of a variety of fabrication techniques has revealed enormous developments of bioimplants. Conventional forming methods have shown sustainable development in the fabrication of bioimplants which includes casting, sintering and compression moulding establishing milestone in the field of medical science for highly efficient as well as decent characteristics of the implants. Presently, commercial metallic orthopaedic prosthetic products are manufactured mainly from either wrought or cast bar stock [9]. If Titanium and its alloys are taken into account, around seventy percent of the market is covered by wrought products [10]. At the outset of 21st century, there was an emergence of wrought Co-Ni-Cr-Mo alloys. It is reported that wrought and casted Co alloys are highly corrosion resistant with the property of having identical abrasive wear resistance [11]. Moreover, various experimental studies have shown that, the casted Ti-6Al-4V alloys with post-investigations has shown improved crack propagation resistance if compared to wrought ones [12]. According to Jovanovic’ et al.[13], under controlled cooling rates and annealing temperatures, it is possible to increase the tensile stress and hardness of casted Ti alloys. Lin et al. [14] showed that in Ti alloys, the most fundamental reason of the fatigue cracks is due to the existence of the casting induced surface pores. The experimental study of Dewidar et al.[15] revealed that the human bones have almost similar mechanical properties as compared to Powder metallurgy manufactured porous 316L stainless steel. But, the major disadvantage of Powder Metallurgy stainless steel is that the porosity can pave the way in the decrease of corrosion resistance property for the increment in the reaction area [16, 17]. Ning and Zhou [18] also exercised Powder Metallurgy for the bioimplants manufacturing from titanium and hydroxyapatite powders. In 1980s, after the advent of materializing the technology, Additive manufacturing (AM) has become an area of research in the domain of fabrication technology [19].

3. Application of additive manufacturing technologies for bioimplant

The layer-by-layer fabrication technology has emerged a new era in the field of medical science and technology with the advent of additive manufacturing which provided the opportunity for manufacturing bioimplants in contrast with the physiological as well as anatomical needs of patient by virtue of proper geometric data from 3D Computer-aided design. It can also be performed by Computed tomography derived models. Thus, any complex shaped objects or implants can be manufactured. Using 3D scanning of a particular patient specific bone, the cloud data is generated through which a patient specific implant can also be formed using additive manufacturing. However, joint arthroplasty, pelvis rebuild, maxillofacial reconstruction and many more disease are cured in last few decades using bio implants. The acceptance of AM applications for the fabrication of implants is increasing at a tremendous rate for product developments in medical science-based industries. In the Table 1, various categorisation of additive manufacturing has been done with various process methodologies. Also, the ink used for different methodologies are mentioned with some of their advantages. In the last few decades, various AM technologies have been flourished [20].

4. Multi-functional biomaterials for additive manufacturing of bioimplants

In terms of substitution of bone, an ideal metallic biomaterial fabricated should not only possess biocompatibility but also have good mechanical as well as biological functional properties by fulfilling the design requirements for better sustainability for replacement and regeneration of bone. The idea of synthesising and processing of multi-material having upgraded physical characteristics, mechanical performance and chemical composition can be achieved by virtue of powder metallurgy. The cell attachment by the surface modification, has shown the pathway for developing multimaterial AM based products with higher technologies.
| Methodology                  | Process technology          | Energy source                  | Material used                        | Merits                                                                 |
|-----------------------------|-----------------------------|--------------------------------|--------------------------------------|------------------------------------------------------------------------|
| VAT polymerization          | Stereolithography (SLA)     | Laser and Ultraviolet         | Metal powder, Ceramic powder, (Resin, Plaster) | High part resolution, costly supply materials, over curing in nature, high building speed |
| Material Extrusion          | Contour crafting            | Thermal energy                 | Metal pastes, Ceramic slurries, Thermoplastics, | Limited part resolution, multi-material printing, inexpensive extrusion machine, Low material, low process cost, high surface finish |
| Material Extrusion          | Contour crafting            | Thermal energy                 | Metal pastes, Ceramic slurries, Thermoplastics, | Limited part resolution, multi-material printing, inexpensive extrusion machine, Low material, low process cost, high surface finish |
| Sheet lamination process    | Laminated object manufacturing (LOM) | Laser beam | Ceramic tape, metallic sheet, Plastic film | Limited part resolution, multi-material printing, inexpensive extrusion machine, Low material, low process cost, high surface finish |
| Material Jetting process    | Poly-jet/Inkjet printing    | Thermal energy and UV light    | Ceramic tape, metallic sheet, Plastic film | Limited part resolution, multi-material printing, inexpensive extrusion machine, Low material, low process cost, high surface finish |
| Binder Jetting Process      | Indirect inkjet printing (binder 3D Printing) | Thermal Energy                 | Metal powder, Ceramic powder, Polymer powder (Resin, Plaster) | Limited part resolution, multi-material printing, inexpensive extrusion machine, Low material, low process cost, high surface finish |
| Powdered bed fusion         | Selective LASER sintering (SLS) | LASER Beam with high power    | Polyamides/Polymers                  | Powder handling and recycling, high specific strengths and stiffness, high density parts, high detailed accuracy |
| Directed Energy Deposition Technique | Wire Arc Additive Manufacturing, Laser Engineered Net Shaping, Rapid Plasma Deposition | Electron beams or LASERS or plasma arcs | Molten metal powder                  | Functionally graded material printing, repair of damaged/worn parts |
Additive Manufacturing

Thus, the technological advancement in the development of Ti-, Mg, Fe- and Bioceramics-based biomaterials for bone substitutes, has established the milestone for the advancement in multi-material-based AM technologies.

4.1. Ti-based biomaterials

Titanium and its alloys for long-term replacement of bone act as optimistic biomaterials due to their promising features of compactness, lightness, higher mechanical strength with its resistance to corrosion. In order to use for permanent replacement of bones, titanium and its alloys must have bone-mimicking characteristics that can be achieved by using AM technology and indicated by the geometry of a porous structure [24 - 30]. In orthopedic and craniofacial applications, the patient-friendly routes of using AM Ti-based bioimplants have shown significant improvement than other substitute approaches as they are fabricated to heal the defects of bone. In case of orthopedic executions, based bioimplants by virtue of AM have been reported to be patient-specific without causing any impairment to the bone tissue, in which the distal tibia bone deformity is replaced by multiple cracks in the talus as well as foot [31]. Hence, AM-specific projects have upgraded the stable nature of Titanium installation equipment. The incorporation of phosphorus and calcium compounds as well as the intervention of nanoparticles onto the surface of Ti-6Al-4V bioimplants has been shown for inducing AM biomaterials having antimicrobial characteristics against *Staphylococcus aureus* (MRSA) which is methicillin-resistant [32]. In *in situ* Ti-CaP and Ti-6Al-4V-HA composites, various compounds like Ca₃(PO₄)₂ and CaTiO₃ have been formed, forming a tribological layer that protects the surface of the biomaterial [33, 34]. In addition to the hardness as well as durability of the coating, the in-situ development of β-phase Titanium alloys is also required for the improvement in the similarity between the expandable Titanium-based biomaterial module with the bone. AM Titanium-based alloys have demonstrated promising solutions for treating of complex deformities in bone. Most of the experiments on the Ti-based products by virtue of AM is focused on the micro structural development as well as mechanical properties, thus, considering a large space for biocompatibility compliance.

4.2. Mg-based biomaterials

Magnesium and its alloys though experimental procedures has paved the way for the development of prosthetic orthopedic implants and has shown profound impact in low load-bearing areas with high potential [35]. Magnesium, due to its low elastic modulus, helps to resist any type of mechanical failure. The degradation of Magnesium is very fast leading to the release of hydrogen which can be a problematic issue in case of bone replacement. Because, during bone healing, the excessive release of hydrogen may give rise to mechanical disturbances. Coating Magnesium alloys with Si [36] and Ca-P [37, 38] serves as protective layers that may decrease corrosion levels and prevent from any primary mechanical losses. To decrease the rate of biodegradation, the magnesium of the magnesium-based biomaterial has to make an alloy with the rare earth (RE) elements. Thus, to improve the corrosion resistant property by virtue of conventional powder metallurgy processes, the inclusion of RE elements, such as Y [39, 40], Nd [41], Gd [42] and Dy [43] to magnesium should be done. In Present days, in the market three types of bone screws based on magnesium are found made from pure Mg [44], Mg-Ca-Zn [45] and Mg-Y-RE-Zr [46]. Recent technological advancement of solvent capillary-derived process by manipulating binder jetting has paved the way in the reduction of the metallurgical complications entailed in the AM of Magnesium alloys [47]. Besides, using SLM technology, various studies are done on *in situ* Additive Manufacturing of Mg-based biomaterials by powder getting blended to control biodegradation by enhancing the antimicrobial property with increased mechanical strength [48]. Several studies have been conducted focusing on the decay behavior of biomaterials based on Mg. Clinical evaluation of Mg-based orthopedic screws has removed the rust-resistant paradise to a new concept of temporary bone grafting.
4.3 Fe-based biomaterials

Till date, the research has been done on Iron and its alloys which has reflected that it can used for transitional load-bearing replacements of bone due to their higher ductility and mechanical strength [49].

Table 2: Outline of the use of 3D printed bioceramics in Bone tissue engineering [50].

| Materials Used | Method | Model (In Vitro / In Vivo) | Summary | Reference |
|----------------|--------|---------------------------|---------|-----------|
| Photopolymer + liquid sodium polyacrylate + HA | Use of a ball crusher was seen for milling all the materials for 12 hrs. for making a slurry having the content of solid of 10–60 wt%. Fabrication of Ceramic scaffold was performed with the help of digital light processing (DLP) technique. | In the condition of α-Minimum Essential Medium (4% penicillin-streptomycin, 10% fetal bovine serum), Mouse osteoblast precursor cells were cultured. | 3D printed scaffold revealed higher biocompatibility and also be able to assist proliferation of osteoblast | [51] |
| Polyethyleneimine + biphasic calcium phosphate (HA/β-TCP = 60:40) + ZrO$_2$ | With printing speed of 100 mm/min, extruded at pressure of 600 kPa. At 1100 °C, Constructs were sintered. | Investigation was done on osteoblast like sarcoma cells due to cytotoxic behaviour and in case of differentiation potential of scaffolds, Human mesenchymal stem cells cells were used. | Scaffolds having improved mechanical properties at 10% (w/w) of ZrO$_2$ was noticed with upgraded BMP-2 expression. | [52] |
| β−TCP/polycaprolactone | β−TCP powder having particle size of 550 nm were used to makecylindrical scaffolds having 350 μm pore size. | Using human fetal osteoblast cells, the Composite scaffolds were examined for 3, 7 and 11 days of incubation period | Improved early bone formation having effectiveness for precisely regulated release of alendronate | [53] |
| β−TCP/sphingosine 1-phosphate | The scaffolds were printed in different sizes into 4 layers to suit in 6-well and 12-well plates. Sintering of Printed scaffolds were then done for 3 hrs at 1100 °C. | Investigation of potential of Immuno regulation on macrophages was done and the osteogenic ability was analysed on stromal cells of rat bone marrow of the | Advanced bone tissue regeneration, highly biocompatibility | [54] |
scaffolds which are coated.

If any comparison is done with magnesium-based biomaterials, it is observed that the Fe-based materials significantly possesses advantageous property of not freeing up hydrogen due to their feature of degradation. Various methods thus obtained which includes powder metallurgy techniques encompassing Mn alloying or involvement of noble metals which by fortifying with bioceramics has shown profound acceleration in biodegradation rate by undergoing various investigations with the diminish in the magnetic effects of iron [55]. Trace of manganese exhibits a vital role in bone resorption as well as osteogenesis [56]. In addition to Mn, the use of various noble metals, for example Pt, Pd, Au and Ag [57-59] leads to the generation of secondary phases in alloys based on Fe such as, Fe-Pt, Fe-Pd, Fe-Au and Fe-Ag. It may help in micro-galvanic mixing to boost up the biodegradation of Fe without causing any injury to the neighbouring tissue [60]. Generally, during the degradation of Fe-Mn-Si alloy, normal blood homeostasis is seen. Technological advancement in AM has opened up the space for developing biodegradation portrayal of Fe-based biomaterials by multi-material designs through porous topology. Anti-ferromagnetic characteristics are seen in phases ε and γ - Fe - Mn [61]. Researches are going on for the implementation of AM for porous Fe-based biomaterials not only in the upgradeation of biodegradation features but also to recognise the cause of biodegradation which affects strongly the biocompatible behaviour of Fe-based biomaterials.

4.4. Bioceramic based materials

Bioceramic based materials can also be used for the bone tissue engineering if undergone through selective processes in additive manufacturing. According to the researchers, the non-invasive observation of pure iron and iron fortified with mainly Tricalcium phosphate (TCP), Biphasic calcium phosphate (BCP), Hydroxyapatite(HA) inserted in sheep forelegs for a period of sixty days has exhibited trivial decrease in the biomaterial’s sizes [62- 64]. The overview of the functionalities of bioceramics for the purpose of bone tissue engineering by virtue of additive manufacturing are shown in the table 2.

5. Conclusion

Noticeably, Additive Manufacturing based technologies congenitally furnish the potential for multi-material production which still not have been considerably investigated by experiments for bone implant purposes leading to the advancement in medical science. The probability of high-perfection in manufacturing of porous biomaterials having complexity in micro- and macro-architecture by means of the AM technologies directly links for the fabrication of bone implants to the metallic biomaterials at future destiny. Researches are going on for the development of the metallic biomaterials through AM which would be extrusion of multi-material leading to the enhancement in abilities for introducing materials of varying compositions typically within the structure at a few micrometre scales. Hence, Additive Manufacturing technologies extrusion of multi-material significantly promises in the advancement of state of the art for the development of alternative metallic multi-functional biomaterials for repairing bone with the enhanced biocompatibility.

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