The Effect of Nanotubes on the Shape Memory Alloy Surface and Biological Properties of Nickel-Titanium (Nitinol) in Orthopaedic Implants
(A review paper)

Abstract

Introduction: An increasing population of the elderly has led to increasing demand for orthopedic implants. Excellent biocompatibility of orthodontic wires, drug delivery systems, cardiovascular stents, and orthopedic implants has attracted widespread attention by researchers for use in medical industries. In some cases, however, superficial properties such as corrosion resistance and other biological behavior are not sufficient for clinical application. Infection caused by the presence of implants in the body is one of the most common complaints of patients. Since the bacteria play important role in patients 'disability, the development of antibacterial properties has been considered.

Methods: Nanotubes, created on the surface of nitinol through anodizing, can be one of the useful solutions in creating antibacterial properties. Also, the ability of these structures to carry drugs such as antibiotics can solve the problems caused by implantation of orthopedic implants in the body.

Results: In order to increase the long-term antibacterial ability of orthopedic implants, the researchers have improved the physical properties by modification of nitinol levels by anodizing method and the formation of nanotubes on its surface and drug loading.

Conclusion: The effect of different parameters on morphology, nickel ion release, corrosion behavior, biological and drug delivery, applicable in orthopedic implants, is discussed.

Keywords: Shape memory alloys, Nitinol, prosthesis implantation, Nanotubes, drug delivery

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Introduction

Natural bone is a complicated and dense connective tissue with excellent mechanical properties that supports the human body, facilitates movement, protects internal organs, and produces stores, and releases blood cells and minerals for the body's metabolism. Bone is a polymer-ceramic composite with excellent bone mechanics composed of nano, micro, and macro hierarchical structure. Bone has an inherent potential for self-healing damage in non-critical sizes below 6 mm, but self-healing is a major challenge in repairing large bone defects due to trauma, tumor resection, infection, or genetic disease.

Autografts, allografts, and xenografts are widely used treatments for bone loss. Autograft transplants have problems such as deficiency and complications at the transplantation location, and allografts are associated with the risk of disease transmission and inadequate immune response [(1)]. Damaged bones can be replaced with decellularized xenograft bones to regenerate bone tissue as a natural scaffold [(2)]. Currently, treatment methods take longer to work, the high expenses of healthcare associated with dealing with this condition are only going to rise [(3, 4)]. The main goal of bone tissue engineering is to make biocompatibility with the osteoconductive and osteoinductive ability of bone in

regenerating tissue [5]. Biocompatibility indicates the implant ability to respond appropriately to the host without side effects such as cytotoxicity, mutagenicity, carcinogenicity, immunogenicity, and gene toxicity [6]. Osteoconductive bone reflects the ability of biomaterials in cell adhesion, as well as proliferation and formation of extracellular matrix by Osteoblasts and supports bone growth. Appropriate ossification represents the implant potential to directly connect with the host bone tissue without forming an undesirable fibrous tissue layer. Other properties of biomaterials for clinical applications include stimulation of ossification, meaning the ability of the material in the osteoinductive bone differentiation of mesenchymal stem cells to osteoblasts [7, 8, 9].

The production of fully biocompatible biomaterials with proper physical, chemical, and mechanical properties has greatly challenged the researchers. Mechanical properties can significantly affect ossification between implants and surrounding tissues and cellular behaviors. Natural bone has biomechanical properties with Young's Modulus in 15-35 GPa. Ideal implants should imitate bone strength, stiffness, and mechanical behavior, with Young's Modulus close to the bone modulus to prevent the effects of post-operative shielding stress, which causes bone resorption and implant failure. Biomaterials used in bone tissue engineering are usually classified into polymeric, ceramic, metallic, and composite materials [10, 11]. Titanium (Ti) and its alloys, stainless steel, cobalt (Co) and its alloys, magnesium (Mg) and its alloys, nickel-titanium (NiTi (Nitinol)), and tantalum (Ta) are common metal biomaterials widely used as bone implants due to their corrosion resistance, long life, tensile strength, and high durability [12]. The mentioned metal biomaterials have some limitations, such as the possible release of toxic metal ions and abrasion residues that cause acute or chronic reactions after implantation due to friction during long-term use. The current research process in biomaterial engineering focuses on surface changes to improve the biological and biomechanical behavior of bone implants. Surface modifications and biomaterial coatings improve the osteoconductive and osteoinductive capabilities of bone, of which organic, inorganic, and composite coatings are examples [13, 14]. Physical or chemical modifications of the biomaterial surface provide a more conducive environment for cells to improve cell adhesion, proliferation, and migration [14, 15]. In addition, coatings containing metal ions, such as silver, zinc, copper, and lithium, transmit antibacterial properties to the biomaterial and reduce the risk of infection at the implant site [16]. Different implant surface modification strategies may be performed using electrophoretic deposition, sol-gel technique, physical vapor deposition, laser, plasma spray, hydrothermal method, spattering, and anodizing. In addition to changing surface chemistry, these strategies also affect topography, morphology, wettability, mechanical properties, and improved surface biocompatibility ([17, 18]. Biomaterial surface topography plays an essential role in the early stages of ossification and prevents implant failure. Surface roughness positively affects cellular response, including adhesion, proliferation, and cell differentiation. In addition, it increases macro-porosity (pore size > 50 µm), ossification, and cell growth. However, the Micro porosity structure (pore size < 2 micrometers) enhances the surface area, contributing to the higher protein adsorption capacity of biomaterials and adhesion of osteoblasts and osteoporogenic cells (bone stem cells) as a main factor to establish the proper interaction between cells and biomaterials. Micro porosity also supports the formation of the apatite-like layer at the planting surface because it increases ion exchange and affects biomaterials' bioactivity [19]. Therefore, proper surface performance plays an effective role in the implant effectiveness. Reviewing the previous studies on nitinol surface modification can help researchers address challenges, such as improving implant cohesion and loosening due to infection by

anodizing and the effect of nanotubes on the surface of the alloy on its biological properties in orthopedic implants.

Nickel-titanium shape memory alloy

Nickel-titanium (NiTi), copper-zinc-aluminum, and copper-aluminum-nickel can be mentioned as important types of shape memory alloys. The most popular shape memory alloy is the nickel-titanium alloy, known as nitinol, which has been noted for its corrosion resistance, good abrasion, excellent mechanical properties, and good biocompatibility [20, 21]. According to Iranian researchers, domestic production of nitinol behaved similarly to foreign samples in terms of biocompatibility [22]. The stress-strain behavior of nitinol1 is very similar to bone and tendons (Figure 1). Therefore, they have been considered for use in orthopedic implants for bone repair because of the usefulness of their low modulus to prevent tension shields [23, 24]. The shape memory properties of nitinol can be used in various forms such as wire [25] or strip 26 in medical applications. In addition to orthopedic applications, nitinol has also been considered in soft tissue. This nitinol shape memory behavior can be used in composite structures used in medicine, including NiTi/silicone intelligent composite structures for artificial muscle [23,26].

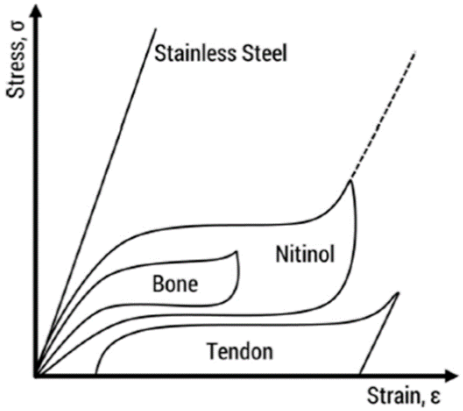

Figure 1. Stress-strain of nitinol, stainless steel, bone, and tendon tissue (23)

Nitinol has not shown any toxicity such as neurotoxicity, gene toxicity, or allergy in terms of biocompatibility compared to clinical reference control material such as stainless steel AISI 316 LVM. However, there is still concern about the release of nickel ions with long-term use in the body due to the significant amount of nickel in nitinol, and care must be taken to minimize threats to the medical use of nitinol especially corrosion and biocompatibility [27]. Surface modification methods have been used to achieve the goal. Different surface modification strategies may be performed using chemical surface modification, Electrophoretic deposition, Sol-Gel technique, Physical vapor deposition, Laser, Plasma Spray, Hydrothermal, Spattering, and Anodizing methods. In addition to changing the surface chemistry, these strategies affect the topography, morphology, wettability, and mechanical properties and improve surface biocompatibility. Careful control of surface roughness can help minimize the formation of biofilm, the presence of which may lead to infection. For example, the chemical surface modification method and the subgrade increase in the silicon-nitinol intelligent composite interface can be used in artificial muscles. Coating thin layers on the surface of nitinol can help improve biocompatibility, which is related to the production method [28, 29]. Experiments on fabricated alloys showed that alloys produced by powder metallurgy are more resistant to pitting corrosion [30].

Nickel: titanium ratio is essential for the production of nitinol because of its significant influence on the behaviour of super elasticity and shape memory. Studies have shown that nickel-rich nitinol has a super-elastic property, and the alloy has a more negligible memory effect but increases its ability to withstand the heat treatment when the nickel: titanium ratio closes to 60%. Nitinol requires 54.57.5% by weight of nickel with titanium balance for ASTM F2063 medical implants [31]. Experimental studies on the ability of bacteria to adhere to biomaterial surfaces and surface roughness below 30 nm showed that surface topography is vital to minimize implant-related infections since the adhesion of bacteria to biological materials is greater in coarse materials. Similarly, the regulation of the TiO2 oxide layer formed on nitinol surfaces improves ossification and increases corrosion resistance [32].

Methods

Anodizing

Anodizing is one of the methods of modifying the surface of metal implants, which is simple and economically viable. This technology is defined as the oxidation of metals (titanium, zinc, and magnesium) through an electrochemical method that allows the formation of oxide films with different nanoscale morphologies on the surface of metals and their alloys. Since anodizing is an electrochemical process, all the elements in alloys can be oxidized with the help of an electric field, and non-oxidized sub-layers, such as nickel-rich layers in NiTi, can be removed after thermal oxidation. Control of parameters such as voltage, anodizing time, formulation, and electrolyte pH in the acidic pH range <5 allows the creation of optimal topography on biomaterial surfaces by controlling the dimensions of the Nanotubes. Nanotubes cannot grow anodically on nitinol levels as oxide surfaces but can be produced on treated alloy. Non-uniform porous structure and uniform structure can be produced when the surface is mirrored and sanded with 600 meshes and 400 meshes, respectively [32] (Figure 2).

Nanotubes are appropriate for increased adhesion, proliferation, and bone differentiation due to their unique topography with hollow cylindrical capacity and high surface area for drug loading. Invitro and In vivo studies have shown the widespread effect of drug release on accelerating and enhancing ossification [33].

Anodic growth of Ni-Ti-O nanotubes on nitinol was first reported in 2010, which is sensitive to electrolyte composition due to the high nickel concentration in the alloy [34]. Other parameters such as voltage, time, and anodizing temperature affect the growth of nanotubes on the nitinol surface ([35, 36, 37]. The diameter and length of the nanotubes rise with increasing voltage, but a larger voltage decreases both. In addition, the diameter of the nanotubes does not change significantly with increasing the anodizing temperature, but the length decreases uniformly because the chemical dissolution of the mixed oxides is more sensitive to temperature than the anodic growth. Therefore, a low anodizing temperature is required to produce long nanotubes. Furthermore, anodizing time affects the surface length and morphology of nanotubes. Prolonged time leads to complete dissolution of the nanotube layer and impairs its growth [38-42].

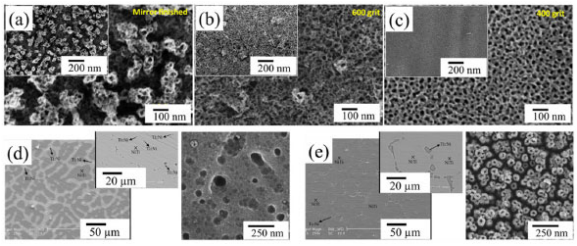

Figure 2. SEM images of the effect of NiTi surface matrix properties on the growth of nanotubes [40, 41, 42]

The effect of heat treatment on the microstructure of Ni-Ti-O nanotubes

Heat treatment is usually performed to crystallize amorphous Ni-Ti-O nanotubes for better bioactivity. When the temperature is less than 600°C, the surface and cross-sectional morphology of the nanotubes is preserved. Higher temperatures lead to the structural collapse of nanotubes. As the temperature increases, the walls of the nanotubes become uneven and small cracks are observed after heat treatment at 600°C (NT-600). Temperatures below 400°C indicate amorphous microstructure. Heat treatment at 600°C converts the amorphous structure to TiO2 anatase [43,44,45].

Release and corrosion behavior of nickel ions from Ni-Ti-O nanotubes

Although nickel is effective in cellular functions such as energy metabolism, protein synthesis, cell cycle, glucose transfer, and DNA repair is an essential element, which is overuse allergenic, toxic, and even carcinogenic. The corrosion behavior of nitinol is especially critical in contact with body fluids as an implantable material [32]. Nitinol is clinically accepted because its surface is coated with a dense, protective oxide film with poor solubility in contact with body fluids. However, the oxide film is quite thin (4 nm) with a weak self-healing ability after an

injury, possibly due to the accumulation of nickel beneath the surface oxide layer, mainly composed of TiO2 [46]. Anodizing thickens the surface oxide layer, but increases the corrosion density by forming nanotubes and increasing their diameter and length [47]. The corrosion resistance of nanotubes can be increased by heat treatment. Heat treatment in the temperature range of 400 to 600°C causes more thickness and compression of the oxide film at the interface between the matrix and the nanotubes and prevents ion migration across the oxide film.

In contrast, higher temperatures convert the amorphous structure to anatase or rutile, which may create voids and cavities. Defects in the oxide layer may serve as channels for the migration of nickel ions and reduce corrosion resistance [48]. According to studies, anodizing nitinol reduces corrosion resistance despite forming a thick oxide layer on the surface. Mechanically polished alloys release the least nickel compared to anodized groups, while smaller nanotubes release fewer nickel ions than larger ones. The release behavior of nickel ions corresponds to the corrosion current density (NiTi-25V). All samples were annealed at 450°C for 2 hours. The potential dynamic polarization and corrosion current density of samples on different days are shown in the right-side figure [38, 47].

Studies have shown that alloy samples coated by Poly Lactic Glycolic Acid (PLGA) biopolymer show the highest corrosion resistance compared to uncoated samples. The protective effect of polymer coatings on metal layers has been confirmed as a physical barrier against electrolyte access, which reduces the leaching of metal ions to the environment and prevents charge transfer at the electrode/electrolyte interface. The coating eliminates the concern for nitinol implants about releasing toxic Ni ions into the tissue around the implant [47, 49, 50, 51, 52].

Biological performance of Ni-Ti-O nanotubes

Ni-Ti-O nanotubes should have proper cellular compatibility as a coating on implantable nitinol implants directly related to nickel ion release. Although the released amount of nickel ions increases after forming the nanotube structure, no significant cytotoxicity is confirmed by fluorescence staining. In other words, the amount of nickel released by the cells is tolerated [38] (Figure3). The researchers have found that the released amount of nickel ions from the anodized sample is far less than tolerable inside the body. Therefore, Ni-Ti-O Nanotubes have proper cellular compatibility [41].

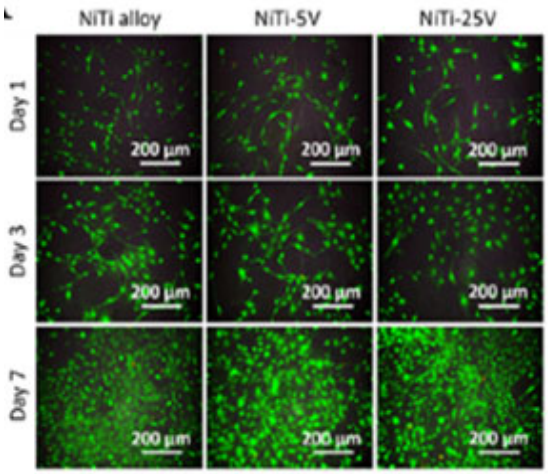

Figure 3. Fluorescence stained images for osteoblast cells after culture for 1, 3 and 7 days on NiTi alloy and nanotube coated samples at 5V (NiTi-5V) and 25V (NiTi-25V) Under the anodizing process [38].

Growth of hydroxyapatite on orthopedic implants

The ability to grow hydroxyapatite is the key to bioactivity for orthopedic implants because hydroxyapatite is the predominant inorganic component of bones. Heat-treated nanotubes at 450°C cannot induce the growth of hydroxyapatite after immersion in simulated body fluids (SBF), but a thick layer of hydroxyapatite is produced on the nanotube film after heat treatment at 600°C [53] (Figure 4). TiO2 nanotubes have been reported to increase the formation of hydroxyapatite compared to pure polished titanium due to their large specific surface area and great core locations. Hence, it can be inferred that Ni-Ti-O nanotubes accelerate the growth of hydroxyapatite on nitinol [54, 55].

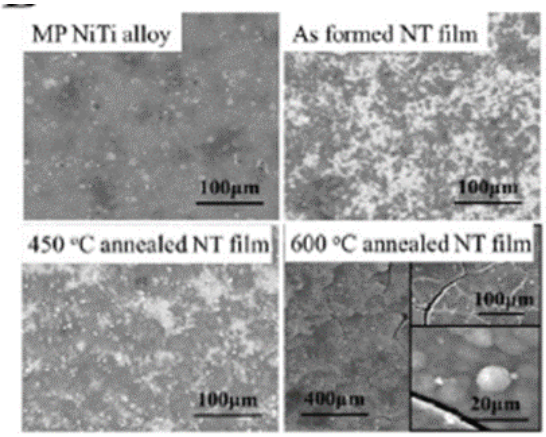

Figure 4. SEM images of polished samples and heat treatment at 450 and 600 ° C after immersion in SBF for 14 days [54, 55].

Results

Effect of implant surface hydrophilicity on cellular responses

Anodizing is a popular surface modification process to increase the biocompatibility of titanium base alloys. Many researchers have reported that anodized alloys have better biocompatibility than uncoated ones [56, 57]. Increased biocompatibility of anodized Ti surface is achieved by increasing surface hydrophilicity due to the formation of the TiO_2 layer. The morphology of the new surface is beneficial for activating the cellular response, and increased hydrophilicity at the Ti level increases in surface energy, facilitating cellular responses in the early stages [58]. Cellular responses, such as adhesion, are affected by the morphology of the substrate surface. Therefore, the anodized layer on the cellular response in the early stage enhances biocompatibility [59]. However, reports on the initial cell response to NiTi alloy are rare when 50% atomic nickel is used as the alloy element. Nickel in the NiTi alloy substrate is, in most cases, in the anodized layer. For this reason, the formation of a nickel-free TiO_2 layer by anodizing is generally difficult [60].

Controlling the release of nickel ions from the anodized surface is helpful for allergic reactions and cellular cytotoxicity limitations, and activation of the initial cell response under the control of surface hydrophilicity and morphology is also an essential factor in improving biocompatibility. The nickel: titanium ratio increased from 0.09 to 0.22. Increasing this ratio showed a decrease in cell proliferation because the release rate of nickel ions increased. The increase in nickel ion release from the anodized nitinol surface is due to the formation of nanometer-sized cavities on the alloy surface. Anodizing nitinol in an electrolyte containing nitric and phosphoric acid resulted in forming a hydrophilic surface, increasing cell adhesion function and initial cell activity at the alloy surface (Figure 5). However, the release of nickel ions from the alloy surface is a barrier to cell adhesion, and its proliferation is shown to increase the culture time from 4 to 72 hours (Figure 6). Thus, the positive effect of anodizing with the negative effect of nickel ion release is an inhibition of the appropriate cellular response. Anodizing with the mentioned electrolytes increased hydrophilicity and cell adhesion in the early stages of cell culture and worsened cellular response to the alloy. Therefore, preventing the release of nickel ions from the alloy surface is an essential factor in improving the cellular response [61,62].

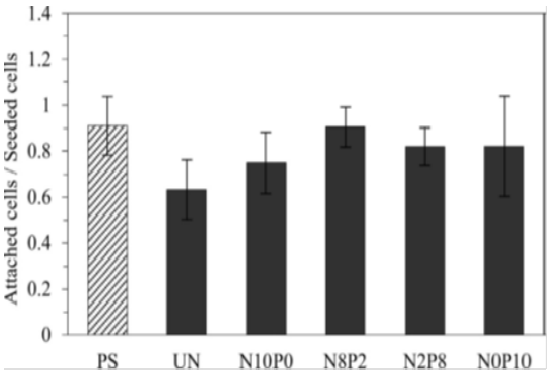

Figure 5. Number of MC3T3-E1 cells on unmodified and anodized NiTi surfaces after four hours of culture [62]

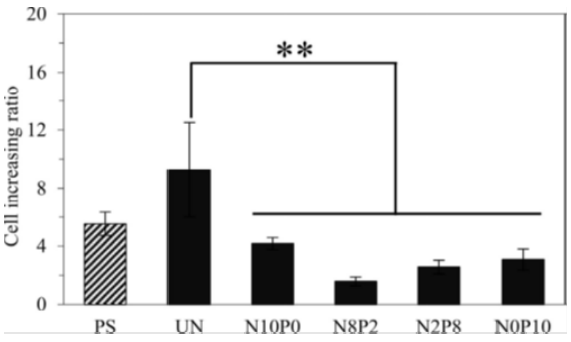

Figure 6. MC3T3-E1 cell growth rate during culture period from 4 to 72 hours on unmodified and anodized surfaces [62]

Drug release platform from nanotubes

Currently, antibiotics are the clinical treatment for prosthetic infection after surgery. Most drugs delivered by conventional methods have several drawbacks, including poor biological distribution of antibiotics, uncontrollable pharmacokinetics, and serious side effects for non-target organs. Low drug concentrations at the infection site cannot effectively kill the bacteria, and increasing drug concentrations can lead to drug overdose and cytotoxicity. Therefore, creating an antibacterial implant with properties that disrupt bacterial adhesion and reduce the risk of a drug overdose is necessary. The use of surface coatings with nanotubes to release the drug at the implant site is produced by modifying the surface to prevent post-operative prosthesis infection. Anodized grown nanotubes can continuously be used as drug reservoirs at the desired location. Combining these nanotubes and materials such as polydopamine can facilitate their use in alternatives coming in contact with soft and hard tissues [63]. Studies have shown that nanotubes containing antibiotics such as gentamicin and vancomycin have a robust bactericidal ability on various bacteria, but fully drug-filled nanotubes can cause side effects due to rapid release [64]. Various solutions have been investigated to control drug release from these nanotubes. Degradable polymer coatings are one of the effective methods in modulating the drug kinetics of release from nanotubes. Chitosan and polylactic glycolic acid (PLGA) are major candidates for their high biocompatibility, antibacterial ability,and improved ossification. Coated nanotubes provide adjusted drug release kinetics compared to uncoated polymer samples in terms of reduced explosive and long-term release in the treatment range for osteomyelitis. Uncoated nanotubes containing Vancomycin antibiotic release about 49% of the loaded drug, followed by the release of the entire drug before 96 hours in the first six hours of exposure to a physiological environment. The polymer coating effectively controls vancomycin secretion up to 26% and approximately 50% of the loaded drug for more than seven days. Drug release is placed in the treatment window with the least negative effect on biocompatibility [65, 64].

Discussion

Effect of Coating Thickness on Drug Release from Nanotubes

Drug molecules should pass through coatings to reach their surroundings. Therefore, the thickness of the coating plays a crucial role in this process. Drug release duration is greatly reduced by increasing the thickness of longer coating layers and drug-related toxicity. However, the excessive thickness may delay the release of the drug. The drug-containing nanotubes were prepared with PLGA coating with 50, 250, and 800 nm thickness. The results showed that the 250 nm coating is the best release kinetics, which is very slow compared to the 800 nm coating, and the deficient concentration of the drug could not have a practical antibacterial function.

Further research is needed to determine the optimal coating thickness for the long-term requirements of the antibacterial effect. Drug release through nanocarriers can lead to the simultaneous release of multiple drugs, increase the stability of the released drug in the body, extend the release time, and reduce the cellular cytotoxicity due to the over-concentration of one agent [63, 66]. Coatings with expanded drug release ability are expanded to simultaneously treat implant loosening and topical infection treatment [67].

Conclusion

Generally, prevention and treatment of implant-induced infection in the body after surgery are clinical challenges. This report reviewed studies related to the growth of nanotubes on nitinol by anodizing and examining their effects on its biological properties and drug release behavior for use in orthopedic implants.

Although nanotubes reduce the corrosion resistance of nitinol and increase nickel ion release, no side effects were found at the cellular level, and the nanotube structure

adjusted cell function to provide desirable biological properties. Nanotubes show promising potential as biomedical coatings with drug release capability, but more research is needed on electrochemical stability for clinical application. Self-responsive systems can respond automatically to infection in the early stages. Future research should be conducted on drug delivery methods with long-term antibacterial goals and a thorough evaluation of their safety in orthopedic implants.

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