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Reducing the Issues of Implements in the Human Body by Applying Hydroxyapatite (HAP) in Modern Biomedicine: Review

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Abstract. Hydroxyapatite (HAP) is a naturally occurring mineral that has received increasing attention as a biomaterial for use in biomedical applications. HAP is biocompatible and has excellent osteoconductivity and bone-bonding properties, making it a promising candidate for use in a range of medical applications, including bone regeneration, dental implants, and drug delivery. This comprehensive review provides an overview of the current state of knowledge on the use of HAP in biomedical applications. The review covers the basic chemistry and properties of HAP, as well as its synthesis and processing techniques. It also discusses the different forms in which HAP can be used, including powders, coatings, and composites, and their respective advantages and limitations. The review goes on to discuss the various biomedical applications of HAP, including bone regeneration, dental implants, and drug delivery. For each application, the review examines the specific properties of HAP that make it suitable for the given purpose, as well as the challenges associated with its use. The review also addresses some of the limitations and challenges associated with the use of HAP in biomedical applications. These include the relatively low mechanical strength of HAP compared to other materials, its susceptibility to degradation over time, and its potential to elicit an immune response in some patients. Overall, this review demonstrates the potential of HAP as a building block for better health and highlights the need for continued research and development in this field to fully realize its potential in biomedical applications.

Keywords: implements, human body, hydroxyapatite, biomaterials, corrosion reduction, biodegradable.

1. Introduction

The Egyptians developed a similar custom of cutting precious metals and pegging them onto the jawbone some 2,000 years later. In an Egyptian pharaoh from 1,000 B.C., a metal implant was discovered for the first time [1], [2], [3]. Numerous skulls with fake or transplanted teeth made of elephant ivory or precious stones like jade have also been discovered by archaeologists. Dr. Wilson Popenoe and his wife Dorothy Popenoe discovered a young woman's skull in Honduras in 1931. Three of her lower jaw's teeth were gone, and shells had filled the spaces. The shells were fashioned to resemble the form of teeth. These teeth were created for function rather than beauty since there was bone development and calculus. Dental implants are now the standard treatment for tooth loss, thanks to modern technology [4].

The study of biomaterials is crucial for humankind's survival and longevity, as well as that of the elderly population, who need biomedical implantation to extend their lives, and some of the less fortunate people born with congenital heart disease [5]. Geriatric doctors are needed to treat various illnesses in the elderly since the body's components have worn down after years of performing their intended functions. One of the most common ailments, arthritis, affects individuals of all ages, including sometimes young people. It damages their quality of life by making them immobile and causing excruciating pain. Despite significant scientific discoveries, the etiology of this illness is still unclear [6]. Young and active individuals, such as athletes, often need replacements owing to fractures and excessive strain, in addition to sick patients. The demand for biomaterials was particularly urgent following the two world wars, and in the modern environment of international terrorism, this topic has acquired considerably more relevance [7].

The usage of iron and gold in dentistry [8], wood for toe replacements, and linen for sutures by the Romans and Egyptians date back more than 4,000 years, although these civilizations had little understanding of the issue of corrosion at the time [9], [10]. After World War II, additional materials such as titanium, stainless steel [11], [12], [13], [14], silicone, Teflon, and nylon were utilized. Implantology has grown in importance, and bio-implants are frequently utilized in veterinary medicine, experimental surgery, histopathology, immunology, neurosurgery, cardiovascular surgery, ophthalmology, dentistry, orthopedics, and plastic and reconstructive surgery [15]. This is due to the availability of improved diagnostic tools and improvements in our knowledge of substances and surgical techniques (Fig. 1). For the fabrication of bioimplants, a variety of materials, including composites, ceramics, polymers, alloys, metals, were employed extensively. These implants interact with bones and tissues in various biological settings with extremely varied physic-chemical makeups, which is a challenging issue.

The biomaterial acceptance by the live body is the most important criterion for selecting. The implanted substance must not result in any negative side impacts, including toxicity, inflammation, or allergy, immediately after surgery or throughout recovery. In addition to fracture toughness and fatigue strength, biomaterials must have adequate mechanical strength to withstand the forces they are exposed to without breaking. A bioimplant must have extremely high wear and corrosion resistance in highly corrosive body environments and under different loading conditions. A biomaterial should last longer and not stop working before the individual dies. It is clear from this criterion that elderly patients must serve a min of 15 to 20 years, whereas younger patients must serve a min of more than 20 years. Three key elements greatly influence a biomaterial's or implant's success: i) the biomaterial's qualities (tribological, chemical, and mechanical); (ii) the implant's biocompatibility; and (iii) the recipient's health and the surgeon's skill. Despite working effectively in the human system [16], the presently utilized materials chosen based on the above characteristics often fail after 12 to 15 years, necessitating revision surgery to restore the system's performance. Their failure may be attributed to various factors, including production, biocompatibility, and surgical, chemical, mechanical, and tribological problems. The implant failure in corrosion has remained one of the most difficult clinical difficulties out of the complications.

The following is a comprehensive list of the many different applications that make use of biomaterials, which are used by medical professionals, academics, and bio-engineers [17]:

- implants in medicine include dental implants, implants for hearing loss, tendons, ligaments, prosthetic joints, grafts, stents, heart valves, and devices that stimulate nerves;
- techniques that hasten the recovery of human tissues, such as staples, clips, and sutures for the closure of wounds, as well as dressings that dissolve on their own;
- human tissue regeneration is accomplished by incorporating biomaterial supports or scaffolds, cells, and bioactive chemicals into the process. One example is a hydrogel that can regenerate bone, while another is a human bladder that was created in a lab;
- molecular probes and nanoparticles are capable of penetrating biological barriers and contributing to molecular-level imaging and treatment of cancer;
- biosensors that can determine the presence of a drug, as well as its concentration, and send that information. Instruments that measure blood glucose levels and sensors that track brain activity are two examples;
- systems for the delivery of pharmaceuticals that may either transport or administer drugs to a disease target.

A few instances of this would be drug-coated vascular stents and implanted chemotherapy wafers for patients with cancer.

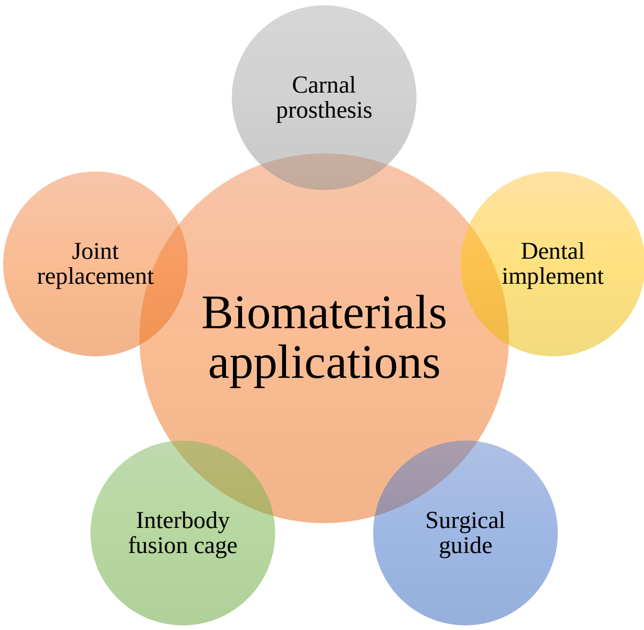

Fig. 1. - The biomaterials applications [18]

2. Types of biomaterials

2.1 Natural

Chitosan, bone, collagen, and starch are examples of natural materials, while ceramics, polymers, and metals are the raw ingredients that laboratories use to produce synthetic materials. With hybrid materials, both types of materials are included into the final product. Because of their one-of-a-kind mechanical, biological, chemical, and physical properties, these are the types of materials that are chosen to be used as biomaterials. These properties allow them to be used both within and outside of the human body. There are a variety of methods in which non-metallic and metallic biomaterials may be coupled, including ionically, covalently, and both ways. Cell therapy is an innovative approach that is still in the process of evolving as a strategy for healing a damaged heart. Tissue engineering may be used to make cardiac patches that have been modified and filled with bone marrow or mesenchymal stem cells to provide a repair that is as close to seeming natural as is humanly feasible. Research has been done in this field on both naturally occurring and artificially produced biomaterials.

Osteoinduction is a technique of bone healing that is gaining in popularity. This approach encourages the creation of bone by either changing the surface of the damaged location or infusing growth factors or bone marrow stem cells there. Without the need for invasive and uncomfortable surgery, this might speed up the process of bones healing. It's possible that mesenchymal stem cells are the parents of ligament fibroblasts. On the other hand, stem cells extracted from bone marrow have the potential to be of great use in the field of skin tissue engineering. It's possible that stem cells originating from fat might speed up the healing process in wounded tissue by boosting collagen production and the migration of skin fibroblasts.

2.2 Synthetic

2.2.1 *Bioceramics*

Bioceramics are frequently employed in a variety of medical procedures, including dental implants, bone transplants, artificial tendons, and hip replacements. Although black pyrolytic carbons are easy to produce and are extremely compatible with human tissues, they are not suitable for implant that is visible from the outside, like the ones employed in the mouth. This includes dental implants. Heart valves, ligaments, tendons, and composite implants are all examples of applications that need great tensile strength, and these materials are used in all of these areas. In addition, bioceramics are being investigated as a potential method for the delivery of medicines, genes (for use in gene therapy), and cancer therapies.

Bioceramics do not cause inflammation, are not carcinogenic, do not cause toxicity, and do not cause cancer. In addition to having a pleasing appearance, they have a high compressive strength and may be dyed to any color chosen. In addition to this, they are resistant to corrosion and generate excellent articulating surfaces. Nevertheless, they are limited in scope due to their brittleness, which renders them prone to shattering when subjected to significant force, as well as the difficulties associated with making them. They might be classified as inert, biodegradable, or bioactive based on their distinct characteristics. This section contains resorbable alumina [19], [20], zirconia [21], [22], carbons, glass ceramics, hydroxyapatites, aluminate, and calcium phosphate. In situations requiring electrical conductivity, inert metals of the third kind are often used. However, for suture materials, biodegradable options are preferable. When used in applications such as vascular stents, bioabsorbable materials offer a framework for healing processes that are both permanent and temporary at the same time. Tendons, ligaments, hips, artificial bones, teeth, and Knees are all examples of places that use resorbable materials. Resorbable materials are also used in orthopedic surgery (calcium aluminate) and dentistry (calcium phosphate). In areas where more bone is required, glass ceramics and several other materials that are either semi-inert or bioactive are applied.

On the other hand, hydroxyapatite is used to manufacture coatings, fillers, and bone grafts for metallic implants [23]. Inert bio-ceramics [24] such as zirconia and alumina are used in the construction of hip and dental implantation. Carbon may be found in bone scaffolds and heart valves, as well as in chemicals that stimulate cartilage regeneration. Silicon nitride is used in the fabrication of spinal fusion implant.

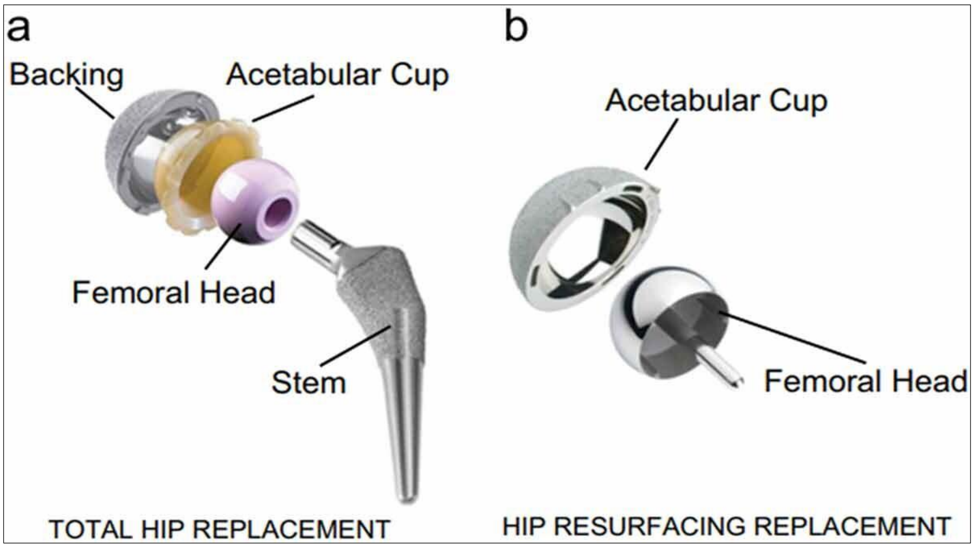

Fig. 2. - Hip implants can use bioceramics [25]

2.2.2 *Polymers*

Natural polymers, including collagen and starch, were accessible and degraded quickly, making them suited for use in biomaterials. Implants, single-use medical equipment, and dental and prosthetic components are increasingly often made utilizing synthetic polymers. Interestingly, materials like polyurethane (PU), polyethylene terephthalate

(PEEP), polymethyl methacrylate (PMMA), polyethylene (PE), and polypropylene (PP) were developed for non-medical uses in numerous biomedicine due to how closely their physical and mechanical properties resemble human body tissues.

PP may be utilized to make extra-corporeal membrane oxygenation (ECMO) membranes, hernia mesh, artificial blood vessel grafts, ECMO membranes, and suture material. PMMA and PEEP are also utilized to create vascular grafts for dental implants and bone types of cement. In addition to medication delivery mechanisms, PU is utilized to create wound dressings, breast implants, blood artery grafts, and patches for the heart muscle. PE is often utilized to create tubes for surgical implants, hip socket liners, and drainage for catheters.

Probes that potentially enhance positron emission tomography (PET) imaging are made from polymers. Polymer is utilized in Microelectron Mechanical Systems (MEMS), sometimes called lab-on-a-chip, which lowers the price of single-use devices. Because of their exceptional capacity for adsorption, polymers are increasingly being used in drug-eluting stents (DES). In order to strengthen the arterial wall, they might, among other things, be coated with anti-inflammatory drugs, anti-plaque steroids, or endothelial cells. Other possible coatings include: Gene-eluting stents are an example of a potential future breakthrough that might deliver a domestic production of RNA or DNA in order to inhibit certain genes that contribute to restenosis [26]. Polymers make it easy to create low-cost fibers, films, sheets, or synthetic latex. They are susceptible to pollution from outside the body because of their quick assimilation of protein and water [27]. Their sensitivity to heat and chemicals makes sterilizing more difficult. Another drawback is their propensity to release undesired substances into the fluids they touch with. They often wear out or break down as well. Eventually, due to their extreme misuse and delayed biodegradability, plastics have already been phased out.

2.2.3 Metals

Metals is frequently utilized in medical devices including pacemaker wires, vascular stents, and implants for hip and knee joints because it is very resistant to corrosion and has a high level of mechanical strength. When it comes to various applications, alloys and pure metals are both put to be used [28], [29]. As a protective coating, either bioceramics or very thin coatings of polymer are added to the metals. There are occasions when these qualities are innately incorporated into the surface. These biomaterials have a powerful memory, and it is not difficult to sterilize or create them according to the requirements. On the other hand, they could be inflexible and difficult to produce, both of which could make osseointegration more difficult. Even allergic reactions might possibly be triggered by them [30].

Most metallic biomaterials may be categorized as belonging to one of these three groups: alloys of cobalt and chromium; stainless steel; or pure titanium or its alloys. Titanium alloy is superior to the other two in terms of its low weight, strength, and resistance to corrosion in human tissues [31], [32]. These characteristics make titanium alloy a very useful material. Electrode leads, joint prostheses, and internal screws may all be fabricated using this material. Titanium, on the other hand, has a joint surface function that is inferior to that of other materials, which results in quick wear and increases the risk of osteoarthritis. Vanadium, which is often included in these alloys, is known to cause tissue damage over time. Along the same lines as aluminum, it may also have a role in the development of neurological diseases such as Alzheimer's disease (AD). Stainless steel has shown to be a useful material for a variety of medical applications, including bone plates, guide wires for endoscopic procedures, and blood vessel transplants. Cobalt-chromium alloys are used in the treatment of fractures and may be found in artificial heart valves, joint prostheses, dental implants, screws, and plates.

3. Metallic Implants

Surgical stainless steel 316 L (SS-316L) [33], cobalt-chromium (CoCr) alloys, and Titanium (Ti) alloys seem to be the bio-metallic inert metals that are the most often used for bone remodeling, angioplasty, and fracture repair [34]. Due to its better mechanical qualities and long-term stability under highly reactive in-vivo environments [34], this is a significant factor. While it is believed that these materials have a low rate of corrosion, it is essential to bear in mind that material deterioration may be caused by wear, friction, and a very hostile microenvironment [35]. This might result in the release of metallic ions that are undesirable. Inflammatory reactions, local tissue damage, including progressive osteolysis of adjacent tissues, systemic injury, and metal hypersensitivity are some of the potential outcomes of this. Osteolysis has the potential to affect the fixation of the implant as well as, in the long run, its loading and force transmission, which may lead to the failure of the implant, the need for corrective surgery, or issues following the treatment [36].

3.1 Challenges with Permanent Metals Implants

We have previously demonstrated that 3D printing can adequately support the load-bearing capacity of injured musculoskeletal tissue, better matching the anatomical specifics of each patient. Researchers have also discussed the controlled introduction of porosity to match the implant's Young's modulus and stiffness to the nearby cancellous and cortical bone (Table 1), thereby limiting stress shielding. This severe issue frequently leads to the refracture of the already weak bone. The stresses on that region of bone tissue directly affect bone development and density. Because titanium alloys are more than ten times stronger than cortical bone, utilizing them drastically reduces the stresses applied to the bone, leading to loss of density and deterioration [37]. These advantages may be achieved while maintaining strong compressive resistance and adequate compressive strengths and the added advantage of better osseointegration.

Hard-tissue replacement implies that the bioceramic device will be used for load-bearing applications. Although it is desirable to have a device with a sufficient porosity for the surrounding tissue to infiltrate and attach to the device, the most important and immediate property is the strength of the device. In order to accomplish this, one must manufacture a bioceramic implant with a density and strength sufficient to mimic that of bone. However, if the bioceramic part is significantly stronger than the surrounding bone, one runs into the common problem seen with metals called stress shielding. The density of the bioceramic greatly determines its overall strength. As the density increases so does the overall strength of the bioceramic. Some of the techniques used to manufacture dense bioceramics are injection molding, gel casting, bicontinuous microemulsion, inverse microemulsion, emulsion, and additives [38].

Table 1. The differences between the mechanical characteristics of metal implants with bone tissue [39], [40]

Tissue/Material	Modulus of Young (GPa)	Yield Strength (MPa)	Compression Strength (MPa)	Tensile Strength (MPa)
Cortical bone	7–30		(1–2.3) x10^2	(1.64–2.4) x10^2
Cancellous bone	0.01–3.0		2–12	
Ti_6Al_4V (cast)	1.14 x10^2	(7.6–8.8)x10^2		(8.95–9.30) x10^2
Ti_6Al_4V (wrought)	1.14 x10^2	(8.27–11.03) x10^2	(8.96–11.72) x10^2	(8.6–9.65) x10^2
SS-316L	1.93 x10^2	(1.7–3.1) x10^2	480–620	(5.4–10) x10^2
CoCrMo Alloy	2.4 x10^2	(5–15)x10^2		(9–15.4) x10^2
Mg (99.9%, cast)	41	21	40	87
Mg (99.9%, wrought)	41	1 x10^2	(1–1.4) x10^2	1.8 x10^2
Hydroxyapatite	50	6.91 x10^2	9.17 x10^2	10.2

On the other hand, inert metal scaffolds could not be easily filled in situ with bioactive chemicals or cells, which partly restricts their application for full tissue regeneration. This is in contrast to biodegradable ceramic and polymer [41]. Consequently, controlling surface chemistry necessitates post-processing, including functionalizing the surfaces with pharmaceutically relevant biomolecules, including paracetamol [42], coupled onto phosphonic acid-based self-assembled monolayers.

Moreover, there is a possibility that the leaching of metallic ions from SS, Ti, and Co-Cr and Ti alloys [43] into the peri-implant milieu may rise due to the insertion of interconnected pores, which considerably increases the surface-to-volume proportion. Since surface oxide coatings are recognized to restrict ion release in-vivo, this might be especially important once utilized in situations with low levels of dissolved oxygen [44]. The presence of proteins, cells, and inorganic ions in bodily fluids may speed up ion release even more. Worrying and stress-related wear may encourage the production of metallic ions and the elimination of the oxide. The interactions between anions, water molecules, and highly reactive ions might also be influenced by the inorganic salts, oxides, hydroxides, and other chemicals that emerge from these reactions. Sarcoma might form because of ions' interactions with host cells.

3.2 Biodegradable Biometals

When full tissue regeneration is anticipated, utilizing biodegradable metals instead of permanent metallic implants may result in considerably superior methods of fracture fixing. For cardiovascular and orthopedic uses, zinc (Zn) [22], iron (Fe), and magnesium (Mg) alloys seem to be currently the best investigated biodegradable metals because they provide good in-vivo biocompatibility, a controlled degradation profile, and enough mechanical strength to support bone throughout the regeneration process. Bioresorbable polymers, such as polylactic-glycolic acid (PLGA), polyglycolide (PGA), or copolymer polylactide (PLA), are brittle and might not be appropriate for applications in which significant forces have been applied to the implant. In contrast, bioresorbable metals exhibit superior mechanical behavior [37], [45]. In addition, unlike Mg, Fe, and Zi, whose biodegradation byproducts are readily metabolized by the host cells, polymer breakdown byproducts may cause necrosis and inflammatory tissue reactions [39].

3.3 Toxicity

A Biomaterial should carry out its intended task inside a live organism without harming other tissues and organs. Biomaterials should be non-toxic to avoid unintended interactions with organs and tissues. The compounds that are released from a biomaterial when it is in-vivo are considered to be poisonous. A biomaterial should not release any substances into the environment unless that is what it is designed to accomplish. Nontoxicity refers to a biomaterial's lack of pyrogenicity, allergenicity, carcinogenicity, compatibility with blood, and inflammogenicity [46]. A biomaterial may be created with toxicity for a specific purpose. For instance, hazardous biomaterials are investigated during cancer immunotherapy testing, both in vivo and in vitro, and toxic biomaterials are utilized to manipulate and control cancer cells [47]. According to a recent study: "Advanced nano biomaterials including liposomes, polymers, and silica are essential for the transport of immunomodulators and pharmaceuticals. These nano biomaterials-based delivery methods have the potential to concurrently lessen harmful side effects while successfully promoting antitumor immune responses [48]." This illustrates how a biomaterial's biocompatibility may be changed to generate any desired function.

4. Hydroxyapatite

A common bioceramic utilized as a biomaterial for bone replacement is hydroxyapatite (HA), which is the calcium phosphate with the chemical formula $Ca_{10}(PO_4)_6(OH)_2$. HA has many applications, such as bone fillers, scaffolds for bone tissue creation, implant coatings, soft tissue healing, and drug delivery systems [49]. It is also intriguing due to its biocompatibilities, osteoconductivity, non-inflammatory qualities, and mechanical properties. About 60–70% of the inorganic material in bone tissue is hydroxyapatite [50]. According to Figure 3, the calcium phosphate compound family is made up of molecules with the molecular formula $Ca_{10}(PO_4)_6(OH)_2$, which are mostly made up of the elements phosphorus and calcium.

Because of its bio-mimicking qualities, this bioceramic is compatible with natural bone. For the manufacture of HA, several synthetic approaches have been widely described [51]. Although several synthetic techniques have been devised to produce HA with certain properties, it is still difficult since harmful intermediate intermediates might arise. The sol-gel technique, hydrothermal reaction, co-precipitation reaction, and mechano-chemical approaches may all be utilized to synthesize HA [52].

Fig. 3. - HAp-Coated Femoral Stem of Hip Surgery Implants [53]

4.1 Crystal Structure of HAP

With the chemical formula $Ca_{10}(PO_4)_6(OH)_2$, hydroxyapatite (HAP) seems to have a crystalline hexagon structure. Hydroxyapatite nanoparticles (nano-HAP) have two different binding sites. For instance, nano-HAP contains positively charged calcium cations (Ca^{2+}) on the sides and negative charges phosphate anions (PO_4^{3-}) at both ends, as seen in Figure 4. Human bones need HAP since they are made up of 30percent collagen, 70percent low-crystalline or amorphous apatite, and 5% bone marrow cells [54].

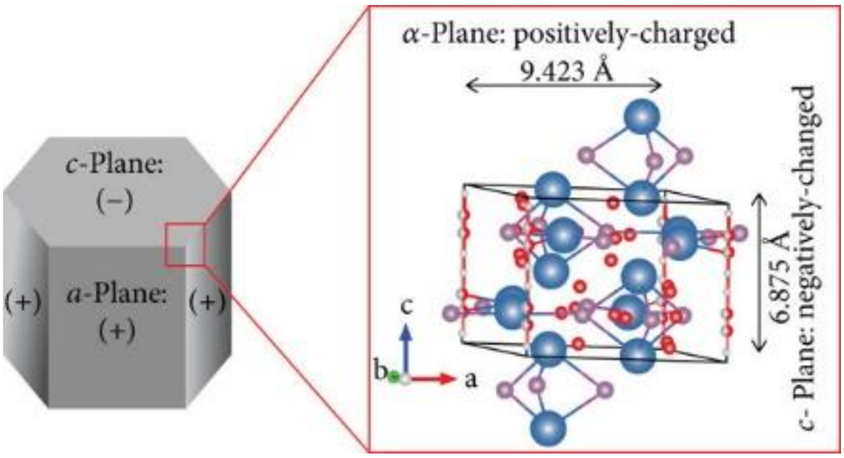

Fig.4. - The Crystalline Structure of HAP [55]

4.2 Properties and Advantages of HAP

The Magnitudes provided for HAP's physical characteristics, its mechanical and physical qualities, and some of its benefits are demonstrated in Table 2. The fracture toughness, tensile strength, and bending strength of an extremely dense HAP. The ranges of HAP's tensile strength, compressive strength, and bending Magnitudes are 38-300 MPa, 120-150 MPa, and 38-250 MPa, respectively. Numerous elements, including the random strength distribution and the impacts of ion impurities, grain size, and residual micro-porosity, all contribute to the huge scatter. The strength rises with increasing Ca/P proportion, peaks at Ca/P of 1.67, and then rapidly falls to Ca/P less than 1.67. In dense HAP, Young's modulus ranges from 35 to 120 GPa based on impurities and residual porosity. Because of grain boundary slip, dense HAP ceramics demonstrate super-plasticity at temperatures between 1000 and 1100 degrees centigrade [56].

Bone's mechanical characteristics are significantly influenced by humidity, the kind and direction of the applied force, and the bone's position inside the body. When it comes to direct bonding with bones, osteoconductivity, bioactivity, and biocompatibility, HAP demonstrates important features as a biomaterial. However, its mechanical characteristics were subpar, as demonstrated by its low fracture toughness (K_{IC} is 0.7 to 1.2 MPa m0.5). As a result, this drastically limits its scope of use in orthopedics. Nevertheless, it is still a fantastic choice for covering metal prostheses or fixing tiny bone flaws [32], [56].

Table 2. Principal characteristics of HAP [56]

Characteristics	Magnitude	Characteristics	Magnitude
Density	3.16 g/cm^3	Poisson's proportion	0.27
Decomposition temp	Less than 1000 degree centigrade	Fracture Energy	2.3-20 J/m^2
Dielectric constant	7.40-10.47	Fracture toughness	0.7-1.2MPa.m$^{0.5}$ (reduction in porosity)
Thermal conductivity	0.013 W/cm.K	Fracture hardness	3-7 GPa (dense)
Melting point	1614 degree centigrade	Bio-compatibility	High
Tensile strength	38-300MPa (dense) ~3MPa (porous)	Bio-degradations	Low
Bending strength	38-250 MPa (dense) 2-11 MPa (porous)	Bioactivity	High
Compressive strength	120-900 MPa (dense) 2-100 MPa (porous)	Osteo-conduction	High
Young's elastic modulus	35-120 GPa	-----	-----

Due to its advantageous biological features, such as osteoconduction, bioactivity, bioaffinity, biocompatibility [57], osteoinduction [58], and osteointegration [59], HAP bioceramics have found widespread use as artificial bone replacements (in certain conditions). Because HAP only possesses calcium and phosphate ions, no adverse reports of either local or systemic toxicity have been from any studies conducted. When the implant is placed, the newly created bone bonds directly to the HAP via a layer of carbonated calcium-deficient apatite that is located at the bone-implant contact [60], [61]. The HAP surface allows for osteoblastic cell adhesion, proliferation, and differentiation. As a result, new bone is produced by creeping substitution from the live bone that is next to the defect. HAP scaffolds have the ability to bind to and concentrate bone morphogenetic proteins (BMPs) in vivo, making them suitable candidates for use as delivery vehicles for cytokines [62].

A vital component of the process of regeneration is the interaction of apatite with the biological tissues of the body. Changes in manufacturing technique, size, the nature of materials, and other factors are causing conceptual shifts in mineralization and tissue contact. These shifts are bringing about new ways of thinking about these processes. Scaffolding has been used to initiate the earliest stages of bone regeneration. Otto Herbert Schmitt is credited with first using the word "biomimetics" in the 1950s. This biological process causes the creation of highly ordered materials with hybrid composition. It starts by designing and synthesizing molecules that can self-organize spontaneously to higher-order structures [60]. This biological process also causes the production of highly ordered materials with hybrid composition.

The HAP's interactions with the tissues are very significant. Understanding the in vivo host reactions while dealing with HAP is essential. In general, the action mechanism of a biomaterial is regarded to be biocompatible, bioinert, biotolerant, and bioactive, and it also includes materials that are bioresorbable. These modifications in knowledge result from improvements in the characteristics and manufacturing technology, as well as a greater comprehension of how materials interact with the tissues. The most recent developments in nanotechnology have led to the creation of HAP in a more bioactive or bioresorbable form, leading to this field's cutting edge. Even if the foreign body is biocompatible, the tissue response to it will still create a capsule, resulting in the foreign entity being isolated. Bioinert materials will not demonstrate any beneficial interactions and will not release any hazardous elements. Encapsulation describes the measurement of the bioinert-ness of a substance, and the body or host tissue will separate such compounds via encapsulation [60].

4.2.1 *Disadvantages*

Because synthetic HAP has desirable qualities as a biomaterial, including osteoconductivity, bioactivity, and biocompatibility, this material has found widespread use as a replacement for bone, a covering for metallic implants, a scaffold for tissue engineering, and a carrier for the transport of drugs. For use in biomedical applications, HAP may be formulated into various forms, including coatings, cement, paste, granules, and dense and porous blocks [63]. One of the most significant drawbacks of HAP is its low strength, which makes it impossible to manufacture high load-bearing implants wholly out of HAP [64]. This is the case even though HAP has various beneficial properties. The nanocrystalline HAP found in bones and teeth is the primary structural component. Grafting with HAP is performed in sinus augmentation, ridge reconstruction, and bone defect repair procedures.

Brittleness, poor tensile strength, and fracture toughness are just some of the issues associated with HAP. Nevertheless, because of its weak mechanical qualities, hydroxyapatite cannot be employed in its bulk form for load-bearing applications, including orthopedics. Specifically, the material's fatigue properties are to blame for this limitation. When utilizing HAP as a delivery system, one of the most significant drawbacks is that the sintering process may lead to the particles' agglomeration, which, in the context of gene delivery, results in a reduction in the effectiveness of the delivery system's ability to transfect cells. Simple ultrasound-assisted precipitation with the addition of glycosaminoglycans was used in the research carried out by Han et al. [65], which resulted in the production of well-dispersed HAP nanoparticles.

Typical bursitis or tendinitis of the shoulder may be caused by the deposition of hydroxyapatite crystals in the tendons and bursae of the shoulder. The area above the greater trochanter is the second most prevalent place for the deposition of this substance [66]. Additionally, it may produce discomfort in the region of the wrist or elbow. Hydroxyapatite has been reported to deposit in soft tissues in several systemic disorders, including renal osteodystrophy, dermatomyositis, and scleroderma. This phenomenon has been seen. Nevertheless, individuals have lately appeared with hydroxyapatite deposition in many tendinous and soft tissue locations despite the absence of an underlying systemic illness [67].

The ineffective adhesion of HAP to the metallic surface is the primary source of worry throughout the process of applying HAP coatings. This is because the adhesive connection between the metallic load-bearing locations and the HAP layer is weak [68]. As a result of HAP's less-than-perfect crystalline structure, the HAP film connection on the metallic surface begins to weaken and abruptly breaks down [69]. Due to this failure, metallic ions are discharged into the bodily environment as the metal surface becomes exposed to the surrounding environment [70]. To improve the adherence of HAP films, surface modifying agents are necessary. These agents contribute to creating a durable coating atop the metallic surface, which helps achieve the desired goal. Because of its biocompatibility, HAP, the primary inorganic component of hard tissues (bones), has been used in various biomedical applications over the last half-century. On the other hand, research conducted in the past and published found that HAP has the characteristics of brittle ceramics that cannot resist the weight of a load [71].

4.3 HAP Preparation Methods

Techniques that are often used to manufacture HAP include, but are not limited to, the hydrothermal process, the precipitation technique, the solvothermal technique, the spontaneous combustion technique, the micro-emulsion technique, the ultrasonic synthesis technique, the bionic approach, and the solid-state reaction technique, which includes both the wet technique and the dry method. The hydrothermal technique, the solvent, the thermal technique, and the precipitation chemical technique [72] are the main techniques used by scientific research workers in recent years. These three procedures also have the most widespread application, the lowest cost, and the best HAP complete properties achieved. The HAP was produced by Chaudhari et al. [73] by the use of the following reaction:

$$10\mathrm{CaO} + \mathrm{K_2HPO_4} + 4\mathrm{H_2O} \rightarrow \mathrm{Ca_{10}(PO_4)_6(OH)_2} + 12\mathrm{KOH}$$

Some of the processes demand a high processing temperature, a significant investment in the necessary raw materials, and an intricate procedure for the actual synthesis. The chemical precipitation approach provides several benefits, including the capacity to create nanosized HAP powder in large quantities and with a high degree of purity, as well as simple equipment and a cheap cost. The primary properties of HAP, such as its Ca/P proportion, crystal size, and morphology, determine the particular applications that may be carried out with this material [74].

Many research investigations have shown that using high-power ultrasound during the wet-chemical synthesis process may increase hydroxyapatite levels [75]. Sono-synthesis, also known as ultrasonically aided synthesis, has shown to be an extremely effective method for the manufacture of nanostructured hydroxyapatite of a high grade [76]. The manufacturing of nanospheres with a core and a shell, as well as composites, is made possible through the ultrasonic approach, which results in the formation of nanocrystalline and changed hydroxyapatite particles [77].

A technique for synthesizing hydroxyapatite nanoparticles was created utilizing Ca and P sources from a chemical reaction of 99.0% $Ca(OH)_2$ and 85 percent H_3PO_4. This approach aimed to decrease or eliminate hazardous emissions, often the results of most synthetic methods used to make hydroxyapatite. Because these chemicals do not leave behind any leftover hazardous anions, there was no requirement for extra cleaning [78].

4.4 Applications of HAP

The interaction between protein molecules and inorganic materials is of pivotal interest in industry, biochemistry, biosensors, biomineralization, and biomaterials. As mentioned earlier, HAP crystals have two binding sites, for example, calcium cations (Ca^{2+}) and phosphate anions (PO_4^{3-}), owing to their chemical composition and specific orientation. A depiction of the most significant applications is placed below [79], [80], [81]:

4.4.1 *HAP as a Coating Material*

Designing a bone-implanting material that may be utilized to repair a bone defect and rebuild the bone is essential for restoring a damaged bone. The process of creating appropriate materials for bone implants is not without its challenges. For example, the first challenge often arises when synchronizing the implanting material and bone throughout the bone remodeling process (resorption and reparative). The implant substance should not negatively impact the immune system. Nevertheless, the materials utilized for implanting sometimes resorb prior to osteogenesis, making them useless. Other times, infections brought on by the implants cause illness and even death, which is exceedingly expensive for the patient and society. Due to these factors, a method for creating acceptable bone tissue regenerating implantation must be developed. Recently, a method of enhancing the bioactivity and compatibility of the implanting material included coating an implant with a biocompatible and bioactive substance. HAP is the most often utilized coating agent. Additionally, applying HAP to the surfaces of implanting substances (such as titanium alloys) improves osteointegration with bone [80], [82].

4.4.2 *HA P as a Drug Delivery Carrier*

The "P" and "Ca" locations on HAP and its rough surface make it easier for proteins to attach to them during mineralization. The interactions of amino acids with HAP have demonstrated the significance of the rough surface. HAP nanorods and nanoparticles are utilized as a medium for the transport of different medicines and proteins (growth factors). For instance, the drug-loaded/modified HAP nanorods/nanoparticles have been combined with a polymeric solution to deliver the drug-loaded HAP to the target region [83].

4.4.3HAP-Based Composite Materials

Most polymeric composites employ HAP as an enforcer to give the composite material mechanical strength and bioactivity. There has been much written on HAP's role in bone tissue regeneration. By grafting proteins and medications onto the surface of HAP, scientists have created HAP/polymer scaffolds that may be utilized to distribute pharmaceuticals, promote bone tissue repair, and treat conditions like osteoporosis. [23], [84].

4.4.4 HAP-Based Ceramics in Bone Tissue Regeneration

The use of HAP in pristine, composite, or ceramic types for the regeneration of bone tissue was already made possible by the resemblance between HAP and the inorganic cement of real bone. The chosen materials for an implantation must-have qualities comparable to those of natural bone to accomplish the intended aim (safe and acceptable bone regeneration). Several HAP bio-ceramics were developed that resemble real bone. Nevertheless, as was already said, the implantation should provide a setting similar to the natural one. For instance, in addition to other things, the implant must be mechanically strong near the bone [23], [85].

In addition to being an implantable material, HAP has been employed in cancer treatment, gene delivery, and bio-imaging. Gene therapy has long been recognized as holding promise for the treatment of a variety of incurable diseases by replacing the missing or damaged genes, catalyzing the destruction of cancer cells, usually causing the cancer cells to transform back into normal tissue, encouraging the growth of new tissue, or stimulating regeneration of the damaged tissue [86]. Nevertheless, largely due to the absence of a reliable and capable vehicle for the delivery of genes, this promise remains unmet [23], [85].

5. Methodology

The current review presents the behavior of pure implements and the improvements in these implements after applying HAP [87]

6. Results and discussion

To increase the biocompatibility of metal dental implants and bone osteointegration, Fathi and Azam [87] developed and manufactured a unique surface composite coating on metal substrate. In order to create a unique double-layer hydroxyapatite/tantalum (HAP/Ta) coating, SS-316L was employed as the metallic substrate. Physical vapor deposition was utilized to create the tantalum coating, while plasma spraying was utilized to apply the HAP layer. X-ray diffraction (XRD) and scan electron microscopy (SEM) methods were utilized to study the coating characteristics. In order to assess the corrosion behavior of the coated and uncoated samples as a sign of biocompatibility, electrochemical polarisation experiments have been carried out in two kinds of physiological solutions at 37±1degree centigrade. According to the findings, corrosion current density significantly decreased for specimens coated with HAP/Ta and was substantially lower than the value measured for SS-316L that had not been coated. The innovative double-layer HAP/Ta composite coating may enhance the SS-316L dental implant's biocompatibility by reducing corrosion.

Figure 5 depicts the HAP/Ta composite coating on SS-316L XRD Pattern. There have been many sharp peaks and a low backdrop in the plot of intensity against 2θ, which is a sign of the HAP/Ta composite coating's crystalline structure HAP coating.

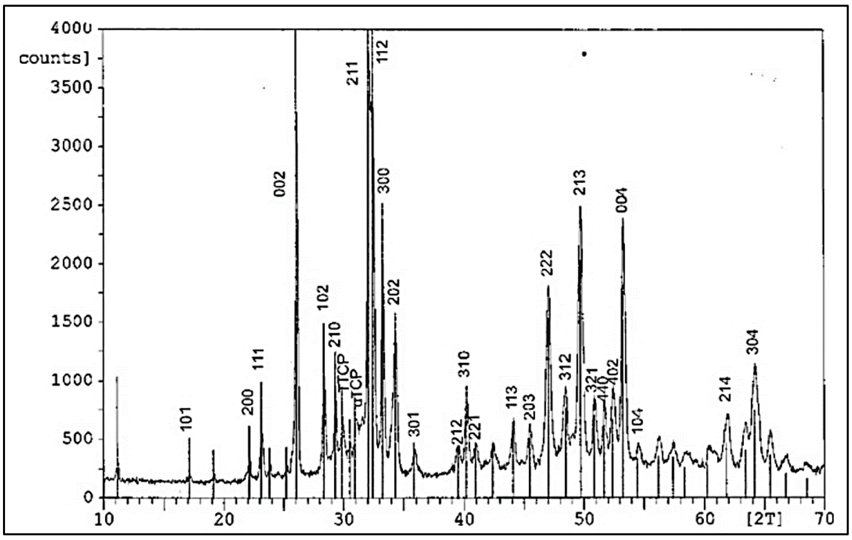

Fig.5. - XRD pattern of the composite coating on SS-316L with HAP/Ta [87]

Figure 6 displays the potentiodynamic polarisation curves of the SS in the normal saline solution with and without the HAP/Ta composite coating. Figure 7 demonstrates the parallel curves that Ringer's solution produced. Since the retrieved data from these curves were the closest to the average magnitude of the present densities of every set of samples, they were chosen. The corrosion current density of HAP/Ta coated SS-316L in Ringer's, and normal saline solutions are reduced due to the HAP/Ta coating's good impact on the metal substrate's resistance to corrosion. Additionally, it can be demonstrated that the uncoated SS-316L has a lower potential for pitting corrosion than the HAP/Ta coated SS-316L [curves (a) and (b), respectively]; this suggests that the corrosion will be inhibited at a certain potential by utilizing the HAP/Ta coating. As a result, utilizing the innovative HAP/Ta coating would lower the current density of corrosion and increase the propensity for pitting corrosion compared to SS-316L that is not coated. The innovative HAP/Ta coating's greater pitting corrosion potential demonstrates that it is efficient at preventing corrosion[87].

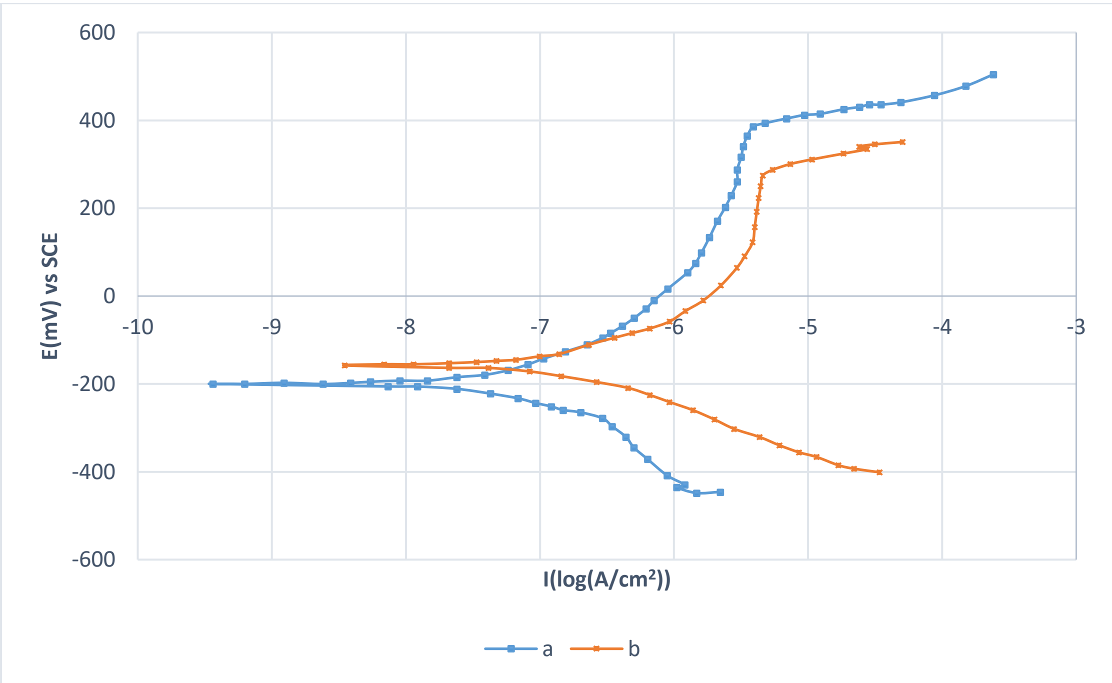

Fig. 6. - Polarization curve: (a) uncoated SS-316L,(b) coated by HAP/Ta in normal saline solution (0.9 wt.% NaCl) [87]

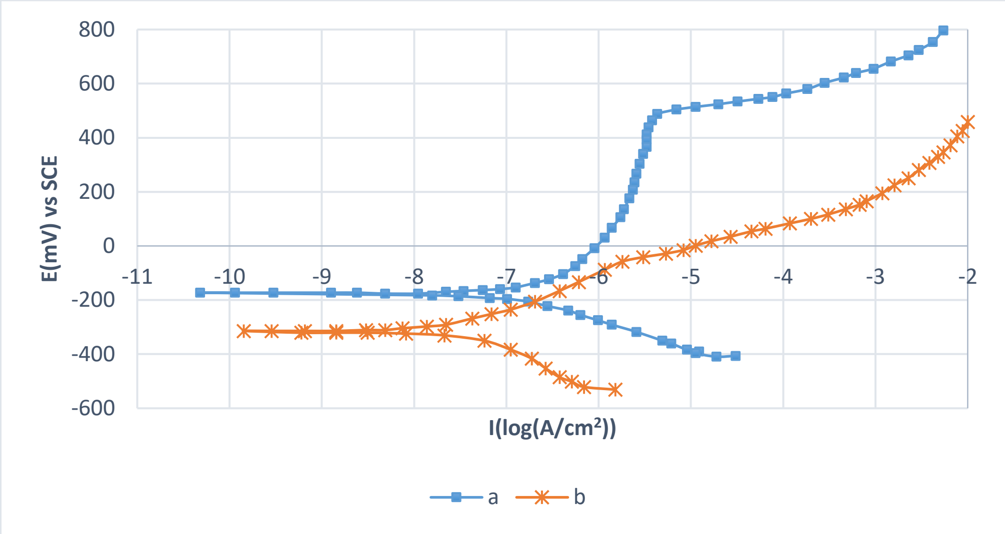

Fig. 7. - Polarization curve: (a) uncoated SS-316L,(b) coated by HAP/Ta in Ringer's solution [87]

Gnanavel et al. [88] utilized the pulsed laser deposition approach to deposit hydroxyapatite (HAP) ceramics on Ti-6Al-4V and SS-316L. XRD, scanning electron microscopy with energy-dispersive spectroscopy (EDS), and atomic microscopy were utilized to evaluate the coated thin film. Correction investigations on uncoated and coated samples were conducted utilizing potentiodynamic polarisation tests in a simulated bodily fluid (Hanks' solution). Their bioactivity was assessed by submerging the HAP-coated specimens in Ti-6Al-4V and SS-316L for nine days in simulated bodily fluid. The existence of HAP was verified by XRD and EDS investigations. According to the corrosion investigations, treated specimens exhibit excellent resistance to corrosion than substrates made of SS-316L and Ti-6Al-4V. The HAP-coated substrate bioactivity was indicated by the development of apatite on treated specimens. Ti-6Al-4V substrates with HAP coating provide greater corrosion resistance than those made of SS-316L.

The XRD pattern's crystalline phase of Ti-6Al-4V and SS-316L has been examined. CuK radiation ($\lambda = 0.1548$ nm) has been utilized, and the specimens have been scanned at a rate of 0.5°/min from 20° to 70°. XRD analysis was utilized to analyze the phases that developed on the surfaces of HAP-coated Ti-6Al-4V and SS-316L, and the results are demonstrated in Fig. 8. The SS-316L with calcium phosphate (Ca/P) XRD forms are consistent with JCPDS#00-003-0429. Calcium phosphate is present, as demonstrated by the peaks at 27.02°, 20.38°, 24.33°, and 39.39°. Furthermore, the XRD pattern of the Ti-6Al-4V of Ca/P are consistent with JCPDS#01-086-1585. The peaks at 44.25°, 45.21°, 48.63°, and 60.20° demonstrate that calcium phosphate is present. The coating contains calcium phosphate, which resembles the composition of bone and has the extra benefit of promoting osseointegration.

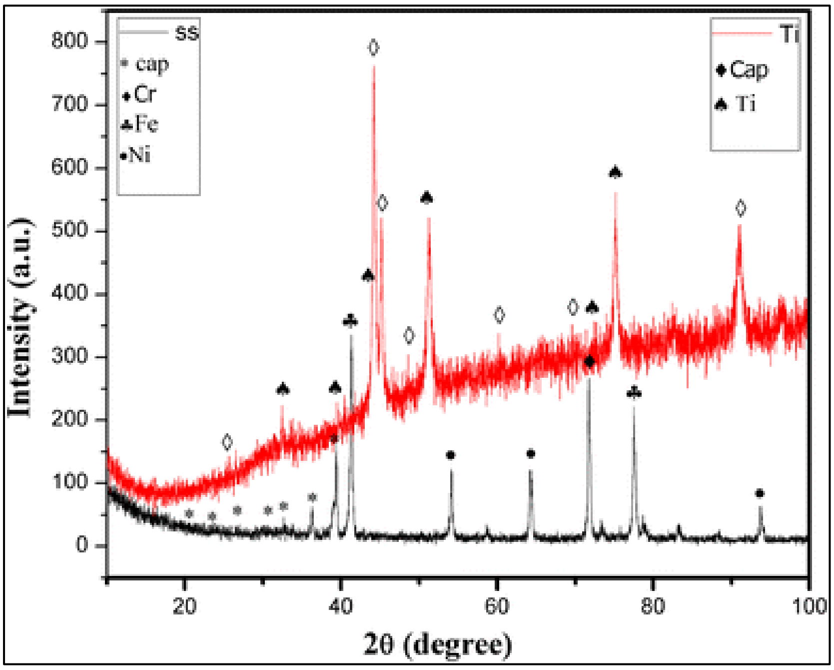

Fig.8. - XRD pattern of Ti–6Al–4V alloy and SS-316L coated by HAP [88]

In Hanks' solution (pH ranges from 7.2 to 7.6), the potentiodynamic polarisation curves of the material and HAP-coated specimens (Ti-6Al-4V and SS-316L) are demonstrated. On specimens coated with SS-316L and Ti-6Al-4V, the Ecorr magnitudes changed to a more favorable magnitude. This finding concludes that, once compared to HAP-coated SS-316L, Ti-6Al-4V alloys have greater resistance to corrosion [89]. These findings demonstrated that the HAP-coated Ti-6Al-4V combination outperforms the SS-316L in corrosion resistance (Figure 9).

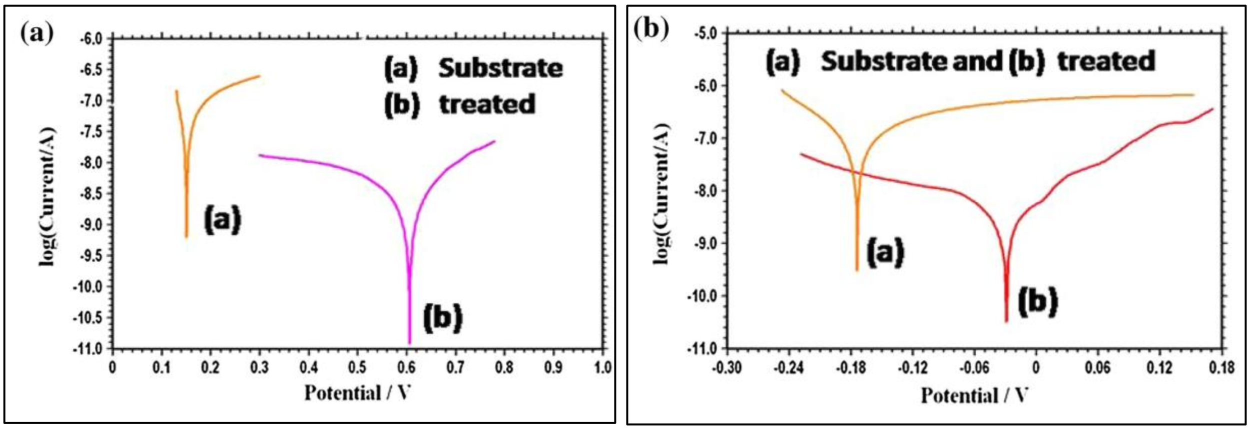

Fig. 9. - Potentiodynamic polarisation a) SS-316L, b) Ti–6Al–4V substrate before and after treatment by HAP [89]

Conclusion

Except for the calcium carbonate otoconia of the inner ear, HAP represents the chemical counterpart of biogenic apatite, the main constituent of all hard tissues in the human body because of the great degree of crystallographic and chemical similarity between the inorganic component of teeth and bone. It drew attention to itself in the early stages of biomaterials science due to the biocompatibility predicted from this similarity. Additionally, HAP has a benefit over biocompatible but bioinert ceramics like titania, alumina, and silica because of its bioactivity, which enables it to interact more closely with the cells and tissues in the biological environment. Additionally, several very straightforward synthesis techniques for HAP were developed, enabling the researchers to create particles with precisely defined shapes and sizes. Moreover, utilizing the powerful physisorption capacity of the polyvalent ions that make up the surface of the HAP particle, functionalization and surface modification of HAP may be accomplished by similarly straightforward, noncovalent interactions.

Thanks to all these benefits, HAP is a good option for various biomedical applications in tissue engineering, medical implants, medication delivery, gene therapy, and bioimaging. Although utilizing HAP has many advantages, there are certain drawbacks and side effects that must be carefully considered before a particular application is chosen. For instance, HAP particles' osteoconductivity is necessary for tissue engineering scaffolds and medical implants, yet this property is insufficient to provide a useful and effective tissue replacement. In certain tissues, it is necessary to create prostheses and scaffolds that can withstand high loads and cyclic stresses. To get around this problem, HAP must be combined with polymers or other kinds of nanoparticles to improve its brittleness and poor fracture toughness. Most of the suggested solutions are still in the research stage, and the consensus is that additional study is necessary before the therapeutic objectives are reached.

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