Heliyon 7 (2021) e06892

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Review article

Additive manufacturing of Ti6Al4V alloy via electron beam melting for the development of implants for the biomedical industry



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ARTICLE INFO

Keywords: Additive manufacturing Powder bed fusion Titanium Electron beam melting Implants Biomedical

ABSTRACT

Additive Manufacturing (AM) or rapid prototyping technologies are presented as one of the best options to produce customized prostheses and implants with high-level requirements in terms of complex geometries, mechanical properties, and short production times. The AM method that has been more investigated to obtain metallic implants for medical and biomedical use is Electron Beam Melting (EBM), which is based on the powder bed fusion technique. One of the most common metals employed to manufacture medical implants is titanium. Although discovered in 1790, titanium and its alloys only started to be used as engineering materials for biomedical prostheses after the 1950s. In the biomedical field, these materials have been mainly employed to facilitate bone adhesion and fixation, as well as for joint replacement surgeries, thanks to their good chemical, mechanical, and biocompatibility properties. Therefore, this study aims to collect relevant and up-to-date information from an exhaustive literature review on EBM and its applications in the medical and biomedical fields. This AM method has become increasingly popular in the manufacturing sector due to its great versatility and geometry control.

1. Introduction

Manufacturing is a production technique that dates back to the very origins of the human race and reflects humans' need to adapt the world to their needs. Therefore, it can be defined as the process of transforming raw materials into final products. Manufacturing also involves activities in which the manufactured product itself is used to make other products [1]. Since it is a tool directly linked to human beings, it has been forced to evolve at the same pace as humanity, which means that new needs and manufacturing processes arise as humankind advances. Additive Manufacturing (AM) is one of the existing manufacturing techniques. It makes it possible to materialize objects designed using a Computer-Aided Design (CAD) software or scans of a real object [2]. The various AM technologies have led to significant advances in important fields of engineering and medicine such as aerospace, automotive, and biomedical engineering; construction; and dentistry.

In the medical field, different AM techniques have been recently used to obtain metallic implants, which, when fabricated through conventional manufacturing methods, present some disadvantages in terms of machining, come in standard sizes, and make it difficult to obtain porous structures that facilitate osseointegration [3]. Alongside the development of new implant manufacturing technologies and their innovation processes, biocompatible materials have been increasingly studied. These materials must efficiently serve their intended purpose as implant materials and have certain properties such as excellent biocompatibility, biofunctionality, yield strength, hardness, elasticity, corrosion and wear resistance, and fatigue strength [4,5]. In recent decades, various AM methods—initially known as rapid manufacturing techniques—have been developed to produce fully dense metal parts. One of their main applications has been the manufacture of customized biomedical implants using computerized tomography scans of a patient's affected area [6]. This type of implants are quite difficult to obtain through conventional methods such as Computer Numerical Control (CNC) machining.

One of the AM techniques used to produce customized implants is Selective Laser Melting (SLM). Besides being employed to manufacture customized dental implants [7], complex biomedical structures [8], and porous parts (e.g., bone substitutes) [9], this method has shown promising results in hip arthroplasty (particularly Resurfacing Hip Arthroplasty [RHA]) [10]. However, in laser technology, materials melt while the parts are at relatively low temperatures, which may induce residual

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https://doi.org/10.1016/j.heliyon.2021.e06892

Received 2 December 2020; Received in revised form 27 January 2021; Accepted 21 April 2021

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stresses that can cause the components in service to fail. Electron Beam Melting (EBM), another AM method, has also demonstrated a great potential for the manufacture of different implants, including customized orthopedic hip stems with good material properties [11] and open-cell titanium pieces with acetabular and integrated structures [12]. In the late 1980s, products obtained with the EBM technique were reported to achieve mechanical and chemical properties similar to those produced using other traditional manufacturing methods such as casting and forging [13, 14, 15]. In other studies, EBM-processed implants for cortical and trabecular bone applications have shown a biological performance similar to that of conventionally machined and forged parts [16].

In implant development, the design of an EBM-machined part, such as a femoral stem, involves several steps. First, a Three-Dimensional (3D) model of the femoral canal is generated via computed tomography imaging to obtain a digital representation of this canal in the bone after surgical curettage [17,18]. These 3D images of the canal serve as reference to design the hip stem implants as per the patient's bone size using a CAD software. This CAD model is also used to make the necessary adjustments based on each patient's needs and to prepare all the details before the manufacturing process. For example, if the implant is to be manufactured by EBM, the first step is to define its orientation and support in the impression area. One design is prepared for each build, and between 15 and 20 implants can be produced per build Conversely, in CNC-manufactured parts, preparation is done for each implant separately, which reduces the number of parts to be produced [6]. Due to the highly rough surface finish obtained with the EBM method, some post-processing operations are required to polish the sides of the part, while, in CNC-machined implants, a post-treatment with titanium powder is commonly employed to create a rough surface in the middle of the part. Subsequently, the middle part of the stem is coated with hydroxyapatite to favor bone ingrowth, and then, the implant is sterilized to have it ready for surgery [6]. Another important aspect to consider is the load supported by the prosthesis. The part of the stem that goes deep in the femur is stiffer than the bone around it, which results in a greater associated load. Therefore, the bone close to this part of the stem loses mass and, in most cases, eventually causes a loosening of the implant [19,20]. Some studies have reported a higher peak bone density at the ends of stems with high stiffness than in implants with low stiffness, as well as an improvement in the stresses around the femur thanks to a proper implant fit [21,22].

To reduce the effects of excessive stress, some important factors to consider include implant's rigidity, as well as implant–bone fit and adhesion. The EBM method offers advantages to solve problems associated with these factors. One of its advantages is the possibility of manufacturing prostheses with open-cell structures (lattice structures) to obtain properties similar to those of a bone (e.g., its rigidity). For instance, it has been demonstrated that the EBM technology is capable of producing porous Ti4Al6V parts with a compression strength and a

Young's modulus compatible with those of a natural bone [23]. Likewise, the EBM technique can be used to design porous structures in the middle part of the stem to favor bone ingrowth. Additionally, EBM-manufactured parts have a more suitable surface structure for bone adhesion. Nevertheless, this structure must be evaluated to review its potential use or analyze whether it is necessary to modify it to make it functional both in terms of bone ingrowth and good mechanical properties. The remarkable biocompatibility of titanium alloys makes them ideal candidates to replace hard tissues and to be implanted in the body. As mentioned above, the formation of a passive layer is responsible for their good biocompatibility and corrosion resistance thanks to its high physicochemical stability [24, 25, 26]. However, the surface of titanium and its alloys do not have favorable mechanical and tribological properties, which may cause damage to the material when it is subjected to a dynamic or static load [27], [28]. Different surface modification techniques help to improve the surface properties of these materials, thus allowing the formation of coatings that lead to a better chemical bonding to the bone.

In recent years, anodizing has gained great attention as a low-cost method to modify the surface structure of titanium alloys. This process allows the formation of a thicker oxide layer whose composition, properties, and morphology are modified depending on certain process variables, such as voltage control, current, temperature, and electrolyte composition [29, 30, 31]. The coatings obtained with this process present a variety of morphologies, and their composition depends on the elements present in the anodizing solution, which enables the formation of biocompatible compounds in the coating. Likewise, these coatings have better mechanical properties and low coefficients of friction, thus preventing the material from wearing down and the parts of the body with which they will be in contact from being affected [32], [33]. In addition, besides being environmentally friendly, as no toxic emissions are released into the environment, the parameters of this process can be easily controlled to produce the required coatings, which present good adhesion to the substrate. Thanks to its versatility, this technique can be easily implemented at an industrial scale [34].

2. Additive manufacturing

Additive manufacturing, or 3D printing, makes it possible to obtain, at low costs and in short times, CAD prototypes that can be transformed into 3D objects, which are built layer by layer [35]. For this reason, the American Society for Testing and Materials (ASTM) defines AM as the "process of joining materials to make parts from 3D model data, usually layer upon layer" [36,37]. This technique consists in producing a part completely from scratch using a model previously designed in a CAD software. Examples of this type of software include 3D Slash, 3DPrinterOS, FreeCAD, Fusion 360, and TinkerCAD [38]. Figure 1 shows the basic steps involved in rapid prototyping.



Figure 1. Product life cycle [39].

Another advantage of using AM is the reduction in the costs associated with the manufacture of fully customized and low-cost objects and components with complex geometries that are difficult to obtain through conventional manufacturing processes. This is why this technique is being widely used in fields such as automotive, aerospace, and biomedical engineering; electrical component manufacturing; medicine; and dentistry [40]. In recent years, AM has exponentially grown in important sectors, thus generating multiple needs that have, in turn, led to the development of novel and innovative techniques. AM technologies are not limited to replacing traditional manufacturing processes; they also have the ability to create new business models, products, and market foci. Thanks to the efforts of the scientific and academic communities, customized prototypes that are in line with the requirements of the end user have been able to be produced by means of AM techniques. Through the various AM technologies, products and prototypes are developed using engineering materials such as metals, polymers, and ceramics and the combination of these. This opens up new paths to solve problems in different applications [41], [42]. In 2015, ASTM classified AM technologies, under the ISO/ASTM 52900 standard, as follows [43]:

2.1. Binder jetting

In this method, a binder liquid (bonding agent) that is selectively deposited to bind powdered materials is injected through nozzles. These nozzles move along a previously designed path until pieces are obtained layer by layer [43]. Although the parts fabricated by binder jetting have well-defined finishes, they do not exhibit good mechanical properties, which is why this method is not often used for prosthetics.

2.2. Powder bed fusion (PBF)

This technique employs a high-energy source that selectively melts a bed of powdered material (preferably metallic materials) layer by layer. It is used to develop functional prototypes and functional engineering pieces in general. The parts obtained with this method have high durability and favorable mechanical properties. PBF is further divided into two techniques depending on the type of energy source used [43]:

- Electron Beam Melting (EBM), which uses an electron beam.
- Selective Laser Melting (SLM), which employs a high-power laser.

2.3. Photopolymerization

This method uses a photosensitive polymeric resin that solidifies when selectively exposed to an Ultraviolet (UV) light source. The UV light is responsible for initiating the chemical selective crosslinking reaction of a layer of the photosensitive polymeric material in order to cure it. Then, another layer of the polymer is cured over the preceding one and so on until the prototype is completed [44]. As in binder jetting, the models produced with this method do not stand out for their good mechanical properties; hence, photopolymerization is often employed to obtain appearance models and prototypes. This technology comprises the following techniques: Stereolithography (SLA), Continuous Liquid Interface Production (CLIP), and Digital Light Processing (DLP) [44]. Parts with high resolution and excellent mechanical properties can be obtained using SLA. However, since the parts are not completely cured after the printing process, a subsequent heat treatment is necessary to achieve the desirable mechanical properties.

2.4. Directed energy deposition (DED)

This technique employs a direct energy source (laser, electron beam, or plasma arc) to melt a material that is, in turn, deposited on the build tray. It uses a flow of injected metal powder or metal wire as the raw material. Although it stands out for being a high-speed method and is used to develop prototypes and functional parts and to repair metal parts

and accessories, the pieces obtained with it do not exhibit suitable mechanical properties. DED is further divided into two methods depending on the raw material used [43]:

- Method based on a welding process, which employs a metal wire as the raw material.
- Laser Engineered Net Shaping (LENS), which uses a powder flow as the raw material.

2.5. Material extrusion (ME)

This method uses an extruder that selectively distributes a material, layer by layer, on a tray, generally at high temperatures to ensure that the part is properly adhered to the bed. The material softens when heat is applied and is extruded under pressure through an orifice or die while following the designed trajectory of the digital model of the prototype [44]. It is characterized by being a low-cost and high-speed technique mainly employed with polymeric materials. It produces parts with fine finishes but low mechanical properties. ME is further divided into two techniques:

- Fused Deposition Modeling (FDM), which is used with different materials, especially thermoplastics. This technology has some drawbacks associated with the direct production of prototypes from polymers and ceramics, as it requires additional processes such as melt extrusion [45]. In FDM, a continuous filament is fed into an extrusion nozzle. Then, it is heated in the nozzle until it melts and continuously deposited on a build platform to produce, layer by layer, a 3D prototype [46].
- Contour Crafting (CC), which is a large-scale 3D printing process developed in 1998 by Berokh Khoshnevis to print real-life houses [47]. This technology focuses on the printing speed and, therefore, is closely associated with productivity. It employs a low-resolution printer, and given its high speed, it may have an impact on some of the mechanical properties of the materials (e.g., their resistance) [48].

2.6. Sheet lamination

In this process, sheets are cut according to the designed geometry using a CO_2 laser or an ultrasonic energy source and then joined together with a bonding agent to form the 3D part. When an ultrasonic energy source is employed, the interfaces of the stacked sheets are bonded, layer by layer, by diffusion to form the 3D part without using heat sources [43].

2.7. Material injection

Like material extrusion, this method is used with polymeric materials. It consists of a printing head that injects the material (a photopolymer with a consistency similar to that of wax) in a given pattern to form each layer. This technique employs a printing head where the drops of the material are deposited and then dry when solidified by the action of a UV light source. In this process, the parts are built layer by layer [44].

3. Powder removal from additively manufactured parts

During the manufacturing process, it is common that some proportion of the solid bed (metal powder) does not melt nor fuse into the manufactured part, which is why such unsintered and partially sintered powder must be removed from it. For this purpose, different devices or systems are employed in the AM process. Table 1 summarizes the different techniques used to remove residual powder from the additively manufactured parts.

Some studies have evaluated the effect of these techniques on the final properties of additively manufactured parts. For instance, Islam et

Table 1. Powder removal systems used in additive manufacturing processes.

Technique or system	Reference
Vibration	[49, 50, 51, 52, 53]
Temperature/Pressure	[54, 55]
Ultrasonic vibration	[56, 57]
Escape holes in a CAD model	[58]
Vacuum	[59]
Air	[60]
Magnetorheological fluid	[61]
Gas	[62, 63]

al. [64] found that submerging the parts in liquid nitrogen and exposing them to ultrasonic vibrations allows an effective powder removal. Additionally, their mechanical and metallurgical properties showed no significant changes [64]. For their part, Drescher et al. [65] analyzed the optimization of the EBM process by removing the semi-sintered powder using a powder blasting system. The authors reported an average productivity improvement of approximately 20% without any detriment to the mechanical properties of the parts [65]. Moreover, a more recent study revealed the dependency of the ductile behavior of additively manufactured parts on the powder removal system employed. Ultrasonic vibration treated parts were found to have a fragile behavior, while those treated with the traditional powder recovery system displayed a ductile behavior [66]. However, further research is required to obtain more conclusive results.

4. Trends in additive manufacturing materials, processes, and applications

Table 2 provides an overview of the AM market. As observed, products manufactured by AM are mainly used in the industrial machinery, aerospace, and automotive industries. Applications in the health (medical and dental) sector are expected to significantly grow in the coming years [67].

Table 3 shows the results of a relevance analysis conducted in a project co-funded by the Erasmus Program of the European Union [67].

Table 2	. Applications	of additive	manufacturing	[67].
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Application	Market participation
Industrial machinery	20%
Aerospace sector	18.9%
Automotive sector	16%
Consumer products/electronics	11.7%
Medical/Dental industry	11.3%
Academic institutions	7.9%
Government/Military	5.1%
Architecture	1.9%
Other	7.0%

Table	3.	Relevance	of	the	various	additive	manufacturing	processes	in	Europe
[67]										

Additive manufacturing process	Percentage of relevance
Powder bed fusion	87%
Material extrusion	56%
Directed energy deposition	45%
VAT photopolymerization	40%
Material jetting	35%
Binder jetting	29%
Sheet lamination	19%

According to this analysis, PBF is currently regarded as the main AM process. This is confirmed by a patent review performed to evaluate the maturity of the different AM technologies (Figure 2), which showed that PBF processes have the highest number of registered patents. Additionally, an analysis per sector indicates that PBF accounts for around 25% of the total AM processes (Table 4) and has experienced a significant growth in the health sector in recent years (Figure 3).

Finally, regarding the materials used in AM, metals and polymers are the most commonly employed due to their suitable properties required for different AM applications. Metals are slightly more used in PBF, possibly because of their greater ease of implementation with PBF techniques and given the different applications that require this material (Tables 5 and 6).

5. Metal additive manufacturing methods used in the biomedical field

AM technologies have been widely employed in the medical domain, and their functionality and use have surprisingly extended to the field of implants and prostheses thanks to the possibility they offer of obtaining unlimited designs and complex geometries in short times [68]. Figure 4 illustrates the different medical fields in which AM techniques have been successfully applied, which include prostheses, implants, surgical instruments, surgery planning and training models, assistive tools, tissue engineering, and artificial organs for transplant [35].

EBM and SLM are presented as the most appropriate techniques to manufacture metallic implants [68]. Unlike other methods, both make it possible to obtain, at low cost, mass implants with complex geometries and in accordance with patients' specific needs [68]. However, these techniques also have some drawbacks. EBM, for instance, is limited, as it only processes a narrow range of materials given its closed system. Another limitation of these methods concerns the dimensional precision of the cellular structures and the trapping of powder within them. These problems can be solved by reducing the point of the laser or electron beam, which leads to a higher precision. Although these and other limitations have prevented EBM and SLM from being fully employed in the biomedical sector, both techniques are considered the most promising to obtain implants when compared to traditional manufacturing processes [68]. The following subsections describe how the SLM and EBM methods work.

5.1. Selective laser melting (SLM)

This technique uses a high intensity energy source (a fiber laser). To fabricate the parts, a layer of material powder with a thickness varying between 0 and 100 mm is spread over the table. Then, the recoating blade distributes the powder across the build table that was preheated to 200 °C. Subsequently, the laser selectively melts the powder layer based on the CAD model (see Figure 5) [68]. The parts produced by means of this technique are built in two steps. First, the contour of the part is built, and then, the powder inside the contour is melted until the complete part is obtained [68].

5.2. Electron beam melting (EBM)

Another metal AM technique that is being widely employed to manufacture implants is Electron Beam Melting [68]. Since it involves melting a powder bed using an electron beam as the energy source, the whole process is carried out in a vacuum chamber [68]. Arcam AB, a Swiss brand founded in 1997 and later acquired by GE Additive in 2017, is currently the leader in EBM prototyping, with both companies being pioneers in this technique [69]. EBM operates cyclically, rotating between the following four steps:

5.2.1. Application of the granular material

A powder bed is formed by spreading the granular material over the work area [70]. This area must be preheated to ensure the stability of the part.



Figure 2. Relevance of the various additive manufacturing processes (number of patents)¹. a) Powder bed fusion, and b) other additive manufacturing processes.

5.2.2. Powder heating

Once the material is already distributed across the build plate, it starts to be heated, maintaining a constant temperature, so that the layer is slightly sintered to increase the electrical conductivity of the powder [71]. While the part is being built, the temperature inside the chamber should be around 700 $^{\circ}$ C to reduce the residual stresses [68].

Table 4. Additive manufacturing	processes	used j	per	sector	in	Europe	and	the
project partner countries [67].								

Additive manufacturing process	Sector	Percentage of participation
Powder bed fusion	Aerospace	25%
	Automotive	25%
	Consumer goods	24%
	Health	23%
	Electronics	25%
Material extrusion	Aerospace	18%
	Automotive	18%
	Consumer goods	20%
	Health	19%
	Electronics	18%
Directed energy deposition	Aerospace	15%
	Automotive	15%
	Consumer goods	12%
	Health	13%
	Electronics	14%
VAT photopolymerization	Aerospace	13%
	Automotive	14%
	Consumer goods	14%
	Health	14%
	Electronics	14%
Material jetting	Aerospace	12%
	Automotive	11%
	Consumer goods	12%
	Health	11%
	Electronics	12%
Binder jetting	Aerospace	10%
	Automotive	11%
	Consumer goods	11%
	Health	13%
	Electronics	10%
Sheet lamination	Aerospace	7%
	Automotive	6%
	Consumer goods	7%
	Health	7%
	Electronics	7%



Figure 3. Patent evolution of powder bed fusion in the health sector.²

5.2.3. Powder melting

The electron beam scans the powder layer at a low speed (usually 4 mm/s) and melts the powder particles in the areas where they remain solid [72].

5.2.4. Layer renewal

After the layer is melted, the plate goes back to its position, but it first places the newly created layer at the level of the granular material feeders. Then, it returns to step 1.

Figure 6 illustrates an EBM system. In this system, a gun emits electrons that are accelerated by a voltage of 30–60 kV. These electrons are, in turn, focused using a series of electromagnetic lenses and electromagnetically scanned by means of a built-in CAD program. The focused beam initially passes at a speed of approximately 10^4 mm/s and with a power of around 30 mA to preheat the first layer of the pulverized material, leaving it at 80% of the melting point After preheating, the power of the beam drops to about 5–10 mA; and its speed, to around 10^2 mm/s (its normal working conditions). The electron beam scans the plane comprised by the x- and y-axes, and the shape of the prototype to be developed starts to be defined. This system is fed by a series of cartridges that, by means of gravity and with the help of a roller, distribute the pulverized material over the work plate. This latter lowers as each layer of the prototype melts completely. As the work plate lowers, the Z dimension of the prototype is formed (See Figure 6).

¹ Data obtained from lens.org.

² Data obtained from lens.org.

 Table 5. Materials used in additive manufacturing [67].

Material	Percentag
Metals	38%
Polymers	29%
Ceramics	16%
Biomaterials	11%
Food	6%

Table 6. Materials used in powder bed fusion [67].

Material	Percentage
Metals	44%
Polymers	30%
Ceramics	16%
Biomaterials	10%

EBM has some advantages over SLM, such as its spot size which is much smaller and more efficient, as well as its high scanning speed and beam deflection [74].

6. Metal alloys used in electron beam melting for biomedical applications

The remarkable mechanical properties of metallic materials (e.g., toughness, rigidity, and impact resistance) have led to their widespread use in the biomedical field, as, for instance, in the manufacture of hip and knee prostheses, fracture fixation plates, screws, among others [75]. One of the main factors limiting the use of metal AM techniques in the industrial sector is the availability of suitable alloys. For EBM to work, the pulverized material must have good electrical conductivity because, otherwise, there will be no flow of electrons to restructure the material. The proper selection of materials to be used in the manufacture of prostheses via AM techniques will guarantee their success and compatibility when implanted. The most common metal alloys employed to produce implants are titanium alloys (Ti–6Al–4V, Ti–Al–Nb, and $\alpha + \beta$ alloys), cobalt–chrome alloys (Co–Cr–Mo, Co–Ni–Cr, and Co–Cr–W–Ni), stainless steel (316L), and titanium–nickel (Ti–Ni) alloys [75]. The most popular metal alloys used in EBM to fabricate implants for the biomedical industry are presented below.

6.1. Chromium-cobalt alloys

Chromium–cobalt (CoCr) alloys have been widely used to manufacture implants thanks to their excellent chemical and mechanical properties, such as their favorable corrosion, wear, and mechanical resistance; high rigidity; and long useful life [76]. For instance, the Co–29Cr–6Mo



Figure 5. Selective laser melting [44].

femoral prototypes with a mesh structure that Murr et al. [77] obtained via EBM exhibited good and compatible bone stiffness (see Figure 7).

6.2. 316L steel

Stainless steels (304, 316, and 316L) have an outstanding combination of properties such as favorable biocompatibility, corrosion and wear resistance, hardness, and ductility [78]. Yet, in applications involving complex body movements and contact with body fluids, they are likely to react with the material and cause implant failure. This may also trigger some of the main implant problems (e.g., possible fracture of the prosthesis, loss of adhesion, and release of metal ions due to corrosion) that could lead to a new intervention [79]. In [80], the authors analyzed the hierarchical structures of EBM-manufactured 316L steel prototypes.

6.3. Titanium alloys

Titanium (even in its pure form without alloying it) is one of the most common metallic materials employed in AM (with EBM being one of the techniques that mostly uses it) given its good chemical properties, such as its high corrosion resistance, a key property for the manufacture of surgical implants and prostheses. Besides being lightweight and harder than steel, this material has a considerably high resistance to (environmental and chemical) corrosion. However, it does not have good thermal or electrical conductivity [81]. Thanks to its suitable chemical and mechanical properties, this metal has been very useful in different



Figure 4. Applications of additive manufacturing in various medical fields [35].



Figure 6. Schematic operation of an EBM machine [73].



Figure 7. Co–29Cr–6Mo femoral prototypes obtained via electron beam melting [77].

industries, including the space, air, and medical (mainly prosthetics and dentistry) ones. Other sectors, such as the automotive one, have also taken advantage of its characteristics, and even, in the sports field, some applications have been reported. For example, some golf club heads are coated with this material. Despite its remarkable mechanical, physical, and chemical properties, certain applications require titanium to be alloyed with other metals in order to control some of its properties (e.g., its ductility). Likewise, its interesting physicochemical and bioactivity characteristics make it ideal to be used as a biomaterial. Its good biocompatibility is explained by the chemical stability of the oxide film (1.5-10 nm) formed on its surface under ambient conditions. Microstructural titanium alloys can form alpha (α) and beta (β) phases and their combinations depending on the alloying elements that stabilize one or the other phase according to the desired properties. Currently, more than 100 titanium alloys are known to exist, but only about 20 of them are used commercially and can be grouped based on their phase.

• α alloys

These alloys contain α -stabilizers and have an excellent corrosion resistance, weldability, and toughness. An example of this type of alloys is Ti–8Al–1Mo–1V, which is used for blades in military engines.

• $\alpha + \beta$ alloys

Since these alloys contain an α -stabilizer and a β -stabilizer, they have the properties of both, thus making them ideal for different industries. The best known or most used alloy in this category is Ti6Al4V, which is mainly employed in the aerospace and implant sectors. Ti6Al4V is the most industrially used titanium alloy, which accounts for half of the titanium production, given the excellent balance between its mechanical properties, corrosion resistance, good behavior at high temperatures, and ability to be worked mechanically, as well as due to the fact that its properties can be easily modified through heat treatments [82]. Table 7 shows the chemical composition of the registered Ti6Al4V biomedical alloy, in accordance with the ASTM F136-13 standard.

Titanium (Ti6Al4V) and cobalt (CoCrMo) alloys, as well as stainless steels (304, 316, and 316L), have a remarkable combination of properties such as good biocompatibility, corrosion and wear resistance, hardness, and ductility [78]. Yet, in applications involving complex body movements and contact with body fluids, they are likely to react with the material and cause implant failure. This may also trigger some problems (e.g., possible fracture of the prosthesis, loss of adhesion, and release of metal ions due to corrosion) that could lead to a new implant intervention [79]. Other disadvantages (see Table 8) associated with the release of aluminum (Al) and vanadium (V) ions when the Ti6Al4V alloy is employed have been reported to cause certain diseases such as Alzheimer's and osteomalacia [84]. In addition, aluminum has proven to have neurological and genotoxic effects [85]. Titanium alloys used for orthopedic implants must have a low Young's modulus (E) to avoid the stress-shielding effect induced by the difference between the Young's modulus of the implant and that of the bone [86]. Despite having a Young's modulus (around 110 GPa) higher than that of the cortical bone (around 10-30 GPa), this alloy is still employed for orthopedic implants [86] (see Figure 8). Nevertheless, the use of other titanium alloys such as Ti-7Nb [87], Ti-42Nb [3], β Ti-Nb-Sn [86], Ti-Nb-Zr [88], Ti-Nb-Ta-O [89], and Ti-Al-Nb [74]) (which could have a better performance) for the manufacture of such implants has recently been investigated. Niobium, zirconium, and tantalum (β-stabilizers) have shown to have adequate biocompatibility and nontoxicity [87].

• β Ti alloys

bone formation [92].

Table 7.	Chemical	composition	of the	Ti6Al4V	alloy fo	r biomedical	applications
[83].							

Element	Composition (% by weight)
Nitrogen, max.	0:05
Carbon, max.	0:08
Hydrogen, max.	0:012
Iron, max.	0:25
Oxygen, max.	0:13
Aluminum	5:5–6:5
Vanadium	3:5-4:5
Titanium	Balance

Table	8	Advantages	and	disadvantages	of the	Ti6A14V	allov
lable	о.	Auvantages	anu	uisauvaillages	or the	110AI4 V	alloy

Advantages	Disadvantages
 Excellent biocompatibility when contact with bone and tissues is required [90]. Good mechanical properties and high corrosion resistance [91]. Most widely used alloy in the additive manufacturing of orthopedic implants [90]. High probability of promoting osteoblast maturation, as an osteogenic environment is established when cells similar 	 Low wear resistance and fatigue strength [93]. Formation of bacterial biofilms on the implant's surface [86]. Risk of causing health problems such as Alzheimer's disease, neuropathies, and osteomalacia (5), as well as allergic reactions, due to the release of Al and V ions [94]. Risk of leading to implant loosening due to its high Young's modulus [84].
substrate which could improve	

These alloys contain β -stabilizers (e.g., vanadium). Although they stand out for their ductility and low weight, they are not suitable for high-temperature applications. An example of this type of alloys is Ti-10V-2Fe-3Al, which is used for the landing gear of the Boeing 777. β Ti alloys have been reported to have a Young's modulus lower than that of $\alpha + \beta$ Ti allovs due to a softening of the lattice near the initial martensitic transformation temperature and because the ω phase, which has a very high modulus of elasticity, can be prevented from forming [86], [95]. The β phase of Ti can be stabilized by adding β -stabilizers such as Mo, W, V, Nn, and Ta [96]. Ternary alloys, like β Ti-Nb, could have a much lower modulus of elasticity if alloyed with elements that prevent the formation of the ω phase, such as Sn [86], [97]. In this regard, Hanada et al. [86] studied the use of β Ti–Nb–Sn ternary alloys (Ti: 27.5-37.5% and Nb: 2.5-11.25%) with a low modulus of elasticity for orthopedic implants and found that the cold rolled Ti-35Nb-3.75Sn alloy exhibited a Young's modulus of 36 MPa. Moreover, the behavior of β Ti alloys, like Ti–15Mo–5Zr–3Al, during cold forming is better than that of Ti-6Al-4V, which reduces production costs [85].

• Ti-Nb alloys

Shape memory alloys such as Ti-Nb can effectively replace titanium alloys in orthopedic applications [98]. Thermomechanical treatment has been found to significantly improve the functional properties of Ti-Nb alloys [98], which, with a Ti40Nb composition, can achieve a Young's modulus ranging from 55 to 68 GPa when cooled from very high temperatures [79]. Weinmann et al. [96] evaluated the viability and proliferation of human cells (fibroblasts and osteoblasts) on Ti-42Nb alloys and compared the results with those on Ti-6Al-4V alloys. The authors reported favorable outcomes regarding their use in the implant sector. For instance, the metabolic activity of the human cells responsible for bone development and growth (osteoblasts) on the Ti-42Nb alloy was found to increase by 17% compared to that on the Ti-6Al-4V alloy, which decreased by 29% on the surface of the specimen. The performance of the Ti-42Nb alloy was, thus, better than that of the Ti-6Al-4V alloy [96]. For their part, Woo et al. [99] observed that the mechanical and biocompatibility properties of sintered samples of Ti-42Nb from mixed and ground powders are higher than those of Ti-6Al-4V.

• Ti-Nb-Zr alloys

Ti, Nb, and Zr in Ti-Nb-Zr alloys have been reported to satisfy certain aspects required from biomaterials in terms of biocompatibility, corrosion resistance, mechanical properties, and ionic cytotoxicity [100]. Additionally, Nb makes it possible to stabilize the β phase in Ti alloys, thus improving their mechanical properties and wear resistance. Ozan et al. developed various Ti-Nb-Zr alloys with an excellent mechanical behavior to be used in the manufacture of temporary orthopedic implants. Such remarkable mechanical properties included low stiffness, high mechanical strength, excellent cytocompatibility, significant plastic deformation, and an elongation at break between 9.9 and 14.8%, which constitute very appropriate characteristics for applications in the biomedical sector (bone tissue implants) [85]. In addition, the Young's modulus of the different Ti-Nb-Zr alloys were found to range from 62 to 65 GPa. Hussein et al. [94] sintered a nanostructured β Ti-20Nb-13Zr alloy containing nontoxic elements such as Nb and Zr to replace Al and V using Spark Plasma Sintering (SPS). This alloy showed improved mechanical properties and a great potential to be employed in the manufacture of orthopedic implants.

• Ti-Nb-Ta alloys

These alloys have a high biocompatibility and outstanding mechanical properties, which ensures protection against high stresses in tension and avoids possible implant replacements [96]. They can also be used to



Figure 8. Modulus of elasticity of various titanium alloys used in the orthopedic industry [84].

produce orthopedic implants by means of AM techniques such as SLM and EBM, thus making it possible to obtain a wide variety of patient-specific implant designs [96]. Sheremetyev et al. [98] applied a thermomechanical treatment (cold rolling and annealing) to a Ti-19.7Nb-5.8Ta alloy and analyzed its superelastic behavior during loading and unloading mechanical tests. According to their results, its Young's modulus decreased from 40 to 25 GPa.

• Ti-Cu alloys

Thanks to the low toxicity of Cu + 2 ions and the low price of copper, Ti-Cu alloys have a great potential to be used in the orthopedic industry [101]. Zhang et al. [102] evaluated the corrosion resistance, as well as some mechanical and antibacterial properties, of Ti-Cu alloys with 2.0, 3.0, and 4.0 by weight of copper and observed antibacterial rates of 90.33% and 92.57% in the Ti-3Cu alloys and the Ti-4Cu alloys, respectively. They also found that their hardness, elastic limit, corrosion resistance, and antibacterial rate increased with increasing copper content. Another study [93] investigated the use of a nanocrystalline Ti-Cu intermetallic alloy as an orthopedic material and evaluated its mechanical, antibacterial, toxicity, corrosion, and osseointegration properties. This alloy was found to have a high hardness (10 GPa), an adequate toughness (8.14 MPam1/2), an antibacterial rate of approximately 98% (S. aureaus and E. coli), a high cell viability (osteosarcoma cells), and a high osteoblast formation rate, which demonstrates the considerable potential of these alloys in the orthopedic sector.

7. Biomedical applications of electron beam melting

Metals have been the preferred material in the manufacture of implants given their suitable mechanical and chemical properties. However, implants produced using traditional manufacturing techniques come in standard sizes and present difficulties associated with osseointegration [3]. AM is, therefore, one of the best options when it comes to fabricating medical devices with highly complex designs [35]. In particular, AM technologies have led to significant advances in the medical and biomedical fields, as they have made it possible to print surgical guides [3], skull [103] and mandibular prostheses [104], pelvic implants [105], among others.

7.1. Ti6Al4V biomedical implants obtained via electron beam melting

Unlike conventional techniques for processing titanium alloys such as casting, machining, and powder metallurgy, AM offers a more suitable surface structure for bone adhesion (osseointegration). Nevertheless, special considerations must be taken into account when producing titanium alloy parts by means of AM due to the high reactivity of titanium with the gases contained in the air, even at temperatures below the melting point. For this reason, while titanium is being processed, an adequate atmosphere must be maintained, especially during material melting [106, 107, 108, 109]. This implies that its processing requires adopting technologies with a precise control of the process parameters and variables to prevent the material from being contaminated by external elements that are difficult to remove through subsequent processes. In addition, these technologies should control the fabrication of parts with a degree of densification and properties suitable for their intended application.

Some commercial implants produced via AM are subsequently subjected to Hot Isostatic Pressing (HIP [110], [111]) to reduce the risk of internal defects due to an incomplete powder melting or spaces between the particles [112]. Femoral stem replacement prostheses are manufactured with Ti alloys given their high corrosion resistance, high tensile strength (100-120 GPa), and good biocompatibility [4], [113], [114]. Nonetheless, their low wear resistance prevents them from being employed in joint contact areas [115]. Mazzoli et al. [116] proposed an automated method to produce customized titanium cranial implants using EBM and CT technologies, which enables efficient and fast reconstructions, as well as the reduction of surgical errors. Harrisson et al. [11] analyzed the finite element design and fabrication of titanium implants (hip stems) via EBM and evaluated some of their mechanical properties. According to the authors, manufacturing hip stems with the EBM technology allows the porous bone ingrowth surfaces to be built in at the same time, thus reducing the number of manufacturing steps.

Furthermore, Yan et al. [104] produced a Ti6Al4V mandibular prosthesis using EBM from a 3D model that was completely designed thanks to a CT (medical imaging) instrument. With this instrument, a volunteer's skull was scanned, and the resulting images were later processed with Mimics ® (version 15.0, Materialise NV, Leuven, Belgium). This software generated a 3D STL file suitable for being modified in a CAD program using Geomagic Studio v12.0. The model obtained from the tomography was retouched, and the teeth were removed from it. The model's design contained relevant data (e.g., porosity and pore size) that the authors had to consider in the geometry. Porosity had to be kept between 50 and 90%; and pore size, in the range of 100–500 μ m. These two values had to be maintained within an accuracy of 80-90% to be able to correct errors during the design phase. After this, a Finite Element Mesh (FEM) was generated, thus obtaining, with the help of a finite element analysis, an optimal geometry. Tang et al. [117] fabricated Ti6Al4V ankle implants, cervical and sacral vertebral fusion cages, and hip stents using EBM to be successfully implanted into patients. An ankle implant was found to have an adequate functioning two years after being implanted into a patient's body at the Chinese traditional medicine hospital. Thompson [118] designed and fabricated, via EBM, a Ti6Al4V pelvic implant with a lattice structure to later be implanted into a patient's body. The final machining of the part was performed using CNC machining. Figure 9 shows some examples of applications of the EBM technique in the manufacture of biomedical implants.

8. Structure and microstructure of Ti6Al4V alloy prototypes obtained via electron beam melting

EBM-manufactured samples generate a macrostructure and a microstructure that later confer them different (physical, chemical, and biological) properties for them to be implemented in various applications. The macrostructure comprises the design of the lattice structure of the sample, which is, in turn, made up of a unit cell (see Figure 10). Several studies have analyzed the relationship between the different unit cells and mechanical properties [120], [121]. Nevertheless, this should only be considered when a similar surface roughness and similar internal defects are assumed [120]. A study that employed open cubic unit cells to control the lattice structure with porosity gradients of the EBM-manufactured samples managed to simulate the characteristics of



Figure 10. Design of a structure manufactured by electron beam melting (lattice structure and real manufactured unit cell [128].

human bones with inhomogeneous porosities, as well as their mechanical behavior [122]. However, surface characteristics and internal defects such as the uncomplete melting of powder particles and the orientation of the internal pores generated during the melting of the powder bed, which lead to failures in the samples when performing mechanical tests on them, have proven to be determining for the properties of manufactured samples [123, 124, 125, 126, 127]. Internal pores or those on the surface of the structure formed by the unit cells develop between the unmelted powder particles [124, 125, 126, 127] due to the trapping of argon in the powders during the atomization stage or of hydrogen as a result of the decomposition of the absorbed water vapor on the powder surfaces [124]. Figure 11 shows some of the typical defects that can occur in EBM-manufactured parts.



Figure 9. Ti6Al4V alloy implants obtained via electron beam melting. a) Cranial plate [116], b) mandibular prosthesis [119], c) cervical vertebral fusion cage [117], d) pelvic implant [118], e) hip stems [11], and f) ankle prosthetics [120]. Human skeleton (taken from Wikipedia).



Figure 11. Possible defects found in parts manufactured by electron beam melting. a) High surface roughness [129], b) cracks [130], c) unmelted powder particles [128], d) internal pores due to the trapping of gases [131], and e) internal porosity between unmelted powder particles [131].

In terms of fatigue strength, the as-fabricated surface roughness must be reduced by means of subsequent machining processes [131]. In this regard, various studies have evaluated alternative techniques to polish the surfaces of parts manufactured by AM, with the purpose of improving their surface roughness and porosity, using fine abrasive finishing processes in horizontally- and vertically-manufactured parts [132]. Other studies have assessed the machinability of EBM-fabricated samples in assisted surface finishing treatments using different cooling techniques [133], [134]. The internal porosity defect can be reduced by subjecting samples to subsequent treatments such as hot isostatic pressing and other heat processes [135]. Another important aspect are the scanning strategies employed during the EBM process [136], as they could play a role in minimizing internal porosity, a characteristic that reduces fatigue strength. Scanning strategies such as spot melting and raster melting are able to control these properties. With respect to raster melting, spot melting minimizes internal porosity, which is reflected in lower gas porosity defects, a condition that allows subsequent processes such as hot isostatic pressing and other heat treatments to be properly applied. The build orientation of samples can also have an impact on their properties. Wang et al. [137] analyzed vertically-, diagonally-, and horizontally-built samples and the effect of each build orientation on their internal porosity, microstructure, and mechanical properties. Their results showed that the main axis of the generated internal pores tends to be perpendicular to the build direction. When a mechanical stress load was applied, the horizontally-built samples presented greater resistance because, in this case, the internal pores tended to close up. Conversely, in the diagonally- and vertically-built samples, this orientation between the shape of the internal pores and the applied load intensified the stress concentration at the sharp corners of the pores, thus leading to fractures. According to these authors, the deterioration in the mechanical performance caused by an undesirable orientation of the internal pores can be somewhat compensated by the microstructure obtained in the samples. Unlike in the diagonally-built samples, in the vertically-built ones, the strong directionality of the columnar phase helps, for instance, to achieve a greater resistance. The authors concluded that the columnar β grain boundaries are desirable in enhancing the mechanical performance if the tensile load is parallel to the columnar boundaries.

Moreover, as reported in the studies that will be considered further below, the presence of elongated columnar prior β grains along the build orientation of samples influences their mechanical performance. This microstructural characteristic is derived from the thermal history of the material [138, 139, 140, 141]. As mentioned above, microstructures are key to define the behavior of the final properties of EBM-manufactured samples. As is known, titanium solidifies in the β phase (cubic structure centered on the body), in which it remains stable above the β -transus temperature (980 °C for Ti–6Al–4V alloys), while, in the α phase (hexagonal structure), it remains stable at lower temperatures [142]. The β to α allotropic transformation is, thus, conditioned by the presence of the other two alloying elements: aluminum (α -stabilizer) and vanadium (β -stabilizer) [143]. Consequently, a great variety of transformations and microstructures with different properties can be achieved depending on the heat treatments applied as per the cooling rates established during the manufacturing process. This makes it possible to adjust the mechanical behavior required for different applications.

According to the processing defined during the manufacture of samples by EBM, the microstructures obtained at room temperature can be classified into three types: completely laminar microstructures, completely equiaxed α grains, and microstructures containing equiaxed α grains in a laminar (bimodal) matrix [144]. Each microstructure has been found to give manufactured samples different mechanical properties For example, the laminar microstructure has lower strength and ductility but better resistance to fatigue propagation when compared to an equiaxed structure [145], [146]. The bimodal microstructure, for its part, presents a good high-cycle fatigue performance given the equiaxed microstructure's high resistance to crack initiation; in addition, the laminar structure retards crack propagation [147]. Other studies have meticulously characterized this type of dual ($\alpha + \beta$) structure [148], [149] and classified it as a fine lamellar α morphology and a small volume fraction of retained β [150]. Depending on the cooling rate of the deposited melt pool, the β phase can be transformed into martensitic α' , α_m massive, and $\boldsymbol{\alpha}$ microstructures. Different phase transformations and microstructures have been reported as a function of the critical cooling rate during the EBM process [151, 152, 153]. Due to the small thickness of the struts in the unit cells of the lattice structures (Figure 10b), martensitic α ' microstructures are the most commonly obtained in EBM-manufactured samples. By means of subsequent heat treatments, the martensitic structure can be modified to achieve a better balance between ductility and resistance. A typical micrograph of an EBM-manufactured sample will show prior β grains, which, in turn, consist of a transformed $\alpha + \beta$ microstructure with colony and Widmanstätten morphologies from the martensite decomposition [131]. Other more in-depth analyses of the microstructures generated by the EBM process can be found in [148], [154].

The reuse of Ti–6Al–4V alloy powders in EBM has also been investigated. Various studies have compared samples made of such recycled powder with those made of virgin powder and reported no differences in the microstructures of both samples. The difference in the mechanical performance of the two samples is associated with the existence of surface defects in the recycled powder particles and their residual surface oxidation during stress and fatigue tests [155]. In the case of samples fabricated with recycled powder, hot isostatic pressing only manages to improve their mechanical performance to a level similar to that of untreated samples made of virgin powder. Based on this description, a detailed analysis of the different properties of EBM-manufactured Ti–6Al–4V samples will be provided below, considering that their structure, microstructure, and internal defects determine their properties and performance for different applications.

9. Properties of EBM-manufactured Ti-6Al-4V implants

9.1. Tensile strength

Being one of the most widely used mechanical tests, tensile strength has been established as the parameter to compare the mechanical performance of EBM-manufactured samples under different process conditions, materials, post-manufacturing treatments, among other factors. Additionally, in the case of implant applications in the human body, baseline information on the moduli and tensile strength of bones that can be replaced with EBM-manufactured parts is currently available. Likewise, there exist standardized values defined by several standards, such as ASTM 1472-14 and ASTM F2924, which are used as reference points for comparative studies [156], [157]. A summary of different papers that examine such conditions and characteristics in EBM-manufactured samples, as well as their mechanical characterization by means of tensile testing, is presented below. In [158], the reuse of Ti-6Al-4V alloy powder in EBM was analyzed in samples subjected to tensile strength testing. This alloy powder was reused up to 30 times in horizontally- and vertically-built parts. The microstructure of the specimens consisted of prior β grains oriented parallel to the build direction. Hence, when a tensile load is applied, these grains appear parallel to the build orientation in vertically-built samples and perpendicular in the horizontally-built ones. Nonetheless, there is a greater risk of failure in vertically-built samples because they exhibit a higher surface roughness. This, in turn, suggests a greater yield strength, ultimate tensile strength, and percentage of elongation in horizontally-built samples although their modulus of elasticity is slightly lower than that of vertically-built samples. With regard to the reuse of Ti-6Al-4V alloy powder, the authors of [158] found that the higher the number of times the powder is reused, the higher the modulus of elasticity, yield strength, and ultimate tensile stress, but the lower the percentage of elongation. In addition, they reported that, after reusing the powder in 25 sequential cycles, the modulus of elasticity decreased.

The build orientation of EBM-manufactured samples has also been associated with tensile strength in horizontally-, vertically-, and diagonally-manufactured parts [137]. Under these conditions, the authors of [137] concluded that the tensile strength of specimens is more affected by their internal porosity than by their microstructure. They define the anisotropy of porosity in terms of the orientation of the pores, which is why a highest yield strength is observed in horizontally-manufactured samples. This is explained by the fact that their pores tend to close up because their major axes are mainly parallel to the applied tensile load, which does not occur in the vertically- and diagonally-manufactured samples, in which the orientation of the pores causes a stress concentration effect that leads to failures. The anisotropy of the microstructure marks the difference between vertically- and diagonally-manufactured samples, with the former having a greater yield strength due to the fact that the applied load is transferred along the prior strong β grains, which, in the vertically-manufactured samples, are parallel to the load direction.

The size of fabricated specimens can also have an effect on their microstructure and mechanical performance. For instance, Wang et al. [157] extracted samples of tensile specimens from a large fabricated part (6 mm \times 180 mm \times 372 mm), some from the bottom and others from the top of the build plate. The tensile test revealed that the yield strength and ultimate tensile strength of the top samples were lower than those of the bottom samples. The authors attributed this to an increase in the α lath width and its different thermal histories along the build height. Moreover, Hrabe and Quinn [159] had previously reported a slight influence of sample size on yield strength and ultimate yield strength and suggested a possible relationship between the α lath width and the mechanical properties. In high-performance applications such as aeronautics, the mechanical performance of EBM-manufactured parts at high temperatures must be evaluated because they have started to be used in this field. Their mechanical performance, for instance, has been assessed by means of Creep tests. Aliprandi et al. [135], [160] investigated the mechanical behavior of EBM-fabricated parts at temperatures between 400 and 600 °C. They reported that a better tensile performance at these temperatures is driven by a subsequent surface smoothing and observed in samples whose microstructure (basket weave) is aligned to the loading direction and has elongated grains along the tensile direction.

9.2. Compressive strength

Regarding compressive strength, there is an important effect of unit cells on the design of the lattice structure of specimens. They produce a structure that can be more dense or porous, thus making it possible to, for instance, adjust the modulus of elasticity of the EBM-manufactured material to values close to those of human bones to fabricate structures that replace bones and avoid the stress shielding effect, which is important in these applications [23], [161], [162]. However, implants that support high loads may exhibit a low yield strength, which is why the cell design must be adjusted to reduce stress concentrations in the material.

In [120], the design of the lattice structures of EBM-manufactured samples and its mechanical response were thoroughly analyzed for their potential use in orthopedic implant applications. This study evaluated lattice structures formed by cubic, dodecahedron, diamond, and hexagonal unit cells with densities ranging from 1.63 to 1.68 g/cm³. The results showed that the compressive yield strength, ultimate compressive strength, and fatigue strength of structures with cubic unit cells are higher than those of dodecahedron lattices, assuming that surface roughness and internal defects are similar. Additionally, the compressive properties of the lattices under analysis were found to increase with increasing density, with their ultimate compressive strength and modulus of elasticity being comparable to those of the human cancellous bone. Also, yield strength was reported to be higher in cubic and diamond cells.

Another study [163] evaluated different cell shapes (cubic, G7, and rhombic dodecahedron) and determined the compressive strength of unit cells by the coupling of the buckling, bending, and deformation of their struts. According to the results, the struts basically deformed by buckling in the cubic unit cells and by bending in the G7 and rhombic dodecahedron structures. In addition, the cubic unit cells exhibited the highest compressive strength, whereas the G7 unit cells had the lowest. For their part, Wu et al. [122] analyzed open cubic unit cells determining the porosity gradients of fabricated structures and assessed them using compression testing. For this purpose, the authors manufactured samples with gradual changes in the porosity of their structure (high, transition, and low porosity regions) and others with sudden porosity variations (two regions without transition). The samples with gradual changes in porosity presented a higher compressive strength, with failure in the higher porosity region, while, in those without gradual changes, failure was observed in the interface region from lower to higher porosity.

In [164], the authors also studied structures manufactured with cubic unit cells and showed the influence of cells' geometry on the compressive

properties in terms of their pore size and the width of the struts that comprise them. Considering variations in these two parameters, structures with porosities ranging between 49.75 and 70.32% were obtained, with an effective stiffness ranging from 0.57 to 2.92 GPa and a compressive strength ranging from 7.28 to 163.02 MPa. Variation in the thickness of the struts was found to be relevant for similar porosity values (49.75–50.75%), with compressive stiffness (modulus) and compressive strength varying up to 80.5% and 93.54%, respectively. Through numerical analyses based on the uniaxial compression testing of cubic Ti6Al4V structures with different porosities, it has been possible to estimate the compressive behavior and the respective modulus of other titanium alloys. For instance, in [165], this was possible by predicting the relative density of the structure and its relationship with the mechanical properties using the Gibson-Ashby model. The new alloys simulated as implants were found to increase bone stress, which minimizes the problem of stress shielding in a proximal cementless fixation.

9.3. Fatigue

Fatigue is a type of failure that often occurs in implants due to the conditions to which they are subjected during their use. Several studies have been developed to evaluate the fatigue behavior of EBMmanufactured samples. In particular, an in-depth review conducted by Chern et al. [131] allowed the identification of four specific scenarios in which fatigue behavior must be evaluated: (1) horizontally- and vertically-built specimens that did not undergo hot isostatic pressing and machining, (2) horizontally- and vertically-built specimens that were not subjected to hot isostatic pressing but did undergo surface machining, (3) specimens that were subjected to hot isostatic pressing but did not undergo machining, and (4) specimens that underwent both hot isostatic pressing and machining. In such study, the effective stress values and the corresponding failure cycles were plotted, thus allowing the authors to statistically model fatigue behavior. According to the results of such analysis and comparative study, scenario 4 (specimens that underwent both hot isostatic pressing and machining) makes it possible to obtain samples with higher fatigue strength, since both post-treatments help to reduce internal porosity and surface roughness (conditions that lower the performance of EBM-manufactured samples).

Similar studies confirm that machining the surfaces of EBMmanufactured samples to remove surface defects and applying hot isostatic pressing to them to reduce the sizes of defects improves their fatigue performance [166]. Other papers have reported that a proper fatigue behavior for dental or bone replacement applications can be achieved by adequately controlling the porosity of the as-fabricated lattice structures [120]. Regarding the ratio of ultimate fatigue strength to ultimate compressive strength, the authors of [120] found that it is lower in EBM-manufactured samples than in the dense Ti–6Al–4V alloy (0.15–0.55 *vs.* 0.65). This is attributed to the high porosity of the open cells, the rough surfaces in the sections of the unit cells, the internal defects, the sensitivity of the notches in the alloy, and the inhomogeneity of the microstructure. According to this, EBM-manufactured cubic unit cells with a porosity of 63% can replace spongy bones, the cortical fibula, and the humerus in the human body.

In general, to manufacture implants with structures based on cubic unit cells, a balance in terms of density must be found, in which when increasing it, the mechanical resistance requirements are satisfied, but the size of the void (which leads to the entrapment of more powder particles in the lattice design, thus affecting the performance of the sample) is reduced. The effect of the unit cells of the as-fabricated structures on fatigue strength has also been analyzed, and dodecahedron-shaped structures have been improved using another dual structure containing cubic cells in the nucleus and a G7 cell in the external part in order to obtain a structure with an interesting combination of low density, high fatigue strength, and energy absorption [167]. The impact of fatigue on EBM-manufactured samples regarding internal defects and residual stresses has also been examined by comparing untreated samples, samples with stress relief, and samples treated with hot isostatic pressing. In [168], stress relief was found not to induce an increase in fatigue strength, whereas hot isostatic pressing significantly led to a higher fatigue strength. This increase was attributed to a reduction in internal porosity and void content, which are generally the cause of crack propagation. Moreover, it has been reported that microstructural thickening increases resistance to crack propagation while reducing resistance to crack nucleation [146].

9.4. Tribology

The wear properties of EBM-manufactured samples are also an important factor to consider, especially in aerospace and biomedical applications. In [169], a comparative analysis was performed to evaluate SLM-manufactured parts, EBM-fabricated parts, and parts obtained by conventional forging methods. The wear of the sample material was analyzed in terms of hardness and ease of surface delamination. According to the results, the AM-fabricated samples were found to have a greater wear resistance compared to the forged ones. The EBM-manufactured samples showed a lower wear rate compared to the SLM-fabricated ones. This is explained by the presence of vertical cracks in the former, which reduces delamination, while, in the later, horizontal cracks were observed. Regarding hardness, the SLMand EBM-manufactured samples exhibited the highest values again although that of the former was slightly higher, which is attributed to the presence of a fine microstructure and a martensitic phase. Conversely, the microstructure of the EBM-fabricated samples consisted of a singular α bulge phase distributed in the columnar prior β grains.

Furthermore, various studies have investigated the wear experienced by tools when machining the surfaces of EBM-manufactured samples to improve their finish. For instance, the tool wear mechanism has been analyzed based on the cooling conditions during machining and the microstructure of the machined samples [134], [170, 171, 172]. Specifically, the use of liquid nitrogen as a coolant has been reported to reduce crater wear [173].

9.5. Corrosion resistance

In [174], Mah et al. analyzed corrosion in specimens that could potentially be used as orthopedic implants and found that the corrosion resistance of EBM-manufactured samples was lower than that of forged samples although their levels remain above the recommended minimums. Combined effects resulting from the process, such as cooling rate, lead to fine microstructural changes that promote a greater formation of stable oxide, unmelted powder particles that favor surface roughness, and the formation of defects or voids that generate small holes on the surface, which can later grow larger and propagate corrosion. Other studies have demonstrated that the corrosion mechanism in EBM-manufactured parts is strongly influenced by their porosity characteristics (in terms of pore morphology or size) during the formation of the passive film, which promotes corrosion resistance. Large and interconnected pores have been reported to favor the free flow of electrolytes and a supply of oxygen adequate for the formation of the passive film, which allows a higher resistance to pitting corrosion [175]. Conversely, small and isolated pores have been found to have a relatively low corrosion resistance [176], [177].

However, there is a lack of consensus regarding the effect of porosity on corrosion resistance. Some studies have reported that corrosion resistance increases with increasing porosity [152], while others have indicated the opposite: a high porosity favors corrosion by cracks [178], localized corrosion [179], electrochemical corrosion [180], [181], and the formation of a less protective oxide film [182], [183]. In this regard, Gai et al. [184] analyzed corrosion performance with respect to pore depth by in-situ monitoring EBM-manufactured samples. For this purpose, they evaluated variations in ion concentrations and surface potential using the pore depth of EBM-manufactured lattice structures. As a result, they found that the presence of pores caused an insufficient oxygen supply and chlorine adsorption on their inner surface, thus generating a thinner passive film containing a higher donor density at the pore depth, which could lead to corrosion inside the pores in long-term applications. Therefore, a suitable pore depth design must be considered when using this type of porous alloys as implant materials. In other studies, corrosion resistance has been improved via Large Area Electron Beam Melting (LAEBM). In this technique, a defocused low-energy pulse of the electron beam is applied to induce high cooling rates on the surface of a given sample. This makes it possible to modify one of its layers using different pulsed treatments (1, 15, and 25 at 1.38 J/cm²) that help reduce surface roughness and contact angle. Additionally, as a result of these treatments and unlike in untreated samples, a martensitic α microstructure is formed, which allows the formation of compact passive oxide layers during corrosion, thus reducing the corrosion rate by several orders of magnitude [185].

9.6. Biocompatibility

From the point of view of their use in biomedical applications, the characteristics of the porous structures of EBM-manufactured samples favor the flow of physiological fluids, oxygen, nutrients, and cells and emulate the flow conditions of the natural bone. Considering this porous structure and the same surface roughness, various changes and adjustments are made to control the different functionalities of implants in the human body. Table 9 presents a summary of different developments in the field and studies that have been conducted using EBM-manufactured samples.

According to the above, given the different properties of EBMmanufactured samples, the presence of internal defects in the fabricated porous structures must be avoided because these defects could have a significant impact on their performance (especially their mechanical performance). Thus, an adequate control of the EBM process is key to minimize the occurrence of such defects. On the basis of a good internal defect control in manufactured parts, special attention should be given to the type of application to which they are intended in order to ensure the minimum requirements in terms of mechanical performance, corrosion resistance, and biocompatibility, among others, are met. In some cases, samples must combine all these properties, whereas in others, biocompatibility or corrosion behavior will be more relevant, to guarantee a minimum mechanical performance. This is important because improving some properties may lead to the detriment of others.

A specific example of this is sample surface improvement: a higher surface roughness reduces tensile and fatigue strength and even corrosion resistance while favoring cell adhesion. Moreover, although the porosity of lattice structures can affect implants' mechanical performance, this property is key to processes that occur within implants because it allows the flow of physiological fluids and the development of other processes between the pores. Likewise, concerning the porosity of samples, it has been reported that corrosion resistance presents discrepancies in terms of a higher or lower porosity of manufactured structures and how this condition affects their performance. Thus, the influence of the surface characteristics and porosity of manufactured structures on their biological and biocompatibility functions has proven to be higher than that of the microstructure obtained in these. Yet, defining this microstructure can be decisive to their successful mechanical and corrosion performance.

10. Surface modification of titanium and its alloys

Titanium and its alloys are one of the most widely used materials for orthopedic or dental implants. However, after being implanted, these biomaterials can trigger difficulties in patients due to infections mainly caused by bacterial adhesion [202, 203, 204, 205, 206, 207]. Their good corrosion performance is mainly explained by the formation of a dense and passive oxide layer on their surface. Nevertheless, in biomedical applications, this oxide film alone does not have enough surface characteristics to provide the material with sufficient resistance to corrosion or premature damage. Therefore, various studies have been developed in recent years to improve the functionality of the surface of titanium implants through surface treatments or modifications, as well as to minimize bacterial adhesion. Some of these treatments include thermal spraying, anodic oxidation (anodizing), sol-gel, Chemical Vapor Deposition (CVD), and high-voltage anodizing processes such as Plasma Electrolyte Oxidation (PEO) [208, 209, 210]. Depending on their type, characteristics, and conditions, titanium surface treatments or

Table 9. Applications of prostheses manufactured by electron beam melting (additive manufacturing).

Application	Result, modification, or treatment
Dental implants	The presence of an oxide layer, such as titanium dioxide (TiO ₂), on their surfaces favors osseointegration, specifically in endosseous dental implants (e.g., screws, rods, posts, and blades) [186].
Osteoblasts	Manufactured structures provide a way to initiate cell migration and impregnation of cells and tissues into the manufactured structure, thus leading to a regeneration of the mineralized extracellular matrix by differentiation of pre-osteoblasts [187], [188]. Regarding their potential use in orthopedic applications, osteoblast organization, as well as adhesion, spreading, and alignment to the geometries of the biomaterial struts, has been observed on the surfaces of EBM-manufactured samples [189]. There is a significant difference in cellular response depending on the pore size of manufactured structures [190]. For manufactured samples, an average surface roughness below 24.9 µm allows for an adequate cell proliferation, while an average surface for samples enables the absorption of fibronectin, a protein that favors osteoblast adhesion and osseointegration [192]. Osteoblast organization, as well as adhesion, spreading, and alignment to the geometries of the biomaterial struts, has been identified within complex titanium surface geometries [189].
Bioactivity	The bioactivity of manufactured and modified samples has been improved via micro-arc oxidation/anodizing, which provides a multimodal surface roughness (nano-, micro-, and macro-scale roughness) [193]. By biologically modifying the surface of samples using bone morphogenic protein-2 and a decellularized extracellular matrix, the bioactivity of porous surfaces can be enhanced. This, in turn, increases the fixation of the implant to the bone surroundings, thus improving long-term stability [194], [195]. Chemically modifying the surface of samples using hydrogen chloride (HCl) and sodium hydroxide (NaOH) has also proven to increase surface bioactivity and bone fixation for a better long-term stability [23,196,197]
Bone defects in diabetic patients	An induced accumulation of induced oxygen species on porous titanium implants is a promising strategy for diabetic patients [198].
Osseointegration and vascularization	Manufactured implants have shown a good performance in favoring osseointegration and vascularization, leading to a living implant after six months of being incorporated [199].
Astragalus osteonecrosis treatment	Through in vivo tests, porous titanium alloy rods have proven to have good biocompatibility, as well as adequate mechanical properties, which makes them suitable to be used to treat early-stage osteonecrosis in this bone [200].
Cell adhesion and proliferation	Each build orientation (horizontal, vertical, and inclined) generates a different surface roughness, with this latter being higher in vertical and inclined orientations. This feature favors a greater vitality and proliferation of L929 cells in <i>in vitro</i> tests [201].

Table 10. Surface treatments for titanium and its alloys via coating application.

Туре	Basis	Substance/Molecule	Reference
By means of physical modification to	echniques		
Bacteriostats	The surface of titanium is modified by altering its TiO_2 surface layer via oxidation or mechanical modification	PLL-g-PEG-RGD macromolecule: RGD peptide + (poly (l-lysine) PLL) + polysaccharide + (poly (ethylene glycol) PEG)	[212, 213, 214]
	(roughness or texture) to electrostatically repel possible	Polysaccharides such as hyaluronic acid and chitosan	[214, 215, 216, 217, 218]
	bacteria. Polyethylene Glycol (PEG)	Antimicrobial Peptides (AMPs)	[218]
	nyarogens and nignly negatively charged or hydrophobic-modified polymers can be used to perform this treatment.	Chitosan and alginates	[219]
		Environmentally-sensitive (smart) polymers: Poly (N-isopropylacrylamide: polyNIPAM)	[220, 221, 222]
Bactericides	They make it possible to kill bacteria using various mechanisms, such as disruption of the bacterial membrane (destruction or synthesis inhibition), prevention of cellular respiration, blocking of DNA replication, or interruption of protein synthesis.	Polyethyleneimine (PEI) biofilms: polyethyleneimine (N,N-dodecyl,methyl-PEI)	[223]
		Cationic Antimicrobial Peptide (AMP) loaded with calcium phosphate	[224]
		Peptide derived from the Parotid Secretory Protein (PSP)	[225, 226, 227, 228, 229]
		Collagen-mimetic protein and synthetic peptides	[230], [231]
		Anodic oxidation of F, Zn, Ca, Cl, I, Cu, Ce, or Se ions	[232, 233, 234, 235, 236, 237, 238, 239, 240, 241]
		Bioactive (photo-functionalized) titanium dioxide (TiO ₂) and reactive oxygen species	[242, 243, 244, 245, 246, 247]
		Copper, zinc, magnesium, silver, and gold nanoparticles (size ranging between 1 and 100 nm)	[248, 249, 250, 251, 252, 253, 254, 255, 256, 257]
		Chemical agents: Hydrogen peroxide (H ₂ O ₂), tooth whitening gel, and citric acid	[258, 259, 260, 261]
		Antibiotics with controlled release and incorporated into polyurethane coatings, biodegradable polymers, and calcium phosphates (carbonate and porous hydroxyapatite)	[262, 263, 264, 265, 266, 267, 268]
		Hydroxyapatite (HA) with silver (Ag+) biocide ions	[248], [269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280]
High-Velocity Oxygen Fuel	In this process, as-cast or partially	Collagen layers loaded with gentamicin	[281]
(HVOF) thermal spraying	molten nanosized titanium powders	Biofilms with silver nanoparticles	[282, 283, 284]
technology	are deposited on titanium substrates at a high velocity via plasma spraying to form a coating that is then biofunctionalized.	Hydroxyapatite (HA) doped with silver and strontium ions	[285, 286, 287, 288]
Plasma-Immersion Ion Implantation (PIII)	This technique seeks to form a plasma layer on the material substrate, where an exchange of positive ions from the plasma with electrons from the material occurs, by implanting an oxide layer of these ions on the surface of the material.	F, Zn, Ag+, P, and Mg ions	[239], [289, 290, 291, 292, 293]
Physical Vapor Deposition (PVD)	Process whereby an inorganic or organic metal is deposited on a conductive matrix via vaporization in high vacuum conditions. This method makes it possible to obtain substrates with good resistance to degradation and a low environmental impact.	Bioactive titanium oxide $(TiO_2) + hydroxyapatite$ (HA) loaded with antibiotics.	[294]
		TiAgN and TiN thin film	[295], [296]
Graphene and its derivatives	A thin film of graphene oxide (GO) with metallic nanoparticles is formed by means of the chemical vapor deposition of graphene on titanium materials via the wet transfer method using polymethyl-methacrylate and a subsequent heat treatment for stabilization.	Silver (Ag) nanoparticles on graphene oxide	[297, 298, 299, 300, 301]
		Graphene oxide (GO) with minocycline	[302]
By means of chemical modification t	echniques		
Chemical Vapor Deposition (CVD)	A metal coating is deposited on a substrate by thermal decomposition or chemical reaction near the hot material while controlling layer thickness, topography, and purity of the deposit.	Thin layer of graphitic C_3N_4 on TiO_2 nanotubes	[303]
		Graphene sheets	[304]
Sol-gel		Silica sol-gels with vancomycin	[305], [306]

(continued on next page)

Table 10 (continued)

Туре	Basis	Substance/Molecule	Reference		
	Mineral phases are formed as thin films	ZnO films with Ag	[307]		
	on titanium substrates by the polymerization of molecular	Copper (II) acetate in TiO ₂	[308, 309, 310]		
	precursors from a colloidal solution or	Silica compound with AgNP (AgNP/NSC)	[311]		
	sol containing organic molecules or nanomaterials.	Ag/HA or Ag/TiSi film	[278], [312]		
Titanium nitride (TiN)	Process used to improve the surface properties and finish of metals. It offers an excellent chemical stability and high resistance to high temperatures and corrosion. Nitride coatings have a high hardness and low coefficient of friction, which demonstrates their good biocompatibility when applied as layers on titanium implants.	Studies into the efficacy of nitride coatings in reducing bacterial adhesion are few and far between.	[296], [313, 314, 315, 316, 317, 318]		
By means of physical and chemi	cal modification techniques				
Plasma spraying and electrochemical deposition	Metallic implants are coated with bioactive calcium phosphate (CaP) ceramics that form an osteoconductive surface that stimulates bone growth and improves prosthesis adhesion. They can also induce the accumulation of osteoblast-like cells and minimize bone cell inflammation problems. CaP biomaterials provide metal substrates with good bioactivity, thus enhancing and accelerating fixation.	 CaP biomaterials: Hydroxyapatite (HA) β-tricalcium phosphate, Ca₃(PO₄)₂ Biphasic calcium phosphate, an intimate mixture of hydroxyapatite and beta-tricalcium phosphate Unsintered CaP or a calcium-deficient apatite (Ca,Na)10(PO₄ HPO₄)₆(OH)₂ 	[319, 320, 321]		

Table 11. Surface treatments for titanium and its alloys via surface modification.

Туре	Basis	Substance/Molecule	Reference		
By means of physical modification techniques					
Grafting copolymerization ("grafting from")	Biomolecules are immobilized on the surface to produce an interface between the biomaterial and its coating. In "grafting from," the aim is to obtain a covalent graft of functional polymers, biomolecules, and/or bioactive molecules on titanium surfaces, which incorporate an appropriate anchor.	Functional polymers: poly (sodium styrene sulfonate (polyNaSS)	[322, 323, 324, 325, 326, 327, 328, 329]		
Grafting copolymerization ("grafting to")	In "grafting to," the aim is to obtain an indirect graft on titanium surfaces (functionalization) with anchor molecules such as silanes, catechols, or phosphates.	Silane	[330, 331, 332, 333]		
		Catechol	[334, 335, 336, 337]		
		Phosphates	[338, 339, 340, 341]		
Silanization: silane anchor	Metal biomaterials are functionalized with biomolecules by means of a suitable chemical reaction with crosslinking agents. This allows the covalent attachment of peptides, proteins, and polymers using molecules such as alkoxysilane.	Melimine	[330], [331]		
		Antibacterial agent SPI031	[332]		
		Vancomycin (VAN) and caspofungin (CAS)	[333]		
Catechol anchors	A polymeric anchor or graft of a catechol group is	PolyNaSS (polyanion)	[334], [335]		
f F i c s F	formed on the titanium surface via direct polymerization on the surface of the substrate using an initiator. A polymer is functionalized and then anchored on the desired surface. The catechol is anchored on the surface of the TiO ₂ film, and then the functionalized polymer is grafted.	Dopamine with carboxymethyl chitosan or hyaluronic acid catechol	[336]		
		Antimicrobial peptide, Magainin I (Mag)	[337]		
Phosphor-based anchor	Phosphonates are covalently bonded on the substrates of metal oxides such as titanium dioxide and used as cross- linking agents. They are more stable than other agents (e.g., silanes).	Myo-inositol hexaphosphate (IP6)	[338], [339]		
		4 Vinylpyridine with Vinylbenzyl phosphonate/ Dimethyl (2methacryloyloxyethyl) phosphonate	[340]		
		4 Vinyl(N)hexylpyridinium bromide and DMMEP: Dimethyl (2methacryloyloxyethyl) phosphonate	[341]		
Anodization (anodic oxidation)	This technique allows the formation of surfaces with nanoscale surface patterns, thus obtaining different ordered geometries, such as stripes, nanotubes, nanopores, or rectangular structures, in electrochemical procedures whereby a metal acts as an anode, oxidizing itself to improve its surface characteristics.	TiO ₂ nanotubes	[342, 343, 344, 345, 346]		
		Plasma Electrolytic Oxidation (PEO)	[30], [347]		
		The oxide layer may contain incorporated chemical species: aluminates, Mg, Al, Ti, Nb, among others.	[30], [209], [210], [348], [349]		

modifications can be grouped into two categories: coating application and surface modification. On the one hand, in surface modification, either titanium's atomic or textural structure is altered [211]. On the other hand, in coating application, the surface of titanium is coated with a layer of a substance. In both cases, modifications are performed by means of physical, chemical, or combined methods, which, in turn, is possible using a variety of chemical and/or physical modification techniques. Tables 10 and 11 show some of the titanium surface treatments reported in the literature, which were classified according to the two categories mentioned above.

Of all the titanium surface modification methods mentioned above, anodic oxidation via PEO is of great interest given its low cost and environmentally friendly nature [30], [347]. Furthermore, the films obtained by means of this method show very good protective properties and high corrosion resistance compared to those provided by conventional anodizing [30]. Additionally, anodic oxidation has several advantages over other surface modification techniques because, for instance, the coatings formed by this technique display good adhesion to the substrate, higher hardness, better corrosion resistance, lower coefficients of friction, greater wear resistance, and good biocompatibility.

Various studies have employed different electrolytes to promote the incorporation of elements required in anodic coatings. The aim is to improve the bioactivity and biocompatibility of implants made of titanium and its alloys because these are bio-based materials and, therefore, chemical integration with bone tissue is not achieved [30], [209], [350], [351]. These properties basically depend on the surface characteristics of the material and the formed oxide film (composition, crystallinity, and morphology) [352]. With alkaline electrolytes of phosphate and calcium compounds, it has been possible to form biocompatible anodic coatings and even biocompatible and bioactive species in the titanium oxide layer. This is the case of hydroxyapatite, a biomaterial with a good osteo-conductive capacity, which facilitates osseointegration. Silicate electrolytes have also been reported to enhance the biocompatibility of anodic coatings, in that silicon species induce bone formation [30], [209], [349]. From the above, we may infer that anodic oxidation via PEO and electrochemical anodizing processes are the surface modification treatments with the best potential to modify implants with complex geometries thanks to, besides the properties mentioned above, their ability to cover the entire substrate surface.

11. Biomedical applications of electron beam melting: case studies

EBM is one of the most promising AM techniques for biomedical applications due to its high efficiency in providing prototypes with complex geometries [353]. However, there are several problems associated with bone compatibility when using titanium alloys in solid and monolithic implants because these alloys can exhibit moduli of elasticity higher than those of the cortical and trabecular bones [354]. Corrosion is another compatibility issue that has been observed in implants made of these alloys and occurs when the TiO₂ protective layers break down due to the action of different factors such as the physiological environment and infections [355]. EBM has, thus, become a promising technique to obtain monolithic, porous, complex, and patient-specific implants [355]. For this reason, numerous studies into the behavior of EBM-manufactured Ti6Al4V implants have been developed in recent years, among which the following stand out:

11.1. Case study 1: knee implant

Murr et al. [355] fabricated knee and hip implant prototypes with porous structures using medical grade Ti6Al4V powders via EBM. Figure 12a) provides a graphical representation of an inner and outer femoral bone structure consisting of a foam cylinder composed of an inner stem and a shell with a density higher than that of the stem. Figures 12b) and 12c) display the EBM-manufactured prototypes.



Figure 12. Solid structures. a) Computer-aided design model of the inner and outer femoral bone structure; and b) and c) Ti6Al4V prototypes obtained by electron beam melting [355].



Figure 13. a) X-ray image and b) incision for knee replacement surgery [355].

Figure 13a) illustrates, by means of an X-ray image, the knee replacement implant consisting of a Ti6Al4V tibial stem and meniscal platform. Figure 13b) shows the incision for knee replacement surgery. In this case, a porous surface is employed in the femoral system to favor femoral bone cell ingrowth. EBM is a promising technique to obtain highly rigid porous structures that can be used as monolithic implants with a lower risk of failure in terms of complexity and mechanical stress.

Figure 14 displays the EBM-manufactured Ti6Al4V tibial stem (knee) prototype with an outer mesh structure. In this case, the longer stem provides greater rigidity and stability to the implant.

11.2. Case study 2: left jaw implant

According to Suska et al. [356], EBM has a high potential in the field of maxillofacial reconstruction because it offers innovative designs of mandible prostheses based on the specific (aesthetic or functional) needs of patients. EBM-manufactured jaw prostheses include porous parts that favor bone ingrowth and secondary biological fixation with solid regions, characteristics responsible for an adequate biomechanical functioning. However, EBM-manufactured implants present some difficulties associated with complex geometries and the surface properties of porous regions, which have not been optimized for some specific medical cases. Suska et al. [356] reported the case of an 84-year-old woman diagnosed with cancer of the left mandible, who had underwent an initial ablative intervention that left her with an apparent defect in the jaw. This led to the decision of manufacturing a customized prosthesis via EBM to begin



Figure 14. Ti6Al4V tibial stem (knee) prototype with an outer mesh structure manufactured by electron beam melting. a) Computer-aided design (CAD) model, b) prototype fabricated via electron beam melting using the CAD model, and c) CAD model with a 45° rotation.

the reconstructive surgical phase. To digitally design the bone prototype, the authors used PowerShape CAD software (version 2014, United Kingdom) and Magics STL editor (version 18.03, Materialise) (see Figure 15). To plan the surgical procedure, they employed a polymer bone replica and placed porous network structures on its upper and lower parts to ensure bone ingrowth and its fixation to the jaw. Finally, the implant was manufactured by EBM using Ti6Al4V plasma-atomized powder with a particle size below 100 μ m.

After the surgical procedure, the patient was followed-up for nine months, period during which the implant showed a good performance from the aesthetic point of view and in terms of stability.

11.3. Case study 3: implant surface modification to improve bioactivity

Ren et al. [357] presented a method that sought to improve the bioactivity and osteogenesis of EBM-manufactured Ti6Al4V implants by fabricating a micro/nano topography on their surface. AM comprises promising techniques in the field of tissue engineering, in that they make it possible to prototype implants using titanium and its alloys. Nevertheless, the biological properties of this metal do not allow its direct adhesion to the bone tissue. For this reason, the authors of [357] proposed to modify the surface of EBM-manufactured Ti-6Al-4V implants via anodic oxidation and ultrasonic-assisted acid etching to remove residual powders and produce micro holes on the implants' surface (see Figure 16). They reported important findings from the *in vitro* and *in vivo* experiments they conducted. For instance, the construction of a hierarchical micro/nano-structure led to an enhanced bioactivity and osteogenesis on the surface of the EBM-manufactured prototypes and favored cell proliferation. Moreover, the in vivo experiments carried out in mice showed an increased bone volume formed around the titanium implants after their surface was modified via anodizing and ultrasonic-assisted acid etching. These results, thus, constitute a great advance in promoting the use of these implants in the orthopedic and dental fields.

11.4. Case study 4: biocompatibility of implants

Wang et al. [353] evaluated the behavior of EBM- and SLM-fabricated Ti6Al4V prototypes in terms of *in vitro* and *in vivo* biocompatibility, cytocompatibility, hemocompatibility, and skin irritation. The authors observed no significant changes in the physical, chemical, and mechanical properties of both prototypes. The EBM-fabricated prototypes exhibited good cytobiocompatibility and hemocompatibility and caused no skin irritation or sensitivity when implanted both *in vitro* and *in vivo*



Figure 15. Designs of the facial skeleton and the jaw implant prototype to be manufactured via electron beam melting [356].



Figure 16. Surface modification of implants manufactured via Electron Beam Melting (EBM). a) In vitro, and b) in vivo experiments [357].

(in rabbits). Figure 17 shows one of the EBM-fabricated Ti6Al4V specimens to be implanted in animals. These specimens were manufactured in an EBM Arcam A1 system using Ti6Al4V Grade 5 powder with a particle size ranging from 45 to 100 μ m.

Figure 18 presents some images of the EBM-fabricated Ti6Al4V specimens implanted in animals, which show no signs of skin irritation.

12. Certification challenges regarding the commercialization of implants manufactured by electron beam melting

The final step in the development of prostheses or implants for their use in humans and commercialization is product certification, a process that ensures that the final product is safe and reliable. In this regard, different standards and certifications for additively manufactured products have been developed. One of the first products to be certified and given green light for its commercialization was an acetabular cup manufactured via EBM using the GE's Arcam EBM technology [358]. Since then, other types of implants have been increasingly produced and marketed, which are backed by different certifications granted by various institutions in Europe, China, and the United States, including the



Figure 17. Ti6Al4V specimen produced via electron beam melting [353].

certifications from the National Medical Products Administration (NMPA) and the China Food and Drug Administration (CFDA), the CE marking, and the Food and Drug Administration's Current Good Manufacturing Practices. Under established international standards, these certifications must meet certain minimum requirements according to the type of application [359]. In addition, various international standards such as ISO 13485 have been defined to allow the implementation of a quality management system within institutions, in such a way that it can provide regulatory or certification services for medical devices across all the stages of the life cycle of additively manufactured products. There are also standards that regulate the sterilization of medical devices (ISO 11737-1: 2018 and ISO 11737 - 2009) and the packaging of sterilized medical devices (ISO 11607-2019) [360].

13. Conclusions

- The defects that may appear in the lattice structure (defined by the unit cells) must be minimized because they can significantly contribute to a deterioration of its properties, especially the mechanical ones. Some of these defects include high surface roughness, unmelted powder particles, and porosity, with this latter occurring in the structs of the unit cells that make up the EBM-manufactured structure. Porosity can develop between the unmelted powder particles and due to the trapping of gases used in the processing, which produces closed internal pores or pores on the surface of the EBM-manufactured samples. Both pore conditions affect the mechanical properties of the parts and promote corrosion.
- High surface roughness and internal porosity considerably lead to fatigue failure, which confirms the need to apply Hot Isostatic Pressing (HIP) and machining treatments in order to polish the rough surface of EBM-manufactured samples. Likewise, the wear experienced by samples is mostly explained by the presence of cracks on their surface (a macro defect).
- On the basis of an internal defect control (either from the processing or using post-treatments such as HIP and machining), the properties of EBM-manufactured samples can be controlled through their microstructure and the shape or geometry of the unit cells that comprise them.
- The microstructure obtained in EBM-manufactured samples possesses a dual structure ($\alpha + \beta$) that provides them with a good fatigue strength and wear resistance (greater hardness). In the case of uniaxial loads such as tension, a microstructure of prior β grains parallel



Figure 18. Ti6Al4V specimens implanted in animals to evaluate skin irritation [353].

to the load orientation offers a higher resistance, as long as the high surface roughness effect does not prevail. In the event it prevails, the use of machining to reduce surface roughness is justified.

- The geometry and shape of unit cells establish important conditions in the final lattice structure obtained in EBM-manufactured samples in terms of its porosity (which depends on strut thickness and pore size), a condition that has the greatest influence on compressive strength. Additionally, the thickness of the struts that make up a unit cell generates a microstructure within it as per the cooling rate during the EBM process, which allows it to support the distributed loads (buckling or bending) under a real load or mechanical test condition. As reported by various studies, cubic unit cells have the best compression strength performance.
- The biocompatibility and interaction of EBM-manufactured implants with living tissues demand different requirements, such as the flow of physiological fluids, oxygen, nutrients, cells, among others, as well as osseointegration, surface bioactivity, vascularization, and cell proliferation and adhesion processes. All these functions are favored by a higher surface roughness and porosity, characteristics that are detrimental to the mechanical and corrosion properties. However, Ti6Al4V alloys show a good balance between their physicochemical properties and biological functionality to be used as implants and bone substitutes in the human body, and their performance can be optimized using post-EBM manufacturing treatments such as hot isostatic pressing, surface machining, and anodizing.
- According to information reported in the literature on surface modification methods for titanium prostheses, different techniques have sought to functionalize manufactured parts used as biomedical implants. Some aspects to highlight from such studies are listed below.
- Although there is still no consensus on which the most appropriate method is, these techniques have been grouped into two categories (coating application and surface modification) based on their type, characteristics, and conditions.
- Depending on the surface modification method used, the aim is to change the chemical structure of titanium at the atomic, molecular, or textural level or apply a layer of a substance to the substrate surface.
- Functionalization can be performed by means of physical or chemical techniques or a combination of both.
- The various implant surface modification methods combine materials or substances with different properties, which, when applied, protect or functionalize the metallic material used for surgical implants.
- Electroless coatings have gained high technological interest because, besides being easy to apply, they make it possible to obtain complex geometries with uniform thicknesses, high wear and corrosion resistance, strong adhesion, and low porosity. In addition, they can be formed on metallic and nonmetallic surfaces.

Declarations

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Funding statement

The authors are pleased to acknowledge the financial assistance of the Instituto Tecnológico Metropolitano (ITM).

Data availability statement

No data was used for the research described in the article.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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