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Current Opinion in
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Biomedical applications of additive manufacturing: Present and future

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Abstract

Three dimensional printing (3DP) or additive manufacturing (AM) of medical devices and scaffolds for tissue engineering, regenerative medicine, ex-vivo tissues and drug delivery is of intense interest in recent years. A few medical devices namely, ZipDose®, Pharmacoprinting, powder bed fusion, HPAM™, bio-printer and inkjet printer received FDA clearance while several biomedical applications are being developed. This paper reviews influence of type of AM method and process parameters on the surface topography, geometrical features, mechanical properties, biocompatibility, in vitro, and in vivo performance of diverse orthopedic applications. Attempts have been made to identify gaps, suggest ideas for future developments, and to emphasis the need of standardization.

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Keywords

Additive manufacturing, Biomaterials, Characteristics, Orthopedic implants, Standards.

1. Introduction

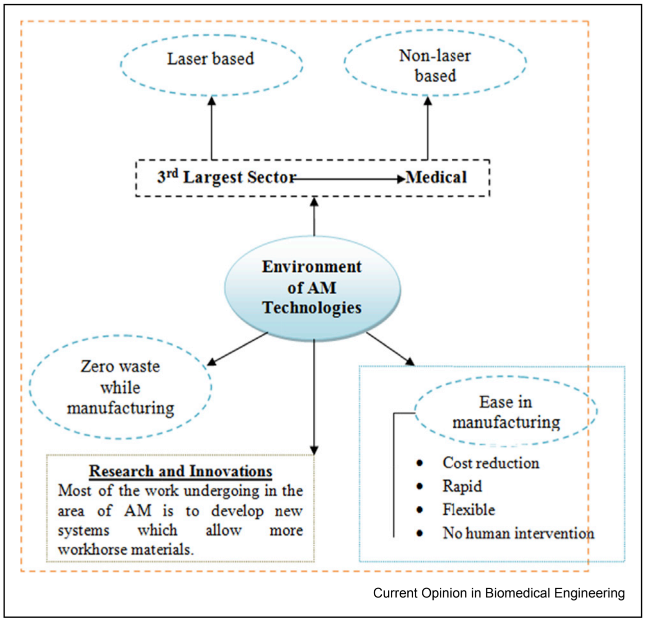
ASTM-F42 Committee defined the additive manufacturing (AM) as *a process of joining materials to make objects from 3D model data, usually layer on layer*, opposite to conventional manufacturing technologies [1]. These technologies utilize an unconstrained environment, as highlighted in Figure 1.

AM researchers are developing a wide range of biocompatible feedstock material and processing systems for medical devices, like hip, knee or articular cartilage joints. The various biomaterials and their applications in biomedical engineering (refer Table 1). Table 2 summarized some of such applications.

The working principle, except the processing of feedstock, is same and the process (specifically in the task of implant development) starts from collection of the work starts with capturing the internal medical data of a patient through are the Computed Tomography (CT) and the Magnetic Resonance Imaging (MRI) technologies [7]. Then the collected images are converted into computer aided design (CAD) model via Digital Imaging and Communications in Medicine (DICOM) directory. The finalized CAD model should be simulated through MIMICS or 3D doctor software for visualizing the fitment [8]. A standardized procedure is available for generating the required *Standard Triangulation Language* (STL) format of implants [9]. After this, as per the requirements of the implant in-terms of desirable quality characteristics the input variables such as slice/layer thickness, printing speed, printing temperature, orientation, raster angle, air gap, contours, environmental temperature/conditions, type of input current, types of laser and its parameters, workhorse material, environmental factors, etc., can be selected on the basis of literature survey or personal experience. Figure 2 shows the schematic of converting human specific data into physical part via AM. The process starts from CT scan data and eventually completes after preliminary surgical verifications.

Issues such as: poor surface characteristics, poor dimensional accuracy, low strength, bio-compatibility, microstructure issues, corrosion of the implants, etc., need the research attentions. It is inevitable that some of the factors critical to the implementation of AM technologies are also important to the adoption of other manufacturing technologies [10]. Particularly, it is of big interest to study the effect of processing parameters on biocompatibility/cell culture analysis as the finally produced structure is liable to alter its properties as the processing conditions change, due to the variation in the material, geometry and integrity of the layers while fabrication task. No matter if the variations analyzed will be limited, but the improvements accomplished would always be supposed to have significations. Moreover, the standard test standards, often come into play while the test and analysis, may not be able to give realistic information because of its differentiation, from the customized orthopedic or tissue, in-terms of geometrical features. Hence, it is highly important to test and

Figure 1



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Environment of AM *(Courtesy: ref.* [1–6]*).*

simulate the laboratory results on the same part which is going to serve. Ducom Instrumentation has already developed apparatus for tribological testing of as-real geometry of the implants. In this review article, the influence of various process parameters on characteristics of orthopedic implant has been reviewed in Section 2, and the information provided will help for the development of required standards as discussed in Section 3.

Table 1

FDA cleared 3D printed biomedical applications.

Material	Application
CP-Ti	Screw and abutment
Ti-6A1-4V	Artificial valve, Stent, Bone fixation
Ti-6Al-7Nb	Crowns, Knee joint, Hip joint
Ti-5Al-2.5Fe	Spinal implant
Ti-15 Zr-4Nb-2Ta-0.2Pd	Crown, Bridges, Dentures, Implants
Ti-29Nb-13Ta-4.6Zr	Crown, Bridges, Dentures, Implants
83%–87%Ti-13%–17%Zr (Roxolid)	Crown, Bridges, Dentures
316L	Knee joint, Hip joint, Surgical tools, Screw
Co-Cr-Mo, Co-Ni-Cr-Mo	Artificial valve, Plates, Bolts, Crowns, Knee joint, Hip joint
NiTi	Catheters, stents
PMMA, PE, PEEK	Dental bridges, articular cartilage, Hip joint femoral surface, Knee Joint bearing surface, Scaffolds
$SiO_2/CaO/Na_2O/P_2O_5$	Bones, Dental implants, orthopedic implants
Zirconia	Porous implants, Dental implants
Al_2O_3	Dental implants
$Ca_5(PO_4)_3(OH)$	Implant coating material

Information gathered by online search.

2. AM based biomedical implants: examples of manufacturing strategies for orthopedics

In this section, we have reviewed the various characteristics of AM based orthopedic implants to highlight the importance of from process parametric study for obtaining better service life, safety, workability and convenience of patient after implantation. All the upcoming characteristics are important to get qualified during pre-surgical verifications after the fabrication of the implant, as highlighted in Figure 2.

2.1. Surface characterization

Implant surface characteristics plays an important role in the osteointegration like: macroscopic, microscopic and nano-metric characteristics [12]. It has been found that the reaction of osteogenic cells to different surfaces was increased on rough surfaces [13], and as compared to smooth surfaces the textured implants surfaces exhibit more surface area for integrating [14] as observed in in-vivo investigations [15]. However, fine surface finish has also been reported as better in case of hip joint applications [16], as fine contact between artificial implant and natural bone structure will help in smooth motion. However in actual, it is not yet standardized that how much rough or fine surface is required for different implants. The authors are believed that for non functional implants, one should prefer textured surfaces and such surfaces are easy to obtain with AM technologies due to the presence of staircase effect [17]. But when the implant is functional such that it has relative motion, then the mating surface should be as fine as possible as roughness could have effect on increased wear [18]. Some of the researchers have used chemical etching [19], mechanically [20] or combinations [21] for improving the surface finish of the titanium implants, however their effects on the chemical composition of the implant material, geometrical scale (to nano level) and other mechanical properties are required to study. Table 3 gives a detail of processing parameter(s) of AM process for surface roughness of produced implants.

2.2. Geometrical characterization

- Dimensional

Developments of exact shape, size and minute geometrical textures on artificial biomedical implants are essentially important for their proper functionality [39,40]. However, it is difficult to produce on an appropriate material and earlier was done by hand crafting from the surgeon [41]. Conventional CNC

Table 2

3D Printed Biomedical Applications under research and development.

S. No.	AM technology used	Application area	Biomaterial	Remarks	University/Lab/group
1	–	3D printing small implants	PEEK	The project intends to develop and extensive toolset for dental implant design and analysis.	University of Southampton
2	Metal on Metal (MOM)	Smart-hip	Silver	New PVD silver bearing coatings were developed to protect against post-operative infection and provide a barrier to minimize metal ion release.	University of Sheffield
3	Electron beam melting (EBM)	Custom design in orthopedics	Ti alloy	Development of metal structures with flexibility closer to the bone.	Mid Sweden University
4	Selective laser melting (SLM)	High-intensity sound for acoustic cleaning	Alginoplast	The sound pressure travels inside the implant is a novel approach.	University of Liverpool
5	–	Customization of biocompatible implant materials for AM	Polycaprolactone	Craniofacial, long bone, ear and nose scaffolds are likely to develop.	EOS and University of Michigan
6	–	Multi applications of AM in biomedical	Various types of polymers	Development of new 3D scaffolds able to induce specific tissue regeneration through engineered surface topology or chemical surface functionality	Brightsland Material Centre
7	–	High Performance Bioactive Structures for Bone Replacement and Tissue Growth	Silver ink	Bone replacement and tissue growth for individuals who have suffered the loss of these structures through congenital defects, trauma or destructive surgery.	Loughborough University
8	Selective laser sintering (SLS)	Processing of new materials by laser sintering	Ti alloy	Phenomenon of processing of polymer nano-composites, thermoplastic elastomers, biomaterials, polyethylene will be understood.	University of Nottingham
9	EBM	Biological mechanisms and optimization of tissue response by pore structure and surface modification	Ti alloy	To probe the structural arrangement, molecular composition and morphology of the bone in-growth in different implant geometries and surface morphologies.	Biomatcell; University of Gothenburg; SP Technical Research Institute of Sweden; Region Västra Götaland; Uppsala University; Arcam AB
10	SLM	Medical imaging techniques	–	Techniques using micro-CT imaging to measure and map deviations due to wear in implants are being developed.	Lawson Health Research Institute
11	–	Theranostic Implants	–	To develop active implants that combine therapeutic and diagnostic functions in a single medical device.	Frounhofer, German
12	–	Design and fabrication of biomimetic and biocompatible Ti-Ta for bone implants	Ti-Ta	To combine structural and materials engineering, additive manufacturing and tissue engineering to develop biomimetic bone-like scaffolds.	RMIT University
13	Bio-printer	Heterogeneous bio printing for in vitro drug toxicology testing	–	–	Drexel University

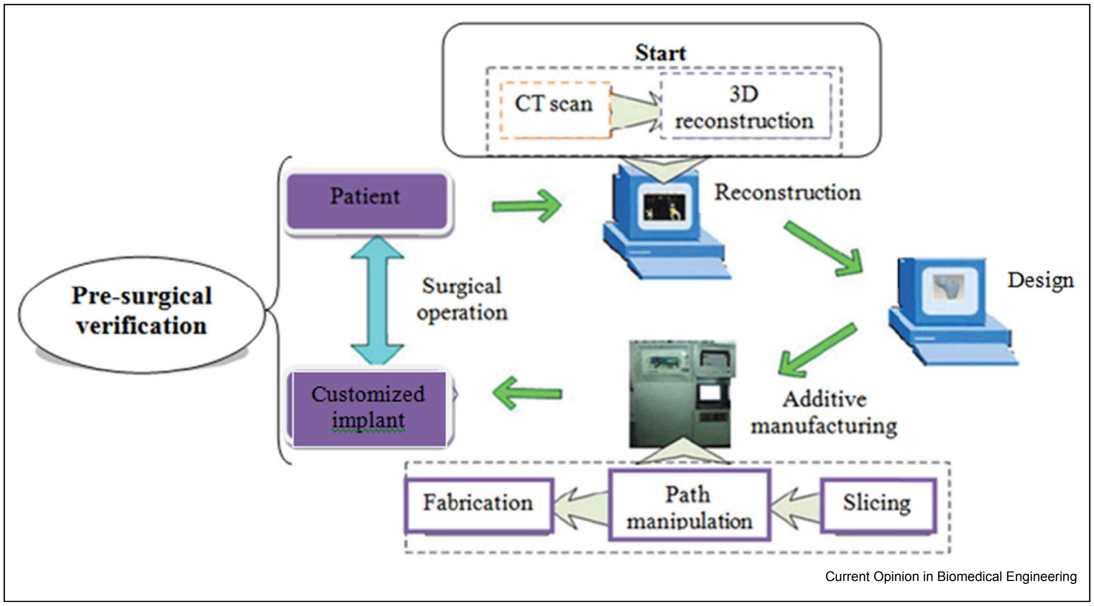
(*continued on next page*)

Table 2 (*continued*)

S. No.	AM technology used	Application area	Biomaterial	Remarks	University/Lab/group
14	–	Hydrogel-based materials for implants	Hydrogel	A locking mechanism for precise actuation and movement of freely moving hydrogel was developed.	Columbia University
15	Fused deposition modelling (FDM)	–	–	This research is a real step forward as it shows how we can use 3D printing to improve biomaterials without the need for achieving high resolution.	Nottingham Trent University
16	–	Heart Implants, 3-D-Printed to Order	A stretchy, FDA-approved polymer	Tailor-made medical devices could give a more detailed picture of cardiac health and may be better at predicting and preventing problems.	MIT University
17	Stereo-lithography (SLA)	3D print biodegradable vascular stents	In house polymer with antioxidant and retinoid properties	Micro continuous liquid interface production to create stents for the treatment of weakened or narrowed arteries.	Northwestern University
18	–	Retinal Implant	–	The developed material is FDA approved.	Restoring Vision Platforms
19	SLS	Liver printing	PCL	3D printing for liver tissue engineering	Northwestern University
20	Bio printer	–	–	Printed a bionic ear by combining biological tissue and electronics	University of Cambridge
21	Bio printer	Bone and cartilage	Stem cells	Regeneration and analysis of musculoskeletal tissues, including bone and cartilage.	Cornell Engineering
22	Bio printer	–	–	Bioprinting for tissue and organ fabrication	Penn State University
23	Inkjet printer	Heart chip	Poly-di-methyl-siloxane	3-D printer builds heart-on-a-chip device	Harvard University
24	–	Cartilage	polymeric bioinks with tailored composition	3D Bioprinting	IIT, Delhi
25	–	Kidney tissues	–	3D Printed Human Skin Tissue	L’Oréal USA & Organovo Team
26	Inkjet printing	Scaffolds	Protein and enzyme	Biosurface engineering through ink jet printing	USA federal science
27	–	–	trithiocarbonate iniferters	Transformation of Parent Gels into Diversely Functionalized Daughter Gels Made Possible by Visible Light Photoredox Catalysis	MIT, USA
28	–	Novel dosage forms	–	3D Printing of solid and semi-solid dosage forms	University of Central Lancashire
29	–	Morphogenetic protein 2, rhBMP-2		3D-printed bioabsorbable scaffold for ACL reconstruction	The Mayo Clinic, USA

Information gathered by online search.

Figure 2



Schematic of AM of customized biomedical part [11].

machining has also been widely practiced to create human femur models but dimensional accuracy of the finished product was subjective of machining orientations [42]. Other processes such as: chemical etching, grit blasting, dies sinking electric discharge machining and ultrasonic machining were also used to produce fine and accurate surface textures [43]. One of the research article highlighted that the dimensional accuracy of the printed implants measured by 3D laser scanning, showed an average of 200 μm, which allows its application in craniofacial structures [44]. Another research article detailed that the scanning and processing pipeline creates a very-high dimension parameter space for which it would be prohibitive from a time perspective to fully investigated [45]. Although the above review of literature is highly supporting that the implants fabricated through AM are highly dimensional stable and are came up with near net features. Further, it has been quoted that the dimensions deviation of 200 μm is suitable for some implants only, not for all. So, the research outcomes are lacking to give a clear picture of parameters affecting the dimensional accuracy.

- Pore consistency

Porous surface having an interconnected pores are recommended for the improvement of bone formation rate and also for the better fixation of the implant [46]. Implant porosity promotes positive results in bone neoformation in-vivo [47], as increased contact area between the biomaterials and bone tissue, result into better implant stability as well as accelerated osteointegration [48]. AM allows full design freedom, in a way by giving the possibility to manufacture regular open porous structures along with high repeatability which enhance both geometrical and mechanical properties [49]. In one of the study on SLM [49], it has been found from biomechanical testing that porous multi rooted implants had a much higher bonding strength at the bone-implant interface than the resorbable blasting media implant. The porosity can be designed in areas based on the patient's need to enhance biological fixation and achieve long-term in-vivo stability [50]. Overall, it has been summarized that there are various machine parameters that affected the pore size and its control overall the geometrical surface and the selection of their levels must need pilot study.

2.3. Mechanical characterization

Human joints or limbs posses certain desirable mechanical properties for ease of functionality as longer as the life. It has been found that the Young modulus, tensile strength, compressive strength and toughness of the human bone are a function of age, gender, and location in the body, amount of water and disease history [51]. Table 4 gives the illustration of mechanical properties of various joints developed through AM technologies. It has been found that the mechanical properties of parts produced with AM technology are competitive to cast material and the ultimate tensile strength variation was a function of orientation and location of the specimens [52]. Some of such comparisons of mechanical properties between cast/ wrought and AM sample are given in Table 5. However,

Table 3

Effect of processing parameters on orthopedic implant characteristics.

S. No.	AM system used	Parameters studied	Remarks	Reference(s)
Surface roughness				
1	Selective laser sintering	Build orientation, layer thickness and laser power	• Build orientation was found to be the dominant parameter affecting surface roughness. • When layer thickness is small, better finish is obtained as compared to higher layer thickness. • Penetration of laser of the same order of energy density may cause over-sintering and hence deteriorate surface finish.	[22]
2	Selective laser melting	Build orientation	• As the inclination angle increases from 0°, higher surface roughness results from the stair step effect. • The trend of measured roughness is mainly constant in the range of 5°–45°, with a relatively slow decrease in the range 50°–90°.	[23]
3	Electron beam melting	Current, scan speed and thickness of sample	The surface roughness increases with increasing sample thickness and beam current, while it decreases with increase in offset focus and scan speed.	[24]
4	Selective laser sintering	Scan speed	Increasing the scan speed resulted into deteriorating the surface topography of the produced parts.	[25]
5	Fused deposition modelling	Geometry of the components/appliance, density of components/ appliance and acetone exposure time	The results of ANOVA highlighted that only part density has contributed significantly (90.29% at 95% confidence level) to the hardness of HVS-processed FDM parts.	[26]
6	Fused deposition modelling	Volume to area ratio, orientation and density of the parts	• The orientation at 0 angles produces the minimum surface roughness and the value of surface roughness increases as the orientation changes from 0 to 90. • Patterns with lesser density produce less surface roughness as compared to solid patterns.	[27]
7	Fused deposition modelling	Layer thickness, orientation, raster angle, raster width and air gap	Raster angle and air gap have a positive influence on flexural strength.	[28]
8	Selective laser melting	Laser power and scan speed	• Higher peak powers tended to reduce top surface roughness and reduce side roughness as recoil pressures flatten out the melt pool and reduce balling formation by increasing wettability of the melt. • Reduced scan speed reduced top surface roughness but increased side roughness.	[29]
9	Laser metal deposition	Laser power	• High laser power increased the surface finish.	[30]
Dimensional accuracy				
1	Fused deposition modelling	Layer thickness, orientation, raster angle, raster width and air gap	• For minimizing the percentage change in length, higher layer thickness (0.254 mm), 0° orientation, maximum raster angle (60), medium raster width (0.4564 mm) and maximum air gap (0.008 mm) are desirable.	[31]
2	Fused deposition modelling	Different geometries	• FDM machine is less accurate in fabricating the circular shape such as a sphere, cylinder and hole as its dimension have exceeded the tolerance value (±0.127 mm) of FDM machine.	[32]
3	Stereo-lithography	Hatch spacing, layer thickness, overcure, blade gap and position on the build plane	• Overcure and build plane have high effect on the dimensional accuracy of the parts.	[33]
4	Selective laser sintering	Laser power, hatch spacing, scan speed, bed temperature and scan length	The shrinkage along X, Y and Z direction is not independent	[34]
5	Electron beam melting	Orientation	• The degree of inaccuracy can be mitigated significantly when the beam energy density is suitably reduced −41.2% to −5.4%.	[35]
6	Inkjet printing	Layer thickness and printing orientation	• The 0.1125 mm layer thickness and X direction were the best printing conditions that offered the highest green strength and dimensional accuracy	[36]

Table 3 (*continued*)

S. No.	AM system used	Parameters studied	Remarks	Reference(s)
7	Direct metal laser sintering	Laser power, scan speed, hatch space and thickness	• With increasing the laser power or decreasing the scan speed, the shrinkage along the sintering (length) direction of the part is more serious. • Increasing the scan speed reduced the dimensional error.	[37]
8	Direct metal laser sintering	Length of the part and scan speed	• The length of the dexel is shorter; the percentage shrinkage is larger because of a higher sintering temperature attained. • When the length of the part was shorter, the shrinkage was higher.	[38]

Table 4

Mechanical properties of AM based implants.

Implant	AM technology	Material	TS	YM	S	H	CS	FL	Ref.
PS	EBM	Ti6Al4V	–	–	0.57–2.92 GPa	–	7.28–163.02 MPa	–	[58]
PS	–	Ti6AL4V-ELI	–	>3.5 GPa	2.9 GPa	–	–	–	[59]
Total knee joint	EBM	Ti-6Al-4V	–	–	2.2 GPa outer and 0.3 GPa inner	3.9 GPa (max.)	–	–	[60]
Ortho	SLM	AISI-Stainless steel	738 MPa (max.)	–	–	250HV	–	–	[57]
Ortho	-do-	Ti-6Al-4V	>150 MPa		>4 GPa	–	–	–	[61]
PS	Lithography	45S5 Bioglass®	40 MPa	–	–	–	0.33 MPa	–	[62]
Dental implants	EBM and LBM	Ti-6Al-4V ELI	–	–	–	–	–	28961SD	[63]
Ortho	EBM	Ti-6Al-4V	833 MPa (horizontal) and 851 MPa(vertical)	783 MPa (horizontal) and 812 MPa (vertical)	–	–	–	–	[54]
–	EBM	Ti-6Al-4V	915 MPa	118 GPa	–	–	–	–	[64]
–	Powder based AM	CP-Ti	414.51 MPa	3.37 GPa	–	–	>400 MPa	–	[55]
Ortho	EBM	Ti-6Al-4V and Co-29Cr-6Mo alloy	–	1.03–110 GPa and 0.51–0.77 GPa res.	–	3.6–4.1HV and 4.6HV res.	–	–	[65]

Note: TS, YM, S, H, CS, FL and PS represent tensile strength, Young's modulus, shear strength, hardness, compressive strength, fatigue life and porous structure.

the tensile elongation values in laser-based AM components, previously reported, lies to be typically 6% and maximum of 11%, which are substantially lower than the 12–17% elongation range observed in wrought conditions [53]. In a study on EBM [54], the effect of post processing operations such as: machining and peening on residual stress, static strength and elongation, fracture toughness, crack growth and on fatigue performance were evaluated. Different orientations and numbers of channels [55], and energy input per unit length [56] affected the characteristics of implants. The optimization of process parameters through design of experiments has the scope to functionally improve the medical implants or instruments [57].

2.4. Biological characterization

- In-vitro

The in-vitro characterization of the artificial implants or medical instruments is the only essential process to be analyzed prior to their use. Study outcomes of in-vitro developments are crucial that provide important for proof of concept and in determination that whether a process/material is suitable for producing biocompatible structures or not. The rough structure of implant has positive influence on cell behavior as reported in numerous studies [70]. Recent innovations in AM technologies, such as bio-printers, have given a breakthrough in medical engineering as they allow 3D cell-printed devices [71]. Numerous histomorphometric studies highlighting the applications of AM for animal [72] and human [73] have documented. Pore size and its structure have significant effect on the cell culture results [71]. It has been found that the various geometrical parameters define the in-vitro results however optimum geometrical features are not defined till date.

- In-vivo

The materials/technologies/structures after getting qualified in in-vitro analysis are proceeding towards in-

Table 5

Comparative mechanical properties of cast/wrought and AM parts.

Material	AM setup	Cast/wrought component			’Additive manufacturing			Reference
		TS (MPa)	Elongation (%)	Yield strength (MPa)	TS (MPa)	Elongation (%)	Yield strength (MPa)	
Inconel 718	SLM	<1000	23%	–	1400	>18%	–	[66]
Ti-6Al-4V	-do-	897	15%	828	1095	8.1%	890	[67]
316L stainless steel	-do-	560	40%	<290	555	13.5%	465	[68]
Ti-6Al-4V	DMLS	979	–	945	1133	–	1096	[69]
SS-316L	-do-	563	–	343	717	–	496	[69]

vivo studies, where the selected implant is planted inside an animal (cat, rat, rabbit, sheep, etc.) [74]; or even directly in human body. The porous Ti6Al4V scaffold prepared by EBM was favorable for bone in-growth after implanted in sheep femoral [75]. In Ref. [76], the effect of porous structures on their biological behavior has been outlined. The effect of AM structures pore size on the in-vivo results is analyzed. Overall, it has been observed that the control of porosity through AM technologies is important.

- Corrosion

Usually, corrosion may appear during the conventional adaption of implants due to the fact that plastic deformation and may break the passive layer of the contact area [77]. AM is capable of producing good corrosion resistance and compatibility [78]. Surface roughness and porosity may affect the corrosion of AM based implants [79]. Potentiodynamic tests for Ti-6Al-4V alloy showed that both EBM and wrought alloy similar corrosion resistance [79]. Heat treatment of the AM manufactured implants is one of the convincing approaches to improve their corrosion resistance.

3. Applicable standards in AM of implants

From Section 3, it has been observed that the research strategies are diverse and hence the results obtained are variable, even conflicting in most of the cases. Hence the time is demanding systematic approaches for the development of particular type of biomedical structure as it is not convenient for the surgery team to carry out pilot studies prior to the operations. Here, standards play an important role in the adoption of a suitable technology. For this significant activities have been taken place, since 2009, through the ASTM International F42 committee which critically worked towards standards in materials and processes, terminology, design and data formats and test methods. Especially in medical sector the growth of the AM industry is slow due to the unavailability of specified standard procedures and human expertise dominates their existence. Due to this the expert usually explore only into those aspects in which they are comfortable rather than a state of the art implant behavior. ASTM F2792−12a, ISO/ASTM DIS 52910.2, ISO/TC 261 and ISO 17296-4:2014 standards are available for the starters. Also, ISO 10993-1 and ASTM F 2129 standards are available for chemical characterization, and ASTM 756 and ISO 10993-6 standards help in testing biocompatibility of the implants. Still researchers need a full proof procedure (from first to last stage) which demands following standards to be available in near future:

- ***Conversion of DICOM files into 3D model;*** its procedure, how to control surface and geometrical feature at earlier stage, critical points to be taken care of; suitable rendering technology.
- ***Preparation of STL file;*** how to adopt the best slicing strategy; how to eliminate the errors occurred, often.
- ***Selection of suitable AM technology;*** since the availability of AM systems is wide so proper selection of AM setup is most important. Through the establishment of standards, one can compare the performance of different AM processes and find out the best.
- ***Selection of AM parameters;*** from literature it has been clarified that processing parameters of the machine are highly contributing towards the output characteristics of the implants. However till now it has not been standardized that for what category of implants which processing parameters are best suitable.
- ***Characterization and testing;*** As most of the mechanical/tribological studies on implants are performed on standard specimens prepared as per ASTM/ISO/ANSI. However, no standard is yet available for testing implants. Here, in regular practices researchers violate the geometrical aspects of the implants that contribute towards certain mechanical properties.

4. Conclusions

Followings are the brief conclusions drawn from the literature review:

- It has been found that AM technologies are promising for converting the customized implants through available scanning technologies like CT/MRI. Till date extensive research work has been carried out for improving the various quality characteristic of AM implants, and reportedly these characteristics are

function of process parameters. Especially, importance should be given to the load bearing implants to achieve mechanical and fatigue performance together.
- The certification of AM critical components has been a critical challenge due to the availability of the conflicting process parameters due to which there exist significant gaps in the selection of their levels. Overall the suggested optimized process parameters are still not at par with the mechanical standard as a result of which the developed components are not immediately ready to use and their post treatment is frequently required.
- Very less work has been done, till date, to simulate the cell responses and cell-tissue growth behavior as a function of process variables.
- There is a myriad of variations for medical devices, in general. This is a benefit, but requires standardization. But, researches focused on the development of norms and standard procedures for such practices are lacking. Moreover we need to seek product opportunities for fabricating regular products (like: screws, plates, etc.) for mass manufacturing point of view.

Conflict of interest

None.

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Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

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