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REVIEW PAPER

Electrochemical and electrophoretic coatings of medical implants by nanomaterials

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Abstract

The demand for medical implants has rapidly increased over the last decades. These artificial devices should possess various properties such as biointegration and mechanical characteristics comparable to that of the replaced body parts. Nowadays, orthopedic, dental, and cardiovascular implants consist mainly of metal-based materials. However, metals suffer from poor osseointegration, some are not biocompatible, and some are not corrosion-resistant. Therefore, surface modification is necessary to enhance and improve the overall compatibility. Electrodeposition methods such as electrophoretic and electrochemical deposition are facile approaches for forming homogeneous and multifunctional coatings on conductive and complex geometries. Moreover, electrochemistry enables driving the deposition of nanomaterials and introduce biomolecules and polymers, by which various properties such as antibacterial activity, cell proliferation, and biointegration can be added to the implant surface. This review aims at describing the recent studies involving electrodeposition methods for coatings of medical implants by nanomaterials.

Abbreviations

BG	Bioglass
CB	Carbon black
CS	Chitosan
DEX	Dexamethasone
GO	Graphite oxide
HA	Hydroxyapatite
PDFE	*Pergularia daemia* Fiber extract
PEEK	Polyetheretherketone
PEI	Polyethylene-imine
γ-PGA-g-AMC	Poly(γ-glutamic acid)-g-7-amino-4-methyl-coumarin
PLGA	Poly lactic-co-glycolic acid
PLL	Poly-L-lysine
PLLA	Poly-L-lactic acid
PVA	Polyvinyl alcohol
PVK	Poly(N-vinyl carbazole)
SF	Silk fibroin
SS	Stainless steel

Introduction

World population as well as life expectancy and quality are rising rapidly due to better health conditions. This growth of the elderly population worldwide leads to a significant increase in injuries, orthopedic diseases such as arthritis, fractures due to osteoporosis, tooth loss, and more. Hence, the demand for implantable devices for dental, orthopedics, cardiology, and wound care has risen dramatically over the last few decades. For instance, in 2018, the dental and orthopedic implants market in the world was approximately 5 and 43 billion USD, respectively, and is expected to reach 7 and 66 billion USD, respectively, by 2028 [1, 2].

Medical implants are mainly manufactured from strong materials such as Ti and its alloys, stainless steel (SS), Mg and its alloys, and polyetheretherketone (PEEK) [3]. These materials should have a modulus of elasticity that is comparable to the replaced body part, appropriate tensile strength, and matching compressive strength to prevent fractures [4]. Additionally, these materials should possess biocompatible and osseointegration capabilities, corrosion resistance, and high durability. In general, metals lack osseointegration, namely, have poor biocompatibility

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with bone tissues due to their bioinert nature. Moreover, the human body represents a complex environment that reacts with foreign object such as implants by the release of different species, e.g., ions and organic and biological substances which reduced the biocompatibility of the implant due to denaturation and fragmentation of adherent proteins [5]. Thus, chemical and physical surface modifications of the implants are essential to ensure good integration between them and the surrounding tissues and to meet clinical demands.

Physical surface modifications such as plasma spray, sputtering, microarc oxidation, chemical acid etching, and anodizing are applied to control and alter the surface topography, including forming nanostructures that improve the implant performance. Anodizing is one of the techniques which allows the formation of a homogeneous porous layer on the substrate surface [6]. These microstructures can increase the corrosion resistance and enhance the adhesion to other bioactive ingredients in the coating process [7]. It has been shown that microarc oxidation can improve the degradation rate of metals, such as Mg-based alloys, by forming a thick oxide layer on the implant surface [8].

Chemical modifications involve adding or changing the chemical functionalities of the implants. This is achieved by either chemically reacting the implant surface or more commonly by coating the implant by an additional thin layer. Clearly, coatings of medical implants should improve the physical and chemical properties of the implants and add to their performance. Coatings can be made of a wide variety of organic and inorganic materials, where the dominants are polymers because of their processability and the ability to fine-tune their chemical and physical properties. Natural polymers, such as chitosan (CS) and gelatin, are biocompatible, biodegradable, and form a good film coating [9, 10]. However, to fulfill the desired requirements for the implant and to improve their chemical and physical properties, additional materials, such as biomolecules and nanoparticles (NPs), should be embedded in the polymeric matrix of the coating [11–13].

The addition of NPs to the coating can significantly improve the corrosion resistance, bioactivity, cell adhesion, and antibacterial activity of implants [14–16]. For example, NPs can act as drug carriers and release nanomedicines in a controlled manner in the desired area [17]. Furthermore, it has been shown that the mechanical properties of orthopedic implants are significantly improved by incorporating NPs in the coating [18]. Another common application is the incorporation of metal NPs such as Ag and Cu into the coating, which provide antibacterial properties that can reduce infections [19, 20]. Moreover, the introduction of hydroxyapatite (HA) NPs into the coating significantly improves the osseointegration capabilities of the implant with the surrounding tissues [21].

Various coating methods have been developed, including spin coating, dip coating [22], plasma spraying [23], plasma electrolytic oxidation [24], magnetron radio frequency-sputtering [25], microarc oxidation [26], electrophoretic deposition (EPD) [27], and electrochemical deposition (ECD) [28]. EPD and ECD are versatile coating methods, which allow the processing of a broad spectrum of materials and can produce bioactive coatings [29]. Furthermore, these methods offer many advantages for coating implants since they are able to control the thickness of the coating and produce a uniform and stable coating on complex geometric shapes as well as on porous and three-dimensional structures [30].

This review summarizes the developments in implant coating by nanomaterials using electrodeposition methods. In the first part, we discuss the types of metallic materials suitable for implants, which can be coated using electrodeposition methods. The second part focuses on electrodeposition methods such as EPD and ECD and their advantages in implant coating. The third part discusses how NPs can be incorporated into the coating of the implant and their role in the coating. Finally, we organize the studies based on the desirable functionalities, such as corrosion resistance, antimicrobial activity, and biointegration introduced by the NPs to the implant coating via electrodeposition methods.

Substrates

Medical implants are made of a variety of materials including metals, polymers, and ceramic. The majority of metal-based medical implants that are being used nowadays are composed of SS, cobalt–chrome (Co–Cr) alloys, Ti alloys, zirconium–niobium (Zr–Nb), and Mg alloys. This is due to their mechanical properties (high strength, low modulus of elasticity, high wear resistance), and biocompatibility [31, 32]. Despite the significant benefits and widespread usage of metal-based implants, they have major limitations. Corrosion, insufficient biointegration to tissues and bones, and stress shielding (i.e., modulus mismatch of the implant material with the natural bone) are known problems that can occur when using bare metal implants [33]. Hence, bioactivation and biocompatibility are necessary and can be achieved by either pretreatment or coating the surface [34]. Evidently, such modification depends on the metal, and therefore, procedures have been developed for the individual metals depending on their mechanical and chemical properties. The following is a brief description of the pretreatment categorized by the different metals.

Titanium and its alloys have some outstanding characteristics such as high strength per density (specific strength), low corrosion rate, and enhanced biocompatibility [31]. However, Ti does not integrate well with the host bone tissue, which can lead to implant failure [32]. To improve Ti

surface compatibility, physical treatment can be accomplished by methods such as sandblasting, plasma treatment, polishing, chemical acid etching, and a combination of those methods [34]. Electrochemical anodization offers an excellent approach for surface pretreatment to form different TiO2 structures [6].

Magnesium has an elastic modulus and density that resemble natural bone better than any other metallic implant. The unresolved challenge comprises the rapid and localized pitting corrosion of magnesium due to an unstable surface oxide layer [35]. Accordingly, substantial efforts have been made to passivate the Mg surface by thermal, chemical, and electrochemical pretreatments [33]. Adjustment of grain microstructure by polishing and anodization has also been shown to decrease the corrosion rate [36, 37].

Stainless steel, in contrast to Ti and Mg, has excellent corrosion resistance; however, the main downside associated with corrosion is cracked areas that can be created as a result of a damaged passivating chromium oxide surface layer [38]. This can provoke the hosting tissue and cause an undesirable biological response. Thus, modifications include grounding and polishing, oxidation, and cold working.

The second way to increase the biocompatibility while preserving the mechanical properties of the metal-based implants is by coating the surface. Although a wide variety of coatings, mostly by polymers has been applied to medical implants, we will focus here only on NP-based coatings. The advantages of such coatings are further discussed in "NPs in medical implant coating." In this section, we will focus on the conductive implant that serves as the electrode for the ECD and EPD of NPs.

Titanium substrate

Implants based on Ti and Ti alloys have shown remarkable properties such as specific strength, excellent biocompatibility, and corrosion resistance. Ti and its alloys have a lower elasticity modulus as compared with SS, and Co–Cr alloys, which are also being used extensively in surgical implantation (Fig. 1). This property contributes to lowering the stress shielding effect, which arises due to the strain mismatch between the bone and the implant [39].

Ti has excellent corrosion resistance because of its stable, continuous, and highly adherent passivating oxide layer on the surface. The passivating mechanism was deeply investigated by Cabrera-Sierra and its coworkers [40]. Nevertheless, the use of Ti is less common in implants that require load-carrying, due to poor fatigue and low wear resistance [41]. These can cause fractures in the oxide layer and lead to a decrease in corrosion resistance in some aggressive or low oxygen environments [42]. Subsequently, efforts have been made to enhance the mechanical properties of Ti and overcome these challenges [43–56]. Most of the studies, reporting an improvement in corrosion resistance, involved the formation of a passivating TiO_2 nanotube (TNT)–based layer by anodization. Khanmohammadi et al. suggested a coating prepared by EPD of bioglass (BG) reinforced with HA whiskers on an anodized Ti substrate [48]. TNTs were deposited as an

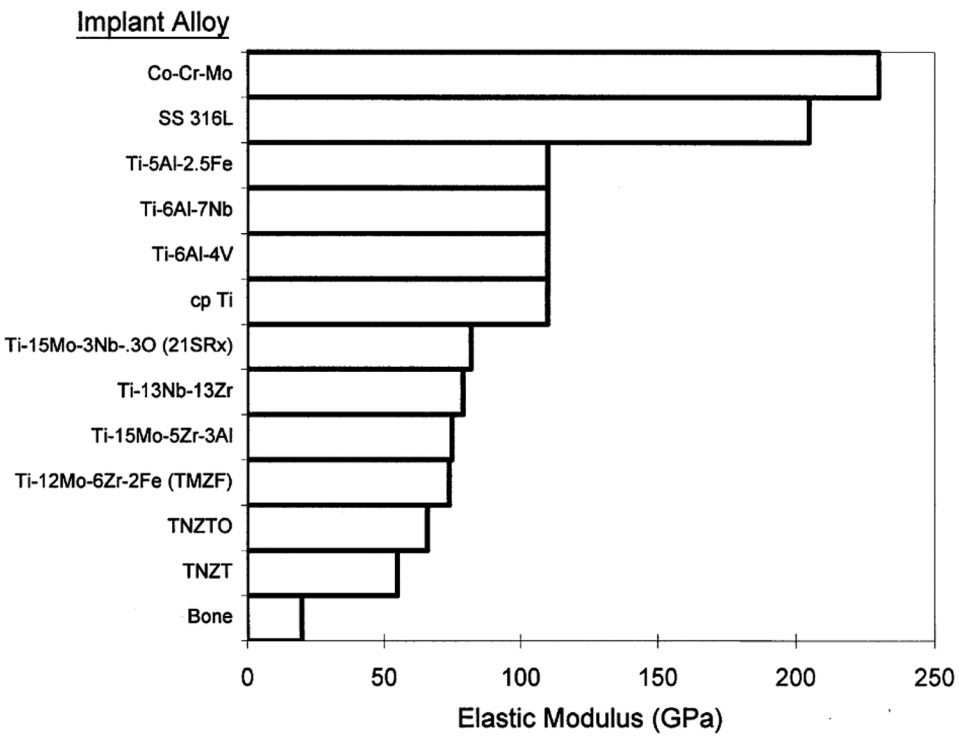

Fig. 1 Comparison of modulus elasticity of Co–Cr–Mo, SS and different Ti alloys. TNZTO and TNZT stand for Ti–35Nb–5Ta–7Zr–0.4O and Ti–Nb–Zr–Ta, respectively. Reproduced with permission from [32]

intermediate layer on the Ti surface to improve the coating adhesion. They showed that the corrosion of bare Ti was reduced from 147 to 17 nA cm − 2 for the anodized Ti, which was further reduced upon assembling the HA layer.

Additionally, different articles have shown that the use of certain NPs such as HA, Au, and graphite oxide (GO) provides protection and increases corrosion resistance. Moskalewicz et al. reported that HA NP EPD on commercially pure Ti (CP-Ti) and Ti–13Nb–13Zr alloy increased the corrosion resistance as shown in Fig. 2 [50]. Besides the HA NPs, they also applied GO, which enhanced the corrosion resistance presumably due to the crack-free morphology.

Another crucial issue that needs to be addressed is the poor osseointegration of Ti, which is vital to bone–implant interaction for the long-term durability of the implant. Surface properties such as microroughness and corrosion directly affect early cell formation and long-term osseointegration. A significant number of studies have shown that the incorporation of different substances and NPs into the coating can improve the implant's topography and roughens the surface, both leading to an increase in the durability of the Ti implants [57].

It has been reported that TNTs, which are used as a passivation oxide layer, can impart bioactivity and chemical bonding to the bone. Such a layer that is composed of smooth and dense TiO_2, can, however, be susceptible to the formation of a fibrous tissue that prohibits osteoblastic cells from firmly attaching to the surface. Thus, improvement of the interface can be accomplished by integrating a larger adhesion area, which requires structuring [58]. Oh showed that the topography of the TNTs, produced by heat treatment at 500 °C, formed an interlocked cell structure that

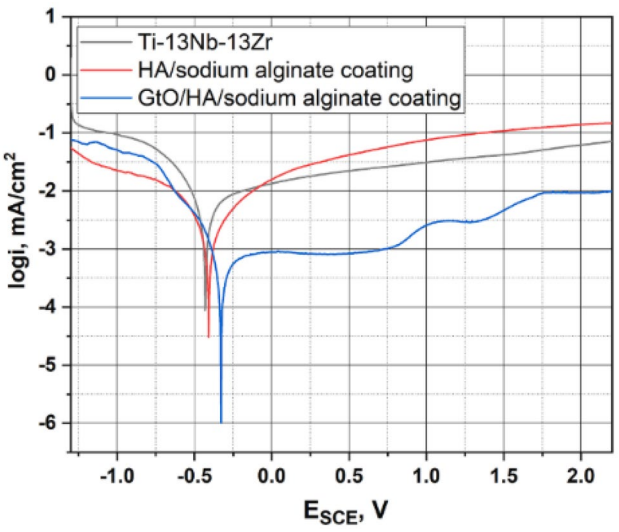

Fig. 2 Polarization curves of HAp/sodium alginate and GO/HAp/sodium alginate coatings on Ti alloy. Reproduced with permission from [50]

accelerated the growing cells into the nanotube pores. Wang et al. introduced Au NP-loaded TNTs, which increased surface energy and improved corrosion resistance as compared with Ti and TNT arrays. This assembly also improved cell–material interaction and, thereby, increased osteoblastic cell attachment and proliferation [55].

Other studies report on various coatings that show improvement of cell proliferation and osseointegration with different pretreatments alongside oxidation [49, 59–65]. Yet, these studies focus mostly on the NPs rather than on the metal surface and therefore are presented under "NPs in medical implant coating."

SS

The most common graded SS used for medical implants are SS 316 and 316L [66]. The major advantages of these SS-based alloys are their corrosion resistance and low cost [67]. Nevertheless, the corrosion of SS alloys is still inferior compared with Co–Cr and Ti alloys. The human body has a mildly corrosive environment with a certain salt level and a low oxygen content, which cause degradation and the release of Cr(III) and Ni(II) ions [68]. This may lead to the denaturation of adhered proteins after implantation and reduce biocompatibility [5]. SS-based implant drawbacks can be treated by coatings that address bioactivity, corrosion resistance, and cell adhesion.

BG and CS are extensively applied as a means of increasing the biocompatibility and corrosion resistance of SS implants [16, 69–77]. It is crucial to demonstrate good adhesion strength between the SS implant and the coating to ensure a long-lasting activity. This has been shown for the first time by Boccaccini et al. who applied PEEK and BG composite coatings by EPD improving significantly the mechanical stability and bioactivity [77]. Rehman et al. showed that the adhesion strength measured on PEEK–BG–Ag coating (3.85–4.09 N for PEEK–BG–Ag coating and 17.6–12.82 N for PEEK–BG coating) applied by EPD can be satisfactory for orthopedic implants [72].

A positive triggered response of the human body towards placing an implant is often the formation of a thin hydrophilic film on the implant surface. Lee et al. claimed that optimal adhesion and growth of the osteoblastic cells result in a water contact angle of 55° [78]. Surface wettability is a good measure for determining protein attachment, which affects cell proliferation at the later stages. Accordingly, Nawaz et al. formed a PEEK/BG as a primary layer by EPD on stainless steel followed by a top layer made of CS/gelatin–Ag–Mn mesoporous BG nanoparticles (MBGN) by EPD as well. The contact angle was reduced from 86° ± 2° to 50° ± 4°. The multistructured coatings enhanced cell viability, attachment, and spreading [79]. The use of MBGN enhanced chemical reactivity and improve bioactivity and osseointegration as

was also demonstrated by Aqib who carried out cathodic EPD to form an Ag–Sr–MBGN-loaded CS-gelatin layer on 316L-SS [69]. The coatings showed less than 5% delamination by an adhesion tape test. EPD was employed by Karbowniczek who formed an antibacterial coating made of sodium alginate-polyvinyl alcohol and ZnO NPs, on top of a primer layer of BG and CS. They showed that while the CS increased considerably the corrosion protection, the addition of BG (that was added to increase the bioactivity) reduced it [71].

Mg alloys

Traditionally used metal implants for orthopedics, dental and cranial implants are based on Ti, Cr, and SS alloys. In some cases, a second surgery is required after implantation for the removal of these metal-based implants because of infections, insufficient bone–implant integration, and healed bone fracture (implant no longer needed) [80]. Therefore, biodegradable materials are suggested to replace traditional metal implants. Mg alloys can potentially replace these implants due to their compatible mechanical properties. Mg exhibits a low young modulus (similar to cortical bone); it is biocompatible and biodegradable, which can be naturally appended to the human body without stimulating toxicity effects. However, the Mg degradation rate in physiological environments is uncontrollable due to its low corrosion resistance in the presence of chloride. This results in pitting corrosion, which causes a fast and local increase in the pH and evolution of H_2, which causes blood circulation blockage. These drawbacks affect the adhesion and cause implant failure. Therefore, it is vital to enhance the corrosion resistance of Mg, which has been targeted by either developing Mg alloys that are more corrosion-resistant or by modifying the Mg surface.

Different nanomaterials have been used for coating Mg implants and to enhance their corrosion resistance. For example, BG NPs (see "Si NPs and BG NPs") could potentially enable bone–implant integration, control the microstructure, improve the mechanical and surface properties of the coating, and, therefore, reduce corrosion. Indeed, Alaei et al. showed that low BG NPs concentrations increased the corrosion resistance [3]. Other studies whereby HA NPs were applied showed a corrosion resistance increase of the Mg [80–85]. Rojaee et al. performed a two steps EPD of HA NPs to form a more homogenous and crack-free coating on Mg AZ91 [81]. The same group has used microarc oxidation as a means of generating an intermediate oxide layer between the Mg and the HA NP layers. The obtained layer ennobled the corrosion potential of the implant and increased the corrosion resistance. As can be seen, the utilization of Mg implants is far from being exhausted, and therefore, there is still much room for additional approaches using electrochemistry and nanomaterials for controlling its corrosion resistance, which will make Mg an attractive metal for medical implants.

To conclude this part, the dominant metals used for mostly orthopedic and dental implants are made of Ti and SS. Recently, different alloys made of Cr, Co, and Ni have been introduced mostly for stents [86]. For both medical implants and stents, different methods and pretreatments have been presented to control the corrosion rate and the biointegration of the metal implants. Following, we will focus on the deposition methods and the substances that lead to the formation of uniform and biofunctionalized coatings.

Electrodeposition methods

Electrodeposition methods, such as ECD and EPD, are among the most frequently used coating approaches [27, 87–89]. A wide range of materials and nanomaterials spanning from metals, through polymers to NPs, can be deposited from solutions and dispersions on conductive surfaces using electrochemistry [90, 91]. These methods are simple, versatile, cost-effective, and applicable at room temperature. The latter allows the deposition of sensitive materials such as proteins and enzymes [91]. Furthermore, electrodeposition techniques enable to control very well the thickness of the deposited layer and form defectless and homogeneous coatings on complex shapes and porous substrates that characterize medical devices. Therefore, electrodeposition methods are attractive for coating medical implants such as orthopedic and dental implants. In this section, we overview the various techniques of electrodeposition and their application in the field of medical implants.

EPD

Electrophoresis is based on the movement of charged particles under an electrical field. Thus, EPD drives the deposition of charged particles onto a conductive surface as a result of a strong electrical field. EPD is often used for different applications such as car painting, making ceramic films, and electronic components. To obtain a good coating, first, the charged particles have to be stable, well dispersed, and move freely in the suspension. Then, by applying an electrical field, the charged particles migrate to the oppositely charged electrode, resulting in the formation of a layer on the surface. EPD can be carried out in aqueous and non-aqueous solvents. The application of an electric field in a protic solvent, e.g., water and ethanol, causes a local increase or decrease in the pH at the cathode or anode, respectively (Eqs. 1–2).

$$2H_2O + 2e^- \rightarrow H_2 + 2OH^- \quad (1)$$

$$2H_2O \rightarrow O_2 + 4H^+ + 4e^- \quad (2)$$

These reactions can promote electrostatic attractions of materials in the dispersion toward the electrodes as well as changes in the zeta-potential, resulting in the accumulation and deposition of various compounds on the electrode [88]. For example, a poly-l-lysine (PLL) film can be deposited onto a metallic substrate by EPD [92, 93]. Dissolving PLL-HBr in water forms a cationic polyelectrolyte (PLL-H^+) that is deprotonated and deposited (Eq. 3) by applying negative potential, which elevates the pH on the cathode (Eq. 1).

$$PLL\text{-}H^+ + OH^- \rightarrow PLL + H_2O \quad (3)$$

EPD has been widely used to coat metallic implants, where in most studies, the implant served as the cathode. Wang et al. developed a cathodic EPD process for the deposition of PLL and HA NPs onto a Pt electrode [92]. The PLL-H + provided stabilization for the HA NPs in the suspension. Clifford et al. developed a one-step cathodic EPD process to form a composite film of catechol modified PLL with HA and rutile TiO_2 NPs [93]. The film exhibited bioactivity and biocompatibility due to the addition of HA and TiO_2 NPs, respectively, as well as good adhesion caused by the addition of the catechol. Yang and his group deposited silk fibroin (SF) onto a Ti electrode in an aqueous solution [94]. This was achieved by applying a constant positive voltage, which oxidized the water, causing pH reduction (Eq. 2) on the Ti surface. The oxidation of water neutralized the SF nanospheres. This reduced the repulsive interactions between the particles and caused the irreversible aggregation of the nanospheres onto the Ti anode.

Although aqueous solutions are environmentally friendly, safe, with easily controlled temperature, and need lower voltage and faster deposition time than organic solutions; pH changes are usually accompanied by the formation of H_2 or O_2 gases (Eqs. 1–2). This gas formation can damage the quality of the deposited layer by forming porous polymer film [50, 95]. Bartmański et al. showed that an increase of the applied voltage resulted in a more porous coating of CS-nanosilver layer deposited onto a Ti electrode due to the gas bubbles formed during the deposition process [95]. Several ways were suggested to overcome this problem. For example, to avoid water hydrolysis, Ahangari et al. demonstrated HA deposition onto Mg through two-step EPD [85]. The first step involved applying relatively high voltage for a short time, followed by a lower potential for a longer time. This led to the formation of a compact structure and uniform HA coating. In another study, CS and BG nanocomposite were deposited onto a Mg alloy by applying a cathodic voltage of 10 V and a deposition time of 5 min with different concentrations of acetic acid [3]. It was found that by reducing the acetic acid concentration from 1 to 0.2 vol.%, the reduction of hydrogen gas on the Mg surface was obtained. This led to the formation of a more uniform and crack-free coating.

Pulsed EPD where the voltage or current is applied in a series of pulses is a popular strategy to reduce the gas bubbles formation and can produce uniform and cracks-less coatings [96]. Ramesh et al. examined the influence of direct and pulsed-direct EPD on the deposition of Pt NPs onto a Pt-Ir electrode [97]. They found that pulsed-direct EPD results in more ordered and uniform surface coating than direct EPD. A follow-up study showed that the coating can be improved even more in a suspension that contained a water–ethanol mixture due to the reduction of gas bubble formation [98].

Working with organic solvents usually generates a more uniform coating than in an aqueous environment, and the formation of H_2 and O_2 gases is prevented [83, 84, 99–101]. It is important to note that it is vital to work with high purity of suspension and to avoid humidity, thus avoiding hydrolysis [81]. This is especially crucial for Mg due to its high water reactivity [83]. On the other hand, relatively high voltage is required in an organic environment, which can cause cracks due to high particle accumulation onto the surface in a short time [65]. Farrokhi-Rad et al. deposited HA NPs onto SS from an organic dispersion with different alcohols (methanol, ethanol, isopropanol, and butanol) [102, 103]. The obtained layer was thicker as the molecular weight was lower due to faster kinetics. The coating obtained using a methanolic dispersion was highly cracked, while those from ethanolic dispersion had fewer cracks. The layers obtained from iso-propanol and butanol were crack-free (Fig. 3).

The quality of the coating is dependent on various parameters of the EPD process, including the applied voltage [95, 102], the deposition time [104–106], the concentration of

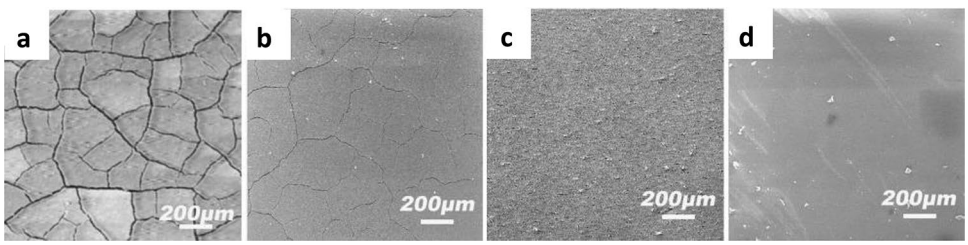

Fig. 3 SEM images of HA coatings deposited from **a** methanol, **b** ethanol, **c** isopropanol, and **d** butanol suspensions. Reproduced with permission from [102]

the materials in the deposited solution [102, 107, 108], and the distance between the electrodes [51, 109–111]. Applying accurate and appropriate conditions enables achieving uniform [49] or porous [54, 112, 113] structures.

Many studies have examined the influence of the applied potential on the deposited coatings [50, 51, 69, 114]. Moskalewicz's group coated Ti electrodes with HA/MoS2/PEEK to increase the corrosion resistance of the substrate [53]. They found that dense and homogeneous coatings were achieved at 90–110 V. Lower voltages led to thin and inhomogeneous layers, while higher voltages resulted in pores in the Ti substrate (Fig. 4). Farrokhi-Rad showed that fiber HA particles were randomly oriented when a high voltage of 60 V was applied. In comparison, horizontally aligned orientation was obtained at a lower voltage (5 V) due to enough space and time for the particles to rotate upon the deposition [115]. Tabesh et al. studied the influence of the applied potential on the deposition of Laponite®: poly(caprolactone) nanocomposite onto a SS surface [116]. An applied voltage of 60 V resulted in the formation of a pore-free and defectless coating compared with a non-uniform coating obtained at 90 V. It was suggested that this was due to the higher speed of movement of the particles in the dispersion, which reduces the compactness of the coating.

The deposition time is another critical parameter that influences the coating morphology and thickness [51, 69, 84, 104, 115]. For example, Cheng et al. EPD double-layered SF nanospheres coating onto Ti implant to obtain a controllable drug delivery system [117]. They found that the thickness of the layer was controlled by the deposition time. When the deposition time increased from 0 to 6 min, the thickness of the layer increased linearly in agreement with the classical Hamaker equation. When the deposition time exceeded 6 min, the coating thickness slowed down due to self-limitation. Qu et al. deposited ZnO NPs onto Mg by applying a potential of 3 V for different deposition times to examine the influence of the corrosion resistance [118]. The corrosion resistance improved as the deposition time raised from 30 to 210 min, which was related to the formation of a thicker protecting layer. Further increase in the deposition time reduced the corrosion resistance due to a decrease in the coating stability.

The possibility to co-deposit different organic and inorganic composites at room temperature is another benefit of EPD, especially for various biomedical applications [50, 76, 113, 119–127]. Humayun et al. EPD CS with Zn-halloysite nanotubes and gentamicin on Ti [128] in an aqueous solution containing acetic acid. They showed that the CS is necessary for the deposition process as it provides a net positive charge at low pH due to the protonation of the amino groups (Eq. 4), which resulted in adsorption onto the NPs. When a negative potential was applied, the pH increased in the cathode (Eq. 1) which caused the CS to deprotonate and deposit (Eq. 5; Fig. 5).

$$CH_3COOH + CS - NH_2 \rightarrow CH_3COO^- + CS - NH_3^+ \quad (4)$$

$$CS - NH_3^+ + OH^- \rightarrow CS - NH_2 + H_2O \quad (5)$$

Deen et al. deposited similarly a composite of CS-halloysite-nanotube-HA onto SS to provide corrosion resistance to the substrate in a simulated body fluid (SBF) [129]. Tomas et al. deposited gentamicin encapsulated in CS NPs and CaP by applying negative potential [122]. The coating contained a high-weight percent of gentamicin and a controlled release of the drug. Nawaz et al. showed that the addition of biologically active metallic ions (Mn and Ag) and molecules (CS) exhibited a strong antibacterial effect [121]. Furthermore, the coating exhibited a negligible toxic effect on the bioactivity due to the inclusion of the Mn and Ag in the matrix.

ECD

As opposed to EPD, in ECD, a faradaic reaction occurs on the electrode when voltage is applied. The main advantage of ECD is the ability to form good bonding between the surface and the coating material without additional treatment, such as heating and sintering [130]. Furthermore, the deposition process can be conducted under mild conditions so sensitive materials such as biological agents can be embedded in the

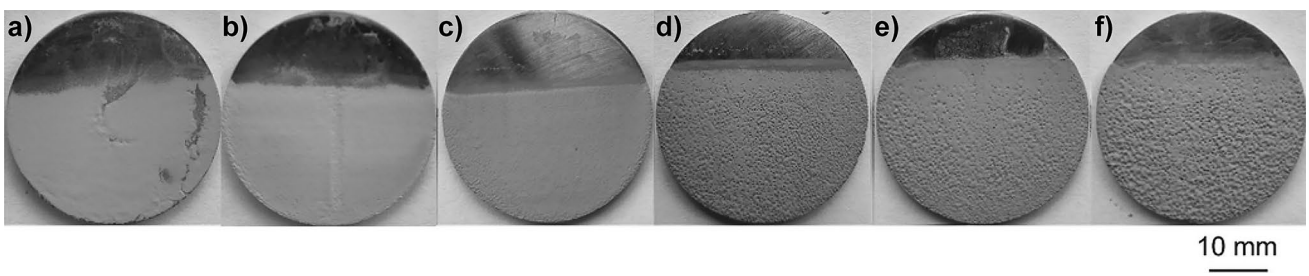

Fig. 4 HA/MoS_2/PEEK coating on Ti alloy substrates deposited a voltage of **a** 50, V **b** 70 V, **c** 90 V, **d** 110 V, **e** 130 V, and **f** 150 V. Reproduced with permission from [53]

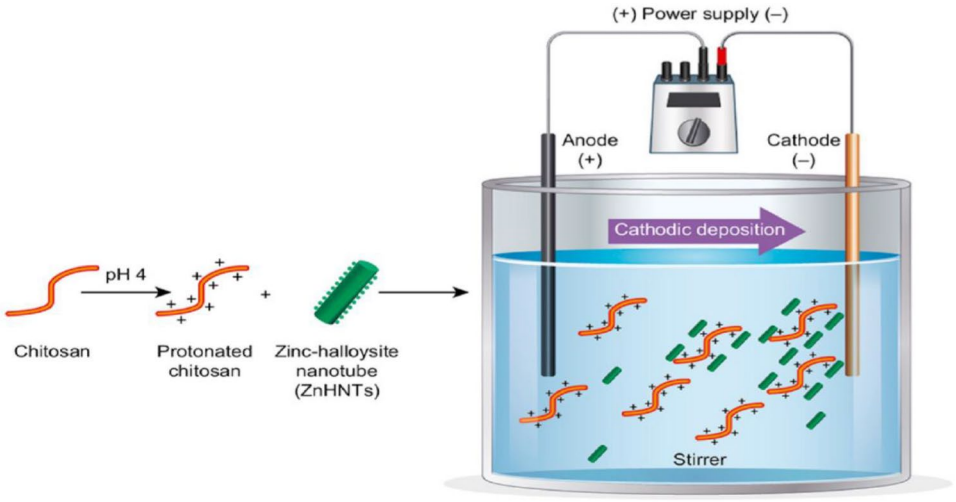

Fig. 5 EPD process of protonated CS with Zn-halloysite nanotube. Reproduced with permission from [128]

coating. This method often produces a uniform and highly crystalline layer with low solubility in body fluids. As in EPD, to obtain the desired properties of the coating, the deposition time, the applied potential, the substrate materials, the composition and concentration of the electrolyte, and the deposited compounds need to be carefully adjusted [131, 132]. For example, Geuli et al. deposited HA NPs dispersed by either citrate or poly(acrylic acid) onto Ti by applying mild positive potentials [133]. The application of positive potential drove water oxidation which reduces the pH on the implant surface (Eq. 2) and generated protons. This reduced the repulsion interactions among the NPs, causing irreversible aggregation of the NPs onto the Ti surface. They found that the thickness of the HA coating increased as the applied potential raised from 1.5 to 2 V and leveled off at higher potentials. Levy et al. deposited latex NPs in a similar approach by applying a constant potential of 2 V for different times [134]. The thickness of the coating arose as the deposition time increased until a maximum thickness of 15 µm was obtained at 900 s or higher deposition times. They showed that the maximum thickness is determined by generating a gradient diffusion layer of protons.

Like in EPD, also in ECD, H_2 gas can form due to the reduction of water that adheres to the surface of the metal, which leads to poor adherence of the coating to the substrate. Studies have shown that by adding H_2O_2 to the deposited solution, the formation of H_2 gas is prevented [135–138]. This can be useful for forming HA NPs, as shown by Gopi et al. [135]. The addition of H_2O_2 to the deposited solution produced excess OH^- ions (Eq. 6), which accelerated the formation of HA NPs on the cathode (Eq. 7) without evolving hydrogen gas.

$$H_2O_2 + 2e^- \rightarrow 2OH^- \tag{6}$$

$$10Ca^+ + 6PO_4^{3-} + 2OH^- \rightarrow Ca_{10}\left(PO_4\right)_6(OH)_2 \tag{7}$$

To further improve the crystallinity and the bonding between the coating material and the substrate, pulsed ECD (PED) was applied [136, 137, 139–144]. Wu et al. co-deposited polypyrrole, HA NPs, and dexamethasone (DEX) onto Ti substrate by applying a series of pulses width of 50 s for oxidation and 300, 600, or 900 s for reduction for 2 h [139]. During the oxidation pulse, polypyrrole was formed, and DEX^- and PO_4^{3-} were doped into the polymerized chain and attracted to the positively charged Ti. Then, by applying a reduction pulse, spherical HA NPs were formed due to the electrostatic interaction of PO_4^{3-} and Ca^{2+}. The duration of the reduction pulse had a significant impact on the composite coating. For reduction width pulse of 300 s, the HA NP size was uneven, while for 900 s pulse, the coating showed agglomeration. When a reduction width pulse of 600 s was used, a uniform size of HA was obtained. Jia et al. applied different pulses during the PED [141]. When applying a moderate pulse voltage, a much uniform, denser, and lower porosity coating of CS-HA was obtained than for lower or higher pulsed voltages. Lu et al. demonstrated the co-deposition of HA and Ag simultaneously by PED, which generated uniform distribution of Ag NPs [145]. Zhou et al. coated Ti porous scaffold with polypyrrole–polydopamine–hydroxyapatite (PPy–PDA–HA) film through a layer-by-layer PED method which resulted in a multiple functionality film [140, 146]. Under electrochemical oxidation, pyrrole monomers were polymerized to form PPy polymer and acted as a stabilizer for HA NPs and prevented their aggregation (Fig. 6).

To summarize, EPD and ECD are powerful techniques that allow surface modification of metallic implants. These methods enable the fabrication of multifunctional coating by introducing various materials such as natural polymers

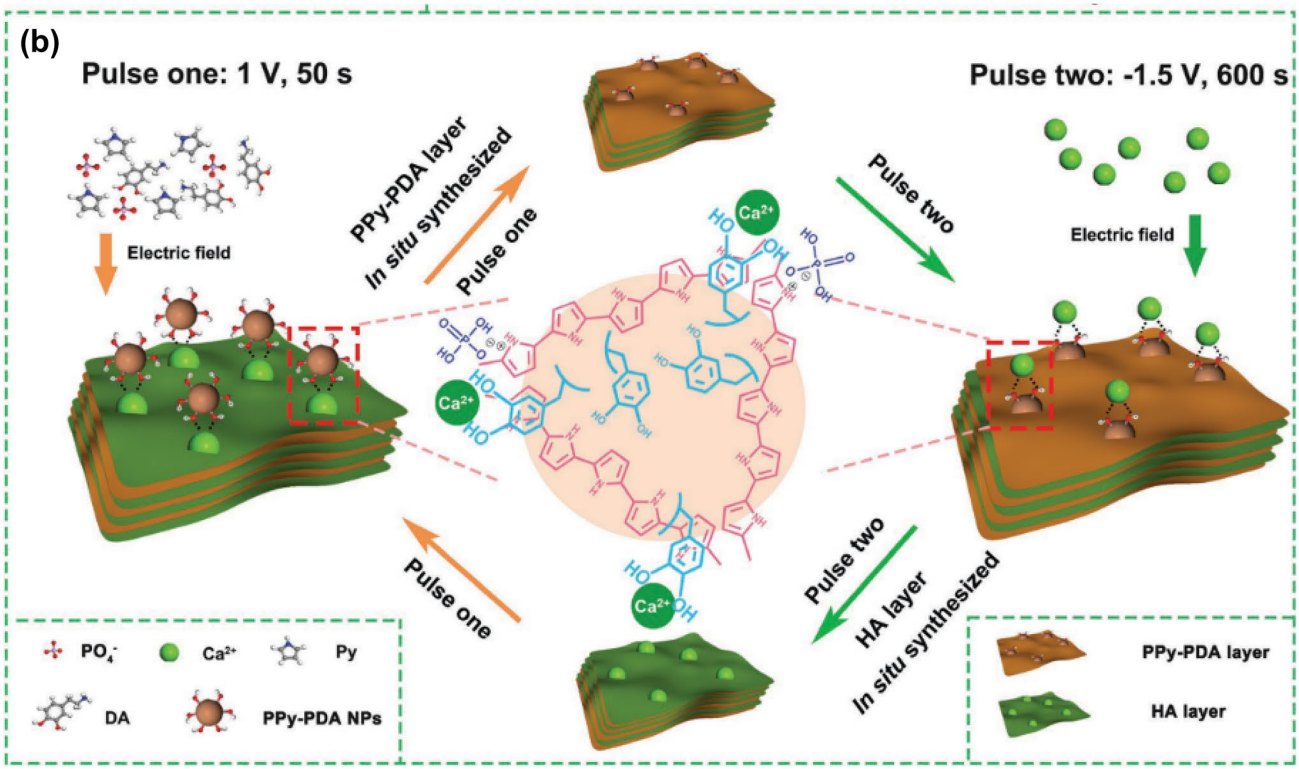

Fig. 6 Preparation of the PPy–PDA–HA film via the LBL–PED process. During this process, each PPy–PDA layer or HA layer was in situ deposited on top of a sublayer. Reproduced with permission from [146]

and NPs. The following section will focus on the addition of NPs to medical implants and their contribution to multiple properties such as corrosion resistance, antibacterial activity, and biointegration.

NPs in medical implant coating

Nanomaterials, such as NPs, nanotubes, and nanorods, are defined as solid particles with at least one dimension that is 1–100 nm. The most studied and applied nanomaterials are by far NPs. These are used in a wide range of applications including medicine, energy storage, sensing, and more. In medicine, NPs are mostly applied for diagnostic and disease treatment, although numerous other applications are also of interest [17, 147, 148]. One of the most appealing applications, which has not been exhausted yet, is the use of NPs as coatings for implants. Coatings based on NPs offer significant advantages, such as controlling the release of drugs and other biomaterials, locally after insertion [149]. Furthermore, NPs can be tailored-made to possess different properties, including biocompatibility, cell viability, antibacterial, and osseointegration activity. Therefore, different approaches have been developed for the adsorption, attachment, or deposition of NPs on medical implants. These can be divided into two major categories where the NPs are applied from either the gaseous or the liquid phase.

Coating of implants from the liquid phase usually requires simple and low-cost instruments and operations and enables homogeneous and controllable layers on a variety of structures including complex geometries. Yet, the formation of stable coatings as well as the ability to form the coatings from the liquid phase require additional capping agents, which are added as a means of stabilizing a homogeneous dispersion and promoting good adhesion of the coating to the surface. The capping agents can be added either in the synthesis of the NPs or applied with or prior to the deposition of the NPs or as a post-treatment after the NPs are deposited.

Computational modeling and numerical testing can attribute for the understanding of the mechanism of NPs and their adverse effects [150]. These computational methods play a complementary role in the prediction of toxicity, bioactivity, degradation, and other properties of nanomaterials. These models can also predict the mechanism of NPs incorporation regarding cellular uptake and cell apoptosis [151]. Furthermore, numeric testing may elaborate the experimental process and contribute for a better understanding of the clinical outcomes of embedded NPs onto medical implants.

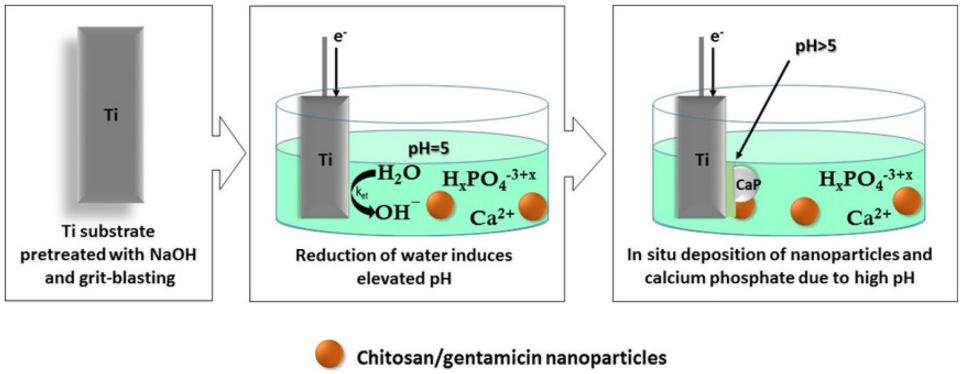

Fig. 7 ECD process of HA with CS and gentamicin (an added drug) through pH elevation. Reproduced with permission from [131]

In the following sections, we summarize most of the studies aiming at the coating of medical implants by NPs. The division is based on the NPs' material and subcategories by the additives.

HA nanoparticles

The main reason for using HA in implants is its osteoinduction. Hence, HA is often used to coat orthopedic medical implants, usually by plasma or thermal spraying and more recently by electrochemical deposition starting with ionic species, e.g., HPO_4^{2-} [152, 153]. The development of nanotechnology has promoted the use of HA NPs as precursors for coatings. Excellent reviews describe the osteoinduction ability and biological responses of HA NPs and different deposition methods (including electrochemical processes) on surfaces [21, 154]. Furthermore, HA NPs are often used to roughen metal implant surfaces and as source materials for assembling bioactive coatings on orthopedic and dental implants [155].

The desired properties of a HA NP-based coating are the overall biocompatibility for both cells and bones, the durability or hardness of the coating, and the corrosion resistance of the produced implant. In a few studies, metal ions such as Zn^{2+} and Mg^{2+}, which play important roles in osteogenesis, are substituted into the HA NPs [156–158]. The doped particles can stimulate cell proliferation and bring additional benefits to the coating such as antibacterial properties. Being versatile and easy to deposit, HA NPs are often used as the model material in method-focused studies of deposition. An example is described in "ECD" concerning Wu et al. and Jia et al. [139, 141] works. While many studies add some sort of an additive to the HA NPs solution to improve their dispersion in the coating, Geuli showed another way to achieve it based on the ECD of HA NPs [133] (see "ECD").

CS is a majorly applied additive to HA NP–based coatings since it can stabilize the dispersions of the NPs and create flexible composites (forming different shapes) [159]. Fabrication of such coatings by electrochemical processes takes advantage of the effect of pH on the solubility of CS. The pK_a of protonated CS is 6.5, which enables its deposition by applying negative potentials that cause a local increase of pH on the electrode surface (Eqs. 1 and 5). Therefore, HA NPs stabilized by CS aggregate and deposit on the cathode due to the deprotonation of the CS. This process can be used for EPD and for ECD, where HA is formed by an electrochemical reaction on the electrode, alike (Fig. 7). Accordingly, numerous stable multilayers with various thicknesses (Fig. 8) were deposited onto SS, Pt foils, and graphite surfaces as reported by Sun et al. [160].

To further improve the durability and functionality of the implant, additional substances are often added along with CS. For example, higher adhesive strength and hardness were achieved by Zhong et al. [45]. They introduced multi-walled carbon nanotubes to their zinc substituted HA NPs dispersion and used EPD to form a coating. The resulted composite layer exhibited better corrosion-resistance

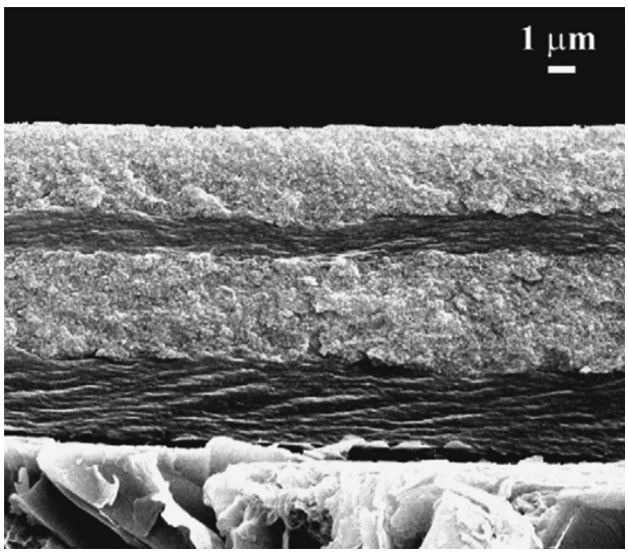

Fig. 8 SEM side image of fractured multilayered coating. Containing alternating layers on graphite with different concentrations of HA NPs and different deposition conditions. Reproduced with permission from [160]

behavior as compared with bare Ti. In their following study using the same coating, they showed improved cell adhesion, good HA formation ability, and differentiation of cells [60]. Moreover, CS is often used for drug delivery, an important feature with possible advantages in medicine. In a study by Eliaz, a coating of HA and CS NPs, in which antibiotics were entrapped, was formed [131]. The antibiotic release showed a steady cumulative release of 60% over 10 days with an enhanced early burst.

Alumina- and yttria-stabilized zirconia nanopowders stabilized by HA were EPD on Ti by Asgari et al. by adding I_2 to an organic solvent, such as acetone [99]. I_2 is known to react with acetone to form H^+, which charged the nanopowders by a positive charge and enabled the EPD.

Considering the high biocompatibility and wide array of possible applications of HA, it is not surprising that many studies have chosen to use it as a model system.

Ag NPs

Ag NPs are among the most studied NPs in medical applications, mainly due to their excellent antibacterial activity. Like in many other inorganic NPs, bacteria do not develop resistance toward Ag NPs [19]. Several hypotheses were proposed for the antibacterial mechanism of Ag NPs, including (i) enhancing the permeability of the bacteria through attachment of Ag NPs on its surface, (ii) production of cell-damaging radicals, and (iii) strong binding between Ag and the thiol groups of cysteine residues of the proteins. The latter hypothesis affects irreversibly the proteins' secondary structure, thus, eradicating the bacteria [161]. Furthermore, Ag NPs can be dispersed easily in very high concentrations, which makes them ideal for deposition by electrochemistry.

CS is one of the most common materials used as an additive to the coating process with Ag NPs due to the chelating of Ag by CS. Furthermore, CS was suggested to reduce Ag toxicity while retaining its antibacterial activity [162]. Xie et al. examined the dual release of Ag ions and cytokines, with CS acting both as the stabilizing agent to chelate Ag ions and as the electrostatic immobilizer of the explanatory cytokine [132]. The complex coating was formed by the ECD of a solution that consisted of Ag^+ complexed with CS and $H_2PO_4^{2-}$ and Ca^{2+}. In the course of the ECD, Ag^+ was reduced to form Ag NPs and HA. The electrostatic repulsion of the CS discouraged aggregations of the NPs, and results in a uniform distribution. Same electrostatic interactions also contributed to the introduction of a second layer containing the cytokine. A significant focus was given to their long-term release, and the functionality of the coated implant, demonstrating its usefulness for its high osteoinductivity and antibacterial properties both in vitro and in vivo.

Nawaz formed a bioactive two layers coating by EPD on SS of CS-gelatin/Ag–Mn-doped mesoporous bioactive glass NPs [79]. Gelatin was selected to improve both the biocompatibility and the attachment of CS to the implant. This approach was based on the creation of two distinct layers by EPD: The first layer controlled the surface area and roughness, creating a porous structure, while the second layer contained the active NPs. They found that the addition of Ag NPs to the coating caused the formation of HA crystals and enhanced the cell viability while retaining the antibacterial activity against bacteria. Another interesting usage of Ag NPs and CS in EPD-based coatings of implants was studied by Ma et al. [163]. Ma EPD Ag NPs stabilized by CS, followed by oxidation of the Ag NPs to form AgCl and Ag_2O. The resulting coating showed uncompromising antibacterial and biocompatible activity with less than 1 w/w % degradation after a month of incubation in fresh sterilized phosphate-buffered saline (PBS) solution. Pawłowski also used EPD to create an Ag NPs/CS layer that included also the cationic copolymer Eudragit E 100 [51]. The latter is known to reduce the degree of degradation of such coatings [164] and is also pH-sensitive; hence, it could be codeposited by a change of Ph [165]. The obtained coating exhibited good corrosion resistance and strong sensitivity to a reduced pH environment, which is crucial for applications in controlled drug delivery systems.

BG is another useful ingredient when it comes to coating metal surfaces with Ag NPs, as it offers osteoinductive properties, which lead to the stimulation of osteogenic cells to form a bone matrix [166]. In many cases, BG is coated along with other stable materials such as biomedical polymers, e.g., PEEK. Previous researchers, such as Boccaccini, deposited uniform, microporous, and reproducible PEEK/BG composite coatings using EPD where they optimized the conditions for deposition [111, 167]. Boccaccini has extensively worked on Ag NP–based coatings [72, 73, 77]. In their most recent study, a thin Ag nanocluster–silica composite coating was deposited by radio frequency on top of an EPD PEEK/BG/mesoporous BG NPs (MBGN) layer (Fig. 9). By employing this approach, a controlled release of Ag^+ was achieved and a structure resembling HA was formed on the surface of the coatings upon immersion in SBF.

Dopamine, a self-polymerizing substance, was introduced by dip-coating as a sandwich layer in between two layers of Ag NPs by Liu et al. [146, 168]. While the first layer was formed by electrospinning, the third layer was EPD. The poly(dopamine) layer enhanced the surface adhesiveness through hydrogen and π–π interactions, preventing the peeling of the coating. The layer contributed to a steady and slow release of Ag, improving the long-lasting bioactivity of the coating. Moreover, the resulted coating promoted the nucleation and growth of HA on the surface, making it biocompatible.

In summary, Ag NPs are well-studied agents in electrochemically coated medical implants with a range of advantages given

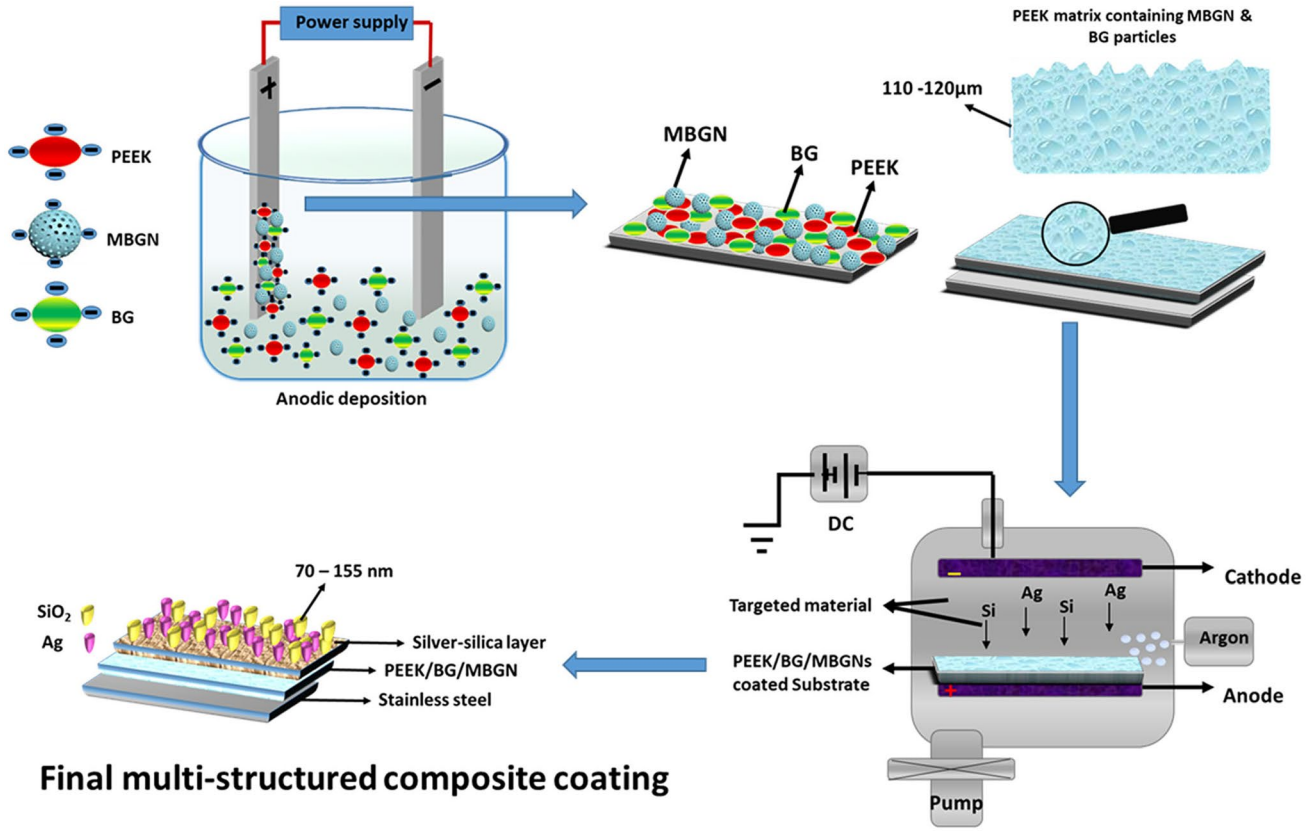

Fig. 9 Experimental setup to obtain multi-structured coatings via EPD and radio frequency co-sputtering. Reproduced with permission from [73]

the proper modification. Their excellent local antibacterial activity as well as their conductivity are decisive factors in their incorporation.

Metal oxide NPs (TiO_2, ZnO, Fe_3O_4, and others)

A few metal oxide NPs are of significant interest in orthopedic and dental implant research because of their biochemical properties such as antibacterial activity, drug delivery, and mechanical strength [18]. However, some metal oxide NPs are toxic to human tissues. Their nanotoxicity is a function of not only the metal oxide itself but also the size, shape, and concentration [169]. The most common metal oxide NPs used in implants are TiO_2, ZnO, and Fe_3O_4.

TiO_2 is often applied for implants as it can readily be formed by anodizing a Ti alloy surface (see "Titanium substrate") as well as added to the deposition solution as NPs. There are excellent reviews discussing the antibacterial mechanism of TiO_2 NPs, where the dominant pathway is photochemistry [170–172]. Tangestani et al. utilized TiO_2 NPs along with HA NPs and poly(caprolactone) as an additive to create a series of biocompatible coatings for SS implants [100]. Corrosion resistance, sliding, microhardness, and adhesion strength measurements led them to conclude that TiO_2 NPs acted as a reinforcement of the composite coating. This improvement is in part contributed to the electrostatic interaction between the NPs and the added binder. Clifford et al. conducted a somewhat similar experiment with TiO_2 and HA NPs that were capped with a catechol functionalized poly(lysine) that enabled their EPD on Ti [93]. The capping agent significantly increased the adhesion to inorganic particles and resulted in a high surface roughness coating at high voltages (50 V). This procedure allowed the co-deposition of both NPs, combining their biocompatibility, and stability to form a uniform bioactive layer. An elegant example of the formation of TiO_2 nanotubes formed by anodization of Ti coated with HA doped with Ag was demonstrated by Yan et al. [56]. Applying negative potential to the TiO_2/Ti in an aqueous solution that contained HPO_4^{2-}, Ca^{2+} and Ag^{+} caused the formation of OH^{-}, which promoted the formation of HA doped with Ag. The TNT enhanced the adhesion of the NPs through an anchoring effect. This process allowed for significant antibacterial and osteogenic properties and enhanced corrosion resistance.

ZnO NPs are also often embedded in implant coatings because of their antibacterial and relatively low toxicity to

humans [20, 173]. One such example of applying ZnO NPs to a metallic structure by electrochemistry was published by Qu et al. [118]. Specifically, ZnO NPs were coated by EPD onto Mg alloy, followed by heat treatment to delay initial corrosion. Their work proved to form a 99% corrosion-effective protection layer on the alloy. However, without biocompatible and antibacterial tests, it seems that this coating is not yet ready for wide application. In a different approach, suggested by Karbowniczek, complex organic/inorganic coatings containing ZnO NPs and BG were successfully deposited on SS by EPD [71]. While the BG improved the in vitro bioactivity of the coating, the high reactivity of BG negatively affected other properties.

Fe_3O_4 NPs are rarely studied as additives in implant coatings. While they are sometimes used for their magnetic properties to attach bioactive ingredients to the layer, other properties of the coating might be affected [174]. For example, the incorporation of Fe_3O_4 NPs in a HA matrix showed an increase in osteoconductivity and chemical durability, which resulted in better stimulation of bone growth during the healing process [175]. Zhuang et al. incorporated Fe_3O_4 NPs into a mineralized magnetically responsive coating of Ti using alternating potential-ECD [138]. Thanks to the magnetic abilities of the NPs, the mechanical stimuli and deformation were controlled under an external magnetic field. They reported an improvement in the mechanical properties and enhanced osteogenic results. In a procedure containing multiple materials, Singh et al. managed to coat a Mg alloy with Fe_3O_4, HA, BG, and CS, by synthesizing nanocomposites containing the four materials and depositing them by EPD [113]. The crystallinity of the coating was enhanced with the incorporation of Fe_3O_4 NPs, producing a crack-free hydrophilic coating.

Other metal oxide NPs were studied by several groups as a means of depositing coatings or modifying them and their functionalities. This includes CeO_2 [176], Y_2O_3 [177], MgO [80], and Mn_3O_4 NPs [7]. Accounting for the large number of possible metal oxide NPs possessing attractive functionalities, it is very likely that additional future studies will appear attempting to incorporate them in implant coatings.

Si NPs and BG NPs

Si NPs have been often used for drug delivery and as optical imaging agents. The main advantages they offer are their precisely synthesized microscopic form, mesoporous structure with pore size between 2 and 50 nm, and chemical functionality as an adhesive to antibiotics [178, 179]. Mesoporous silica (MSi) nanotubes have been explored as an appealing modification of Ti for drug loading purposes, cell adhesion, and osteogenicity [180, 181]. The motivation for modifying Ti is described in "Titanium substrate." MSi nanotubes, CS, and collagen EPD enabled the loading of therapeutic molecules safely at high quantities, as well as the release in a sustainable and controlled manner [61]. The authors reported the in vitro early interactions with stem cells (derived from rat bone marrow). They found that mineral crystallites formed in a sustained way over 30 days, hinted at a substantial and continual apatite mineral induction, and suggested a high level of acellular bioactivity. The induced polarization of drug-loaded MSi NPs in a biologically focused study was reported by Luo et al. [182]. The coating process was EPD with CS as an additive on Ti, after the formation of TiO_2 by anodization. The added NPs showed favorable cytocompatibility, as well as a drug storage capability (less than 30% cumulative release of the drug was measured over 4 days incubation in PBS). While they report enhanced osteogenic differentiation behavior, the MSi NPs showed clear dose-dependent cytotoxicity, limiting this approach for further investigations.

Ballarre and her team contributed significantly to the study of implant coatings [30, 63, 119, 183–185]. They deposited by EPD synthesized silica–gentamicin on SS and Ti in one and two-step procedures. The two-step coating involved spraying BG and EPD of NPs and biomaterials, forming a carrier system with improved biocompatibility. Through these approaches, an amorphous structure that allowed particle degradation and release of antibiotic drugs was formed on the implant surface. The mechanical and morphological characterization of the coatings was tested on SS and Ti. They found that CS and gelatin were excellent biopolymer holders for Si and silica–gentamicin NPs, as strong uniform and homogeneous coatings were generated.

BG has not only been described as an additive to other NPs throughout this review, but can also be applied as the main material in coatings. The main advantages of BG (and BG NPs) are its osteoinductive properties and cell simulating capabilities. Excellent reviews describing the origin of BG properties, such as its delivery of inorganic therapeutic ions and the antibacterial activity of the composites that it forms, have been published [186–188]. A few studies deposited a layer of BG NPs onto metals, where the aim was to create a better-controlled morphology of the implant through the creation of microstructures or nanostructures (nanocomposite coating) [189–191]. Patel et al. developed composite coatings of CS and BG NPs on Ti by EPD that showed favorable cell adhesion, drug delivery capability, growth, and stimulated osteogenic differentiation [126]. In this case, BG acted as the bioactive inorganic component of the implant, while the CS positive charge allowed for cathodic EPD. Alaei et al. constructed a similar coating to the latter on top of a Mg alloy with different BG and CS contents [3]. They reported the deposition of a crack-free uniform CS-BG NPs layer on the substrate with increased wettability and surface roughness, good adhesion, corrosion resistance, and apatite formation ability.

Considering the reported Si NP properties, it is not surprising that they have often been used in drug-delivery systems. Yet, while the release of antibiotics can aid in short-term antibacterial activity, the shift towards inorganic or metal NPs in implant studies is expected to grow as it proves to have long-term advantages.

Other NPs

Even though most studies of electrochemically deposited NPs on implants comprised inorganic or metal NPs, several reports describe the use of organic or biological NPs. This section demonstrates the effects of organic biopolymer-based NPs and SF NPs for implant coatings. One such example of organic NPs was demonstrated by Liu et al. in the construction of advanced drug-eluting stents [192]. Their primer layer was made of organic N-nitrosomelatonin-loaded poly(D,L-lactide-co-glycolide) NPs acting as the active ingredient. The top layer of the coating was a collagen layer, deposited to reduce the immunological defensive reaction. Both collagen and the organic NPs are based on biodegradable polymers that would fully degrade, subsequently producing less inflammation in long-term applications [193]. The stent showed sustained delivery of nitric oxide, significantly reducing platelet aggregation in vivo. Attempting to improve the biocompatibility and anticorrosion properties of Mg let Sun et al. apply a coating with an organic/HA hybrid NPs via EPD [83]. The coated Mg showed, indeed, improved degradation and corrosion resistance in vitro with greater cell viability and cell adhesion. CS-gelatin NPs with and without the addition of a cationic antibiotic drug were successfully fabricated as a layer on Ti through EPD by Cai et al. [62, 194]. Mechanical testing demonstrated enhanced interlocking in the coating-Ti interface for a high concentration of the drug.

Yang and his team published a novel additive-free EPD coating assembly procedure from pre-assembled SF NPs [94, 117]. Using this method, the controlled and sustained release of antibiotics was enhanced by a factor of 1.38 with prolonged drug release by 21 times without observed cytotoxicity. More recently, they created a bilayer of two distinct SF NPs (from *Antheraea pernyi* and *Bombyx mori* for the top and bottom layers, respectively). The need for two types of SF NPs is reasoned both economically and chemically based on the different rarity and stabilizing effects on some biological compounds of alternative silk proteins [195].

Evidently, the incorporation of different NPs in implants proves to be advantageous for various applications. Specifically, they show improvements in antibacterial properties, corrosion resistance, and other biological effects. Hence, it is expected that we will witness additional studies, whereby more sophisticated NPs will be used to coat implants electrochemically.

Significant properties of medical implants

In this review, we have described a variety of coatings based on a broad range of substances for medical implants by electrodeposition methods. The incorporation of different materials took advantage of the metal-based implants and enhanced or modified surface properties. A combination of NPs and additives such as natural polymers provide multiple functionalities. Composite coatings allow (i) improvement of corrosion resistance of the metal implant surface; (ii) biointegration, osseointegration, and cell proliferation; and (iii) antibacterial performance. Tables 1, 2, and 3 summarize most literature studies that target surface modification of implants via electrodeposition methods. Further description and comparison of the tables can be found in the text.

Table 1 Improvement of corrosion resistance

NPs	Additives	Substate	Method	Ref
HA	CS GO	Ti	EPD	[44]
HA		Ti_6Al_4V	EPD	[104]
HA	PEI	Ti Ti6Al4V	EPD	[196]
HA Cu		Ti13Zr13Nb alloy	EPD	[46]
HA–ZrO_2		Ti6Al7Nb	EPD	[47]
HA TiO_2	PLL Catechol	Ti	EPD	[93]
HA GO	Sodium alginate	CP-Ti Ti13Nb13Zr alloy	EPD	[50]
GaHA	PDFE PVK	Ti	EPD	[49]
HA ZnHA	SF CS	Ti	EPD	[45]
HA		Ti (Grade 4)	PEO-EPD	[54]
HA TiO_2		Ti Ti6Al4V	PEO-EPD	[6]
HA TiO_2	Ag	Ti	ECD Anodized	[56]
HA/TiO_2		316 SS	EPD	[106]
HA	CB	316 L SS	EPD	[82]
HA	Methanol Ethanol Butanol Isopropanol	316 L SS	EPD	[103]
HA	Tris (tris(hydroxymethyl) aminomethane	316 L SS	EPD	[102]
HA		316 L SS	EPD	[82]
HA-chitosan $BrTiO_3$	Tri-ethanolamine	316 L SS	EPD	[75]
HA TiO_2	Polycaprolactone	SS	EPD	[100]
HA	Graphene Carboxymethyl cellulose	Mg alloy (AZ31)	EPD	[85]
HA	PLGA	Mg	EPD	[84]
γ-PGA-g-AMC/HA		Mg	EPD	[197]
γ-PGA-g-AMC/HA		Mg	EPD	[83]
HA	Ethylene glycol Triethanolamine ZrO_2	Zr	EPD	[8]
HA	Silicate Phosphate	Nb	PEO-EPD	[112]
Fe_3O_4 HA-BG- CS		Mg alloy(AZ91)	EPD	[113]
HA CS $RuCl_3$		Mg alloy(AZ91)	Pulsed ECD	[141]
($Ca_2ZnSi_2O_7$)		SS 316L	EPD	[198]
BG	CS	Mg alloy (AZ91)	EPD	[3]
Ag	CS Eudragit E 100	Ti (grade 2)	EPD	[51]
TiO_2 ZnO		Ti6Al4V	EPD	[52]

Table 1 (continued)

NPs	Additives	Substate	Method	Ref
ZnO	Sodium alginate PVA CS BG	SS 316L	EPD	[71]
ZnO		Mg alloy (WE43)	EPD	[118]
$MgSiO_3$ TaN		Mg alloy	EPD	[199]
Mn_3O_4		Ta	EPD	[7]
Au	TNT	Ti	ECD	[55]
CeO_2	SF	Ti	Electrospinning ECD	[176]

Table 2 Improvement of biointegration, osseointegration, and cell proliferation

NPs	Additives	Substate	Method	Ref
HA	CS GO	Ti	EPD	[44]
HA	PEI	Ti Ti6Al4V	EPD	[196]
HA ZnHA	SF CS	Ti	EPD	[45, 60]
GaHA	PDFE PVK	Ti	EPD	[49]
HA TiO_2	PLL Catechol	Ti	EPD	[93]
HA	Triethanolamine	316L SS	EPD	[105]
HA	Tris (tris(hydroxymethyl)aminomethane	316L SS	EPD	[105]
HA	CB	316L SS	EPD	[82]
HA/CS $BaTiO_3$/CS	Tri-ethanolamine	316L SS	EPD	[75]
HA		Mg alloy (AZ91)	EPD	[81]
γ-PGA-g-AMC/HA		Mg	EPD	[197]
HA	CS $RuCl_3$	Mg alloys (AZ91D)	Pulsed ECD	[141]
HA	Ethylene glycol Triethanolamine	Zr	EPD	[8]
HA	Silicate phosphate	Nb	PEO-EPD	[112]
HA		Ti (grade 4)	PEO-EPD	[54]
HA		Ti Ti6Al4V	ECD	[133]
HA	Polypyrrole DEX	Ti	ECD	[139]
Pd–Ag-HA TiO_2		Ti	ECD	[200]
HA TiO_2	Ag	Ti	ECD	[56]
SiC HA		Ti	ECD	[201]
HA Ag	L-cysteine Cysteine acted	Ti	Pulsed ECD	[145]
HA	Polypyrrole DEX	Ti	Pulsed ECD	[139]

Table 2 (continued)

NPs	Additives	Substate	Method	Ref
$Ca_3(PO_4)_2$	Nucleic acids	ITO	EPD	[202]
$Ca_2ZnSi_2O_7$		316L SS	EPD	[198]
BG	CS	Mg alloy (AZ91)	EPD	[3]
BG	CS	Ti	EPD	[126]
BG Nanodiamond	Alginate	316L SS	EPD	[203]
Ag nanocluster–silica mesoporous BG	PEEK	316L SS	EPD	[73]
Mesoporous silica nanotube	CS Collagen	Ti	EPD	[61]
Mesoporous silica	DEX CS	Ti	EPD	[182]
Silica–gentamicin	CS Gelatin	316L SS	EPD	[30]
Ag–Sr-doped mesoporous BG	CS Gelatin	SS	EPD	[69]
Ag–Mn-doped mesoporous BG	CS Gelatin	PEEK/BG SS	EPD	[79]
Ag	CS Vancomycin	Ti	EPD	[70]
Ag	Bone morphology protein-2 HA CS Heparin	Ti	EPD	[132]
Ag	BG Polysaccharide CS	Ti6Al4V	EPD	[96]
Ag $Ag/Ca_3(PO_4)_2$	HA	Ti	ECD	[204]
Ag encapsulated in mesoporous silica nanocarriers	CS	Ti	EPD	[124]
Ag	PEEK BG	SS	EPD	[77]
Ag nanocluster–silica	PEEK BG	SS	EPD	[72]
Ag	Collagen	Ti	ECD	[28]
Ag		Ti6Al4V	ECD	[107]
Ag	HA	Ti	ECD	[205]
Ag	Dopamine CS	PLA/Ag	Electrospinning ECD	[168]
Ag	Dopamine Polypyrrole	PLA/HA	Electrospinning ECD	[146]
Ag	Lysozyme CS HA	Ti	Electrospinning ECD	[206]
MgO	PLLA	Ti	EPD	[207]
Mg-doped chitosan/gelatin	CS Gelatin	Ti	EPD	[62]
MgO		Mg	EPD	[80]
$MgSiO_3$	TaN	Mg alloy	EPD	[199]
Fe_3O_4	$CaCO_3$ HA Gentamicin	Ti6Al4V	EPD	[208]
Fe_3O_4	Collagen	Ti	ECD	[138]
Fe_3O_4	HA-BG-CS	Mg alloy (AZ91)	EPD	[113]
CaSi		Ti	ESD	[59]

Table 2 (continued)

NPs	Additives	Substate	Method	Ref
Au		Ti	ECD	[55]
CeO_2	SF	Ti	Electrospinning ECD	[176]
GO	GO Gelatin Methacrylic anhydride Bovine serum albumin	Ti	EPD	[123]
Poly(D,L-lactide-co-glycolide)	N-nitrosomelatonin Collagen	SS	EPD	[192]
SF		Ti	EPD	[94]
Dexamethasone-loaded mesoporous silica	$Ca_3(PO_4)_2$	CS-alginate-gelatin on SS	ECD	[74]
CS/gelatin/Si-gentamicin	Sol–gel CS Gelatin Gentamicin	Ti	EPD ES	[63]
γ-PGA-g-AMC/HA		Mg	EPD	[83]

Table 3 Improvement of antibacterial properties

NPs	Additives	Substrate	Method	Ref
Ag		Ti	EPD	[107]
Ag	CS	Ti	EPD	[70, 124]
Ag	CS Gelatin	Ti	EPD	[163]
Ag TiO_2		Ti	EPD	[209]
Ag	Collagen	Ti	ECD	[28]
Ag	HA	Ti	ECD	[205]
Ag ZnO TiO_2	CS Gelatin	Ti	ECD	[210]
Ag HA		Ti	ECD	[204]
Ag	CS HA	Ti	ECD	[132, 206]
Ag	Polypyrrole	PLA/HA/polydo-pamine	ECD	[146]
Ag	PEEK BG	SS	EPD	[72, 73, 77]
HA		Ti	EPD	[127, 204]
HA	CS Gentamicin	Ti	EPD	[122, 131]
HA	CS GO	Ti	EPD	[44]
HA Cu		Ti	EPD	[211]
HA Fe_3O_4	CS	Mg	EPD	[120]
BG	CS Gentamicin	Ti	EPD	[63]
BG	CS	SS	EPD	[76]

Table 2 (continued)

NPs	Additives	Substrate	Method	Ref
BG	PEEK Ag ions Mn ions Chitosan Gelatin	SS	EPD	[79, 121]
BG ZnO	Alginate CS	SS	EPD	[71]
MoS_2	CS	Ti	EPD	[212]
Halloysite nanotubes	CS Gentamicin	Ti	EPD	[128]
Chitosan–gelatin nanosphere		Ti	EPD	[194]
MgO	PLLA	Ti	EPD	[207]
Fe_3O_4	$CaCO_3$ HA Gentamicin	Ti	EPD	[208]

Conclusions and perspectives

The field of medical implants is rapidly growing and involves mostly orthopedic, dental, and cardiovascular stents. The impact of these artificial devices has revolutionized medicine and improved dramatically the life quality of millions of patients. Due to the required mechanical properties, most implants are still made of metals and in particular stainless steel, titanium, magnesium, and other alloys. Yet, the surface properties of these metals and alloys do not always provide the biocompatibility, osteoinduction, and other essential properties that implants should possess. Therefore, the basic metal structure is often coated with a proper layer, which can be made of nanoparticles and other nanostructures. The advantage of nanoparticles is their ability to accommodate additional organic and biologically active substances that can be released locally. Electrochemistry is ideally suited for coating such conductive implants with functionalized nanoparticles. Electrophoresis and electrochemical depositions that are carried out at room temperature and under mild conditions do not harm the organic and biological compounds and at the same time allow to control very well the thickness of the coating on implants having complex geometries.

We believe that only the tip of this iceberg is currently seen, and we anticipate that the incorporation of more nanostructures made of mostly organic and biological polymers will further and significantly increase. As such, electrochemistry is clearly going to play a major role first in laboratory studies and eventually in commercial processes in coating medical implants.

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