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Review

Antibacterial Pure Magnesium and Magnesium Alloys for Biomedical Materials—A Review

Qingfeng Song [1], Lingzhi Yang [1], Fang Yi [2,3,*], Chao Chen [4], Jing Guo [2], Zihua Qi [2] and Yihan Song [2]

[1] School of Minerals Processing and Bioengineering, Central South University, Changsha 410083, China; 245612087@csu.edu.cn (Q.S.); yanglingzhi@csu.edu.cn (L.Y.)
[2] Xiangya School of Stomatology, Central South University, Changsha 410008, China; 8302220120@csu.edu.cn (J.G.); qizihua0922@163.com (Z.Q.); syh030104@163.com (Y.S.)
[3] Hunan Xiangya Stomatological Hospital, Central South University, Changsha 410008, China
[4] College of Materials Science and Engineering, Taiyuan University of Technology, Taiyuan 030024, China; chenchao@tyut.edu.cn
* Correspondence: yifangcsu@163.com

Abstract: Implant-related infections are one of the major challenges faced by orthopedic surgeries. Developing implants with inherent antibacterial properties is an effective strategy to address this issue. Biodegradable magnesium and magnesium alloys have become a research hotspot due to their good bioactivity, mechanical properties, biocompatibility, and excellent antibacterial ability. However, magnesium and its alloys have rapid corrosion, and the difficulty in expelling harmful magnesium ions and hydrogen gas produced by degradation from the body. This review summarizes the mainstream surface modification techniques such as laser surface modification, friction stir processing, and micro-arc oxidation, along with their impact on the antimicrobial properties of magnesium-based materials. This paper reviews the latest research progress on improving the antibacterial properties of magnesium alloys through alloying and introduces the antibacterial effects of mainstream magnesium alloys and also elaborates on the antibacterial mechanism of magnesium alloy materials. It is expected to provide more basis and insights for the design of biodegradable magnesium alloys with antibacterial properties, thereby promoting their development and clinical application.

Keywords: antibacterial property; magnesium alloys; biodegradable magnesium material; surface modifications; biomedical implants

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1. Introduction

Biomaterials are materials used to diagnose, treat, repair, or replace tissues and organs of the body or to enhance their functions [1]. In contrast, bio-implantable materials are used for implantation into the human body. They interact with human biological +tissues and have strong biocompatibility. Bio-implantable materials have specialized roles in the body and can repair and replace damaged tissues and organs. Bone healing sparked the development of bio-implantable materials. People implanted materials to heal shattered bones. Antimicrobial properties and biocompatibility of bio-implantable materials are two important factors [2].

Initially, non-biodegradable implant materials such as iron and copper were chosen. After bone healing, these materials must be surgically removed. The patient's cost and risk increase with this second procedure. These compounds also inflame neighboring tissues upon implantation. People must use antibiotics to manage inflammation to prevent bacteria from causing significant injury. This may lead to bacterial resistance and, in severe cases, may even require surgery to eliminate the inflammation. These issues restricted implantable material use. To address these issues, the researchers propose a new strategy that uses a drug delivery system based on porous alloys and oxide nanotubes. These

systems can be filled with antibiotics to prevent inflammation from occurring. In the design of drug delivery systems, the application of porous nanomaterials such as porous silicon nanoparticles (pSiNPs) and mesoporous silica nanoparticles (MSNs) is also progressing. These materials could be designed as smart drug delivery systems to control drug release and reduce reliance on antibiotics [3]. Degradable implants are a better alternative to non-degradable implants. By modifying the surface and incorporating antibacterial metal elements, they can also achieve an antibacterial effect, reducing reliance on antibiotics, which is currently a hot topic of research.

Degradable implant materials can degrade independently after some time in the body. The degradation products are eliminated from the body via the kidneys, avoiding the surgical risks associated with the secondary surgical removal of traditional implanted materials [4,5] and the possibility of secondary infections. This reduces the patient's risk of new complications, which aids recovery and lowers costs. Magnesium metal is one of nature's most abundantly stored elements, with numerous sources and low prices. Magnesium alloy has excellent mechanical properties and good biocompatibility as a degradable material. And magnesium is one of the essential nutrients in the human body, participating in various metabolic processes. Therefore, magnesium-based materials are promising metal materials in the field of biomedicine.

The breakdown rate of degradable implant materials is crucial. The rate of deterioration should mirror the rate of tissue repair. It should not be too rapid to prevent function loss before completing its supportive task. And it shouldn't be too sluggish to inhibit tissue growth and healing or induce localized inflammation. Controlling the complete deterioration period of the implanted material is also necessary. Handling degradation time suits different applications. The implanted material must be mechanically robust and biocompatible. The implant also needs to be bacteria-resistant. The body can easily absorb and eliminate its breakdown products. Currently, there are specific issues with using magnesium as an implant material. In vivo, degradation is speedy [6–9], rapidly weakening mechanical characteristics. In vivo study in male Sprague-Dawley® rats showed that the degradation rate of pure Mg was initially 0.4 mm/year and was less than 0.2 mm/year at week 4 and week 12. In vitro experiments showed that when the material was placed in Dulbecco's modified eagle's medium (DMEM) supplemented with 10% fetal bovine serum (FBS), the degradation rate of pure magnesium was 0.75 ± 0.45 mm/year in the first week, and significantly decreased to 0.32 ± 0.04 mm/year after four weeks [10]. When magnesium is in the body, the antibacterial ability was weakened and reduced [11]. And the degradation process produces hydrogen accumulation in the tissue affecting tissue healing [12]. Surface alteration and alloying can fix these issues [13]. The surface modification method delays magnesium corrosion and ensures complete operation. Some specific elements can also be added in the modification process to give the implant material other unique properties [14]. Alloying is one of the known methods for improving the corrosion resistance of magnesium alloys. Various aspects of the properties of magnesium alloys can be enhanced by adding different alloying compositions. Alloying is a research priority in the biomedical field. The article describes surface modification methods, including laser surface modification technology, micro-arc oxidation (MAO), hydrothermal method, layer-by-layer assembly (LBL), electrophoretic deposition, and chemical conversion. And the article explains the principle of surface modification to enhance material properties, discussing the different antimicrobial effects of different coatings and other property improvements. Alloying can alter material characteristics and structure. Magnesium alloy characteristics depend on the elements used [15,16]. Silver, zinc, copper, tin, iron, and gallium are common antimicrobials [17,18]. As shown in Figure 1, this article begins with an overview of the basic knowledge of magnesium alloys as biomaterials, and then delves into a discussion of their advantages and disadvantages. Next, the interaction between magnesium alloys and bacteria is analyzed, which is key to understanding their biocompatibility and potential antibacterial performance. Subsequently, the specific antibacterial effects of two commonly used methods to enhance antibacterial performance (surface mod-

ification techniques and alloying) are introduced, and finally, the antibacterial mechanisms of magnesium-based materials are explored.

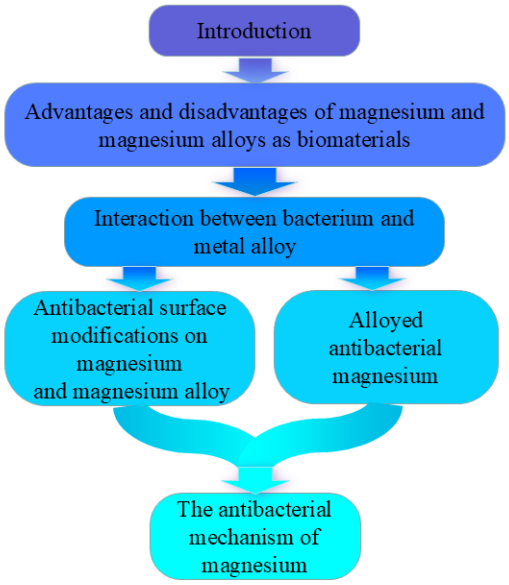

Figure 1. Introduction diagram of the article content.

2. Advantages and Disadvantages of Magnesium and Magnesium Alloys as Biomaterials

2.1. Advantages of Magnesium and Magnesium Alloys as Bioimplant Materials

For a long time, there has been extensive research on biodegradable implant materials, and magnesium and magnesium alloys have stood out among many biological implant materials due to their excellent biocompatibility, similarity to human bones, and the ability to promote osteogenesis.

The mechanical properties of magnesium are superior to those of other implant materials. Magnesium has mechanical properties similar to those of human bones, which gives it a natural advantage over traditional inert biological implant materials [19]. Magnesium has a natural advantage over traditional inert bio-implantable materials. Magnesium has a density of 1.74 g/cm^3, similar to human bone (1.75 g/cm^3) [7]. Magnesium's Young's modulus is akin to that of the human body. It can obviously avoid the stress shielding effect in the replacement of hip joint, knee joint and some fracture fixation devices. However, other conventional implant materials are difficult to avoid stress shielding directly. For example, titanium metal's modulus of elasticity (106.4 GPa) is much higher than human bone. To solve the problem of excessive mismatch between the modulus of elasticity of titanium implants and the modulus of elasticity of human bone, titanium has been made into a porous material [20]. This strategy eliminated the elastic modulus mismatch-induced stress shielding effect. However, the surface area increases after the cloth is absorbent, which significantly increases the cost of titanium surface modification. Porous titanium fabrication is complicated and difficult to mass produce. The density of stainless steel is 7.86 g/cm^3 and the elastic modulus is 110 GPa, which is also much larger than the human bone and difficult to match [12,21]. Magnesium and magnesium alloys do not have this problem, as shown in Table 1, and the mechanical properties of magnesium and magnesium alloys are a good match for bone. The density of magnesium alloys is basically controlled at 1–2 g/cm^3, and the elastic modulus is about 40 GPa [22–24], which is relatively close to the elastic modulus of human bone at 30 GPa [25]. Its low elastic -modulus can effectively reduce the stress-shielding effect of implants in the body. This makes Mg-based materials have obvious advantages in mechanical properties for some hard tissue replacements in vivo.

Magnesium has innate good biocompatibility. Magnesium is one of the nutrients required for the human body to function correctly and is involved in various metabolic

processes. Magnesium is essential for the normal physiological functioning of many tissues and organs, particularly the heart, brain, muscles, and skeletal system. And Magnesium is synthesized and associated with nucleic acids and more than thirty enzymes in the human body. Human serum magnesium ranges from 0.75–0.95 mmol/L [26]. The body fluid can destroy magnesium-based implants. Some of the magnesium is absorbed into the body, while excess is eliminated through the body's metabolic processes. Magnesium in the body also has a diastolic effect on coronary vessels [27].

Furthermore, magnesium promotes osteogenesis. Magnesium can enhance osteogenesis in the human body in at least two ways, and Nie et al. [28] reviewed and explained the mechanism of magnesium-based materials to promote osteogenesis. One method is that magnesium ions can activate the MAPK/ERK signaling pathway in vivo, which promotes bone growth, as shown in Figure 2 [29]. This signaling pathway can regulate bone development and metabolic processes of bone. The other is that magnesium ions enhance osteogenesis by modulating Wnt/β-Catenin, as shown in Figure 2 [29]. The regulating method is that magnesium ions induce the phosphorylation of GSK3 to impede GSK3 binding to β-Catenin, increasing the content level of β-Catenin. And it stimulates β-Catenin to form new bone and expedite skeletal healing.

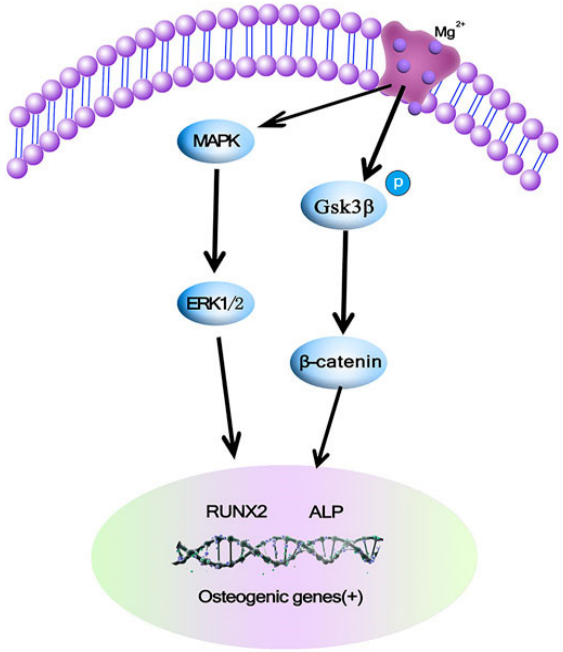

Figure 2. Schematic diagram of magnesium promoting osteogenesis [29].

Table 1. Performance parameters of bone and various implant materials (Partial reference [30]).

Sample	Density g/cm^3	Modulus of Elasticity GPa	Yield Strength (MPa)	Fracture Toughness (MPam1/2)	Corrosion Rate	Reference
Cortical bone	1.75	3–30	130–180	3–6	N/A	[7,12,21,25,31]
Pure magnesium	1.74–2.00	41–45	60–100	15–40	0.2–0.4 mm/year	[10,12,21,25]
Titanium alloy	4.4–4.5	110–117	758–1117	55–115	N/A	[12]
Ti6Al4V	4.51	110	900	N/A	Passivation, Corrosion potential −254 mV	[25,32–35]
AZ91	1.81	45	160	N/A	3.6–4.11 mm/year	[22,23,36]
WE43	1.84	44	170	N/A	5.04–6.19 mm/year	[23,37]
Mg-6Zn	N/A	42.3	169.5	N/A	2.32 ± 0.11 mm/year	[24]
Stainless steel	7.86	110	170–310	50–200	Corrosion resistant	[12,21,38]

2.2. Current Problems with Magnesium and Magnesium Alloys

Magnesium and magnesium alloys, as biomaterials for implants, still have certain issues. The main problems at present include the excessively fast corrosion rate of magnesium-based implant materials in the body, the increase in surrounding environmental alkalinity due to the production of hydroxide ions during the degradation process, and the corrosion process produces a large amount of magnesium ions and hydrogen gas, causing adverse reactions.

Magnesium's high breakdown rate in the body is an issue [19]. The corrosion degradation rate of magnesium-based implants is higher than the rate of human bone development and healing, and this causes the magnesium-based substance to degrade before the bone is supportive, losing its tissue-supporting and cell-adsorbing properties [39].

The corrosion of magnesium will increase the alkalinity of the surrounding environment. In living organisms, the corrosion of magnesium or magnesium alloys releases hydroxide ions, which raise the pH of the surroundings. Magnesium is degraded and corroded vivo via the reaction $Mg + 2H_2O = Mg(OH)_2 + H_2$. Wang et al. [20] found that soaking titanium-magnesium (Ti6Al4V-Mg) alloys in saline for two days produced enough hydroxide ions to elevate the ambient pH above 10. The high pH would surely be a significant issue for the organism. It also increases the alkalinity of the surrounding environment in the body, but much more gently than outside the body, and the body neutralizes alkaline substances produced by degradation [11]. However, it is also faced with the problem of insufficient antibacterial effect, because the antibacterial effect of magnesium mainly depends on the increase of alkalinity in the environment to kill bacteria. If the alkalinity in the body environment is not high enough, the bactericidal effect may also be affected.

At the same time, there are many magnesium ions accompanied by hydroxide ions produced. Although the human body contains a certain amount of magnesium ions, if the magnesium ion content is too high, it will cause hypermagnesemia, magnesium toxicity, and other adverse reactions. In addition to producing enormous volumes of alkaline material and magnesium ions, the corrosion process of magnesium also has hydrogen gas. One mole of magnesium creates around 22.4 L of hydrogen gas. If hydrogen generation exceeds tissue cell absorption, hydrogen will clear the implant. The collected hydrogen will also diffuse into softer and looser tissues to generate air pockets, which can interfere with wound repair and exacerbate the patient's sensation of foreign body experience. Although such cavities can be released through puncture, this is impossible in all cases. For example, in some in vivo vascular procedures, using a prick to alleviate the problem of gas cavities is not ideal [40].

3. Interaction Between Bacterium and Metal Alloy

3.1. The Role of Bacteria and Implant Materials

The antimicrobial properties of bioimplants are critical, and the ability to prevent bacterial growth and spread is essential because they significantly reduce the risk of inflammation and infection, thereby ensuring the success of the implant procedure and patient safety, as well as protecting patients from potential complications. Especially magnesium as an implant material for already infected bone tissue, such as infectious osteomyelitis, contaminated fracture wounds, etc., has obvious advantages. The antibacterial properties of magnesium-based implant materials can effectively prevent further infection and inflammation.

Biomaterials and microorganisms interact complexly. When bacteria encounter the surface of a biomaterial and begin to proliferate, two significant processes occur. The first process is the attachment of bacteria to the surface of biomaterials by some physicochemical effects or specific structures on the bacterial surface [41], which permanently change the surface's structural characteristics and physicochemical properties through their own secreted metabolites [42]. The second process is that the bacterial community produces macromolecular exopolymers on the biomaterial's surface. The macromolecular exopolymers form a biofilm to protect its structure, provide a better habitat for bacterial

development and resist external drug effects [43]. Finally, the bacteria begin to proliferate on the surface of the material.

There are two kinds of interactions between bacteria and materials. The first type is the interaction of microorganisms with metal ions in the environment. The implanted material keeps a higher concentration of metal ions in the surrounding environment. Bacteria will interact with metal ions before touching the bioimplant material [44–46]. The second type of interaction is between the bacteria and the surface of the implant material. After contacting biological material, bacteria will interact with the surface [47,48].

The interaction between alloys and bacteria is mutual; nearly half of the biochemical reactions within bacteria are catalyzed by enzymes containing metal ions. Bacteria need to maintain metal ions at an appropriate concentration to meet their normal physiological needs. Some metal ions themselves possess antibacterial properties. In a liquid environment, the surface of the alloy is constantly eroded by bacteria, causing changes in the surface structure of the alloy and producing metal ions, which in turn kill the bacteria [15,16,49–51]. At the same time, the alloy will also resist bacteria, and the strength of its antibacterial ability depends on the alloying ingredients.

3.2. The Performance of Some Mainstream Antibacterial Metals

The antimicrobial strength of bio-implantable materials depends on their type, concentration, and degradation rate in the body. The type and content of the elements in the material affect these factors. At present, many elements have antibacterial effects, including silver, aluminum, arsenic, cadmium, cobalt, chromium, copper, iron, gallium, mercury, molybdenum, manganese, nickel, lead, antimony, and zinc [17,18,52]. Among them, silver, copper, and zinc are common antibacterial implant materials. By degradation in the body and creating metal ions, these materials compounds are potent, broad-spectrum antimicrobials. The specific antimicrobial concentrations of these metals have been collated in Table 2.

Table 2. Antimicrobial properties of metal elements.

Element	Antibacterial Substances	Minimum Inhibitory Concentration (μM)	Reference
Silver	Silver ion	<1	[53,54]
Copper	Copper ion	12	[55]
Zinc	Activated oxygen	156	[56]

Magnesium also has certain antibacterial properties, but the antibacterial performance of magnesium alone as an implant material is limited. An in vitro antibacterial experiment was conducted using the spread plate method to evaluate the antibacterial rates of planktonic bacteria in culture dishes and adherent bacteria on samples. The tested bacterial species included *Escherichia coli*, *Staphylococcus epidermidis*, and *Staphylococcus aureus*. The results showed that pure magnesium has a certain antibacterial ability. On the first and third days of the test, the antibacterial effects on planktonic *E. coli* were 59.9% and 77.6%, on planktonic *S. epidermidis* were 50.8% and 72.4%, and on planktonic S. aureus were 50.3% and 70.1%. The antibacterial effects on adherent *E. coli* were 70.5% and 88.8%, on adherent *S. epidermidis* were 63.8% and 83.0%, and on adherent *S. aureus* were 65.2% and 81.4%. It can be seen that in the case of magnesium alone for antibacterial action, it has a certain inhibitory ability against adherent bacteria, with an antibacterial rate reaching 60–88%, while the antibacterial ability against planktonic bacteria is weaker, with an antibacterial rate of only 50–70% [57]. Based on the different antibacterial rates of magnesium against planktonic and adherent bacteria, the antibacterial action of magnesium mainly occurs on the material surface, belonging to the second type of interaction, whereas the antibacterial effect produced by the first type of interaction is relatively weaker.

Antimicrobial silver is fantastic. It inhibits most bacteria, fungi, and viruses. Its efficient bactericidal action renders medical surgical instruments and other items antibacterial.

Today, silver is used as an antibacterial substance in surface-modified devices rather than silver-made devices [42]. For example, Catalano et al., Aleksandrova et al., and Tiller sought to employ silver nano-ions to produce antimicrobial film coatings [58–60]. McQuillan et al. [61] found that reactive oxygen species from silver influence cell membrane function, thereby achieving antibacterial effects.

Copper degradation generates reactive oxygen species and copper ions [62]. Salah et al. [63] found that under the action of reactive oxygen species and the increasing concentration of copper ions, the bacterial membrane is severely damaged by reactive oxygen. Subsequently, copper ions and the reactive oxygen they release cause bacterial death. The DNA inside the bacteria is also destroyed as copper ions enter the cells [64].

Zinc has a medium antibacterial action. Zinc inhibits bacterial activity but does not kill bacteria [65]. Gudkov et al., Li et al., and Sirelkhatim et al. [66–68] showed that zinc oxide-based compounds are more effective at killing microbes. Especially after being made into nano-zinc oxide, the antibacterial ability is stronger.

4. Antibacterial Surface Modifications on Magnesium and Magnesium Alloy

Magnesium alloys have been shown to have the ability to promote osteogenesis and effectively avoid the stress masking effect. Because of its biodegradable properties and biocompatibility, it has a promising future in human implantable biomaterials. However, the excessive corrosion rate of magnesium alloys in vivo has always affected their application. Many factors are related to magnesium corrosion rate and biocompatibility, such as the proportion of alloying, the primary type of alloying, the technology of processing methods [69], the surface modification of magnesium alloys [70], and so on. Surface modification techniques for magnesium alloys are one of the finest solutions for improving the problem of excessive corrosion rate of magnesium alloys in vivo [70–74]. There are numerous surface modification techniques for reducing the corrosion rate of magnesium alloys. This paper focuses on several surface modification techniques for increasing antimicrobial properties, such as laser surface modification [75,76], friction stir processing (FSP) [77,78], micro-arc oxidation (MAO) method, hydrothermal method, layer-by-layer assembly (LBL) technique, electrophoretic deposition method, chemical conversion method, and sol-gel method. Representative methods are listed in Table 3. This table details the class of substrate material to which the coating is attached, the coating reference material and the antibacterial properties of the coating.

Table 3. Surface modification methods and their effects.

Method	Subject	Mixed Substances	Antimicrobial Properties	Reference
Laser surface modification	MA8 (Mg-Mn-Ce)	Nothing (superhydrophilic) or fluorosilane (superhydrophobic)	After 48 h, treated superhydrophilic samples showed a bacterial titer of 10^{-8} for both *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*, with a clear antibacterial effect.	[79]
Friction stir processing	AZ91-D (Mg-9Al-1Zn)	HAP (Hydroxyapatite)	AZ91-D Mg alloy surface treated to prepare nanoscale hydroxyphosphate lime composites. Better antimicrobial properties against *Staphylococcus aureus*, *Candida albicans*, and *Aspergillus fumigatus*.	[80]
Micro-arc oxidation method	Mg-2Zn-1Gd-0.5Zr alloy	Cu	Copper ion release gives the material an antimicrobial rate of up to 96% (*S. aureus*).	[81]
	Mg-3Zn-0.5Sr alloy	Ag	Strong antimicrobial properties against *E. coli*	[82]
	AZ31 (Mg-3Al-1Zn)	TA (Tannic acid)	There were 147 CFUs of *E. coli* in the untreated alloy sample dish, while there were only 10 CFUs in the TA-coated alloy sample dish	[83]
	AZ91 (Mg-9Al-1Zn)	Ag	In the inhibition zone test of *Staphylococcus aureus*, it was found that the inhibition zone diameter of the Ag coated sample was 40 mm, and the inhibition zone of the non-Ag coated sample was 15 mm	[84]
Hydrothermal method	$Mg_{68}Zn_{28}Ca_4$(at%)	HA/ZnO (Nano-hydroxyapatite/ZnO)	In the antibacterial experiments against *Staphylococcus aureus* and *Escherichia coli*, the plate counting method was used, and the samples with HA/ZnO coating achieved an antibacterial rate of 100%.	[85]

Table 3. *Cont.*

Method	Subject	Mixed Substances	Antimicrobial Properties	Reference
Layer-by-layer assembly technology	APTMS/Mg ((3-aminopropyl)trimethoxysilane/Mg)	AgNPs	Samples coated with AgNPs on agar plates at 37 °C showed an inhibition zone diameter of 22.10 mm against *E. coli*, which is larger than the inhibition zone diameter of uncoated samples (14.86 mm).	[86]
	AZ31(Mg-3Al-1Zn)	AgNPs/PMTMS	The antimicrobial efficacy of $(AgNPs/PEI)_5$ multilayer film and $PMTMS/(AgNPs/PEI)_5$ film against S. aureus was 98.40% and 85.00%, respectively	[87]
Electrophoretic deposition method	TiO_2/MgO	Ag-Zeo-Hap (Ag-zeolite-hydroxyapatite)	The inhibition zone of the Ag-Zeo-Hap coating against *E. coli* is 3.86 mm, and the number of *E. coli* colonies in the petri dish decreased by 94%.	[88]
Chemical conversion method	AZ31B (Mg-3Al-1Zn)	MgO-MgF_2	Through the *E. coli* antibacterial experiment, the antibacterial rate of the alloy samples with fluoride coating reached 99.99% after 24 h.	[89]
Sol-gel method	Mg	$Mg(OH)_2$	After 30 h of sol-gel treatment, the inhibition ability of the samples against Enterobacteriaceae was significantly enhanced compared with the hydrothermal treatment materials, and the optical density of *E. coli* at 600 nm was between 0.2 and 0.3.	[90]

4.1. Laser Surface Modification

Laser surface modification technology uses a high-energy laser to treat the surface of magnesium alloy. Make the melting-solidification process happen to modify the microstructure. Laser treatment changes the surface properties of magnesium alloy. Varying the intensity and speed of the laser can obtain different forms of microstructure and surface properties. As shown in Figure 3 [91]. Emelyanenko et al. [79] used a surface laser to process the MA8 magnesium alloy. He chose *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* for the antimicrobial experiments. After comparative experiments, the highly hydrophilic alloy with laser processing performed better against *Pseudomonas aeruginosa* than the MA8 standard polishing alloy. After 48 h, the antibacterial performance peaking, and the antimicrobial effect is more than 60% stronger than the original alloy. The treated material was a bit more antibacterial against *Klebsiella pneumoniae* than polishing.

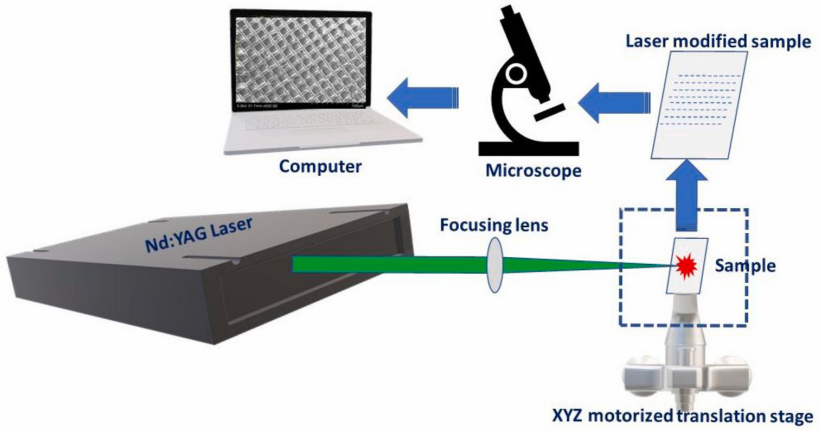

Figure 3. Laser surface modification technology [91].

4.2. Friction Stir Processing

Friction stir processing technology is derived from friction stir welding technology. Rotating the cylindrical head at high speed violently rubbed and exothermic the material surface, causing substantial plastic deformation. The surface microstructure is homogenized, refined, and densified [77]. The specific formation process is shown in Figure 4 [92]. Nasiri et al. [93] observed that homogenized dispersed particles strengthen brittle alloy components and improve magnesium alloy tensile characteristics. This method is useful for coating the surface of magnesium alloys. Kundu et al. [80] used friction-stirring composite coating on the surface of AZ91-D magnesium alloy to create hydroxyapatite

surface composites. Using *Staphylococcus aureus*, *Candida albicans*, and *Aspergillus fumigatus* as experimental strains, the material's antibacterial performance was more than three times that of the raw material. Even rubbing and stirring the material does not prepare HA composite layer. Antibacterial activity against various experimental bacteria rose by 60–90% after treatment.

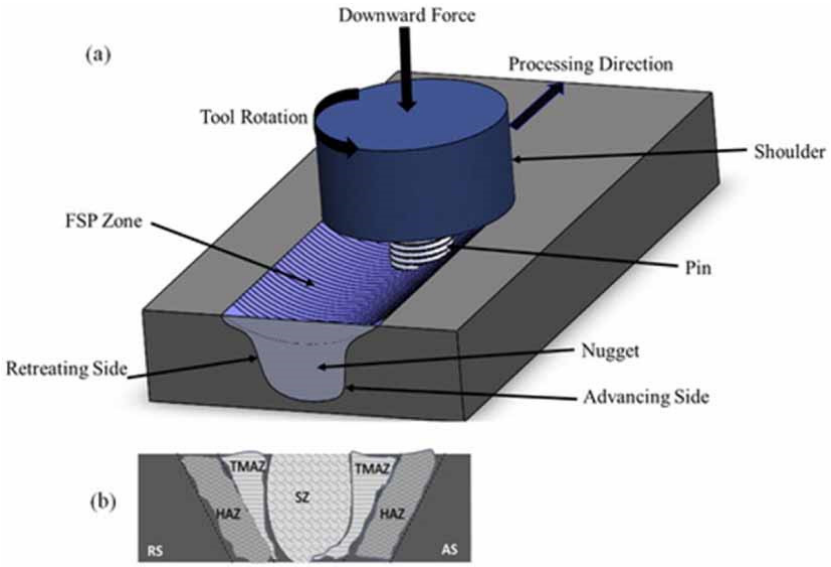

Figure 4. Schematic of (**a**) FSP and (**b**) transverse cross section view of FSPed region [92].

4.3. Micro-Arc Oxidation Method

The main principle of surface modification of micro-arc oxidation is that the metal surface grows a ceramic film layer with matrix metal oxide and electrolyte compounds as the main components under the action of instantaneous high temperature and high pressure produced by arc discharge. Figure 5 depicts the formation process of the coating, with the yellow part indicating the molten oxide, the red area denoting the reaction zone, and the green part showing the oxide after cooling and solidification [94]. Ceramic micro-arc oxidation (MAO) coating adheres well to magnesium alloys. Its surface has a distinctive porous morphology [95]. Due to their microporous topology, MAO coatings can combine more closely with other materials. And this allows the micro-arc oxide coating to be used as a base coating. Different surface-modified materials can comprise to the surface of the micro-arc oxide coating. The participation of silver, zinc, and copper elements can create antibacterial coatings. It's important to note that too much metal can harm human cells [96]. Chen et al. [81] used MAO technology to fabricate a coating containing copper on the surface of magnesium alloys. The coating was found to have good corrosion resistance, with a corrosion rate of 0.16 mm/y after two weeks. At the same time, the release of copper ions in the coating also inhibited the proliferation of bacteria, and the antibacterial rate against *Staphylococcus aureus* reached 96% after 12 h of culture. Cui et al. [83] found that adding tannic acid (TA) to MAO coating reduces micropore size and microcracks. MAO-TA coatings are thicker than MAO coatings, and TA-magnesium complexes can slow magnesium alloy corrosion. In in vitro antimicrobial testing, the TA-MAO coating increased antimicrobial ability. Silver is often added to MAO coatings to boost their antibacterial properties. Sukuroglu et al. and Chen et al. [82,84] incorporated silver into the MAO coating. In the *Staphylococcus aureus* test and the antimicrobial test for *E. coli*, almost no bacteria survive on the silver-coated surface, showing strong antimicrobial ability.

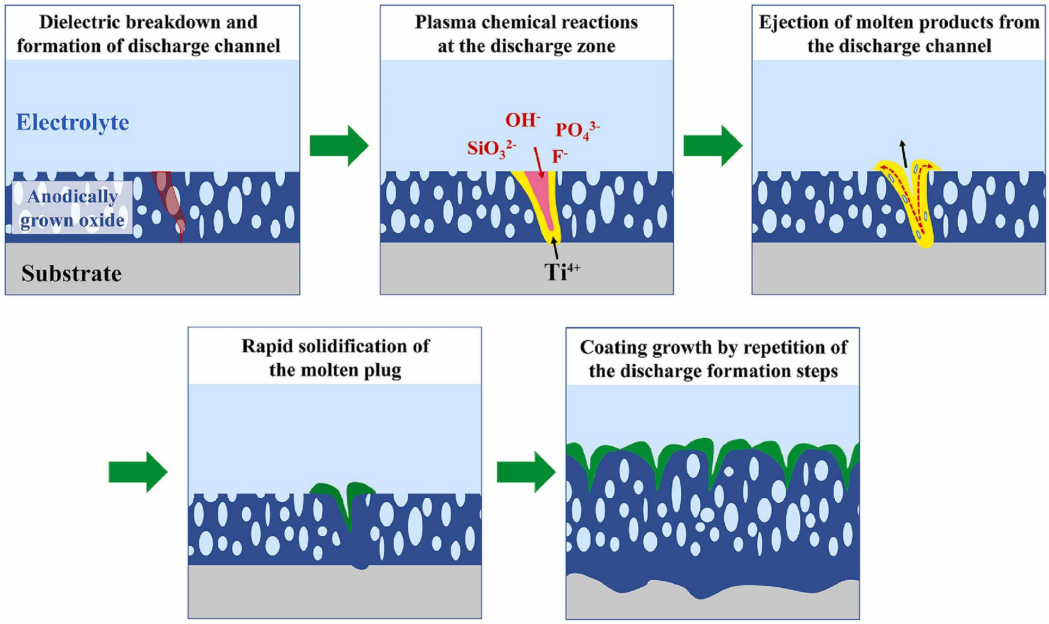

Figure 5. Formation process of micro-arc oxidation coating [94].

4.4. Hydrothermal Method

The hydrothermal method involves placing the metal in a container at high temperature and pressure. The metal surface absorbed particles from the liquid. The particles crystallize and precipitate. Precipitates produce a uniform, complete, smooth, and dense covering on the substance [97–99]. As shown in Figure 6, Ca-P and $Mg(OH)_2$ composite coatings were prepared on magnesium based materials by hydrothermal method at 120 °C [100]. This approach increases the corrosion resistance and biodegradability of magnesium alloy surface coatings [99,101–103]. Ji et al. [97] produced a dense, seamless HAp coating. The HAp coating made magnesium alloys corrosion-resistant and extended Gentamicin Sulfate (GS) release. Song et al. [99] used a hydrothermal approach to create a three μm thick magnesium hydroxide coating on the surface of magnesium-lithium alloys with outstanding corrosion resistance. Zhou et al. [85] prepared a 16 μm thick HA Nano-hydroxyapatite/ZnO coating on the surface of $Mg_{68}Zn_{28}Ca_4$ by one-step hydrothermal method. The overcoat material showed good biocompatibility and excellent corrosion resistance, and the antibacterial rate against staphylococci was close to 100% in vitro antibacterial experiments.

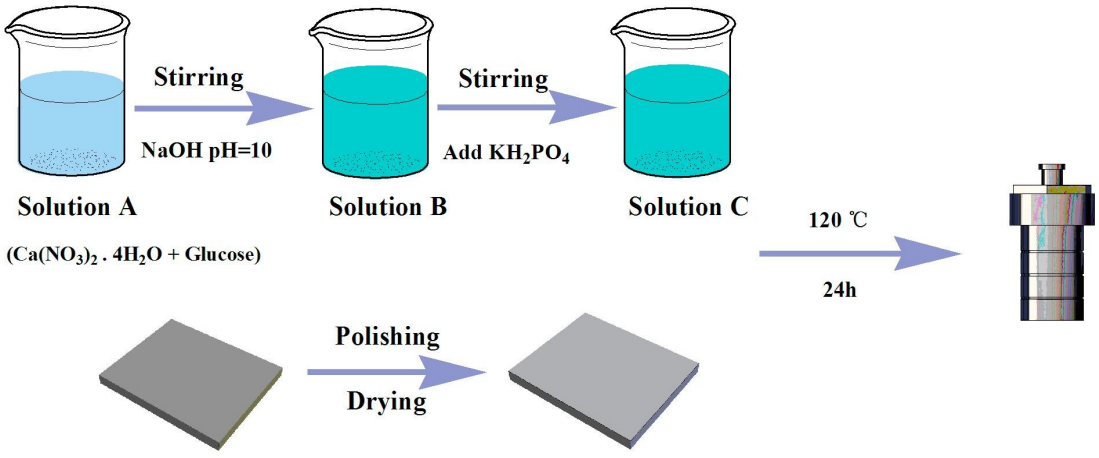

Figure 6. Schematic diagram of composite coating prepared on pure magnesium by hydrothermal method [100].

4.5. Layer-by-Layer Assembly Technology

Layer-by-layer assembly (LBL) technology enables coatings with diverse functions to be composited together [104,105]. Figure 7 illustrates the specific formation process of the layer-by-layer assembly coating, where rods and sheets of different colors correspond to one-dimensional (1D) and two-dimensional (2D) structures formed by molecules of various substances [106]. Zeng et al. [86] used a self-assembly technique to immobilize silver nanoparticles on the surface of an APTMS-modified magnesium alloy. The breakdown voltage of the treated material is −1040 mV, and the diameter of the inhibition band for *E. coli* is up to 14.86 mm. The material exhibits better corrosion resistance and excellent antimicrobial properties against *E. coli*. Zhao et al. [87] made silver nanoparticle-polysiloxane composite coatings. Composite coatings improve antibacterial and corrosion resistance. The slow-released silver ions in the coating played a major bactericidal role, and the sterilization rates of $(AgNPs/PEI)_5$ multilayer materials and $PMTMS/(AgNPs/PEI)_5$ multilayer materials against *Staphylococcus aureus* were 98.4% and 85.0%, respectively.

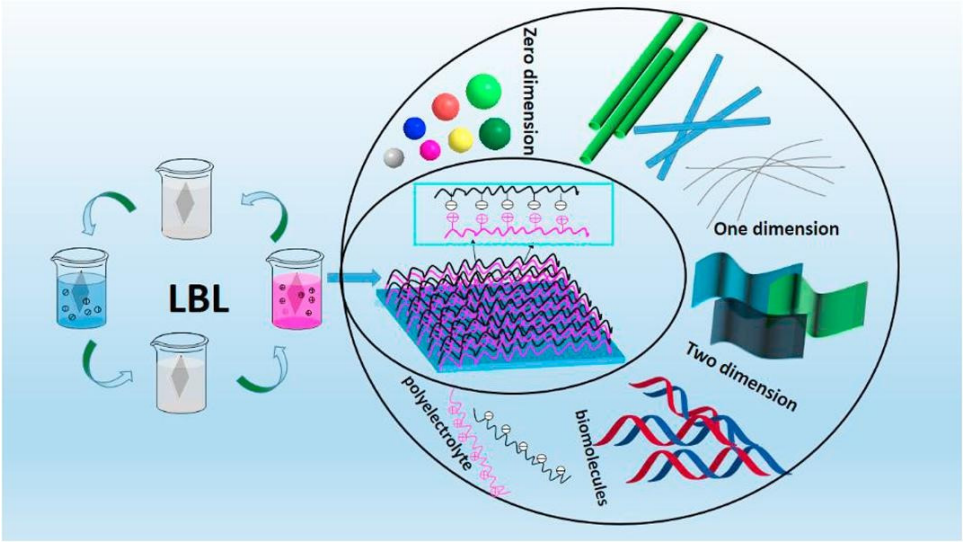

Figure 7. General scheme of the LbL process with a wide variety of assembly materials [106].

4.6. Electrophoretic Deposition Method

The electrophoretic deposition method uses direct current to transport charged ions in a suspension in a specific direction, depositing and attaching to the material's surface to form a coating. As shown in Figure 8, a voltage was used to drive the nano-silica to attach to the prototype material to form a coating [107]. The formation of a coating on Mg-based materials is similar, as long as the anode material is replaced by a Mg-based material, the electrophoretic deposition method can be used to prepare a coating on the surface of Mg-based materials. Energization period and voltage intensity affect coating properties [108]. This method offers several advantages. For instance, coating preparation is delicate and does not cause heat stress or high temperature-induced material brittleness. The coating can be applied uniformly to alloy material in all directions, recessed places, and delicate components. The coating can be adjusted from 1 μm to 100 μm. The downside is that the material must be conductive. Conductive layers must be produced before electrodeposition for non-conductive materials, which adds cost and process [13]. Bakhsheshi et al. [88] used PVD-assisted electrodeposition to complete the silver-doped zeolite hydroxyapatite (Ag-Zeo-HAp) coating on the surface of magnesium alloy with titanium dioxide coating. The corrosion potential of the material is −1540 mV and the corrosion current is $0.7 \mu A/cm^2$. And showed excellent antimicrobial rates in Petri dishes of *E. coli*, with a 94% reduction in colonies. The range of the suppression band with the Ag-Zeo-Hap coating material is 47% larger than the range without the Ag-Zeo-Hap coating material.

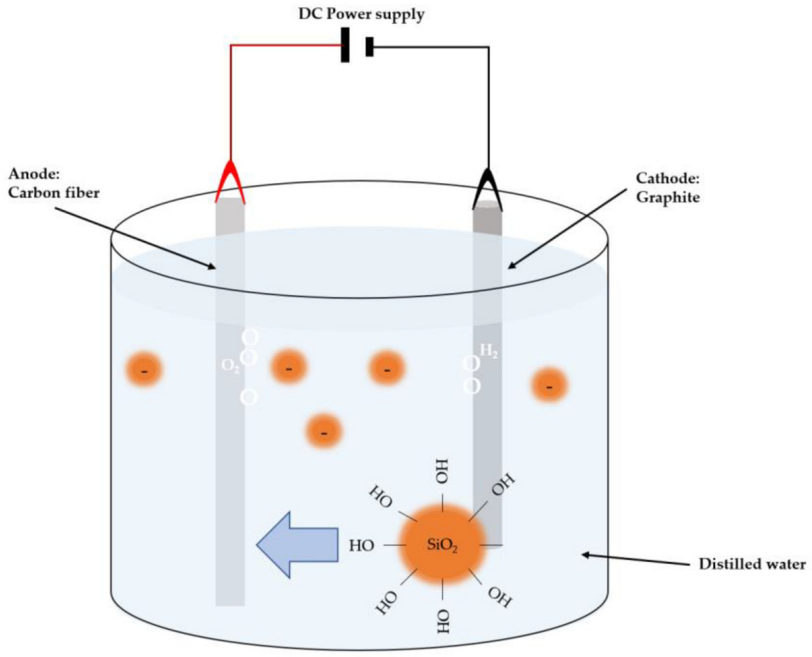

Figure 8. Schematic illustration of EPD configuration for CF surface modification [107].

4.7. Chemical Conversion Method

The chemical conversion method uses the surface of the substrate to undergo complex chemical reaction with the components in the solution, and the reaction product film is generated on the surface, as shown in Figure 9 [109]. The surface of the material reacts with phosphoric acid ions and metal ions in the solution to form a dense coating. For magnesium-based materials, complex surface reactions result in the formation of a coating of magnesium oxide, magnesium hydroxide, or other oxides and hydroxides on the surface. The chemical conversion method uses components in a solution. The surface reacts to generate magnesium oxide, magnesium hydroxide, or other oxides and hydroxides after complex interactions. This covering grows in situ. The coating has excellent adherence and a strong substrate-coating bond [110]. This method can also be used to pretreat the material for better adhesion of the outer coating to the surface of the material [111]. Yan et al. [89] successfully synthesized a fluoride coating on the surface of magnesium alloy by chemical conversion method in hydrofluoric acid, which significantly improved the corrosion resistance of the material and showed good biological activity in plasma. It has also shown a non-toxic effect in vitro experiments on BMMSCs. In the 24-h *E. coli* antibacterial test, the fluoride-coated sample had a killing rate of 99.99%.

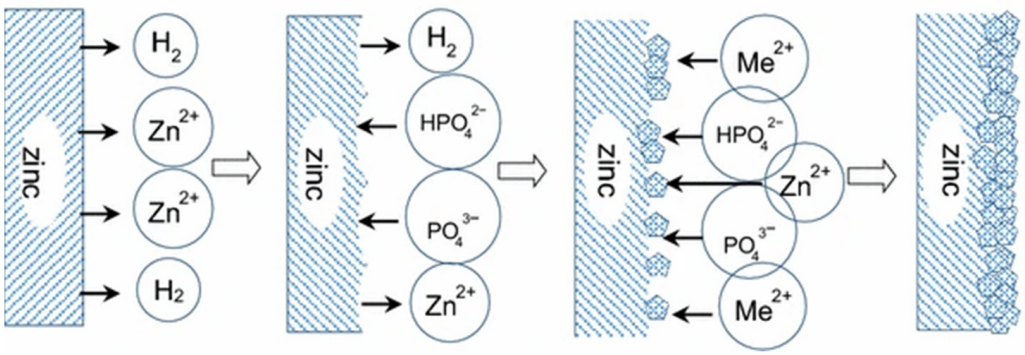

Figure 9. Zinc base material surface phosphate chemical conversion coating process diagram [109].

4.8. Sol-Gel Method

The sol-gel method does not melt the substrate and is carried out at room temperature. This method allows for simple control over the chemical composition of the film. The coating is pure and does not introduce impurities. It is well suited for complex and uneven surfaces. The coating adheres well and bonds directly with the material. However, the coating produced by this process is relatively thin. Its preparation process is shown in Figure 10 [112]. The different colored spheres in the figure represent different kinds of precursors. Tatullo et al. [90] subjected superplastically treated magnesium devices to sol-gel treatment to investigate their bioactivity and antibacterial properties. The study found that the material had excellent cell compatibility. After a seven-day L929 cell viability test, the cell survival rate was 100%, indicating that the material had very good cell activity. The antibacterial performance was also enhanced. Compared to materials treated with the hydrothermal method, materials treated with the sol-gel method showed a lower survival rate of *E. coli* in a 30-h antibacterial test, with an optical density at 600 nm of 0.2–0.3.

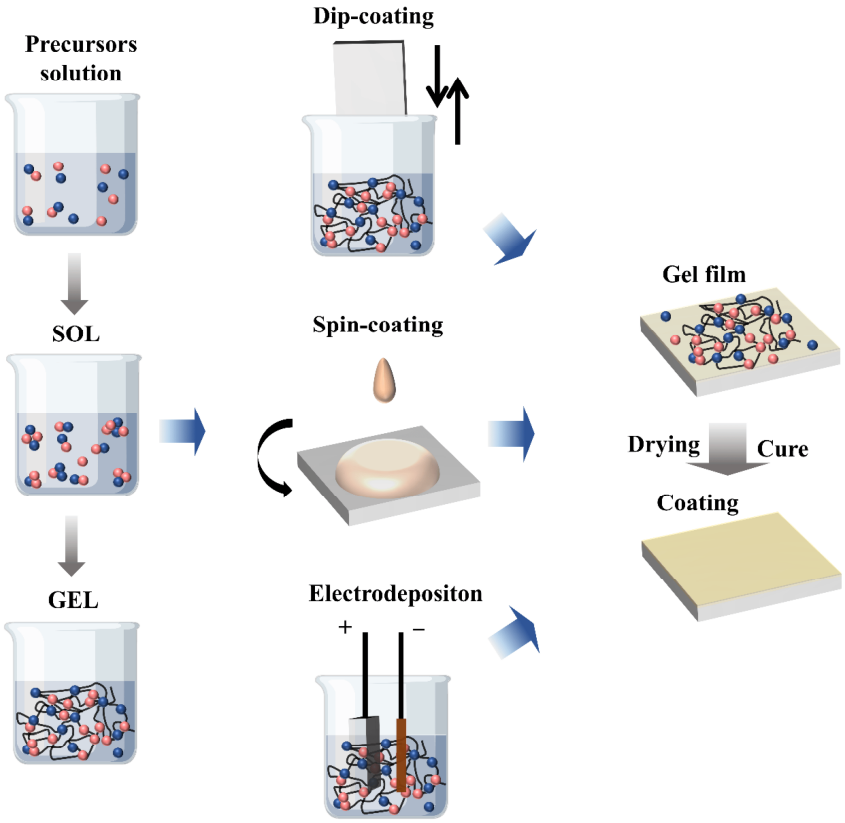

Figure 10. Schematic of steps and processes used to obtain sol-gel coatings [112].

The combined use of multiple methods can obtain superior-performance surface coatings. Shang et al. [113] used the self-assembly method (SAM) and micro-arc oxidation (MAO) to create composite coatings with more excellent corrosion resistance than MAO alone. Multi-method surface coatings on magnesium alloys function better. The combined use of the self-assembly method (SAM) and layer-by-layer assembly method (LBL) preparing chitosan-functionalized graphene oxide (GOCS)/heparin (Hep) multilayer coatings. The coating exhibits high blood compatibility and in vitro corrosion resistance.

5. Alloyed Antibacterial Magnesium

5.1. Properties of Magnesium Alloys

Magnesium bioimplants have some drawbacks. For instance, in vivo, antibacterial activities are suppressed [11], and the corrosion rate is too high [19,39]. Magnesium alloying can fully exploit the benefits of magnesium as a bioimplant material. Magnesium alloy

properties can be enhanced by incorporating various antimicrobial alloy components. Silver, copper, tin, and zinc are common antimicrobial metals in magnesium alloys. Magnesium alloying can dramatically raise the pH of the environment surrounding the implant [114] and has more extraordinary antibacterial characteristics than pure magnesium [114–118]. As element proportions increase, metallic elements' attributes alter. These magnesium alloys with antimicrobial metal components show biocompatibility comparable to pure magnesium [115,116] and better cell adhesion and proliferation promotion [114]. Alloying magnesium changes the degradation rate of the alloy. Magnesium-silver alloys have a reduced corrosion rate after treatment [117]. Many types of magnesium alloys have significantly reduced corrosion rates, such as AZ type, ZK type, WE type, etc. [119,120].

Magnesium alloys are better implant materials than pure magnesium due to their corrosion resistance, antibacterial efficiency, and biocompatibility. Many elements, including silver, copper, tin, zinc, chromium, iron, gallium, and others, can be introduced into magnesium alloys to modify their properties. Among them, silver and copper have a strong antibacterial effect and have obvious advantages over traditional antibiotics in controlling bacterial resistance. Alloying magnesium with tin, zinc or iron improves antimicrobial efficacy, and alloying metals provides a means of physical antimicrobial protection compared to injectable antibiotics, reducing the risk of development of resistance, and can provide long-lasting antimicrobial protection. Various alloys are created by combining one or more of these with magnesium. Table 4 provides specific details on the compositions, preparation methods, and antibacterial properties of mainstream magnesium alloys.

Table 4. Magnesium alloys and their effects.

Alloy	Elemental Ratios	Production Method	Antibacterial and Other Properties	Reference
Magnesia-silver alloy	Mg-4 wt% Ag	Solution treatment, aging heat treatment	The number of bacteria adhering is reduced by 50–75%, the viability of bacteria is reduced by 74–79%, and the sterilizing rate is 90%.	[115]
	Mg-6 wt% Ag	Solution treatment, T4	Bacterial survival was 18.64%. (Mix *S. aureus* and *S. epidermidis* 1 to 1)	[117]
	Mg-8 wt% Ag	Solution treatment, T4	Bacterial survival was 14.75%. High silver content showed poor osteogenic activity and degradation rate.	[117]
Magnesium-copper alloy	Mg-0.03 wt% Cu	Ingot casting method	In the 6 h anti *Staphylococcus aureus* experiment, the remaining bacterial colonies were 4.1 CFU/mL. Best bone formation ability.	[118]
	Mg-0.01 wt% Cu	Ingot casting method	Degradation rate 20 mm/year. Better antimicrobial effects against *MRSA* and *Staphylococcus epidermidis*, CFU stands for 30.3 ± 7.4, 18.7 ± 5.2, and 11.5 ± 3.8	[121]
	Mg-0.25 wt% Cu	Ingot casting method	Rapid release of copper ions, significant antibacterial effect, Rapid release of copper ions, significant antibacterial effect, CFU of *MRSA* and *Staphylococcus epidermidis* stands for 30.3 ± 7.4, 18.7 ± 5.2, and 11.5 ± 3.8	[121]
	Mg-0.5 wt% Cu	Ingot casting method	Degradation rate is more than 50 mm/year. In the 6 h anti *Staphylococcus aureus* experiment, the remaining bacterial colonies were 2.3 CFU/mL. Degradation is faster, with a 3-day degradation rate approaching 90 mm/year. Less osteogenic capacity.	[118]
Magnesia-tin alloy	Mg-1Zn-0.5Sn	Melted in an induction furnace under Ar gas protection and extruded at 300 °C.	In the antibacterial experiment, the optical density was detected at 600 nm, with the optical density of *Escherichia coli* stabilized at 0.4, and that of *Staphylococcus aureus* stabilized at 0.35.	[114]

Table 4. *Cont.*

Alloy	Elemental Ratios	Production Method	Antibacterial and Other Properties	Reference
Magnesium-zinc alloy	Mg-4Zn-xSn (x = 0, 1.0, 1.5 wt%)	Melted in an induction furnace under Ar gas protection and extruded at 300 °C.	The number of *Staphylococcus aureus* colonies in the samples with Sn group decreased by more than 50%, and the antibacterial ability was significantly improved compared to the samples without Sn group.	[122]
	Mg-5.6 wt% Zn	Metal ingot	In the test experiment of the display board method, the Mg-Zn alloy achieved a 1–3 day antibacterial rate of 72.8–96.2% against planktonic *MRSA*, and a 1–3 day antibacterial rate of 62.3–84.5% against adherent *MRSA*.	[123]
	Mg-1Ca-0.5Sr-2Zn	Melting in a high-purity graphite crucible (protected by Ar gas) and thermally extruding at 320 °C	The killing rate of *Staphylococcus aureus* is 76.9%.	[116]
	Mg-1Ca-0.5Sr-4Zn, Mg-1Ca-0.5Sr-6Zn	Melting in a high-purity graphite crucible (protected by Ar gas) and thermally extruding at 320 °C	The bactericidal rates of Mg-1Ca-0.5Sr-4Zn and Mg-1Ca-0.5Sr-6Zn against *Staphylococcus aureus* are higher than 96.6%.	[116]

5.2. Mg-Ag Alloy Properties

Magnesium-silver alloys combine silver's antibacterial qualities with magnesium's outstanding characteristics. Tie et al. [115] successfully fabricated magnesium-silver alloys with enhanced properties using solid solution and heat treatment processes. Comparing magnesium-silver alloys to glass and titanium, alloys showed antibacterial solid action. Bacteria adhering to magnesium-silver alloys were reduced by 50–75%, viability by 74–79%, and death by over 90%. Tie et al. [115] tested biocompatibility for two weeks in cellular tests. Magnesium-silver alloys provide over 95% cell adhesion and survival. Magnesium-silver alloys are more bioactive than titanium and glass. Liu et al. [117] prepared magnesium-silver alloys to enhance antibacterial properties. The alloy was found to be non-toxic to human primary osteoblasts. The corrosion rate of the alloy after T4 treatment was significantly reduced. Furthermore, the bacterial activity (a mixture of *Staphylococcus aureus* and *Staphylococcus epidermidis*) of Mg-6Ag and Mg-8Ag after T4 treatment was 18.64% and 14.75%, respectively

5.3. Mg-Cu Alloy Properties

Magnesium-copper alloys have high biocompatibility and long-lasting bactericidal characteristics. Magnesium-copper alloy kills bacteria by dissolving their biofilm and has obvious antibacterial and fungicidal capabilities [124]. Liu et al. [118] research on magnesium-copper alloys found that the alloys can stimulate angiogenesis, induce osteogenesis, and also provide long-lasting antibacterial properties. In the antibacterial experiment against *Staphylococcus aureus*, under normal pH conditions, the antibacterial effect from 3 to 72 h showed that the magnesium-copper alloy's antibacterial effect was stronger than that of pure magnesium, and the antibacterial effect became stronger as the copper content in the alloy increased. After 72 h, the *Staphylococcus aureus* colonies on both the magnesium-copper alloy and magnesium were eliminated. In a neutral pH environment, the bactericidal effect of the magnesium-copper alloy from 3 to 24 h was somewhat reduced, but it still killed the bacteria after 72 h. Li et al. [121] studied the antibacterial effects and other biological properties of magnesium-copper alloys with 0.05, 0.1, and 0.25 wt% copper content. In the 24-h antibacterial tests against *MRSA*, *Staphylococcus epidermidis*, and *Escherichia coli*, the magnesium-copper alloys performed better than titanium. The number of formed units of bacterial colonies in the Mg-0.1Cu group were 30.3 ± 7.4, 18.7 ± 5.2, and 11.5 ± 3.8, respectively. In the Mg-0.25Cu group, these numbers decreased to 8.2 ± 3.3,

4.4 ± 2.4, and 7.9 ± 2.7. At the same time, biocompatibility is good and did not cause side effects. The antibacterial effect of the magnesium-copper alloys gradually increased with the increase of copper content, which confirmed the research conclusions of Lui and his team.

5.4. Mg-Sn Alloy Properties

Tin is a vital trace element. Tin and magnesium have good solid solubility, and tin can prevent corrosion by increasing magnesium's electrode potential [114]. Zhao et al. [114] found that tin oxide and tin dioxide create a membrane on the alloy's surface as it corrodes. The membrane prevents corrosion of the alloy. Zhao et al. also observed magnesium alloys containing tin have better antibacterial characteristics. In vitro, the alloys demonstrated good biocompatibility, allowing biological cells to cling to the alloy surface and promote cell proliferation. Jiang et al. [122] studied the antibacterial activity of Mg-4Zn-xSn alloys (where the content of Sn is 0, 1.0, 1.5 wt%). The experimental results of antibacterial activity against *Staphylococcus aureus* showed that the number of bacterial units in the 1.0 Sn and 1.5 Sn groups was half that of pure magnesium after 12 h, demonstrating significant antibacterial effects.

5.5. Mg-Zn Alloy Properties

Zinc is another crucial trace element. Zinc additives in magnesium improve mechanical strength and ductility [125]. Yu et al. [123] research indicates that magnesium-zinc alloys have a good antibacterial effect on MRSA. The bactericidal rate of the samples against planktonic MRSA reached 72.8% and 96.2% on the first and third days, respectively, and the bactericidal rate against adherent MRSA reached 62.3% and 84.5%, respectively. In vitro experiments show that the alloy extract can inhibit bacterial growth. The antibacterial test against *Staphylococcus aureus* found that Mg-1Ca-0.5Sr-2Zn exhibited a relatively low kill rate of 76.9%. While the kill rates of Mg-1Ca-0.5Sr-4Zn and Mg-1Ca-0.5Sr-6Zn were higher than 96.6% [116].

6. Antibacterial Mechanisms

6.1. PH and Antibacterial

Degradation of magnesium and magnesium alloys produce hydroxide roots, raising the surrounding pH. A high pH inhibits the growth of bacteria [126]. Alkaline pH suppresses the expression of bacterial agr RNAIII [127] and hinders bacterial multiplication. The solution pH can reach 9–10 after the breakdown of magnesium-based compounds in vitro [126,128]. However, most bacteria thrive at pH 6–8 [129]. Bacterial biofilms thrive in acidic pH 5–6 environments [130]. When pH exceeds 7, biofilms of common bacteria like *Staphylococcus aureus* weaken and are easily eliminated [131]. The alkaline environment created during magnesium breakdown contributes significantly to magnesium's remarkable antibacterial ability. This idea has been supported by experiments [114,118,132–134]. Rahim et al. [135] showed that pH affects antibacterial action in magnesium-degraded supernatants. After increasing the total amount of magnesium, the supernatant had a higher pH and more pronounced bacterial suppression. However, after neutralizing the pH of the supernatant, the antimicrobial effect worsened, and the bacterial inhibitory effect of the supernatant was lost. It shows that alkalinity in the environment is crucial to antibacterial activity.

Magnesium-based alloys induce alkaline environmental changes due to deterioration process. Magnesium breakdown produces alkaline compounds. The anode oxidizes magnesium to magnesium ions. The cathode reduces water to hydrogen and hydroxide [136]. This creates alkaline magnesium hydroxide. Magnesium hydroxide forms an exterior coating on the alloy. The outer film dehydrates, forming a magnesium oxide inner film [132,137–141]. The deposited layer provides some corrosion resistance. However, anions in living organisms can react with magnesium ions [142,143]. This reaction weakens magnesium oxide and hydroxide's protective layer, making them reactive [144].

Thus, chloride ions in the environment quickly combine with magnesium hydroxide to create magnesium chloride [139,145]. This process eventually destroys the outer layer of magnesium hydroxide and exposes the inner layer of magnesium oxide. Yao [141] found that magnesium oxide reacts readily with water. The volume of the resultant magnesium hydroxide expands. The oxide coating will burst if too much magnesium oxide reacts and expands. After the oxide film breaks, the magnesium alloy corrodes. This process generates alkaline chemicals, which increase the alkalinity of the surrounding environment. Lin [133] observed that in alkaline conditions, bacteria must use considerable amounts of their hydrogen ions to neutralize ambient hydroxide ions. This would impair the bacteria's internal proton electrochemical gradient. The internal bacterial electrochemical gradient drives ATP production. Electrochemical gradient disruption restricts ATP synthesis and kills bacteria.

6.2. Biochemical Effects of Magnesium Ions on Bacteria

Another antibacterial function of magnesium implants is the usage of magnesium ions released into the environment to kill microorganisms. Magnesium ions' antibacterial action is intimately linked to their influence on bacterial biofilms [146]. Magnesium ions specifically bind to biomembranes, thereby increasing the permeability of the biomembranes and even destroying them, leading to a significant loss of cellular contents and bacterial death [147]. Magnesium ions also exert immunomodulatory effects by regulating the local immune environment, thereby producing antibacterial effects. Magnesium ions can also regulate the local immune environment to enhance the antibacterial effect. High concentrations of magnesium ions promote macrophage polarization to the bactericidal M1 type and induce the expression of two important substances, TNF-α and iNOS, in macrophages, thereby significantly increasing phagocytic activity against bacteria [148]. It is worth mentioning that in an environment with low concentrations of magnesium ions, magnesium ions can reduce the production of pro-inflammatory cytokines by macrophages by inhibiting the activation of transcription factor NF-κB, such as tumor necrosis factor α (TNF-α), interleukin 6 (IL-6), and interleukin 1β (IL-1β), thereby controlling inflammatory cell aggregation and activation, and enhancing human bone marrow mesenchymal stem cell (hBMSC) chondrogenic differentiation [149].However, magnesium ions cannot be used as the primary force for sterilization. Most bacterial cells contain magnesium ions. For some bacteria, the amount of magnesium ions in them is very high [150,151]. To kill the bacteria alone, magnesium ions must exceed the organism's magnesium ions [133].

In alkaline settings, magnesium ions have a substantially higher antibacterial capacity. Alkaline surroundings increase magnesium ions' antibacterial impact [152]. Magnesium ions and the alkaline environment magnesium creates make magnesium alloys antibacterial [133]. The bactericidal effect of magnesium ions depends on the alkaline environment [152]. Thus, alkaline conditions are necessary for magnesium alloys' antibacterial properties.

6.3. Direct Contact Sterilization

The surface of the alloy directly contacting with bacteria can destroy the bacterial membrane and structure, and it can also inhibit the bacterial adhesion to the alloy surface to achieve antibacterial effects [47,127]. Magnesium has a certain contact antibacterial ability, but its antibacterial capacity is limited. When magnesium forms alloys with other antibacterial metals or forms oxides, it exhibits better antibacterial effects. In vitro antibacterial experiments, Qin et al. used the spread plate method to test the antibacterial effects of magnesium and magnesium alloy (Mg-Nd-Zn-Zr) on *Escherichia coli*, *Staphylococcus aureus*, and *Staphylococcus epidermidis*. The results showed that pure magnesium has a good antibacterial effect on adherent bacteria, and the Mg-Nd-Zn-Zr alloy has a stronger antibacterial effect [57]. Nemanja et al. explored the antibacterial mechanism of magnesium oxide particles and found that the antibacterial activity of magnesium oxide is closely related to its surface properties, and reducing the low-coordinate oxygen atoms on the MgO surface

greatly promotes the antibacterial process of magnesium oxide. Magnesium oxide can undergo hydrolysis reactions in a liquid environment, forming defects or vacancies on the surface, which destroys the original surface of magnesium oxide. When the low-coordinate oxygen atoms on the surface of magnesium oxide are reduced, the MgO surface becomes less susceptible to water, maintaining more of the original surface. The original surface of MgO can destroy the bacterial cell wall through physical contact, causing cell content leakage and thus killing the bacteria [153]. At the same time, MgO slurry powder has shown bactericidal effects on bacteria such as *Escherichia coli*, Salmonella, and *Pseudomonas aeruginosa*, demonstrating a broad antibacterial spectrum [154].

6.4. Affects Bacterial Electron Transfer

Bacteria produce energy substance adenosine triphosphate (ATP) through respiration, which is vital for their survival. The synthesis of ATP in bacteria depends on the electrochemical gradient formed by the transfer of charged particles, and the formation and stability of the electrochemical gradient are very important for the formation, transport, and respiratory function of ATP in bacteria [155,156]. The proton electrochemical gradient is a transmembrane proton concentration difference established by the cell through the electron transport chain (ETC) during cellular respiration. In bacteria, this process usually occurs on the cytoplasmic membrane. Electrons are transferred from NADH or FADH2 to oxygen, while protons (H+) are pumped from the inside of the cell to the outside, forming a proton gradient. This gradient provides the necessary driving force for ATP synthesis [157–159]. As shown in Figure 11(4), electrochemical corrosion occurs between magnesium and other metallic elements in magnesium-based materials, causing electron transfer in the surrounding environment and producing many electrons. The yellow and blue circles in the figure represent different types of metals [48]. Studies have shown that after bacteria encounter magnesium-based materials, many protons are produced, and the proton reserve in the bacterial membrane gap is excessively consumed, thereby destroying the proton electrochemical gradient of the bacteria. The interruption of the transmembrane proton electrochemical gradient can lead to a decrease in ATP synthesis, which in turn limits the formation and maintenance of the glycocalyx, causing metabolic disorders in bacteria [160], and interfering with their normal proliferation. Ultimately, this can lead to the death of bacteria due to their inability to maintain basic life activities or resist environmental stress [161]. While the massive migration of protons also leads to the generation and transfer of many electrons, the process of electron transfer consumes hydrogen ions. Excessive consumption of hydrogen ions can affect the activity of the proton pump inside the bacteria, thus releasing a large amount of ROS [18], thereby killing the bacteria.

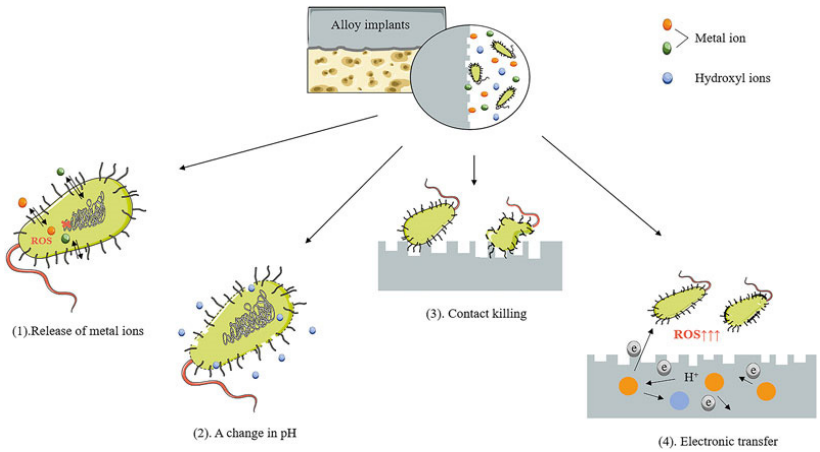

Figure 11. Four mainstream antimicrobial mechanisms for metal implants [48] The diagram describes the four primary mechanisms of alloy antibiosis, and the four mechanisms are: (**1**) release of metal ions, (**2**) a change in pH, (**3**) contact killing, and (**4**) electronic transfer.

7. Conclusions

Despite their potential, magnesium alloys face significant limitations in clinical use due to their rapid degradation rate in physiological conditions. This high corrosion rate makes it challenging to achieve a harmonious balance between biocompatibility, mechanical properties, and corrosion resistance. The future of magnesium alloy development hinges on controlling this corrosion rate effectively. Strategies such as surface modification, alloying with other elements, and other optimization methods are being explored to enhance corrosion behavior and regulate the degradation rate precisely.

Magnesium alloys possess a robust antimicrobial effect in vitro, but this efficacy is reduced in vivo, where the body's neutral environment counteracts the alkaline pH produced by degrading magnesium, thereby diminishing its antimicrobial impact [11]. To optimize magnesium-based implants for enhanced in vivo antimicrobial performance, it is essential to tailor the composition of magnesium alloys to meet the specific requirements of different implantation sites and to modify the surface of magnesium materials accordingly.

Magnesium has a strong antimicrobial effect in vitro, but this effect is weakened in vivo, and the mechanism of this lagged effect is unknown. It is now thought that the in vivo environment neutralizes the alkaline environment created by magnesium degradation products and that disrupting the alkaline environment reduces magnesium's antimicrobial effect. Studying magnesium's in vivo antimicrobial effect can help better target the environmental situation and develop magnesium-based implants with excellent vivo antimicrobial properties. The high degradation rate of magnesium alloys in the physiological environment continues to be a significant limitation for clinical applications. They are still far from achieving a good balance between biocompatibility, mechanical properties, and corrosion resistance. The focus of future development remains the control of its corrosion rate. It combines surface modification, alloying, and other optimization methods to improve corrosion behavior and precisely regulate its degradation rate.

Specific methods include but are not limited to the use of laser surface modification, micro arc oxidation and other surface modification methods, a comprehensive discussion of its modification principles and uses, the formation of a variety of methods of composite application, the collection of different methods of their respective advantages. At the same time, combined with alloying, the substrate metal is optimized, the corrosion behavior of the material is improved, and the degradation speed is accurately adjusted.

Similarly, the design of magnesium alloy should be changed to the overall design of structure and function and the development of composite materials. Specific types of alloys must be developed based on the requirements of different implantation sites to broaden the scope of magnesium alloys' application in the biomedical field. Meanwhile, the transformation of implantable magnesium-based devices is multidisciplinary. It entails material design and preparation, biological testing, and clinical evaluation. Establishing a collaborative platform between research institutes, hospitals, and businesses is necessary to promote the development and clinical application of new magnesium-based implants.

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