Metal-Based Antimicrobial Agents

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Contributor: Thywill Dzogbewu

Due to increasing bacterial resistance to antibiotics, surface coatings of medical devices with antimicrobial agents have come to the fore. These surface coatings on medical devices were basically thin coatings that delaminated from the medical devices due to the fluid environment and the biomechanical activities associated with inservice implants. The conventional methods of manufacturing have been used to alloy metal-based antimicrobial (MBA) agents such as Cu with Ti6Al4V to enhance its antibacterial properties but failed to produce intricate shapes. Additive manufacturing technology, such as laser powder bed fusion (LPBF), could be used to produce the Ti6Al4V–xCu alloy with intricate shapes to enhance osseointegration, but have not been successful for texturing the surfaces of the Ti6Al4V–xCu samples at the nanoscale.

metal-based antimicrobial (MBA) agents | implant infections | surface coating | laser powder bed fusion | nanotextured surfaces

1. Introduction

Biometallic materials are preferred biomedical materials due to their reliability in terms of the stringent mechanical performances required for load-bearing implants. Historically, biometallic alloys have been used successfully and have systematically evolved through different transition stages parallel to advancements in technology and materials science. Pure metals such as gold and iron were used in 1875 as biometals; silver, copper and coated steel were introduced from 1875 to 1925; and cast Co-Cr-Mo alloy and AISI type 316 stainless steel were used during World War II. From the literature, the modern period of producing biometallic alloys with appropriate biomechanical properties started in 1925 [1][2].

Among the biometallic alloys, titanium and its alloys have been identified as “miracle” metals [1], since they have become the backbone material for producing biomedical devices, due to their unique combination of chemical, physical and biological properties. The preference for Ti-based alloys for biomedical applications over other biometals is due to the spontaneous formation of an extremely thin, stable and adherent protective titanium oxide film in an oxidizing environment during the passivation or repassivation process, which prevents corrosion and promotes biocompatibility of the metal [2]. However, it has been found that the same surface properties that make Ti-based implants biocompatible are also responsible for its surface susceptibility for bacterial infections [3][4][5]. The formation of the thin titanium oxide layer under physiological conditions is a good substrate for the adhesion of proteins and cells, which can equally provoke bacterial colonization and biofilm formation on Ti-based implant surfaces. Hence, titanium and its alloys alone cannot meet all the clinical requirements, especially prevention of infections, without the appropriate surface modifications and coatings [5][6][7][8]. The current review, therefore, seeks to examine the previous antibacterial coating strategies that have been used, identify their limitations and emphasize why biomimetic additive manufacturing of Ti-based medical devices with nanotextured (nano protrusions) surfaces and incorporated metal-based antimicrobial (MBA) agents, such as Cu, in the custom implant is the most ideal alternative for the production of the next generation of implants. This paper presents the current challenges limiting LPBF manufacturing technologies from producing nanotextured surfaces. An alternative approach to manufacturing biomimetic nanotextured medical devices and recommendations are reported in the paper. Successful manufacturing of biomimetic medical devices with incorporated MBAs would limit the stress shielding effect, prevent implant infection, enhance osseointegration and avoid bacterial resistance to antibiotics, which is a major health concern.

2. Surface Coatings

The modification of the surfaces of biomedical implants to enhance tissue attachment and prevent implant infections evolved from the mechanical modification of the surface of a medical device (grinding) [9][10], morphological alteration (blast, groove, etching) [11][12][13], physicochemical active surface treatments (chemical treatment and hydroxyapatite coating) [14][15][16][17][18], biochemical active surface treatments (immobilization of biofunctional molecules) [19][20][21][22][23] and, finally, modifying the biologically active surface of the implant by coating it with stem cells and antibacterial agents [24][25][26][27][28]. Since the discovery of osseointegration (*the direct and stable anchorage of an implant due to the formation of bony tissue around the implant*) and the race for the surface (*the race between microbial adhesion and biofilm growth on an implant surface versus tissue integration*) [29], it has been evident that coating of implant surfaces with the appropriate antibacterial agents would enhance osseointegration and prevent infections. Organic antibiotics were the prime antibacterial surface modification agents for implant infection control and have been studied and applied extensively in the clinical treatment of implant infections. However, there are many outstanding issues, such as [8][9][10][11][30][31][32][33]

- potential toxicity,
- depression of the revision process,
- damage to cell functioning,
- a faster rate of elution of the incorporated drugs,
- a relatively low drug concentration at the target site,
- inability to produce coatings that can load and release enough bactericides in a controllable fashion throughout the lifetime of the implant and
- the detrimental effect of bacterial resistance.

According to the World Health Organization (WHO) [13], 700,000 people die each year of drug-resistant diseases. The list of antibiotics that can be used against disease-causing microbes has been dwindling at an exponential rate over the past few decades and it is estimated that if no viable alternative is found, about 10 million people will die per year from disease-causing microbes [12][13]. Essential oils have also always been considered as a prime alternative antibacterial agent that would fight bacterial infection effectively. However, research on the potential surface coating applications of antimicrobial plant extracts (essential oils) is still largely in the theoretical and laboratory experimental stages [34][35].

To overcome the numerous limitations of organic antibiotic coatings of implants, surface coating of implants with inorganic MBA agents was adopted. The major MBAs include silver (Ag), copper (Cu), zinc (Zn), calcium (Ca), nitrogen (N) and some oxide- and nitric-related agents (e.g., titanium dioxide, zinc oxide, tantalum nitride, titanium nitride (TiN), and zirconium nitride (ZrN)) [3][15]. However, the bonding (adhesive strength) between the coating material and the metal matrix is in some cases not as strong as expected, due to the thermophysical differences (thermal expansion coefficient, thermal conductivity, specific heat capacity, etc.) between the MBA coating materials and the metal (titanium alloy) matrix [16]. The major surface coating techniques used for coating the implants with the MBAs are presented in Table 1. These surface coatings are basically thin coatings [36][37][38], which are at risk of been worn out due to the fluidic environment and the biomechanical activities associated with service implants. The thin coatings normally become worn out or delaminate from the metal matrix of the implants and lose their antibacterial potency. The implants therefore become vulnerable to infections in the long term. Probably, the best alternative is producing implants with embedded antibacterial properties [39], thus alloying the custom implant with the MBA agent that can act locally and permanently at the target site.

Table 1. Methods used for coating biomedical objects.

Methods	Advantages	Disadvantages	Nature
Plasma spray [40][41][42]	Can be used to coat a wide range of materials (ceramics, plastics, glass, composites, etc.).	The high temperature operations of the plasma jet can result in carbide formation or excessive oxidation. It is a line-of-sight process, making it difficult or impossible to coat intricate geometries.	Thin film
Physical and chemical vapor deposition [43][44][45][46]	Can be used to coat a wide range of materials (ceramics, plastics, glass, composites, etc.)	It operates at high vacuum and temperature, requiring skilled operators.	Thin film
Magnetron sputtering [47][48][49]	The thickness of the deposition can be effectively controlled	The magnetic field of the target material can affect the efficiency of the deposition.	Thin film
Electroplating [50][51][52][53][54]	Can be used to plate a wide range of metals and prevent them from corrosion	Non-uniform coating of the metal due to the electric field.	Thin film

Methods	Advantages	Disadvantages	Nature
Sol–gel method [52][53][54]	Due to the gel state, it can be used to coat some complex geometries	High permeability, low wear resistance, weak bonding, instability of the gel.	Thin film
Ion implantation [46][55]	Good homogeneity and reproducibility of the profile	The implanted ions can cause damage to the material and even change the material properties. It is a line-of-sight process, making it difficult or impossible to generate surface layers of even thickness for intricate geometries.	Thin layer

tibacterial properties compared with other MBAs and they have been studied and applied extensively in the clinical treatment of implant infections [16][18][20][24]. However, it has been widely reported that silver-coated implants can cause various degrees of cell damage and can even lead to cell death [56][57][58]. On the other hand, Cu ions are more easily metabolized by the human body than Ag ions and, in addition, Cu ions are less easily deposited in the liver as compared with Ag [59]. It has been documented that cell toxicity could occur with a relatively lower concentration of Ag^{+} and Zn^{2+} (LD50 = 3.5 × 10^{-3} mmol/L), but a relatively higher concentration of Cu^{2+} (LD50 = 2.3 × 10^{-1} mmol/L) still had no toxic effect on tissue cells. This indicates that the human body can endure a higher amount of Cu ions than ions of the other antibacterial elements [60]. Gaetke and Chow [59] explained that the homeostatic regulation of Cu via increased Cu absorption or excretion protects the body against Cu toxicity or deficiency. However, they cautioned that, since copper is a heavy metal, it would have a certain degree of toxicity in the human body when used in excess; hence, moderate use is always the best. It has been widely documented that <5 wt.% Cu [31][61] alloyed with Ti-based implants would not cause any harmful effect to the human body in the long term. This empirical evidence has made Cu the preferred MBA for biomedical applications for implant infection control.

Cu and Cu-containing alloys can kill more than 99.9% of microbes that cause infections within two hours of contact (contact killing) [62][63]. Although there are divergent explanations and theories about how the Cu ions kill the bacteria on contact, it is generally understood that the Cu ions kill bacteria by destroying the cell wall and cell membrane, causing the cytoplasm of the bacteria to leak [58]. Cu alloys can effectively kill from ten to a hundred million bacteria per minute by destroying the bacteria's DNA. Cu is the only metal approved by the U.S. Environmental Protection Agency (EPA) in recognition of its antimicrobial properties [64]. Cu is an essential trace element that is required for human health in the formation of red blood cells, absorption and utilization of iron, metabolism of cholesterol and glucose, synthesis and release of life-sustaining proteins and several enzymes [65]. It was also stated that since bacteria have not developed resistance to copper in the last 3000 years, they are unlikely to do so in the future [66][67]. This implies that embedding Cu in a customized implant would make the medical device permanently self-sustainable against implant infection.

Ren et al. [39] produced Ti-based implants with incorporated antibacterial properties by melting commercial medical grade Ti6Al4V–xCu alloys with Cu (x = 1, 3, 5 wt.%) in a 100 g capacity vacuum arc furnace. The Ti6Al4V–xCu (x = 1, 3, 5 wt.%) implant samples demonstrated excellent antimicrobial properties. It was revealed that, as the percentage of copper increased in the Ti-based alloy, the potency of the implant against bacterial infection also increased with no cytotoxicity effects. Zhang et al. [68] reported on preparation, mechanical properties and antibacterial activity of a Ti–xCu (10 wt.% Cu) alloy produced through powder metallurgy. It was concluded that the addition of copper provided the whole alloy with strong antibacterial properties. The studies of Liu et al. [69] focused on the antibacterial activity, cytotoxicity and cell function of a sintered Ti-10 wt% Cu alloy for biomedical applications. The antibacterial activity of the alloy and cytotoxicity were investigated. The results attest that the alloy possesses strong antibacterial properties without cell cytotoxicity. Although moderate usage of Cu less than 5 wt.% was recommended by most clinical investigations, it was also reported that higher percentages of Cu (10 wt.% Cu) were still non-toxic to the human body [39][70][71]. Regarding the effect of the Cu content on the biomechanical properties of the Ti-based alloys, it was reported that Ti-based alloys containing >5 wt.% Cu demonstrated different biomechanical properties due to the presence of the intermetallic compound (Ti_2Cu) as compared with the Ti6Al4V standard for biomedical applications [37][39][40]. Hence, moderately used <5 wt.% Cu, which effectively kills bacteria and does not have any significant effect on the biomechanical properties of the alloy, remains the ideal composition for optimal results.

Although the conventional methods (press and sinter processes) discussed above alloyed the Cu MBA perfectly with the precursor Ti-based powder, the inherent limitations of the conventional methods (milling, forging, sheet forming, perforated/slotted, sheet folding, extrusion, investment casting, etc.) used to manufacture intricate biomimetic structures for biological applications, and the advancement in technology, led to the euphoric expectation of many researchers investigating the possibility of using the additive manufacturing (AM) methods. The AM methods can be used to produce intricate biomimetic Ti-based implants with incorporated MBAs, such as Cu, with a textured surface that would enhance osseointegration and prevent bacterial infection. The AM process does not only produce biomimetic near-net-shapes, but also reduces the time spent on manufacturing, avoids waste of manufacturing materials, eliminates or limits assembly processes, improves performance reliability and results in weight reduction [72][73][74]. Due to the abovementioned capabilities of the emerging AM technologies, it is argued that, currently, AM is the most ideal technology for producing Ti-based alloys such as Ti6Al4V–xCu with the required biomimetic characteristics and embedded antibacterial properties in a custom implant.

4. Metal Additive Manufacturing

Additive manufacturing (AM) is the process by which parts are joined or solidified from a powder feedstock additively, layer by layer, as opposed to the subtractive approach used by the conventional methods of manufacturing [75]. The AM technologies are classified into seven categories by the American Society for Testing and Materials (ASTM) International F42 Committee on Additive Manufacturing (AM) technologies [76]. These categories are: powder bed fusion, photopolymer vat, material extrusion, directed energy deposition, sheet lamination, material jetting, and binder jetting. Of the seven categories, powder bed fusion (PBF) manufacturing technology is the most extensively used in industry for processing metallic powder materials, especially for biomedical applications [77]. The PBF manufacturing technology is comprised of electron beam melting (EBM) and laser powder bed fusion (LPBF) machines [77]. The LPBF manufacturing process is a paradigm shift from the traditional methods of manufacturing and can produce intricate shapes (near-net-shapes) based on a CAD model

[74][75]. The layer-by-layer monolithic eco-design topology optimization technology manufacturing process of the LPBF manufacturing process permits the manufacturing engineer to produce biomimetic implants according to the technical, functional and geometrical dimensions of the affected body parts [72]. Using the LPB technology to produce biomimetic structures would enhance osseointegration. Several researchers have used the LPBF technology to produce biomimetic structures, such as lattice structures for biomedical applications, which had been almost impossible to produce using the conventional methods of manufacturing [73]. Such structures have demonstrated mechanical properties similar to that of bony tissue. It was demonstrated experimentally that the biomimetic lattice structures produced using the LPBF technologies are able to minimize the stress shielding effect (the mismatch between the mechanical properties of an implanted devices and the bone tissue) [41][42][43], which is also another major reason for implant failure.

Taking a step further by incorporating MBAs such as Cu would enable the production of biomimetic implants with antibacterial properties, which would enhance the longevity of orthopaedic implants and sustain the improved quality of life of implant patients. Preliminary investigations of in situ alloying (incorporating) Cu into Ti-based precursor powder for manufacturing biomedical devices using LPBF technology have been conducted [78][79]. The authors based the composition of the alloy (amount of Cu) on what was already known from the conventional methods of manufacturing (<5 wt.% Cu). Since Ti6Al4V is the principal alloy used industrially for manufacturing biomedical objects, few researchers have tried to determine the optimum process parameters that could be used to in situ alloy Cu with Ti6Al4V [48][49]. The current preliminary results revealed issues of agglomeration of the powder leading to inhomogeneity of the Cu in the Ti6Al4V–xCu matrix [80]. The most ideal solution should be producing pre-alloyed Ti6Al4V–xCu alloy for manufacturing the biomimetic Ti-based implants with “inbuilt” antibacterial properties. However, such pre-alloyed powder does not exist currently. Perhaps after successful preclinical in situ alloying of Ti6Al4V–xCu implant samples has confirmed the lab and theoretical results, investors would be comfortable investing in the production of pre-alloyed Ti6Al4V-xCu powder, which could then be used to produce biomimetic implants with antibacterial properties.

5. Effect of Surface Texture on Microorganisms

The surface quality of an LPBF-manufactured sample needs to meet the industrial requirements, especially for sectors like the medical industry where precisely tailored surface quality is required for each type of implanted medical device. This is because the surfaces of implanted medical devices need to be in direct contact with the human body tissue for osseointegration to occur. It has been empirically proven that the anchoring process after implantation is directly affected by the surface quality of the implanted device. Generally, the surfaces texture of LPBF products are reported to be between 6 and 10 m for Ra value and 35 and 40 m for Rz value however, it is well documented that metal surfaces that are nanotextured could prevent infections. Unfortunately, the current LPBF technologies are not able to produce nano 3D structures or nanotextured surfaces. Research is ongoing to improve the manufacturing capability of the LPBF technology to produce objects with multi-material properties at both the macro and nanoscale with nanotextured surfaces for biomedical and engineering applications. A recent review publication of Moshiri et al. on the benchmarking of LPBF machines, which are mainly used for manufacturing biomedical products, revealed that precise nanostructural design via AM still has a long way to go. This is empirically true, because due to the innovation of nanomaterials in parallel with the evolution of additive manufacturing processes, few researchers have tried to incorporate nanoparticles into Ti-based alloys for various biomedical and engineering applications. The preliminary results reveal agglomeration of the nanopowders, settling of the nanopowder particles at the bottom of the powder bed and inhomogeneity and porosity in the final product. Indeed, manufacturing or texturing the surface of LPBF-manufactured products at the nanoscale has a long way to go. Apart from the technical issues regarding the LPBF machines' limitations to manufacture or texture the surfaces of LPBF biomedical products at the nanoscale to prevent infections and enhance osseointegration, issues of environmental stability, health and safety also present challenges in the processing of the nanopowders, as well as the use and disposal of thenano manufactured products [

Despite these challenges, researchers are taking advantage of the surge in technological advancement and are making a continuous attempt to modify the surface of the additively manufactured product at the nanoscale and even manufacture nanoscale 3D objects. The successful resultant effect of these efforts means it is not only the incorporated Cu (in situ alloying) in the Ti6Al4V–xCu implant that would kill the disease-causing organism, but the changing of the texture of the LPBF-manufactured implant surface would also kill the pathogens. This envisaged kind of implant is what the literature refers to as the next-generation implants. These are implants with biomimetic structures, which are able to prevent the stress shielding effect and implant infections and enhance osseointegration in order to improve the quality of life of implant patients. It is reported that texturing of metal surfaces with nano protrusions that can physically rupture the outermost layer of the disease-causing organism without being harmful to the human tissue would be the most efficient and effective way of preventing infection transmissions, thus turning the surface materials of implants into a weapon against pathogens that dwell on them. It is worth mentioning that this new wave of research into the nanotexturing surfaces of materials (especially copper alloys) to provide them with antibacterial properties to kill pathogens immediately on contact is fueled by the Coronavirus pandemic as researchers are trying to find ways to make surface antibacterial agents. This might be a clarion call to the AM community to harness the emerging technologies of nanotexturing surfaces to prevent transmission of infection in the implant manufacturing industry. The success of this kind of surface texturing of biomedical devices would eliminate biofilm
formation. Biofilm formation on the surface of medical implants poses a grievously complicated challenge to the field of medical implant implantation. In a biofilm, bacteria are well protected from the host's immune defense and the bacteria subsequently develop a resistance against the applied antibiotic agent. It is always difficult to eradicate bacteria in biofilms and even high-level local concentrations of antibacterial agents cannot completely destroy the bacteria in biofilms. Developing implants with inbuilt antibacterial properties, such as Ti6Al4V–xCu with nano protrusions that could rupture the outer layer of the microorganism, would probably annihilate implant infections.

Although none of the LPBF technologies have reached industrial readiness and commercialization of the conceptualized nanotextured surface production methods, some examples already exist with other types of 3D printing technology. Sharklet Technologies produces a biomimicry plastic sheet material that mimics sharkskin by using a diamond pattern on the surface, which bacteria are unable to settle on. This is already used on medical devices like catheters, to prevent the catheter from carrying infectious bacteria into the body. The diamond pattern (surface ridges) that rupture the bacteria on contact are about 1/10th the width of a human hair and rupture the outer layer of bacteria with 90% to 99.99% efficiency. It is expected that the diamond pattern would be produced on the surfaces of metallic implants such as Ti-based implanted medical devices in the future. The first-ever such metallic implant surface modification was recently demonstrated by Wandiyanto et al.through hydrothermal etching. The authors hydrothermally produced a random nanosheet texture (topology) surface on a titanium device. They reported that the hydrothermally produced random nanosheet textured surface achieved maximal antibacterial efficiency of 99% against pathogenic bacteria. The nanosheets were produced with sharp edges of approximately 10 nm and exhibited efficient mechanobactericidal activity against both Gram-negative and Gram-positive bacteria. The authors confidently stated that they were the first to produce such a nanostructured titanium topography since the “birth” of nano surface modification of biomedical devices began about a decade ago. Such an approach can be adopted to improve the surface of LPBF Ti6Al4V–xCu biomedical devices.

Selvamani et al. also used a laser texturing mechanism to produce mesoporous nanostructures. The authors argued that due to the simplicity and scalability of the technique, it could be easily incorporated into the existing medical device manufacturing processes. Such a laser nanotexturing technique could be an add-on manufacturing strategy that could be incorporated into the LPBF manufacturing process. Nanotextured surfaces could change the chemical/biological reaction of implanted devices due to the changed implant surface interaction with ions, biomolecules and cells. This change in interactions, in turn, could enhance the rate of bone-to-implant contact (osseointegration) and have the potential of improving the longevity of the implanted devices.

6. Challenges, Further Research and Recommendations

This concept of texturing the surfaces of materials with nano protrusions to kill bacteria on contact is a biomimetic approach based on the “tiny spikes” on the wings of the insect cicada that prevent bacterial cells from being able to settle and grow on its surface. The challenge of producing implanted medical devices with nano spikes is that it might be necessary to remove the dead pathogenic cells from the surfaces of the implanted devices. However, it is reported that “titanium and titanium alloys, pathogenic cells’ debris detach away from the surfaces—essentially making them self-cleaning”. The question is: would the dead pathogenic cells be dissolved and be flushed out of the body through excretions just like dissolvable implants. Further research is required to understand how the dead pathogenic cells caused by the nano spike killing can be removed from the body.

Since it has been empirically proven that it is the surfaces of an implanted device that determine the anchorage process after implantation, it is obligatory to improve the LPBF manufacturing process to produce biomimetic objects with surface textures that would prevent implant infections and enhance osseointegration. Alternatively, it might be recommended that add-on technologies (laser texturing, hydrothermal etching, etc.) could be used to texture the surface of LPBF biomimetic Ti6Al4V–xCu samples. The challenge of using such add-on technologies is that they cannot be used for intricate shapes, but only for flat and "simple” 3D structures. Such an approach would nullify the monolithic nature reported extensively regarding LPBF technologies. The applicable AM processes are still not sufficient to stand on their own monolithically without being complimented by other add-on technologies.

The current nano surface texturing (nano protrusions) is an improvement on the nano surface modifications (nanomaterial coatings) that emerged about two decades ago along with nanotechnology's evolution when the surfaces of medical devices were coated with nanoparticles/nanomaterials. This new trend of nanotexturing of implanted medical devices is due to the inherent drawback of the coating material leaching off from the medical device and the detrimental effect of bacterial resistance to antibiotics. Research in this field of direct nanotexturing of material surfaces without coating is quite young and reports cover preliminary preclinical experimentation. There is a need for detailed substantive data to confirm most of these claims. The exact size of the nano protrusions that could kill bacteria on contact by rupturing the outer layer of the bacteria is not documented in most of the reports.

7. Conclusions

As discussed, it could be stated that the preferred biomaterial (Ti6Al4V) is not sufficient to prevent implant infection without appropriate modifications such as incorporating antibacterial agents into the custom implant. Using the conventional method of manufacturing to incorporate (alloy) MBAs such as Cu was "successful". However, the inherent limitations of the conventional methods to produce biomimetic near-net-shapes have led to the use of AM technologies such as LPBF to produce Ti6Al4V–xCu medical devices. The manufacturing of Ti6Al4V–xCu biomedical devices with near-net-shapes would prevent or minimize the stress shielding effect and bacterial infections and enhance osseointegration. However, the existing LPBF technologies cannot produce medical devices with surfaces containing nano protrusions which could rupture the outer layer of bacteria on contact. Therefore, it is recommended that other add-on technologies be used in conjunction with the LPBF technologies to produce next-generation medical devices, which would prevent stress shielding and bacterial infection and enhance osseointegration in order to extend the improved quality of life of implant patients.

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