Additive manufacturing and characterisation of biomedical materials

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Abstract

At present, additively manufactured biomedical materials find extensive applications in a wide range of avenues ranging from orthopedics to urology. Additive manufacturing (AM) techniques based on layerwise deposition of materials allow for fabricating complex-shaped biomedical components with a high level of accuracy. In this context, the major challenge is to obtain robust and functional engineering components. This may be attributed to a large-scale microstructural inhomogeneity arising due to the aforementioned deposition methodology followed in the AM-based techniques. In addition, the other challenges include size limitations, quality inconsistency, scaling issues and high cost of manufacturing of final parts. This leads to a major limitation of AM-based biomedical components in terms of their mechanical biocompatibility with the adjoining bones and tissues. One of the ways to overcome the aforementioned challenges is to engineer the microstructure in these materials in order to optimise the parameters involved during AM-based fabrication techniques. The present chapter is aimed to provide an overview of the different AM-based techniques involved in the fabrication of commonly used biomaterials and the common characterisation techniques for establishing a systematic structure-property correlation in these materials. Moreover, the future outlooks and challenges associated with these materials have been addressed from the authors' viewpoints at the end of the present chapter.

Keywords: Additive manufacturing, Biomedical materials, microstructural investigation, Correlative Microscopy, structure-property correlation.

1. Introduction

In terms of addressing design complexities and versatility in material selection, additive manufacturing (AM) turns out to be highly advantageous over traditional manufacturing techniques, particularly, in terms of following the 'bottom up' approach where a structure can be fabricated into a pre-designed shape using a 'layer-by-layer' deposition [1]–[4]. These render AM techniques as suitable for most of the industrial sectors, especially the medical sector where AM-based biomedical materials, presently find a number of applications in orthopedics [5]–[8], cardiology [5], [9], [10], respirology [7], [11] and urology [5], [12]. Inspite of the tremendous advantage offered by AM techniques in addressing design complexities in a wide range of materials ranging from metallic materials to Functionally Graded Materials (FGM) [2], [12], the primary challenge still remains in obtaining 'real, robust and functional' objects of engineering interest [3], [13], [14]. Moreover, the other challenges include: (i) size limitations [1], [15], (ii) quality consistency [16], (iii) scaling issues [17], [18] and (iv) high material cost [16], [18], [19]. In this context, there are mainly two parameters: (i) Process parameter which primarily influences material processing during AM and (ii) Structural parameter which provides a 'post-mortem analysis' in terms of microstructural features of AM products and hence, is very essential in selection of materials for AM [20]. Optimisation of these two parameters is extremely necessary for overcoming the aforementioned challenges associated with AM [21]–[40]. At present, there are a number of reports on understanding process parameters in AM techniques for a wide range of materials [41]–[44]. However, there are very few reports on understanding structural parameters especially in the context of AM biomedical materials [18].

A major challenge in the field of biomedical materials (especially metallic biomaterials) is to produce biomedical materials which are mechanically biocompatible with the adjoining bones and tissues [45]–[52]. This is necessary in order to prevent micro-injuries, cell damage, inflammation, necrosis etc. [45], [52]–[55]. The aforementioned mechanical biocompatibility is hugely influenced by the microstructure of the bio-implant [45], [55]–[58]. In the context of mechanical deformation of bio-implants, tensile properties are considered to be the most important for the purpose of preventing any kind of internal fracture inside the human body [59]–[64]. In addition, the other properties of the bio-implants which are largely influenced by the microstructure (of the implant) are the wear and corrosion resistance of these materials

on account of being subjected to a highly erosive and corrosive environment inside the human body [59], [62]–[74]. Nano-scratch and nano-fretting techniques are the two most common techniques for determining the wear resistance of biomedical materials [62], [75]–[81]. On the other hand, a number of electrochemical corrosion testing techniques have been reported for determining the extent of resistance of biomedical materials (especially metallic) towards both general and localised corrosion [82]–[86]. Besides, a number of attempts involving surface modification and thin film coating approaches have been made towards enhancing the overall biocompatibility of biomedical materials [87], [88]. Patterning of surface chemistry (of biomedical materials) has also been used as a technique to exert control over incidents such as cell spreading and attachment [87]. In addition, the common in-vivo techniques which have been reported till date for determining the overall biocompatibility of biomedical materials are implantation, irritation, sensitisation and toxicity testing techniques [8].

On the other hand, the common characterisation techniques used for determining the influence of surface modification techniques on the biocompatibility of biomedical materials are Atomic Force Microscopy (AFM), time-of-flight Secondary Ion Mass Spectrometry (ToF-SIMS), Infrared (IR) spectroscopy and X-Ray Photoelectron Spectroscopy (XPS) techniques [50], [87]. However, AFM provides information on only the surface topography with no information on the surface chemical composition whereas, IR Spectroscopy, ToF-SIMS and XPS techniques provide information on only the surface chemistry of these materials. In the recent decade, the emergence of a novel ‘Correlative Microscopy’ methodology involving the use of a number of different characterisation techniques for correlation of structural information with chemical information from the same region in a particular microstructure, has proven to be an extremely powerful tool for addressing AM-based selection and processing challenges in AM-based metallic materials [41]–[43]. However, owing primarily to challenges in sample preparation, there is hardly any report on employing the novel aforementioned methodology for structure-property correlation in biomedical materials. The present chapter is aimed at highlighting the importance of parametric optimisation along with the need to employ the novel ‘Correlative Microscopy’ methodology as a tool to address the challenges involved in material selection and processing in AM both from both industrial and fundamental viewpoints through a discussion on the recent developments in the field of AM-based biomedical materials based on a number of

interesting case studies in this direction. Moreover, the present chapter intends to provide a future outlook in the direction of AM of biomedical materials from the authors' viewpoint.

2. Classification of biomaterials

Biomaterials interact with biological systems and may be either natural or synthetic [89]. Moreover, in medical applications, they are primarily meant for he purpose of replacing a natural function. Biomaterials may be categorized on the basis of their biocompatibility levels as being bioactive, biodegradable, bioinert, and/or biotolerant. A bioactive material in the environment of a bone tissue may create an environment which is compatible with osteogenesis through the formation of chemical bonds with bone tissues [90]. Bioactive materials may be categorized into two different classes: osteoconductive and osteoinductive materials [91].

Osteoconductive materials (such as Hydroxyapatite and $Ca_3(PO_4)_2$) allow the growth of bone tissues along the bioactive material surface [91]. Osteoinductive materials stimulate the growth of new bone. Some osteoinductive materials (such as Bioactive glasses) are also known as osteoproductive materials by which bone growth can be stimulated away from the site of the implant [92], [93]. When a bioactive material is implanted into the human body, it stimulates a biological response from the body, which leads to a series of biophysical and biochemical reactions between the implant and tissue leading to a strong chemical bonding between the implant and the tissue [94], [95]. Although, biotolerant materials are accepted by the host but they are separated from the host tissue by the formation of a fibrous (scar) tissue. The layer of the scar tissue is induced by the release of ions, and chemical compounds (including corrosion products) from the implant [92], [96], [97]. Most metals and artificial (or, synthetic) polymers fall into this category. Bioinert materials (such as Ti and its alloys) are stable and do not react with body fluids or tissues [98]. Fibrous tissues encapsulate these materials in order to isolate them from the neighbouring bone [98]. This is similar to the tendency of biotolerant materials [94]. Biodegradable materials (such as polyglycolic and polylactic acids, calcium phosphates and Mg) dissolve upon coming in contact with the body fluids [95]. The products (formed after dissolution) are secreted via the kidneys [94]. These materials find applications in medical goods such as surgical sutures, and controlled drug release [95], [97].

3. Classification of additive manufacturing techniques for biomaterial fabrication

A number of AM techniques are available for medical and tissue engineering applications which are:

1. **Powder bed fusion (PBF)**: PBF techniques use either electron beam or laser to selectively consolidate powder particles. These techniques are: electron beam melting (EBM), selective laser melting (SLM) and selective laser sintering (SLS). Among these, SLM and EBM both melt completely and undergo fusion with the powder, while SLS technique heats the powder to the point where it can undergo fusion on a molecular level. In all PBF techniques, there is a layerwise spreading of material powder.
2. **Binder jet 3D Printing (BJ3DP):** Tis technique is similar to the PBF technique in terms of utilization of material powders which are spread one on top of the other layer. However, unlike PBF, which involves melting and fusion of the powder particles, this technique uses a binder as an adhesive for its consolidation across different layers.
3. **Material extrusion (or Fused Deposition Modelling (FDM)):** This technique involves pushing of raw materials in the form of polymer wires through a heated nozzle. The material is deposited in the form of polymer roads which are arranged to define the cross-section of a component and are consequently stacked in a layerwise manner.
4. **Material jetting:** This technique uses a liquid photopolymer resin cured with ultraviolet (UV) or near-UV radiation. Similar to the FDM technique, a nozzle moving horizontally across the build platform, is used to deposit the material. The material is subsequently cured followed by the consolidation of the resulting cross-section in a layer-by-layer manner as the building platform undergoes a vertical motion.
5. **Vat polymerization**: This technique employs photopolymer resins cured with UV radiation in a layerwise manner. In contrast to material jetting, the resin remains in a material vat, where the build platform is submerged. This is followed by the downward (or upward) motion of the build platform depending on the position of the source of radiation in order to create additional layers one on top of the other.

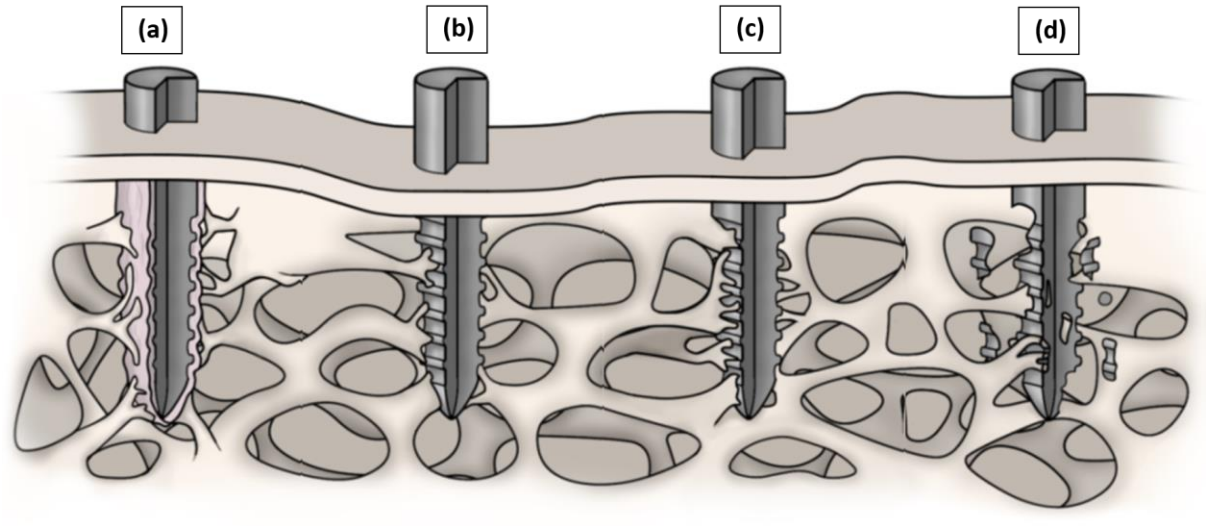


Fig. 1 Bone classifications illustrate using a bone screw: **(a)** Biotolerant, **(b)** Bioinert, **(c)** Bioactive and **(d)** Biodegradable [97].

4. Metallic biomaterials

Owing to an excellent combination of high stiffness coupled with wear resistance, ductility and electrical and thermal conductivities, metallic materials commonly find applications in orthopedic and orthodontic implants, artificial joints, bone and external fixators [99]–[102]. It is due to a unique combination of strength and ductility that even today, metallic implants cannot be completely replaced by the more biocompatible ceramics and polymers [102]–[107]. Biocompatible metals are mainly classified as being biotolerant with the exception of Ti and its alloys, which are bioinert. In addition, Ti and its alloys, stainless steel and Co-Cr alloys have been reported as the most commonly used biocompatible metals [108], [109]. To date, only PBF techniques have been able to successfully process biocompatible metallic materials (for medical grade) [110], [111]. Ti6Al4V is a common material for orthopedic implants owing to its high specific strength, excellent corrosion resistance and unique biocompatibility [112], [113]. Ti6Al4V (α-β Ti alloy) is inert meaning that the material may undergo direct contact with the adjacent bone tissue without introducing any chemical reaction between the implant and the host tissue [114], [115]. Once a bioinert material is implanted into the human body, it undergoes self-passivation by forming an adhesive oxide layer which prevents both electronic and ionic flow in the body fluid or adjoining tissue [113], [116]. The presence of V in the Ti-6Al-4V acts as β stabilizer, whereas Al acts an α stabilizer, which simultaneously contributes to strengthening and a decrease in density of the alloy [117]–[119].

Stainless steel (SS), on the other hand, is a common material for biomedical implants [120], [121]. In addition, it is a low-cost material. The AISI3xx series (mainly 304 and 316L grades)

with a fully austenitic microstructure is utilized in medical applications [122]–[124]. Although the aforementioned SS grades do not offer the same level of biocompatibility as in Ti6Al4V, however, they are biotolerant. **Fig. 2** shows the SEM images (at two different magnification: 100x and 500x) ofTi-6Al-4V alloy fabricated using EBM technique. With surface treatments, it is possible to increase both the biocompatibility and corrosion resistance of the aforementioned SS grades [125], [126]. Owing of the excellent combination of high strength couple with corrosion resistance, SS is often used in bone plates, spinal fixation, knee and hip components [116], [127]. Co-Cr alloys are another class of biotolerant materials. These alloys possess high wear resistance [128]. Cr forms an oxide layer on the surface of the alloy making it corrosion resistant in a biological environment whereas Co ensures a continuous phase resulting in homogeneous properties [129]. This renders Co-Cr alloys as suitable candidates for bone implant applications [130]–[132]. Xie [133] has reported that even though the metals do not express bioactive properties, the biocompatibility of most metals may be enhanced by creating bio-inspired surfaces. Although AM-based metals have been widely used in the dental industry, AM has the potential to set up new possibilities for long-lasting orthopedic implants for load-bearing applications. **Table. 1** summarises the classification, fabrication technique and application of some of the commonly used metallic biomaterials. **Table. 2** different AM-based techniques for the fabrication of metallic biomaterials. **Table. 3** shows a summary of some of the most commonly used AM-based techniques for the fabrication of metallic biomaterials.

Table. 1 Classification, AM-based fabrication techniques and application of some commonly used metallic biomaterials (SLM: Selective Laser Melting, EBM: Electron Beam Melting) [97]

Biomaterial	Classification	Fabrication technique	Application	Reference
Gold	Biotolerant	Powder bed fusion (SLM) and binder jetting	Dental restorations	[134]
Co-Cr-Mo alloys		Powder bed fusion (EBM and SLM)	Orthopedic and dental implants	[135]
Stainless steel		Powder bed	Cardiovascular	[135], [136]

		fusion (EBM and SLM) and material extrusion	stents and orthopedic implants	
Niobium		Powder bed fusion (EBM)	Vascular stents and coating for orthopedic implants	[137]
Tantalum		Powder bed fusion (EBM and SLM)	Orthopedic implants	[138]
Commercially pure Ti	Bioinert	Powder bed fusion (EBM and SLM)	Orthopedic and dental implants	[139]
α-β Ti alloy (Ti-6Al-4V)		Powder bed fusion (EBM and SLM)	Orthopedic and dental implants	[140]

Table. 2 Comparison of different AM-based techniques for the fabrication of metallic biomaterials [141]. (3DP: 3D Printing, SLS: Selective Laser Sintering, SLM: Selective Laser Melting, EBM: Electron Beam Melting, DMLS: Direct metal laser sintering, DMD: Direct metal deposition, EBAM: Electron-beam additive manufacturing) (P: Poor, L: Low, H: High, G: Good, E: Excellent, M: Moderate, B: Big S: Small, F: Fast, Sl: Slow)

AM-based technique	Resolution	Build Speed	Surface roughness	Power Efficiency	Build Volume	Residual Stress	Cost
3DP	P	F	P		B	L	L
SLS	G	Sl	E	P	S	H	H
SLM	G	Sl	E	P	S	H	H
EBM	M	F	G	G	S	M	H
DMLS	G	Sl	E	P	S	L	H
DMD	P	F	P	P	B	H	M
EBAM	M	M	G	G	S	M	H

Table. 3 Summary of some common AM-based techniques used for the fabrication of metallic biomaterials [141] (3DP: 3D Printing, SLS: Selective Laser Sintering, SLM: Selective Laser Melting, EBM: Electron Beam Melting, DMLS: Direct metal laser sintering, DMD: Direct metal deposition, EBAM: Electron-beam additive manufacturing)

AM-based technique	Characteristics	Applicable for metallic materials in biomedical applications	Advantages and disadvantages	Classification
DMLS	• A very thin layer comprising of metal powder particles is spread across the surface to be printed • Slow movement of	Stainless steel, Ti	Advantage(s): • Fabrication of parts free from internal stresses. Disadvantage(s): • Expensive;	Powder Bed Fusion

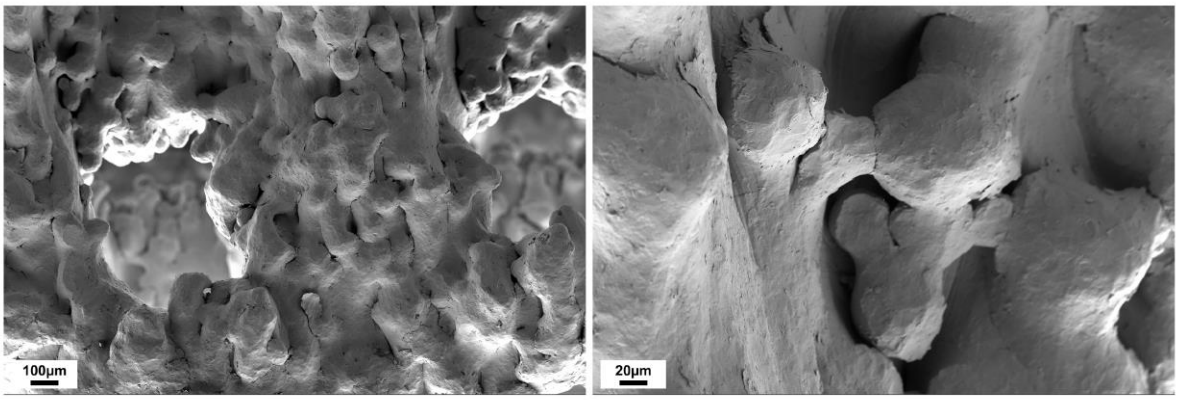
	laser moves across the surface to sinter powder • Sintering of additional powder layers.		limited its use to high-end applications. • Not suitable for low ductility materials. • Heating stage needed for low ductility materials.	
DMD	• Melting of powder particles using laser or other form of energy at the nozzle followed by layerwise deposition.	Fe, Ti	Advantage(s): • No limitation of part. Large metal parts may be fabricated. • Versatile. Disadvantage(s): • Poor surface finish.	Direct Energy Deposition
EBAM	• Conversion of CAD model to CNC code • Deposition of metal using electron beam gun, via layerwise deposition of powder or wire feedstock until the near-net shape is attained. • Heat treatment and machining as finishing treatments	Ti, stainless steel, Zn alloy, Ta, W	Advantage(s): • No limitation of part. Large metal parts may be fabricated. • Good material utilization. • Utilisation of multiple wire feed nozzles with a single EB gun. Disadvantage(s):	Direct Energy Deposition

			• Low processing accuracy (especially then compared to powder bed AM) and poor surface finish.	
3DP	• Depositing binder on metal powder • Curing the binder to hold the powder together • Sintering or consolidating the bound powder • Infiltrating with a second metal (optionally)	Stainless steel, Co-Cr alloys, Fe, Zr, W	Advantage(s): • Ability to create shapes with high design complexity. • No need for extensive laser optimization experimentation • No need of using heat source during the processing. • No need for a build plate. Disadvantage(s): • Fabricated parts needs extensive post-processing • Porosity in final parts • Not available for part reparation	Binder jetting

SLS	• Preparation of powder bed followed by layerwise deposition of powder • Sintering each layer according to the CAD file, using laser source	Stainless steel, Co-Cr alloys, Ti	Advantage(s): • No requirement of support and post-processing. Disadvantage(s): • Heat treatment and material infiltration are necessary. • Porous part and rough surface in final parts. • Thermal distortion in the finished parts. • No option for part reparation	Powder Bed Fusion
SLM	• Distribution of thin layers (20–100 μm) of atomized fine metal powder using a coating mechanism onto a substrate plate, usually metal. • Each 2D slice of the part undergoes fusion by selective of melting the powder particles. • Repetition of the process in a layer by	Stainless steel, Fe based alloys, Ti, Au, Ag	Advantage(s): • Complete melting of the powder particles enables to fabricate fully dense near net-shape components without the need for post-processing. • High processing precision s attained (~10	Powder Bed Fusion

	layer fashion until fabrication is complete		μm). Disadvantage(s): • High quality requirements for metal powders coupled with limited part size. • Distortion caused due to high residual thermal stress.	
EBM	• Reading of the data from a 3D CAD model and subsequent layerwise deposition of powder particles. • Melting of these layers are melted, using electron beam under high vacuum conditions.	Ti alloys, Co-Cr alloy	Advantage(s): • Preheating of the powder helps in the lowering of thermal stresses. • Vacuum environment is maintained. Hence, metal does not oxidize easily. Disadvantage(s): • Complex internal cavities in the fabricated part.. • Rougher texture and lower precision when	Powder Bed Fusion

			compared to laser beam manufacturing technique.	



(**a**) 100×, scaffold (**b**) 500×, scaffold

Fig. 2 SEM images at different magnification; **(a)** 100x and **(b)** 500x of Ti-6Al-4V scaffolds (mean pore size ~800 μm) fabricated using EBM technique [97].

5. Bioceramics

Owing to their excellent biocompatibility, these materials find applications as implants in bones, joints, and teeth. These may be either bioinert or bioactive [142]. Bioactive ceramics may further be classified as either degradable or non-degradable [143]. These ceramics are commonly integrated with bone tissues via chemical reactions which leads to the formation of hydroxycarbonate apatite without any inflammation. The bond (formed between the bone tissues and bioactive ceramics) is stronger than the bone itself [144]. Common examples of these ceramics are bioglass and calcium phosphates [145], [146]. Some calcium phosphates are based on hydroxyapatite (HA) and tricalcium phosphate (TCP), and have been considered for bone replacement applications [146]. HA($Ca_{10}(PO_4)_6(OH)_2$) is a bioactive ceramic with structure and chemistry in close resemblance with bone minerals and finds applications in scaffolds [144]. These ceramics are designed to undergo gradual degradation in a predetermined time frame. TCP ($Ca_3(PO_4)_2$) is another common bioactive ceramic with chemical composition similar to that of bone tissue mineral [142]. It has good resorbability

and bioactivity with higher rates of biodegradation as compared to that of HA under in vivo conditions [143].

Considering the brittle nature and poor fatigue properties of ceramics, they are less suitable for load-bearing applications unlike most metallic materials [133]. However, bioactive materials, (such as HA and bioglass) are used as bioactive coatings on metallic implants for load-bearing applications [147]. Ceramic coatings on metal implants offer three major advantages viz. (i) enhancement of bone formation, (ii) direct bonding of the costing with the adjoining bone, and (iii) reduction of metal corrosion as well as the release of corrosion products. Electrophoretic deposition [148], plasma spraying [149], and dip coating [143], [150] have been reported as common fabrication techniques for bioceramics.

Bioinert ceramics, on the other hand, possess excellent chemical stability and high mechanical strength in vivo. In addition, these are chemically inert and have a lower coefficient of friction and wear rate as compared to that of most metallic materials metals [108]. Hence, these ceramics often find applications as femoral heads of hip implants [146]. Common examples of bioinert ceramics are Al_2O_3 and ZrO_2 [147], [148]. Al_2O_3 (or alumina) has low coefficient of friction, high hardness combined with excellent wear and corrosion resistance [142]. Owing to these properties, Al_2O_3 has been developed as an alternative to surgical metal alloys for orthopedic and dental applications [151]. ZrO_2 (or zirconia) derived from Zr, is commonly used in a number of prosthetic devices owing to its high strength and wear resistance [109]. ZrO_2 is also used as a coating on Ti in dental implants [150]. In addition, it has been shown that ZrO_2 implants accumulate less bacteria as compared to that of commercially pure Ti implants in vivo [113].

AM can be a powerful tool to fabricate dental implants. Not only does the layer-by-layer approach (followed in AM-based techniques) reduce material consumption, but it also allows the fabrication of complex-shaped components. Recently, lithium disilicate glass ceramic dental restorations have been manufactured using a stereolithography-based AM technique, with high flexural strength (> 400 MPa) [152]. Mitteramskogler et al. [152] have utilized vat polymerization technique and utilised a modified digital light processing system for the purpose of improving the geometrical accuracy of 45 vol% ZrO_2 green parts [152]. ZrO_2-toughened Al_2O_3 ceramics have also been fabricated using vat polymerization technique [142]. Liu et al. [153] have manufactured HA porous scaffolds using vat polymerization technique. Moreover, the aforementioned scaffolds have been reported to demonstrate good in vitro biocompatibility for orthopedic applications. Schmidleithner et al. [136] have also used vat polymerization technique to manufacture TCP scaffolds (with < 2 vol.% error in

porosity and < 6% deviation from the mean pore size) for the regeneration of bone tissues. **Table. 4** summarises the classification, fabrication technique and application of some of the commonly used bioceramics.

Table. 4 Classification, AM-based fabrication techniques and application of some commonly used bioceramics (SLS: Selective Laser Sintering) [97]

Bioceramic	Classification	Fabrication technique	Application	Reference
Al oxide	Bioinert	Binder Jetting, vat polymerization	Osteosynthetic devices, bearing surfaces	[154]
Zirconium oxide		Powder bed fusion (SLS)	Fixed partial dentures	[155]
Hydroxyapatite	Bioactive	Vat polymerization, powder bed fusion (SLS), material extrusion and binder jetting	Bone tissue engineering	[156]
Bioglass		Vat photopolymerization	Bone tissue engineering	[157]
Calcium silicate		Powder bed fusion (SLS)	Tissue engineering	[158]
Tricalcium phosphate	Bioactive/ Biodegradable	Binder jetting, vat polymerization, material extrusion	Bone tissue engineering	[159]

6. Biopolymers and co-polymers

From a viewpoint of biomaterials, polymers and co-polymers may be categorised into two different classes namely biodegradable and biotolerant [160]. Among metallic biomaterials and bioceramics, polymers exhibit the minimum toughness (including both strength and ductility) [160]. As a result, biocompatible polymers and co-polymers (also known as

biopolymers and co-polymers) are not used in load-bearing biomedical applications. However, owing to a high level of tunabilityin terms of interaction with the biological, biodegradable polymers are widely investigated for applications in temporal devices [160]. AM-based biodegradable polymers, both natural and synthetic, are used for the fabrication of drug delivery vehicles (for controlled drug release), temporary 3D porous structures such as tissue engineering scaffolds, and temporary prostheses [161]. The degradation of polymers may be further classified as hydrolytical and enzymatical polymeric degradation [161]. Enzymatic degradation refers to a state of degradation wherein the polymeric material undergoes degradation by the enzymes which are secreted by the immune system, tissues, or microbes present in a biological environment [162]. This kind of degradation is common in most natural polymers [162]. In addition, the rate of enzymatical degradation largely depends on the implantation site (especially on the availability of different enzymes in an implantation site) [161].

On the other hand, hydrolytically degradable polymers undergo degradation by the cleavage of hydrolytically sensitive bonds in the polymer, which consequently leads to polymer erosion [161]. Polymer erosion may be divided into bulk or surface erosion, or a combination of both. In surface erosion, erosion starts from the exterior of the material and the interior of the material does not degrade until all the surrounding material has been degraded [160]. On the contrary, bulk erosion is characterized by an equal amount of erosion occurring throughout the entire material [162]. An interplay of these erosion mechanisms determines the suitability of different biomaterials for biomedical applications. For instance, in the context of sustained drug delivery, surface erosion is preferred over bulk erosion [162]. This is advantageous for bone tissue engineering (BTE) applications meant for ensuring a gradual replacement of the scaffold implant with the adjoining bone tissues [162]. **Fig. 3** shows a flowchart of design, fabrication and evaluation of BTE scaffolds.

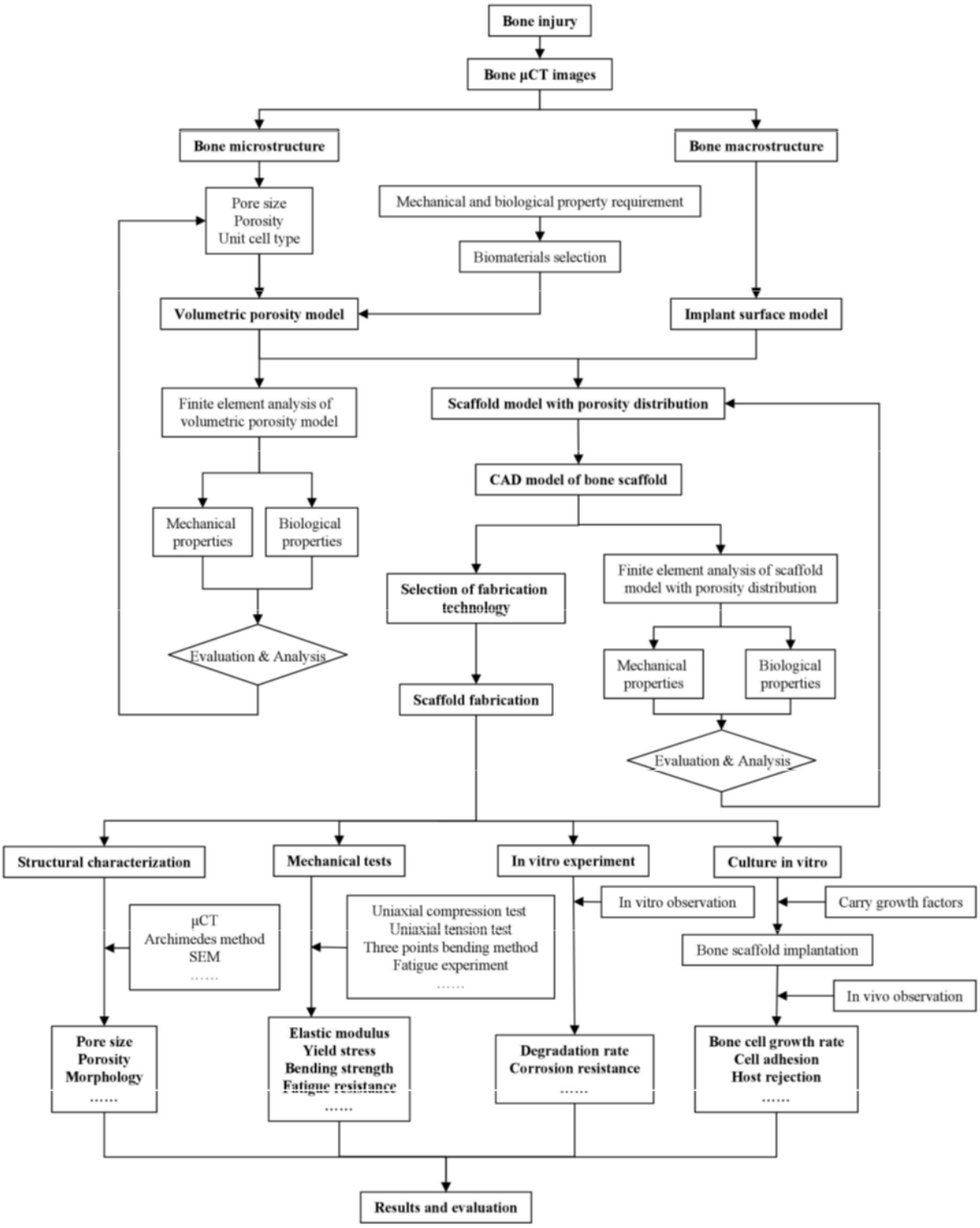


Fig. 3 BTE scaffolds: design, evaluation and fabrication. μCT (micro-computed tomography) [141].

The present research is mainly focussed towards implementing AM-based techniques for fabricating customized implants. Guerra et al. have employed material extrusion technique to fabricate stents using polycaprolactone (PCL)/polylactic acid (PLA) composites [161].

Moreover, the aforementioned printing technique was reported to be suitable for fabricating composite stents with an accuracy of ~85–95% combined with medium degradation rates, and enhanced biocompatibility [162]. Jia et al. [163] have designed and fabricated self-expandable biodegradable vascular stents from PLA using material extrusion technique. However, there are a number of limitations with biodegradable polymers when compared to conventional metallic bone fixators. There is a need to pre-drill holes for the biodegradable screws. Yeon et al. [164] have reported the manufacturing of a PLA/HA/Silk composite bone clip (using material extrusion technique) implanted in rat femur bone. Moreover, the bone clip was reported to show excellent alignment of the bone segments [164]. Zhang et al. [165] have utilized material extrusion technique to fabricate PCL scaffolds with three distinct mean pore sizes (215, 320, and 515 μm) [165]. In addition, the PCL scaffold with mean pore size ~215μm showed fibrocartilaginous tissue formation and enhanced mechanical properties as compared to the other pore sizes [165]. **Table. 5** shows the classification, fabrication techniques and applications of some commonly used biopolymers and co-polymers.

Table. 5 Biopolymers and co-polymers [97]

Biopolymer/co-polymer	Classification	Fabrication technique	Application	Reference
Polyethylene (PE)	Biotolerant	Powder bed fusion (SLS)	Vascular prostheses, cardiac valves and hip joints	[166]
Poly(hexano-6-lactam) (PA6)		Powder bed fusion (SLS)	Intravascular balloon catheters	[167]
Poly(methyl methacrylate) (PMMA)		Powder bed fusion (SLS) and Vat photopolymerization	Anchoring of hip prostheses, vertebroplasties and eyeglass lenses	[168]
Poly(tetrafluorethylene) (PTFE)		Vat photopolymerization	Orthopedy and vascular clips	[169]
Poly(aryletherketone) (PAEK)	Bioactive	Powder bed fusion (SLS)	Orthopedic and spinal implants	[170]
Polyurethane (PUR)	Biostable and biodegradable	Vat photopolymerization	Cardiovascular devices	[171]

Polycaprolactone (PCL)	Biodegradable	Powder bed fusion (SLS) and material extrusion	Tissue engineering and controlled drug release	[169]
Poly(lactic acid) (PLA)		Material extrusion	Bioabsorbable fixation, bone regeneration and fixation and drug delivery	[168]
Poly(lactic acid-co-glycolic acid) (PLGA)		Material jetting and material extrusion	Therapeutic devices, drug delivery and tissue engineering	[167]

7. Characterisation of biomaterials

7.1 Structural and chemical characterisation

7.1.1 X-ray diffraction (XRD)

X-ray diffraction (XRD) is primarily used to determine the structure of materials [172]. A typical powder X-ray diffractometer consists of an X-ray generation source (Co, Cr, Cu and Mo are typically used as the source), a diffractometer (to control the direction of the X-ray and also the sample and detector positions), a monochromator and a detector. In addition, a Bragg-Brentano geometry is followed in a typical powder XRD instrument [172].

In powder XRD technique, a monochromatic X-ray beam is directed towards the material with an interplanar spacing d and the intensity of the diffracted beam is measured as a function of the angle between the incident and diffracted beam (2θ, where θ is the angle between the incident X-ray beam and the atomic plane also known as Bragg plane). Bragg's law is used to used to determine d from 2θ: [172]

$$\lambda = 2d\sin\theta \quad (1)$$

where λ is the wavelength of the monochromatic X-ray beam. 2θ and d provide a number of information such as the crystal structure, lattice parameter, shape and dimension of the unit cell, crystallite size, residual stress and so on.

7.1.2 Infrared (IR) spectroscopy

This is an optical technique for identifying the structure and chemical composition of complex compounds [171]. IR radiation (at various frequencies) is absorbed by different functional groups [141], [173]. This enables IR spectroscopy to detect the presence or absence of different chemical functional groups in a molecule [173], [174]. Similar to XRD (discussed in section **7.**1), this technique is non-destructive and can be used to analyze biomaterials irrespective of their state of matter (solid, liquid or gaseous) [175]. IR photons do not possess a sufficient amount of energy to cause electronic transitions in the valence shells of atoms, however, the vibrational and rotational motion are excited by IR radiation [175]. The IR spectrum comprises of a plot of intensity (of absorption, transmission, or refection) as a function of wavelength or frequency and may be further divided into three different subregions; (i) Near-IR (NIR): extends from ~800 to ~2500 nm, (ii) Mid-IR (MIR): extends from ~2500 to ~15000 nm, and (iii) far-IR (FIR): extends from ~15,000 to ~1,00,000 nm (FIR) [174]. The most common IR instrument is the Fourier transform infrared (FTIR) spectrometer which owing to its high signal-to-noise ratio, is easy to use and is available at low cost[176]. In addition, FTIR is capable of measuring all wavelengths. Thus, whole spectral information is obtained in one go.

In the context of biomedical materials, FTIR has been used for investigating the degree of conversion in dental composites and the process of polymerization [177], [178]. Moreover, another technique named attenuated total reflection FTIR (ATR-FTIR) spectroscopy is being recently employed to characterize biomaterials. The main advantage of the ATR-FTIR is that there is no pretreatment required during sample preparation [179].

7.1.3 Raman Spectroscopy

Similar to XRD (discussed in section **7.1.1**) and IR spectroscopy (discussed in section **7.1.2**), this is another non-destructive characterisation technique. However, unlike XRD which is meant for structural characterisation of materials, this is a spectroscopy technique based on the molecular vibrations of materials and has shown a promising potential as a spectroscopic technique in the field of biomaterials irrespective of their state of matter (solid, liquid, or gas). Unlike the existence of selection rules based on Structure factor calculations (for different crystal structures) in XRD, there exist certain excitations in vibrational mode which are allowed in IR spectroscopy but are forbidden in Raman spectroscopy [180]. The Raman spectra are generated due to the interaction of photons with the specimen molecules and are collected using optical filters. Raman spectra contain information about the chemical composition, molecular structure, and identify the unknown materials. In this technique, the

Raman intensity is plotted as a function of the Raman shift [181]. The Raman shift is defined as the difference of frequencies between the incident and scattered Raman light beam.

7.1.4 X-ray Photoelectron Spectroscopy (XPS)

This is used to characterize the chemical composition of the very top surface (~1-10 nm) of any solid surface based on the photoelectric effect during bombardment of surface with X-ray photons. The ejection of electrons occurs using a monochromatic beam of X-rays in an ultrahigh vacuum (UHV) environment [176]. This is followed by the emission of electrons from the shell of atoms and their kinetic energy and number are simultaneously measured by detectors. The binding energy of electrons is a characteristic of the elements, but it is also influenced by the oxidation state and the local bonding environment between atoms (especially the state of hybridization). Therefore, XPS is capable of determining the chemical nature of the materials [176]. The application of XPS is limited in the context of biomaterials as they have a high chance of radiation damage caused by X-ray photons. Besides, XPS also enables to determine the extent of the functionality and binding of biomolecules onto a number of surfaces. In the context of dental applications [176], XPS has been used to analyse tooth tissues in restorative dentistry for the purpose of understanding of the mechanisms of interaction between the biomaterial and the hard tissue [176], [182].

7.1.5 Ultraviolet (UV)-vis spectroscopy

This technique is based on the absorbance of UV radiation (λ~190-350 nm) to visible light (λ~350-800 nm) (in a material) as a function of wavelength [176], [183]. The absorption (of UV radiation) happens due to the transition (of electrons) from the ground to the excited state with magnitude depending on the Beer Lambert relationship: [174], [176]

$$A=abc \quad (2)$$

Where, A is the absorbance, a is the absorption coefficient (wavelength-dependent), b is the path length through the solution, and c is the molar concentration of the absorbing analyte. This technique is especially useful for providing both qualitative and quantitative information about dental biomaterials and composites.

7.1.6 Nuclear magnetic resonance (NMR) spectroscopy

This is a non-destructive spectroscopy technique for determining chemical composition and conformations of biomolecules [176]. NMR probes the nuclei of atoms and not the electrons. During NMR, the behaviour of specific atoms (1H, 13C, 15N, 31P, 19F) on being exposed to an external magnetic field leads to a spin-nuclei mechanism occurs [177]. NMR has been

applied in molecular level for understanding the mechanisms of biomineralization (the ones used for bone repair and hard tissue regeneration of the teeth) [181].

7.1.8 Mercury Intrusion Porosimetry (MIP)

In recent years, porous biomaterials have gained attention for applications in scaffolds for tissue engineering and drug delivery system. The minimum pore size needed to permit the in-growth of mineralized tissue has been reported as ~50 μm in Ref. [174]. In this context, it is worth mentioning that larger pore sizes degrade the mechanical properties and also lead to an increase in the depth of infiltration of these tissues into the biomaterial [176]. Smaller pore sizes, on the other hand, lead to large surface areas, resulting in a higher adsorption of cellinducing proteins. MIP is used to determine the pore sizes and porosity in a number of biomaterials (especially bioceramics) [176].

7.1.9 Scanning Electron Microscopy (SEM)

This is one of the most widely used microscopy tools for imaging the microstructure and morphology of the materials [176]. In SEM, an electron beam (with low energy) scans the surface of the sample [174]. A number of different interactions occur as the beam reaches and enters the material, which lead to the emission of electrons and characteristic X-rays from near the sample surface [174], [184]. In order to form an image, the receiving signals produced from the electron sample interactions are detected with different types of detectors depending on the mode of SEM being used and the information required [176]. For instance, secondary electrons (SE) generated from near the sample surface provide information about the surface topography whereas back-scattered electrons (BSE) generated from a greater depth in the sample show the atomic number (Z) contrast between the different phase in a given microstructure and can also be used to generate information about the orientation of different grains in a polycrystalline material (through tilting the specimen to ~70° with respect to the horizontal level) by tilting the specimen and allowing the BSEs to undergo diffraction and finally, detecting the Kikuchi bands (formed due to the diffraction of BSEs) through special detectors. This SEM-based technique is also known as Electron Backscatter Diffraction (EBSD) [185]. On the other hand, Energy Dispersive Spectroscopy (EDS) detectors, providing information on the chemical composition of different phases in a multiphase microstructure, detect the characteristic X-rays generated from within the specimen (at a much higher depth when compared with those of SE and BSE). Different modes of SEM are used for the characterisation of biomaterials such as EDS mapping, secondary electron (SE) imaging, backscattered electrons (BSE) imaging. The main components of a typical SEM are:

- The electron gun: for the emission of electrons which are then accelerated to ~0.1-30 keV.
- Hairpin tungsten gun: for the purpose of forming high-resolution images from a high diameter electron beam.
- Electromagnetic lenses and apertures: meant to focus electron beam to form a small high-intensity spot on the specimen.
- High-vacuum environment: for preventing electron scattering.

7.2.0 Transmission Electron Microscopy (TEM)

This technique is used to provide information about the morphology, crystal structure, and chemical composition of biomaterials with a higher resolution than what which may be achieved with a typical SEM. Here, electrons (with energy ~ 120-300 kV) are emitted from an electron gun (aminly of two types: Thermionic and Field emission), are directed by the electrostatic lenses onto an electro transparent specimen (thickness < 50 nm) and undergo dynamic scattering in the specimen [174], [176]. Owing to the dynamic scattering events undergone by the electrons with the electron transparent sample, depending on the sample density, some electrons undergo scattering (or absorption), and some others pass through the sample. These electrons which pass through the thin sample and hit the detector form an image on the fluorescent screen placed at the bottom of the TEM. The denser the sample, the lesser is the probability of electrons to pass through it, and consequently, the image formed (in bright field (BF) mode) is darker [186], [187]. The main limitations is a TEM are smaller field of view as compared to that in an SEM, chances of sample damage if the beam energy is excessively high (very common for sensitive biological materials), poor contrast in low atomic number (Z) materials, sample preparation (both conventional and Focussed Ion Beam (FIB)-based) require huge effort and skills, expertise in equipment handling and data interpretation and low depth of resolution [188], [189]. **Fig. 4** shows the TEM-BF image of human chondrocytes grown at the surface and within the bulk.

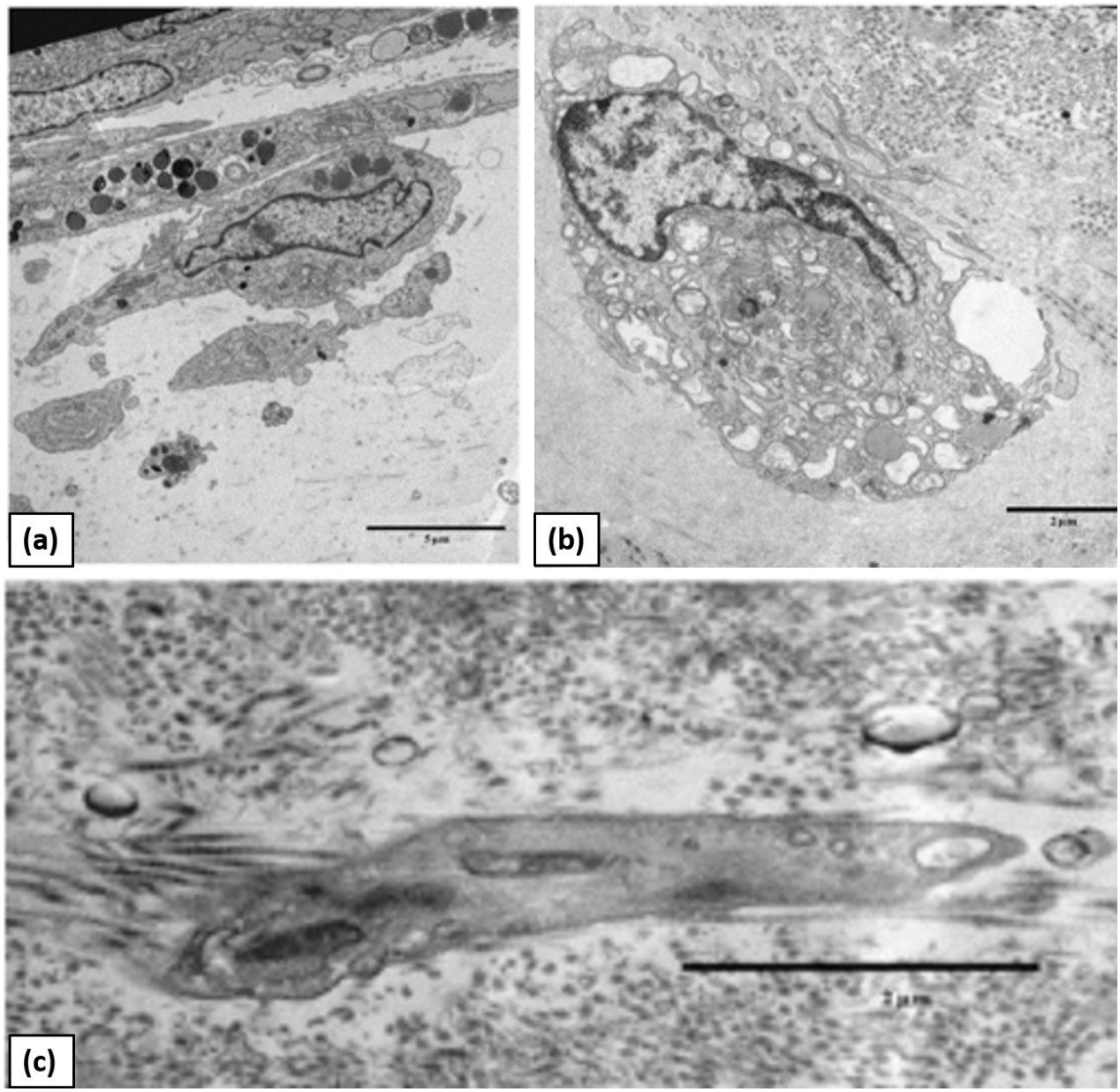


Fig. 4 TEM-BF image showing the morphology of human chondrocytes (grown at the surface and within the bulk): **(a)** unmodified bacterial cellulose, **(b)** articular cartilage bulk, and **(c)** articular cartilage surface [190].

7.2.1 Atomic Force Microscopy (AFM)

This technique is used to image and analyze nearly all kinds of surfaces (hard or soft, insulator or conductor). The image formed by the AFM reveals the 3D surface features with a spatial resolution of the order of a few nm [191]. Here, a sharp tip (nearly one atom thick and made of Si or Si Nitride) is used to record the topography of the sample [191]. The force between the tip and the sample surface leads to an elastic deflection of the beam (which is directly proportional to the magnitude of the interatomic forces) to which the tip is attached.

An optical system is used to image the deflection of the beam [191]. On the basis of the nature of tip-surface interactions, different modes of AFM are:

- Dynamic force (or tapping mode): Oscillation and movement of the tip near the surface of the sample, leading to a periodic contact of the tip with the sample surface.
- Contact mode: Movement of the tip over the sample surface and experiences a strong repulsion from the sample surface leading to the bending of the beam.
- Non-contact mode: Movement of the tip close to the surface (at a distance farther than that for the dynamic mode) and hence, does not come in contact with the sample surface. The interaction forces (between the sample surface and the tip) in this mode are very low (of the order of a few pN). This mode is especially useful for soft biomaterials since this does not damage their surfaces.

7.2 In-vitro characterisation

7.2.1 Cytotoxicity testing

This is a testing technique for determining the cytotoxic effects of a biomaterial in a living organism [192]. It is one of the earliest in vitro techniques meant for the evaluation of biocompatibility of materials [193], [194]. Typical biological endpoints (in cytotoxicity testing) include:

- Morphological assessment: This is performed by using ultrastructural analysis of the cells using either SEM or TEM, depending on the level of accuracy and resolution (required in terms of morphology), and microscopy parameters field of view and depth of field.
- Cell viability and proliferation assays: Common examples are Alamar blue assay, 3-(4,5 dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay, bromodeoxyuridine incorporation assay, 3H-thymidine incorporation assay, and DNA or protein content measurement.
- Cell function assays: measurement of the release of inflammatory markers, glutathione determination, heat-shock protein and apoptosis assay.

7.2.2 Hemocompatibility testing

This is a testing method to analyse adverse effects (e.g., thrombosis, hemolysis, platelet activation) and blood-biomaterial interaction [194]. One of the primary issues associated with hemocompatibility is the absence of adequate standards for anticoagulation. Therefore, it can be difficult to classify a particular biomaterial as either hemocompatible or nonhemocompatible [195]. Some of the very important aspects in hemocompatibility testing

include physical and chemical characteristics, stability of the materials, test conditions, and plausibility aspects.

7.2.3 Genotoxicity and carcinogenicity testing

These are meant to study the genotoxic effect (e.g., gene mutation, change in DNA, and alterations in chromosome) and the carcinogenic effects of an implant on a living organism [196]. Micronucleus assay, comet assay, and Ames test have been used to determine the genotoxic effects of nanomaterials among which the Ames test and Comet assay is known for being quick (in terms of detecting Deoxyribonucleic Acid (DNA) damage) and also for its simplicity and low cost [195].

7.2.4 Reverse transcription-polymerase chain reaction (RT-PCR)

This technique is used for detecting and comparing the levels of messenger-Ribonucleic Acid (m-RNA) and the surface proteins [192]. PCR can be performed as both (i) real-time and (ii) end-point PCR [193]. End-point PCR is a low-cost technique and requires low cost equipments. Measurement of gene expression is the main role of end point PCR [192].

7.3 In vivo characterization

7.3.1 Sensitization, irritation, and toxicity tests

Sensitization may be described as an increase in immune response and delayed hypersensitive response to a biomaterial (in a living organism) which otherwise may result in skin irritation and local inflammation on skin [194]. This can be highly time consuming as it requires a film of chemical agent (in a saline solution) to be placed on the skin followed by the monitoring of the effects of a particular biomaterial with passage of time [195]. Murine Local Lymph Node Assay, Buehler and Guinea Pig Maximisation are examples of sensitization testing. The other common in-vivo tests for determining the extent of irritation caused by the biomaterials in animals are intracutaneous reactivity, subacute systemic toxicity, subchronic systemic toxicity, and chronic toxicity tests [197].

7.3.2 Implantation testing

Here, materials are implanted into the connective tissue, muscle, or into the animal bone to understand the pathological influences (ranging from gross to microscopic levels) of biomaterials on the functioning and structure of the tissues [195]. This may be used to demonstrate tissue necrosis and apoptosis, cell proliferation, thrombus formation, collagen deposition, and endothelization. Both short and long-term testing may be used to determine the immediate and delayed response of the tissue to the implant [196].

7.3.3 Biodegradation test

A number of degradable biomaterials may discharge degradation products (commonly impurities and corrosion products) to the adjacent tissues and even the organs (which may be distant). In-vivo biodegradation tests have an important role for studying of effects biodegradation of biomaterials in living tissues [197]. Biological and tissue responses in a living organism may be identified using histological analysis [195].

8. Summary and future outlooks: From the authors' viewpoint

At present, there is a sufficient amount of information on the different AM-based fabrication techniques for all three different types of biomaterials (viz. metallic biomaterials, bioceramics and biopolymers and co-polymers) as discussed in the **sections 2-6**. Hence, it is reasonable to infer that there is a good amount of information on the process parameters involved in different AM-based techniques or the fabrication of biomaterials. Besides, there are a huge number of reports on the fabrication of different biomaterials using different AM-based techniques getting published frequently. However, the missing aspect in all the present reports is a proper understanding of the microstructure in biomaterials which is important to engineer the biocompatibility (especially the mechanical biocompatibility) of biomaterials. As briefly mentioned in the introduction section (**section 1**), mechanical biocompatibility (between tissues/bones and a biomaterial) is essential in order to prevent micro-injuries, cell damage, inflammation, necrosis etc. [45], [52]–[55]. The aforementioned mechanical biocompatibility is hugely influenced by the microstructure of the bio-implant. Although a number of recent reports have been aimed towards addressing the corrosion and wear resistance and also the tensile, compressive and flexural properties for a number of different biomaterials, however, a systematic correlation between the microstructure and the aforementioned properties is missing in the present reports.

In the recent decade, a correlative approach towards microstructural characterisation has been widely employed towards correlating the structural information with the local chemistry of especially nanosized features in metallic materials. The pre-requisite for such characterisation mainly involves careful sample preparation (which may sometimes be time-consuming) [198]. However, these techniques involve a huge amount of investment and may sometimes lack consistency of experimental results. Moreover, owing to the complexity of structures and of sample preparation in bioceramics and biopolymers (and co-polymers), there is hardly any report (till date) on the correlative characterisation of these materials. In addition, only a few groups have reported the characterisation of biomaterials in an atomic scale using Atom Probe Tomography (APT) technique in the present decade [199]–[204]. Hence, correlative microscopy maybe used as a potential tool for the purpose of correlating the wide range of

interesting properties shown by the biomaterials (fabricated using different AM-based techniques) with both structural and chemical information in their microstructure. This is necessary to establish a systemic structure-property correlation in these materials which, a present, is the least understood in the context of biomaterials.

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