Review

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Studies on Corrosion Behavior and Biomedical Applications of Titanium-based materials: A Comprehensive Review

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Abstract: Titanium and its alloys offer numerous advantages in diverse industrial applications, but the rising demand necessitates a comprehensive understanding and prevention of corrosion failure. Corrosion, caused by electrochemical reactions with the environment, can compromise the appearance, functionality, and safety of these materials. To address this, it is crucial to investigate factors influencing their corrosion behavior, including composition, microstructure, surface treatment, environmental conditions, and mechanical loading. Beyond industrial use, titanium's biocompatibility, corrosion resistance, and mechanical properties make it widely employed in biomedical applications. Its ability to form complexes with ligands enhances biological interactions, showing promise in anticancer agents, bone implants, drug delivery, biosensors, and bioimaging probes. This review aims to provide insights into corrosion mechanisms, prevention methods for titanium and its alloys in industrial settings, and recent advancements in their diverse biological applications.

Keywords: Ti Corrosion; complexes; biological applications; Schiff-bases

1. Introduction

Owing to their preferable qualities of excessive strength to mass proportion, wonderful biocompatible features, as well exceptional corroding resistant effects, titanium (Ti) alloys were extensively utilized in maritime, biomechanics, salt removing of seawater, offshore drilling, as well as chemicals productions [1-5]. A recently discovered close to Ti alloy, Ti-6Al-3Nb-2Zr-1Mo (Ti80), stands out among the major Ti alloys since it is primarily employed as an engineering constructional substance in oceanic demands, while every component's assistance life relies completely on its corroding resistance [6-9]. Ti alloys' greater corroding resistance is almost owing to a passive coating that spontaneously formed on the exterior side [10-12]. But, existing fluorides (F^-) in saltwater, even though tiny doses, hardly destroy inactive protecting coat [13-17] after that guide to corrode Ti substrate completely [18-20]. Due to the remarkable discharge of industrial wastewater containing F^- in the last few years, as well as the dissolution of the exhaust gases from the coastal thermal power plant that contained some F^-, etc. [20]. The service life of a Ti80 component has been extremely hampered by the F^- content in offshore water which rises.

Metals that are easily passivated include titanium and its alloys. With good corrosion resistance and biocompatibility in oxidizing, neutral, and slightly reducing conditions, the surface passivation coating is quite stable. In both human and animal studies, the tissues around titanium implants have been observed to exhibit blackening phenomena. The corrosive disintegration of titanium and its alloys, which were concentrated in the surrounding tissue and degenerating cells, is thought to be the cause of this impact. Unwanted compounds produced by corrosion can enter the body and seriously injure people (e.g., tissue poisoning or cell distortion). Additionally, it results in implant flaws including loosening and early breakage. As such, concerns about titanium alloy corrosion have drawn attention from the scholarly community. Although titanium and its alloys are known for having very high corrosion resistance, titanium can experience pitting corrosion under certain circumstances. The corrosion resistance of titanium and titanium alloy welds is equivalent to that of the base metal in most situations. However, titanium welds are susceptible to more rapid corrosion attacks than base metal when exposed to marginal or active circumstances. In basic terms, researching titanium's ability to withstand corrosion means researching the characteristics of the oxide deposit. The oxide covering titanium is extremely robust and resistant to most chemicals, except high-concentration reducing acids like hydrofluoric acid. Because titanium has a significant affinity for oxygen, it can virtually instantly repair this layer in any environment that has even a small amount of moisture or oxygen. This study aims to discuss a variety of previous investigations on the corrosion of titanium and its alloys in different media, as well as bioapplications and medical dental uses of titanium alloys and complexes, oxides, alkoxides, and Schiff bases [21].

2. Bio applications of Ti alloys

Scientists have utilized biomaterials to recognize diseases, return and restore tissues as well as organs, and restore biological systems. At the end of the 20th century, the evaluation of biological substances recognized spectacular conversion resulted in serious advancements that the general people could feel. This should motivate more studies into these materials. Titanium is one of the elements whose application in biological materials has received considerable research [22]. The explanation for this is that titanium has strong mechanical features [23] besides, high corroding resistance. One of titanium's mechanical features that must be focused on is its tiny particular weight as well importance for implants [23, 24].

Ti-6Al-4V, a kind of utilized alloyed titanium specimen, is firstly made of titanium with 6% aluminum and 4% vanadium. However, it was denoted utilizing these alloys in implants will have negative healthiness outcomes because of the probability of vanadium or aluminum ions being liberated into the anatomy [25]. Besides, these alloys have to some extent unfavorable mechanistic features, like the elevated ratio of flexibility [26]. Moreover, aluminum and vanadium involve allergic reactions just by existing [27] as well aluminum could retard bone mineralization in some cases [28]. Table 1 indicates a comparison between biomedical applications of Ti alloys and Ti complexes.

Table 1: Comparison between biomedical applications of Ti alloys and Ti complexes.

Titanium alloys	**Titanium complexes**
1-Titanium alloys are considered to be the most attractive metallic materials for biomedical applications. Ti-6Al-4V has long been favored for biomedical applications. However, for permanent implant applications, the alloy has a possible toxic effect resulting from released vanadium and aluminum. For this reason, vanadium- and aluminum-free alloys have been introduced for implant applications [29].	1. Bioimaging Probes: Titanium complexes are explored as contrast agents in bioimaging techniques, including MRI and fluorescence imaging, offering improved resolution and detection of biological structures.
2-Trauma devices, such as bone plates, screws, and intramedullary nails, require materials that can withstand the mechanical stresses imparted on them within the human body, which can be superior to those faced by orthopedic devices.	2. Biosensors: Titanium complexes can be integrated into biosensors for detecting specific biomolecules. The unique electronic and catalytic properties of these complexes enhance the sensitivity and selectivity of biosensing devices
3-Spinal implants are somewhat in the between arthroprosthetic and trauma devices, and their required properties can vary greatly depending on the specific application. Titanium pedicle screws are used to stabilize and immobilize the spine: they are inserted into the vertebral pedicles and serve as anchors for other spinal implant components	3. Drug Delivery Systems: Titanium complexes are being investigated for drug delivery applications. Their ability to form stable complexes with drugs allows for controlled release, improving the efficiency and specificity of drug delivery to targeted tissues
4-Titanium and its alloys play a crucial role in the development of cardiovascular devices, contributing to improved patient outcomes in the treatment of various heart and vascular conditions. These alloys possess properties that make them well-suited for devices aiming to restore normal blood flow, enhance cardiac function, and provide structural support.	4. Anticancer Agents: Titanium complexes have shown promise as potential anticancer agents. Their ability to interact with biological macromolecules and exhibit cytotoxic effects on cancer cells make them subjects of research in cancer therapy.
5-Titanium is not commonly used as the primary material for soft-tissue implants, which are typically made from materials that are more compatible with the characteristics and flexibility of soft tissues, such as collagen, silk, and various polymers. Soft-tissue implants are designed to mimic the properties of natural soft tissues, such as skin, fat, and muscle, and they are often used for reconstructive or cosmetic surgery [30].	5. Bone Implants: Titanium complexes are explored for enhancing bone regeneration and integration in implants. Their interactions with biological macromolecules contribute to improved biocompatibility and bone tissue response.

In summary, both titanium alloys and titanium complexes play crucial roles in various biomedical applications, ranging from structural implants to advanced diagnostic and therapeutic tools. Their biocompatibility, corrosion resistance, and versatility make them valuable materials in the field of medicine and healthcare. Ongoing research continues to explore novel applications and optimize the performance of titanium-based materials in the biomedical context.

3. Why do Ti alloys exhibit good corrosion resistance in most environments?

Titanium alloys particularly have densities of around 4.5 g cm^{-3}, which is only about 60% of steel's density. As a result of having substantially greater strength than other metals, alloyed titanium specimens have elevated particular strength (strength/density) of all metal structural materials. In comparison to most materials, titanium has -1.63 V against SHE. However, because of the high affinity across titanium and oxygen, a close-packed inactive layer with a width ranging from a few nanometers to ten nanometers is established onto the exterior side of alloyed titanium specimens in an oxygenated medium (Lu et al. 2008), meaning that the corroding potential of Ti alloys is positive at real assistance circumstances. By hindering the transfer of reactive species, this close-packed passive coating lowers the exterior side active dissolving regions and reduces the corroding rate of titanium alloys (Shukla et al. 2005). Soluble Ti ions swiftly reacted with oxygen resulting in a recent oxide layer, isolating metal from the corroding medium and reestablishing the passive film's self-healing property while the passive layer is damaged as well as base metal inside airy corroding solutions. Therefore, the usage of titanium alloys is widespread in critical industries like shipbuilding, aviation, petrochemicals, and more because they display good corroding resistance in a variety of situations. However, as applications grow, the corrosion issues with titanium alloys become more manifested. If the passive coating is damaged while alloyed titanium specimens were employed to serious acids responsible for reduction or low oxygen grads circumstances, mainly when temperatures are elevated, innate recovery could be difficult and corroding could be the result. (Dai et al. 2016 a,b). The corroding behavior of alloyed titanium specimens, mainly localized corroding, was thoroughly examined in the past few decades in light of the aforementioned circumstances. Galvanic corroding, pitting corroding, crevice corroding, hydrogen-induced cracking, stress corroding crack, microbiological corroding, corroding wear as well corroding fatigue, are principal corroding issues that titanium alloys encounter during the application process. Temperature, pressure, and corrosive medium all have particular effects on the corroding process. Resistance against corrosion is relied on base metal's microstructure, chemical composition, and passive film's compactness. In addition, several application domains for titanium alloys have various corrosion issues. Corroding types, influencing effects, as well corroding issues utilized inside inquires will be discussed in this research **[31-34].**

4. Main Forms of Corrosion of Ti

A thin titanium dioxide coating, ranging in thickness from 1.5 to 10 nm, is created when titanium, a highly active metal, is susceptible to airy conditions. The remarkable corrosion resistance of titanium is due to these oxides, which are typically close-packed, adhering exterior side, as well as chemically steady in several conditions **[32, 33].** Despite this, titanium corrodes in hostile situations. The following corrosion processes can affect titanium: fretting corrosion, erosion, stress-corrosion cracking, hydrogen embrittlement, crevice and pitting, and uniform corroding. Distinct alloys comprising nickel, palladium, and molybdenum were found to address those possible problems. Those metals encourage cathodic processes, aiding metal to be passivated. However involving those metals had high cost. TiO_2's natural thickness may also be increased through surface treatments **[34].** The TiO_2 layer has been thought to be tuned using oxidation processes, notably anodization, to raise its width as well as produce a greatly amorphous phase, with a conclusive target of raising pure titanium's resistance against corroding to the extent of high-cost alloyed specimens. Other approaches include ion implantation, thermal oxidation, and chemical oxidation. In this review, the types of corrosion that titanium experiences in certain typical situations will be covered.

Titanium, like any other metal, is subject to corrosion in some environments. The types of corrosion that have been observed on titanium may be classified under the general headings: general corrosion, crevice corrosion, stress corrosion cracking, anodic breakdown pitting, hydriding, and galvanic corrosion. In any contemplated application of titanium, its susceptibility to corrosion by any of these modes should be considered. To understand the advantages and limitations of titanium, each of these types of corrosion will be explained concerning commercially pure and near commercially pure grade of titanium.

General Corrosion

General corrosion is characterized by a uniform attack over the entire exposed surface of the metal. The severity of this type of attack can be expressed by a corrosion rate. This type of corrosion is most frequently encountered in hot-reducing acid solutions.

Oxidizing agents and certain multi-valent metal ions can passivate titanium in environments where the metal may be subject to general corrosion. Many process streams, particularly H_2SO_4 and HCl solutions, contain enough impurities in the form of ferric, cupric ions, etc., to passivate titanium and give trouble-free service. In some cases, it may be possible to inhibit corrosion by the addition of suitable passivating agents.

Crevice Corrosion

This is a localized type of attack that occurs only in tight crevices. The crevice may be the result of a structural feature such as a flange or gasket, or it may be caused by the buildup of scales or deposits.

Dissolved oxygen or other oxidizing species present in the solution are depleted in a restricted volume of solution in the crevice. These species are consumed faster than they can be replenished by diffusion from the bulk solution. As a result, the potential of the metal in the crevice becomes more negative than the potential of the metal exposed to the bulk solution

Stress Corrosion Cracking (SCC)

This mode of corrosion is characterized by cracking under stress in certain environments. Titanium is subject to this form of corrosion in only a few environments such as red-fuming nitric acid, nitrogen tetraoxide, and absolute methanol. In most cases, the addition of a small amount of water will serve to passivate the titanium. Titanium is not recommended for use in these environments under anhydrous conditions.

Anodic Breakdown Pitting

This type of corrosion is highly localized and can cause extensive damage to equipment in a very short time. Pitting occurs when the potential of the metal exceeds the breakdown potential of the protective oxide film on the titanium surface. Fortunately, the breakdown potential of titanium is very high in most environments, so this mode of failure is not common. The breakdown potential in sulfate and phosphate environments is in the 100-volt range. In chlorides, it is about 8 to 10 volts, but in bromides and iodides, it may be as low as 1 volt.

Increasing temperature and acidity tend to lower the breakdown potential so that under some extreme conditions the potential of the metal may equal or exceed the breakdown potential and spontaneous pitting will occur. This type of corrosion is most frequently encountered in applications where an anodic potential exceeding the breakdown potential is impressed on the metal.

Hydrogen Embrittlement

Titanium is widely used in hydrogen-containing environments and under conditions where galvanic couples or cathodic protection systems cause hydrogen to evolve on the surface of the titanium. In most instances, no problems have been reported. However, there have been some equipment failures in which embrittlement by hydride formation was implicated.

The oxide film which covers the surface of titanium is a very effective barrier to hydrogen penetration; however, titanium can absorb hydrogen from hydrogen-containing environments under some circumstances. At temperatures below 170°F (77°C) hydriding occurs so slowly that it has no practical significance, except in cases where severe tensile stresses are present. In the presence of pure anhydrous hydrogen gas at elevated temperatures and pressures, severe hydriding of titanium can be expected. Titanium is not recommended for use in pure hydrogen because of the possibility of hydriding if the oxide film is broken [35].

5. Titanium uniform corroding

The protective oxide that covers the surface of titanium varies in nature and content depending on the environment in which it is generated. The oxide that forms in aquatic conditions is primarily amorphous TiO_2, with minor contributions from Ti_2O_3 and TiO. When intermediary temperatures often produce slight protecting oxide, in anisate crystals, at high temperatures, rutile, a crystalline and more chemical-resistant form of TiO_2, develops, **Fig. 1.**

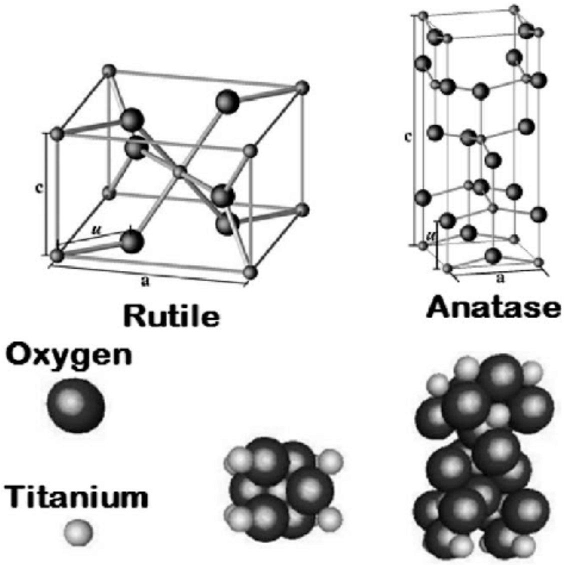


Fig. 1: Structure of anatase and rutile phases of TiO_2 [36].

Anisate and rutile TiO_2 (titanium dioxide) are two different crystal structures of titanium dioxide with distinct properties. Anisate TiO_2 typically refers to a TiO_2 crystal structure with anisotropic properties. The term "anisotropic" indicates that the material exhibits different properties in different directions. Anisate TiO_2 may have varying optical properties along different crystallographic axes. The electrical conductivity of anisate TiO_2 can be direction-dependent. Mechanical properties like hardness and elasticity may vary along different directions within the crystal lattice. The thermal conductivity of anisate TiO_2 can also be anisotropic. Rutile is one of the three main polymorphs of TiO_2, alongside anatase and brookite. The rutile crystal structure is characterized by a tetragonal unit cell, where the titanium atoms are octahedrally coordinated by oxygen atoms. Rutile TiO^2 is optically isotropic, meaning it exhibits the same optical properties in all directions. Rutile is generally a poor electrical conductor in its pure form. It has a high hardness and is often used as a component in ceramics. Rutile TiO_2 has relatively low thermal conductivity. Both anatase and rutile phases of TiO_2 exhibit photocatalytic activity, making them useful in environmental applications such as water purification and air treatment. Titanium dioxide is biocompatible, and rutile TiO_2 is often used in various biomedical applications. Titanium dioxide nanoparticles, especially anatase, are used in solar cells for their semiconductor properties. Titanium dioxide is effective in absorbing ultraviolet (UV) light, protecting sunscreens and UV-blocking coatings.

The corroding resistance of titanium will be investigated by taking into account circumstances such as thermodynamically unbalanced protective oxide. Titanium is inactive throughout a large range of potentials, owing to the Pourbaix diagram (pH-potential) of titanium in aqueous medium [37], as well only becomes vulnerable in strong oxidizing circumstances while oxides are soluble as well in the existence of strong reducing circumstances while hydrides were resulted. Because this range is comparatively intense to chlorides, titanium naturally resists them in conditions that have aqueous chlorides.

Owing to fine oxidation on titanium exterior sides, when titanium is in a passive state, corroding rates match the density of passive current; the average value is less than 0.02 mm/year. Test coupons may show a colored exterior side as well as so much tiny weight gain corresponding to this oxide layer creation. Oxide's color is produced during the involvement of shining rays sent back from metal beneath; as a result, color highly relied on film thickness [38]. Titanium elements are often constructed without any corroding allowance because of the strong passive layers [37]. Uniform corroding happens in reducing circumstances, especially in the acidic medium at elevated temperatures. In a hot high reducing acidic medium, the desolvation of oxide film occurs, besides oxidation of bare metal to dissolved trivalent ions occurred ($Ti \rightarrow Ti^{3+} + 3e-$). While hot acids have dissolved oxygen, the Ti^{3+} ions are oxidized to Ti^{4+} ions, as well the latter consequently hydrolyzes to convert to insoluble titanium dioxide. This layer can minimize corroding progress. Without oxygen, while a powerful corroding attack happened in a hot reducing acidic medium, a matt silver-gray exterior side appeared, owing to the establishment of titanium hydrides on the exterior side [33]. Resistance of titanium's defensive oxide which varies depending on the environment is crucial for the metal's ability to resist corrosion. This section will list the various typical conditions in which titanium is utilized, along with those environments' effects on the metal.

6. Seawater

According to reports, titanium has excellent resistance to common corroding in salt water. Titanium does not experience microbial-induced corroding (MIC) and, despite the possibility of very minor biofouling, no corrosion is seen beneath marine creatures. Titanium is utilized in heat exchangers in desalination plants, while temperature is typically maintained at about 130 °C [34] Titanium is said to be resistant to common corroding up to 260 °C. Commonly, metal is resistant to corroding as well as cavitation up to 36 m/s in this environment.

Even though titanium exhibits superior corrosion resistance in acidic environments, during the service of titanium as chimney lining materials, the corrosion resistance of titanium will be seriously reduced due to the presence of fluoride ions (F^-) in seawater or acidic media attributed to the dissolution of TiO_2 to soluble complex and the direct exposure of the titanium matrix. There exists a critical F^- concentration value in the fluoride-containing condensates. When the F^- concentration exceeds this critical value, the titanium oxide film will lose its protection and make the substrate suffer severe corrosion. This threshold F^- concentration is reported to have a direct relationship to pH. Some reports define this critical value as the maximum concentration of fluoride at which the titanium still stays passivated, and some researchers have determined the maximum F^- concentration using different methods. Wang et al. studied the corrosion behavior of pure titanium in fluoride-bearing H_2SO_4 and believed that there are different corrosion mechanisms before and after the F^- concentration exceeds the critical value. Kong et al. studied the electrochemical behavior of fluorinated $HClO_4$ and analyzed the intrinsic mechanism of the critical F^- concentration from the aspect of electrochemical impedance spectroscopy by theoretical derivation. In the acidic flue gas condensate, there is a certain amount of nitric acid (HNO_3), hydrochloric acid (HCl), and F^- in addition to sulfuric acid (H_2SO_4). It is not clear whether the corrosion behavior of pure titanium in the presence of F^- is different in the three acids. The effect of anions in the condensates on the corrosion of titanium still needs to be clarified [39].

7. The human body

Titanium is a great substance for the construction of orthodontic, prosthetic, and cardiovascular implants because it is biocompatible, has low toxicity, high mechanical toughness, as well low density [34] Corroding resistance is a top trouble because all of these devices must withstand a lifetime of immersing in bodily fluids without the prospect of investigation and care. This is why applications connected to the human body make up the majority of studies on titanium's resistance to corroding. In the current study, a simulated bodily fluid with a pH of 7.4 is the most frequently employed solution to examine the electrochemical behavior of the metal [34]. Composition and pH may change under specific circumstances, such as inflammatory states or orthodontic implants near toothpaste [37].

Titanium's corroding resistance and biocompatibility are closely associated; in fact, less corrosion implies fewer ions liberated into the body, which could result in prosthetic rejection. Additionally, titanium exterior sides can be treated via anodic oxidation, which encourages the growth of its oxide and, if done correctly, may duplicate the construction of hydroxyapatite, one of the important parts of bone. This raises biocompatible importance [38].

8. Use of Ti alloys in dental medicine applications

Owing to its exceptional biocompatible importance, corroding resistance, and nearly low density, titanium, and its alloys are the subject of extensive research in dental medicine. The 1930s saw the first attempts to create implants using titanium [1]. Titanium alloys may contain metals like Zr, Mo, Ni, Nb, and Ta because of their good biocompatibility and status as non-toxic metals once they interact with live tissue. Additionally, these elements are the best alloying components to use when lowering the elastic modulus without reducing the material's mechanical resistance [40, 41]. Numerous techniques for enhancing corroding resistance in titanium alloys were researched [42]. Niobium is a known alloying element that has particularly strong biocompatibility and corrosion resistance in simulated bodily fluids [43, 44] Although studies have demonstrated various Mo-containing Ti alloys, such as Ti-Mo, Ti-Mo-Ta, and Ti-Mo-Zr-Fe, could have excellent mechanical compatibility as well good cytotoxic compatibility, the usage of molybdenum is still contentious [45-50]. In comparison to Nb, Ta, or Zr, Mo has the benefit of being a good stabilizer of phases for Ti alloys [51, 52]. To understand how titanium alloys behave electrochemically as biomaterials that are prone to corrosion in human tissue, these materials have been examined in a variety of physiological media, involving artificial saliva, Hank solution, Ringer solution, and NaCl solution [51-56] The effectiveness of molybdenum content on Ti-Mo alloy corroding resistance in several simulated physiological settings was examined in numerous studies, and one found that the inclusion of molybdenum developed the electrochemical manner [57-62]. Niobium (Nb) is utilized as major alloying element in Ti-Nb and Ti-Nb-Zr systems because it has unique features that enhance stability, reduce elastic modulus, as well raise corroding resistance [63-72].

Finding strategies to develop the features of these alloys with medical applications becomes a remarkable research focus. Therefore, efforts are undertaken to determine the ideal alloy exterior side properties that meet high standards so that the lifetime of alloys could be increased in severe situations of the human body. Some of the most popular biomaterials are still made of titanium-based alloys. These researches were carried out to realize electrochemical manner and potential impacts on the environment and human beings.

A persistent, defensive titanium oxide exterior layer is accountable for the exceptional corroding resistance of titanium as well as titanium alloys. Due to titanium's high reactivity with oxygen, when it comes into contact with air or most other media, the surface oxide types instantly and spontaneously. If moisture or oxygen exists in environment at levels of parts per million, damage caused by the oxide film normally heals rapidly. As a result, titanium alloys have a strong corroding resistance, typically decrease at very low rates, and don't need a corrosion limitation. However, building or repair of the oxide film may be stopped by anhydrous or highly reducing conditions, and corrosion may then become accelerated. Similar to stainless steels, which likewise rely on a protective oxide film on the exterior side of a reactive metal, this type of corroding resistance is seen in alloys made of aluminum, magnesium, and those metals.

The desirable material for biomedical implants is titanium (Ti) and its alloys, although the human body is in a difficult position for any biomaterials owing to immunological, biochemical, metabolic as well as microbiological processes that affect its corrosion resistance **[73].** Besides, the composition, microstructure, and surface treatment of Ti alloys affect how resistant they are to corrode **[74].** Thus that, the particles and ions liberated by the corrosive phenomenon could build up in pre-implant bone as well as reduce functionality, mechanical integrity, and implant mass. This can have an impact on the useful life of the implant by increasing the possibility of failure, bone resorption, infections, as well loosening, or by causing systemic migration to various organs, which could result in long-term health issues **[75].** The passive surface TiO_2 layer on titanium gives it superior electrochemical properties compared to other metals, but the oral cavity is a dynamic medium affected by changes in charge, pH, and corrosive products of dietary metabolism as well as biofilm, which could cause accelerated corroding and harm to the survival of the implant by interfering with the thickness of the oxide layer and the re-passivation processes **[76-78]**. According to Mischler et al. **[79].** Creation of passive oxide layers, the rate of corroding temperature, as well as electrolyte all have an impact on corroding potential.

As a result, the interplay between the biological environment as well as the physicochemical, morphological, besides mechanical characteristics of Ti oxide coating that spontaneously forms on the implant exterior side and provides corroding resistance is directly dependent on the biocompatibility of alloyed titanium samples **[80].** Researchers examine the impact of the chemical construction of Ti alloys on bone-implant contact to determine the best suggestion for those in all operations which it is important in light of modern studies that have shown the genotoxic and cytotoxic potential of nano TiO_2 particles **[80].**

9. Titanium complexes and their biological applications

Titanium is a transition metal that has special effects like high strength, low density, corrosion resistance, and biocompatibility. Those features make titanium and its compounds suitable for various applications in medicine, biotechnology, and environmental remediation. Titanium complexes are compounds that contain titanium atoms bonded to other atoms or groups, such as oxygen, nitrogen, sulfur, or carbon. Titanium complexes can have different structures, shapes, and charges depending on type and number of ligands attached to the titanium center. Some examples of titanium complexes are titanium alkoxides, titanium oxides, titanium oxo-clusters, titanium porphyrins, and titanium Schiff bases **Fig. (2).**

Titanium complexes have been explored for their biological applications in several areas, such as antimicrobial agents, biological sensors, tumor cell-killing agents, gene-targeting devices, and biomaterials. Titanium complexes can exhibit antimicrobial activity against various bacteria and fungi by disrupting their cell membranes or interfering with their metabolic pathways **[81].** Titanium complexes can also act as biological sensors that can detect the presence of biomolecules or ions by changing their color, fluorescence, or electrical properties. Titanium complexes can induce apoptosis or necrosis in tumor cells by generating reactive oxygen species or by binding to DNA or proteins. Titanium complexes can also be used as gene-targeting devices that can deliver specific genes to target cells by using viral or non-viral vectors. Titanium complexes can also serve as biomaterials that can be used for implants, prostheses, or tissue engineering by providing mechanical support, biocompatibility, and bioactivity **[82].**

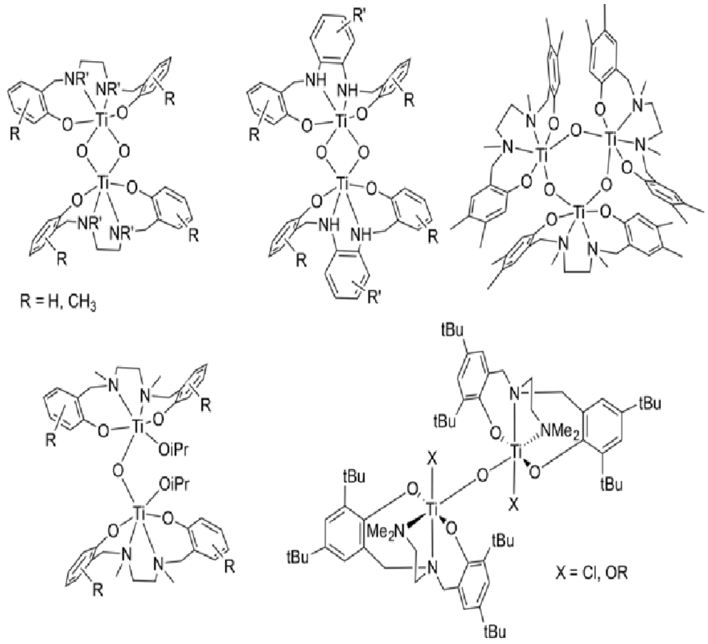


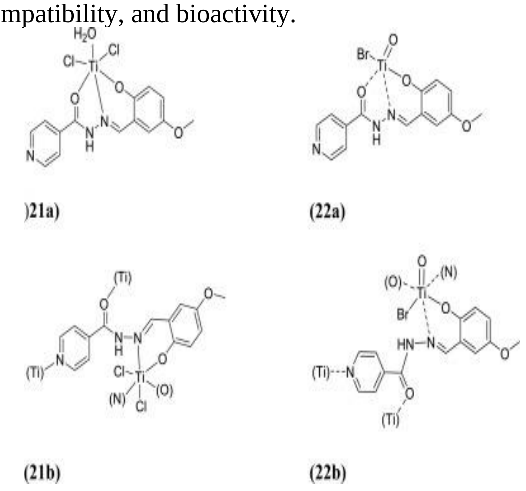
Fig. 2: Titanium complexes **[83]**

Titanium complexes are therefore hopeful possibilities for various biological uses owing to their versatility, stability, as well functionality **[84].** However, there are also some challenges and limitations associated with the use of titanium complexes in biological systems, such as toxicity, bioavailability, specificity, and biodegradability. Therefore, further research and development are needed to optimize the synthesis, characterization, and evaluation of titanium complexes for their potential applications in biology.

9.1. Titanium Schiff bases

Schiff bases are a class of organic compounds characterized by the presence of a functional group formed by the condensation of a primary amine with an aldehyde or ketone. These compounds are named after the German chemist Hugo Schiff, who first reported them in the 19th century. Schiff bases are formed through a condensation reaction between a primary amine (NH_2R) and a carbonyl compound (R'CHO or R'COR'). The key structural feature of Schiff bases is the azomethine (-C=N-) group, resulting from the imine bond formed during the condensation. Schiff bases are commonly named by combining the names of the amine and carbonyl compounds involved in their formation, with the word "Schiff base" included in the name. Schiff bases can exist in E (trans) or Z (cis) isomeric forms, depending on the spatial arrangement of substituents around the imine bond. Schiff bases are widely used in coordination chemistry as ligands for metal ions in the synthesis of metal complexes. They serve as catalysts in various organic reactions. Schiff bases and their metal complexes exhibit diverse biological activities, including antimicrobial, antifungal, antiviral, and anticancer properties. Schiff bases can be employed as sensing materials for detecting metal ions or other analytes. Due to their biological activities and potential medicinal applications, Schiff bases have garnered attention in drug design and development. Schiff bases are used in the synthesis of dyes and pigments, contributing to their applications in the textile and pigment industries. Some Schiff bases exhibit interesting photophysical properties, making them suitable for applications in materials science and optoelectronics. In summary, Schiff bases are versatile compounds with a broad range of applications in coordination chemistry, catalysis, medicine, materials science, and more. Their ability to form complexes with metal ions and their diverse biological activities make them valuable in various scientific and industrial fields. Titanium Schiff base complexes are compounds that contain titanium atoms bonded to Schiff base ligands, which are organic molecules that have a carbon-nitrogen double bond. Schiff base ligands are usually obtained from the condensation of an amine as well as an aldehyde or a ketone **Fig. (3).** Titanium Schiff base complexes have been explored for their biological applications in several areas, such as antimicrobial agents, biological sensors, tumor cell killing agents, gene targeting devices, and biomaterials **[85, 86].**

Titanium Schiff base complexes can exhibit antimicrobial activity against various bacteria and fungi by disrupting their cell membranes or interfering with their metabolic pathways **[84].** Titanium Schiff base complexes can also act as biological sensors that can detect the presence of biomolecules or ions by changing their color, fluorescence, or electrical properties. Titanium Schiff base complexes can induce apoptosis or necrosis in tumor cells by generating reactive oxygen species or by binding to DNA or proteins **[76].** Titanium Schiff base complexes can also be used as gene-targeting devices that can deliver specific genes to target cells by using viral or non-viral vectors **[76].** Titanium Schiff base complexes can also serve as biomaterials that can be used for implants, prostheses, or tissue engineering by providing mechanical support, biocompatibility, and bioactivity.



)21a) (22a)

(21b) (22b)

Fig. 3: Titanium Schiff bases complexes **[87]**

9.2. Titanium alkoxides

Titanium alkoxides are compounds that contain titanium atoms bonded to alkoxy groups, which are derived from alcohols**, Fig. (4).**

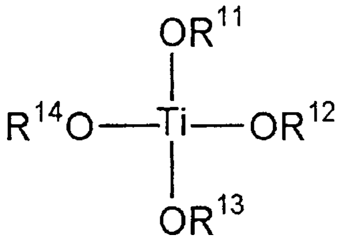


Fig. 4: Titanium alkoxides **[88]**

Titanium alkoxides are extensively employed as precursors for synthesizing titanium dioxide (TiO_2), a material with diverse biological applications. TiO_2, acting as a semiconductor, produces reactive oxygen species (ROS) when exposed to light. This property finds applications in antimicrobial treatment, anticancer therapies, and photodynamic therapy. Additionally, TiO_2 serves as a biocompatible coating for implants, biosensors, and tissue engineering scaffolds. However, titanium alkoxides have some drawbacks, such as high reactivity, low solubility, and poor management over morphology as well as crystallinity of resulting TiO_2. Therefore, chemical modification of titanium alkoxides with organic molecules is often employed to improve their properties and performance in sol-gel processes **[77].** Sol-gel is a technique that involves the hydrolysis and condensation of metal alkoxides to form metal oxides in solution or gel form.

Some examples of organic modifiers for titanium alkoxides are (1) Organosilanes: These are compounds that contain silicon atoms bonded to organic groups. Organosilanes can act as coupling agents between TiO_2 and organic polymers, enhancing the mechanical and thermal properties of hybrid substances. Organosilanes can also introduce functional groups such as amino, carboxyl, or thiol on the surface of TiO_2, which can be used for further conjugation with biomolecules such as drugs, antibodies, or enzymes. (2) Polymers: These are large molecules that consist of repeating units of smaller molecules. Polymers can be used to modify the surface of TiO_2 nanoparticles, improving their stability, dispersibility, biocompatibility, and stealthiness in biological environments. Polymers can also provide stimuli-responsive properties to TiO_2 nanoparticles, such as pH-, temperature-, or light-triggered drug release **[78, 89, 90]**. (3) Small molecules: These are organic compounds that have low molecular weight and simple structure. Small molecules can be used to modify the surface of TiO_2 nanoparticles, enhancing their photochemical features such as absorption spectrum, quantum yield, and ROS generation. Small molecules can also act as ligands for metal ions or chelating agents for radionuclides, which can be used for imaging or therapy purposes. (4) Hydrogels: These are three-dimensional networks of hydrophilic polymers that can swell in water. Hydrogels can be used to encapsulate TiO_2 nanoparticles, providing a biocompatible and porous matrix for cell growth and tissue regeneration. Hydrogels can also modulate the release of drugs or other bioactive agents from

TiO_2 nanoparticles, depending on the crosslinking density, swelling ratio, or degradation rate of the hydrogel [91-94].

9.3. Titanium oxides

Titanium oxides are compounds that contain titanium and oxygen atoms in different ratios and structures. Titanium oxides have many biological applications due to their distinct properties, like elevated refractive index, photocatalytic activity, biocompatibility, and low toxicity, **Fig. (5).** Some of the most common titanium oxides are Titanium dioxide (TiO_2): This is the most stable and utilized form of titanium oxide. TiO_2 has two main crystal phases: anatase and rutile. TiO_2 can be used as a white pigment, a sunscreen agent, a photocatalyst, a biosensor, a drug delivery carrier, a bone implant coating, and a tissue engineering scaffold. TiO_2 can also give reactive oxygen species (ROS) under light irradiation, which can be used for antimicrobial, anticancer, and photodynamic therapy purposes [95, 96]. Titanium monoxide (TiO): This is a rare and unstable form of titanium oxide that has metallic properties. TiO can be used as a magnetic material, a superconductor, a thermoelectric material, and a gas sensor. TiO can also enhance the electrical conductivity and biocompatibility of TiO_2-based material. Titanium suboxides (Ti_xO_y): These are non-stoichiometric forms of titanium oxide that have variable compositions and structures. Ti_xO_y can be used as electrochromic materials, lithium-ion battery electrodes, fuel cell catalysts, and gas sensors. Ti_xO_y can also enhance mechanical strength as well as corroding resistance of TiO_2-based materials [97].

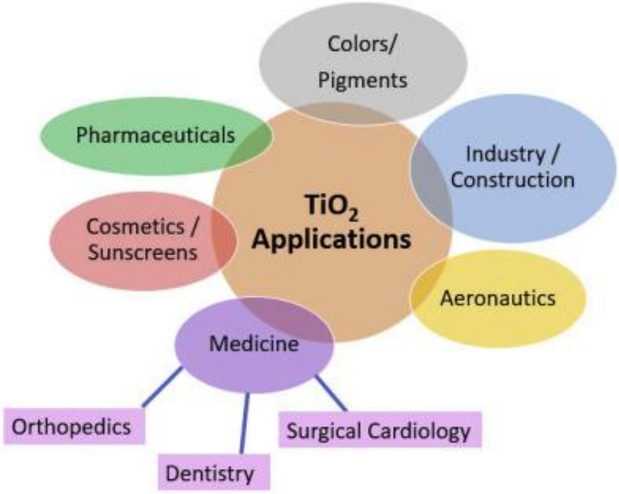


Fig. 5: Titanium oxides applications [98]

9.4. Titanium oxo-clusters

Titanium oxo-clusters are well-known, monodisperse nano-objects that consist of titanium and oxygen atoms arranged in various shapes and sizes, **Fig. (6).** Titanium oxo-clusters can be used as precursors for the synthesis of titanium dioxide (TiO_2) or other titanium-based materials by sol-gel processes. TiO_2 is a widely used material that has many biological applications, like photocatalysis, biosensing, drug delivery, and tissue engineering. Some examples of biological applications of titanium oxo-clusters are:

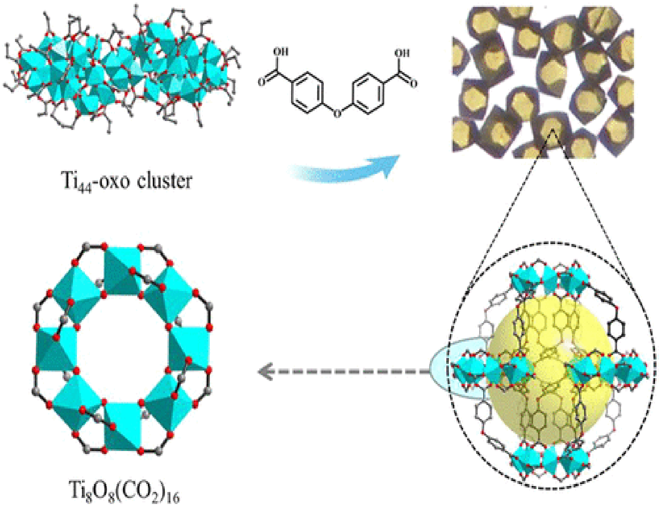


Fig. 6: Titanium oxo-clusters [99]

Photocatalysis: Titanium oxo-clusters can give reactive oxygen species (ROS) under light irradiation, which can be used for antimicrobial, anticancer, and photodynamic therapy purposes. For instance, a family of oxime-based titanium oxo-clusters showed enhanced visible light absorption and photocurrent responses compared to TiO_2 **Fig. (7)** [100].

Biosensing: Titanium oxo-clusters can be used as electrochemical or optical sensors for the detection of various biomolecules, such as glucose, hydrogen peroxide, DNA, and proteins. For example, a Ti8-oxo cluster modified with gold nanoparticles exhibited high sensitivity and selectivity for glucose detection.

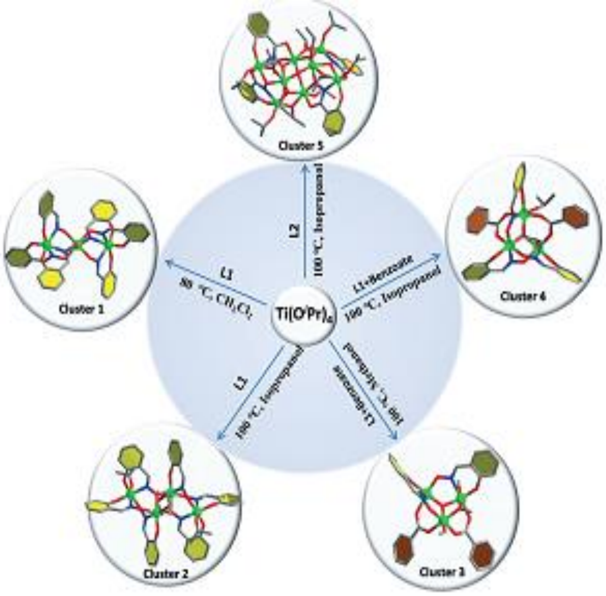


Fig. 7: Titanium oxo-clusters examples [101]

Drug delivery: Titanium oxo-clusters can be used as carriers for the delivery of drugs or other bioactive agents to specific targets in the body. For example, a Ti6-oxo cluster functionalized with folic acid and doxorubicin showed enhanced cellular uptake and anticancer activity against human breast cancer cells [102].

Tissue engineering: Titanium oxo-clusters could be utilized as building blocks for the fabrication of biocompatible as well porous scaffolds for cell growth and tissue regeneration. For example, a Ti12-oxo cluster incorporated into a hydrogel matrix formed a hybrid scaffold that reinforced adhesion as well the proliferation of human stem cells **[103].**

9.5. Titanium porphyrins

Titanium porphyrins are compounds that contain a titanium atom coordinated to a porphyrin ring, which is a cyclic structure composed of four pyrrole units, **Fig (8).** Titanium porphyrins have many biological applications because of their unique optical, magnetic, and catalytic properties. Some examples of biological uses of titanium porphyrins are:

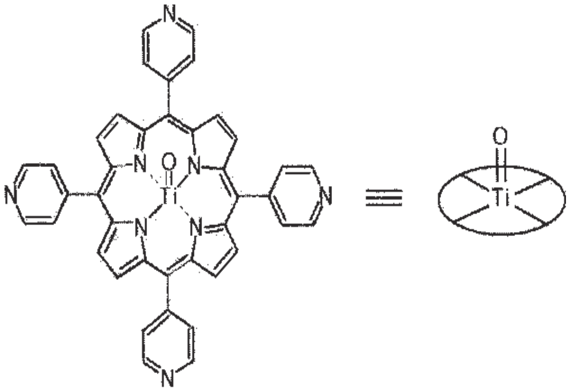


Fig. 8: Titanium porphyrins **[104]**

Photodynamic therapy: Titanium porphyrins can act as photosensitizers, which are molecules that can produce reactive oxygen species (ROS) when exposed to light. ROS can damage the cells and tissues of pathogens or tumors, leading to their destruction. Titanium porphyrins have the advantage of absorbing light in the near-infrared (NIR) region, which can penetrate deeper into biological tissues than visible light. For instance, a titanium porphyrin derivative showed high efficiency and selectivity for killing methicillin-resistant Staphylococcus aureus (MRSA) under NIR irradiation **[105].**

Magnetic resonance imaging: Titanium porphyrins can serve as contrast agents for magnetic resonance imaging (MRI), which is a technique that uses magnetic fields to generate images of the internal structures of the body. Titanium porphyrins can enhance the signal intensity and contrast of the images by altering the relaxation times of the water protons in their vicinity. For example, a titanium porphyrin complex conjugated with a peptide showed high affinity and specificity for targeting amyloid-beta plaques, which are associated with Alzheimer’s disease, in mouse brains **[106-108].**

Biosensing: Titanium porphyrins can be used as electrochemical or optical sensors for the detection of various biomolecules, such as glucose, hydrogen peroxide, DNA, and proteins. Titanium porphyrins can interact with the target molecules through different mechanisms, such as electron transfer, fluorescence quenching, or color change. For example, a titanium porphyrin modified with gold nanoparticles exhibited high sensitivity and selectivity for glucose detection.

Conclusion

Titanium and its alloys, prized for their specific strength, corrosion resistance, and temperature tolerance, find diverse applications in aerospace, automotive, chemical, and biomedical industries. The growing demand for titanium alloys presents a challenge in preventing corrosion failure. Notably, in the medical field, these alloys exhibit excellent biocompatibility, corrosion resistance, and mechanical performance. Interacting with biological macromolecules, titanium alloys form complexes modifying biological activity. Titanium complexes show potential in bioimaging, biosensors, drug delivery, and bone implants. This study offers a comprehensive overview of recent advances in biological applications of titanium complexes.

CRediT authorship contribution statement:

Hoda Abd El-Shafy Shilkamy: Supervision. Conceptualization. Data curation, Writing – original draft, Aly Abdou: Supervision, Conceptualization, Writing – original draft. All authors have read and agreed to the published version of the manuscript.

Data availability statement

The data used to support the findings of this study are available from the corresponding author upon request.

Declaration of competing interest

The authors declare that this manuscript is original, has not been published before, not currently being considered for publication elsewhere, no conflicts of interest associated with this publication, and there has no significant financial support for this work that could have influenced its outcome.

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