

Review

Surface Modifications for Implants Lifetime extension: An Overview of Sol-Gel Coatings

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Abstract: The limited lifetime of implants entails having patients undergo replacement surgeries, several times throughout life in young patients, with significant risks for them and extensive cost for healthcare service. The overcoming of such inconvenience is still today a hard challenge for the scholars of the biomedical and biomaterial fields. The improvement of the currently employed implants through surface modification by coatings application is the main strategy proposed to avoid implants failure, and the sol-gel coating is an ideal technology to achieve this goal. Therefore, the present review aims to provide an overview of the most important problems leading to implant failure, the sol-gel coating technology, and its use as a strategy to overcome such issues.

Keywords: implants lifetime; surface modification; sol-gel method; sol-gel coatings

1. Introduction

In the last decades, changes in population habits and a longer life expectancy have led to an exponential increase in the number of repair procedures with surgical implants. The growing clinical demand for increasing the performance of medical devices together with the advancement in technology has induced a significant expansion of the industries working in the biomedical and biomaterial fields. This phenomenon is related mainly to the devices employed in orthopedic surgery. Nowadays, approximately 1.5 million joint replacements are performed annually in Europe, while 7 million in the United States [1]. Although joint replacement surgery has become common, the implanted biomaterial's long-term durability is not ensured. The failure of the implants can be caused by several reasons, such as adverse immune system reactions, biofilm formation, or mechanical, chemical, tribological, surgical, manufacturing, and biocompatibility problems [2,3]. Despite the research efforts in the development of new materials with high tolerability and integration capability or in improving performances of existing biomaterials, a good combination of mechanical, chemical, and tribological properties and biocompatibility has not yet been reached [4]. Therefore, the average lifetime of an implant is about twenty years. This entails the need for further surgical interventions of prosthetic devices replacement, mainly in young patients. Most revision surgery is more complicated and more expensive than primary joint replacements. For example, the annual hip revision costs constitute 20% of all hip surgery costs [5]. Therefore, revision surgery for failed joint replacements poses a considerable burden for healthcare systems [6].

The need for overcoming the limitations of currently used medical devices has stimulated many research groups to turn their interest toward the techniques able to modify the material surface.

This has an essential role in defining the biomaterial performance [4] since it is more reactive than the core of the material [7]. Therefore, the response of the human body to the material implantation is a function of the reactions that take place at the tissue–implant interface [7]. Many macroscopic material

properties (e.g., resistance to corrosion and chemical agents, hydrophilicity/hydrophobia, bioactivity and biocompatibility, refraction index, reflection, photoluminescence and other optical properties, etc.) are related to the chemical and physic features of the material surface [4]. Hence, surface modification can lead to the enhancement of the implant integration process by the application of functional coatings to biologically implantable materials. This is a promising strategy to give new properties to a material or to modify and enhance some already existent ones [4] (e.g., improvement of wear and corrosion resistance, inhibition of ion release [8], modification of hydrophilicity and hydrophobicity features, the introduction of functionality [9], and the improvement of bioactivity and biocompatibility [10–13]).

In the last years, sol-gel technology has been considered one of the most feasible technologies to manufacture chemically homogeneous coatings with a wide range of properties compared to other deposition techniques. Sol-gel is a method used to produce inorganic and organic–inorganic hybrid materials at relatively low temperature starting from a colloidal solution (namely, “sol”) where hydrolysis and condensation reactions take place leading to the formation of a 3D rigid network (namely, “gel”). The process is easily coupled to some coating techniques, such as dip coating, spin coating, and spray coating. Sol-gel chemistry, indeed, allows the formation of thin layers on substrates of different nature and shape by the instantaneous transition from the sol to the gel (as explained in detail below). Sol-gel coatings are successfully used in a wide area of applications, such as optics, electronics, energy, environment, solar cells, catalysts, sensors, and functional smart coatings [4,14], as well as in biology and medicine where they are used for modifying the surface of the medical devices. Sol-gel coating technology, indeed, allows the production of glasses, glass–ceramics, and calcium phosphate materials of known biological performance [15–17]. Their bioactivity and biocompatibility are ascribable to the presence of residual hydroxyl groups and large specific surface area [18] due to the materials’ intrinsic mesoporosity. These features make the sol-gel materials more performant than traditional glass and ceramics in term of tolerability and biocompatibility [19]. Moreover, the presence of the residual –OH groups induce easier nucleation of the hydroxyapatite (HA, the main biomineral in the human bones with chemical formula $Ca_{10}(PO_4)_6(OH)_2$) on sol-gel materials surface and allows an easy functionalization by suitable biomolecules and ensures an effective adhesion of the sol-gel coatings on the substrate [20] due to their interaction with it [21,22]. Moreover, materials chemistry and high specific surface area promote protein or drug adsorption [23,24].

The use of sol-gel technology for coatings production has several advantages (see Figure 1). The possibility of modulating the synthesis parameters (e.g., sol pH, reagents molar ratios, use of inhibitors or catalysts, and synthesis and annealing temperature) allows the control of the surface chemical composition and functionality, as well as the coating’s microstructure and morphology [4].

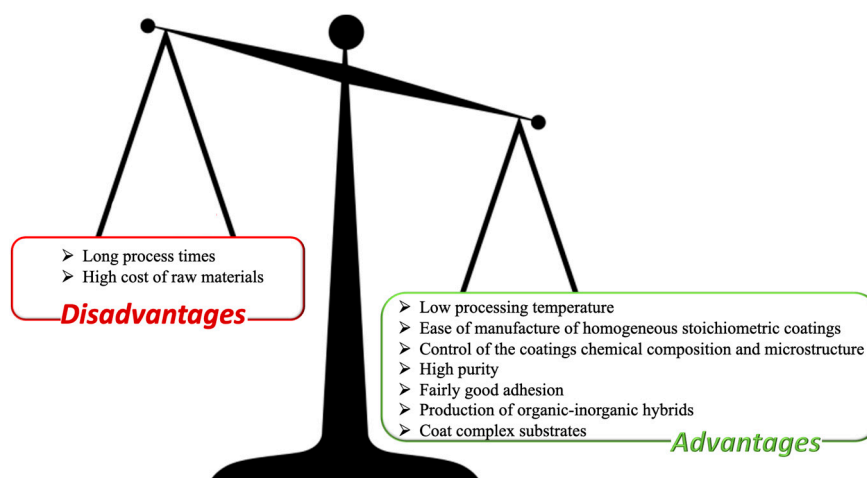


Figure 1. Advantages and disadvantages of sol-gel coating technology.

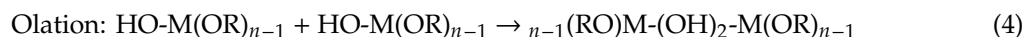
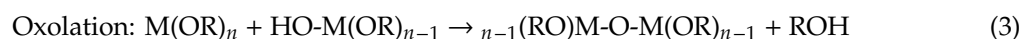
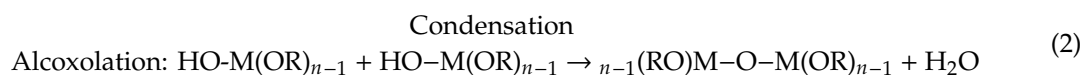
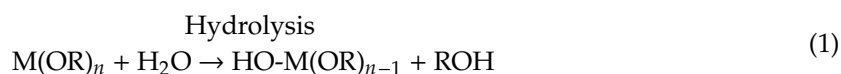
For example, the post-deposition heat treatment conditions (in particular, temperature and time used) can affect the coating microstructure leading to amorphous or crystalline layers [25]. Moreover, the low processing temperature allows the functionalization of coatings with thermolabile molecules (e.g., polymers, drugs, biomolecules, etc.) leading easily to the manufacture of organic–inorganic hybrid (OIH) coatings. The low processing temperature together with the use of pure raw materials and the modulation of the sol ageing time ensure the production of stoichiometrically homogeneous coatings. This is not always ensured using other deposition techniques requiring high processing temperatures due to material thermal instability, the possible formation of secondary glassy phases in the ceramic layer, or the dissolution of some of them in the biological environment, as reported for the HA coating preparation by plasma spray techniques [26,27].

The several articles and review works [20,28,29] published in the last years about the surface modification of implants demonstrate the interest in this issue and the sol-gel coating technology. In this context, the present review aims to provide an overview of the role of the sol-gel coating in the research of new strategies for the implants' lifetime extension with particular attention to the causes and mechanisms underlying the processes leading to the implants' failure. For this purpose, some theoretical aspects of the sol-gel chemistry and the main techniques used for sol-gel coatings deposition are initially described. The following section focuses on the main causes associated with implants failure and the solutions proposed within the sol-gel coating technology. Nowadays, this is still an unavoidable clinical event and its prevention represents a challenge for the researchers working in the biomedical field.

2. Theoretical Fundamentals of the Sol-Gel Coating Technology

2.1. Sol-Gel Method: Some Theoretical Aspect

The sol-gel technique is a wet chemical method of manufacturing inorganic or organically-modified glass and ceramic oxides, at low temperature [4,30]. The process starts with the preparation of the sol, which is a stable colloidal suspension of fine nano-sized particles in an aqueous or alcohol solution. The sol is obtained through hydrolysis and partial condensation of inorganic metal salts or metal–organic compounds, mainly metal alkoxides with generic formula $M(OR)_n$ ($M = Si, Ti, Zr, Al, B$, or other network-forming elements, and $R =$ alkyl group). These sol precursor compounds are generally solubilized in an alcohol–water solution where they are hydrolyzed by water. The alcohol acts as a homogenizing agent since the precursor alkoxides are immiscible in water [31]. Once hydrolysis products are formed the condensation can start and the two reactions proceed simultaneously. Both hydrolysis and condensation reactions take place following an S_N2 mechanism, according to equations below [30]:



Therefore, the condensation reactions can go on between two partially hydrolyzed metal alkoxide precursor molecules (alkoxylation) or between a partially hydrolyzed one and a non-hydrolyzed one (oxolation). In both cases, the reactions lead to the formation of oxygen bridge bonds and water or alcohol as by-products, respectively. Moreover, the condensation can also occur through an olation reaction, leading to the formation of a hydroxyl bridge between two metal atoms [4,30]. The continuation of the condensation reactions and particle agglomeration within the sol leads to the gradual formation of a 3D network retaining the residual solvents and water (namely “wet gel”).

Thus, the conversion from the sol to the gel occurs gradually in this step and is detectable to the naked eye because it is accompanied by the gradual increase in solution viscosity and the achievement of gel point. In the gel phase, the condensation reactions continue and the removal of most solvents and water occurs, leading generally to a significant shrinkage and a stiffness increase of the gel. This step is called syneresis or “ageing” of the gel [4,30]. Afterwards, the drying of the gel is required to ensure the removal of residual solvents and water. In addition to the drying, the gel calcination at high temperature could be required to remove the residual M–OH groups on the network surface.

Several synthesis parameters influence the rate and degree of the hydrolysis and condensation reactions, which in turn affect the microstructure, and, thus, the properties of the final obtained material. The most important are the following [4,30–34]:

- The kind of precursors. The metal atom ability to increase the coordination number beyond the valence, the ionic character of the M–O bond, affected in turn by electronegativity differences between the M and O atoms, the ligand reactivity towards hydrolysis [35], depending on its size and geometry (steric effect) as well as the electron-donating/withdrawing ability of R groups are the main factors influencing the relative rates of hydrolysis and condensation and thus the degree of oligomerization or polymerization. Therefore, different morphologies of products can be yielded by modulating the choice of precursors.
- pH. The use of acid or basis catalysts affects the relative rate of the hydrolysis and condensation reactions. For example, acid or basis catalysts are essential in the sol-gel silica chemistry because the hydrolysis of alkoxysilanes is too slow in a neutral environment. Acid catalysts act by protonation of Si–OH or Si–OR groups oxygen atoms inducing a double effect: the improvement of the electrophilicity of the silicon atom through the withdrawn of the electron density from it and the formation of a good leaving group (water or alcohol). On the other hand, when alkali conditions are employed, the hydrolysis and the condensation proceed through the attack of the central silicon atom by OH[−] or deprotonated Si–OH (that is Si–O[−]) groups, which are more nucleophilic than water and Si–OH groups. The different kinetic caused by the employment of these two catalysts lead to obtaining gels with a whole different structure. In particular, acidic environments allow synthesizing linear-like network containing a high concentration of unreacted silanols, whereas the result of the alkali catalysis process is a branched dense gel.
- Catalysts or inhibitor use and their concentration. Many sol-gel processes involving metal alkoxides require the use of a chelating agent to slow down the hydrolysis and condensation reactions by decreasing precursor reactivity. This outcome is obtained by the reduction of the available metal coordination sites often coupled with an inductive effect and can lead to a less cross-linked network.
- Precursor/water ratio (R_w). The amount of available water affects hydrolysis kinetic and, thus, condensation proceeding.
- Solvents. Depending on the solvent features, interactions with the precursors can take place influencing their reactivity.
- The temperature. Beyond the kinetics of hydrolysis and condensation reactions, the temperature also affects the evaporation of the solvents and water during the syneresis and drying steps, and thus the cracks formation probability.

The shrinkage is one of the main disadvantages of the sol-gel method. As this phenomenon is easier to control in a thin film, the main application of the sol-gel technique is the production of coatings.

2.2. Sol-Gel Coatings: Preparative Techniques

The sol-gel process is easily couplable to a deposition technique, such as dip-coating, spin-coating, or spray-coating (Figure 2). For the coating production, after the preparation of the sol with a

composition suitable to the coating application, its deposition on the substrate is carried out using a deposition technique.

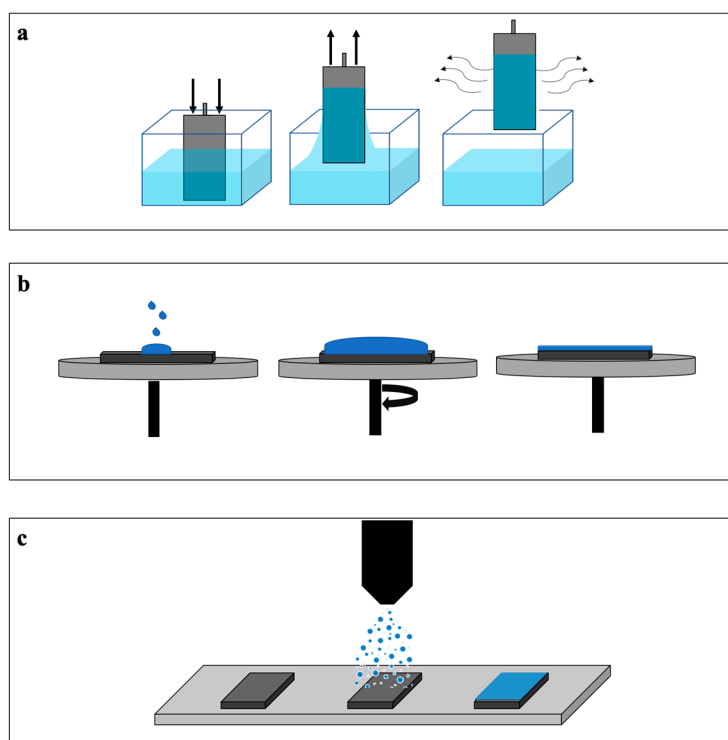


Figure 2. Schematic representation of: (a) dip coating; (b) spin coating; and (c) spray coating.

When the dip-coating process is employed, the substrate is soaked in the sol at a constant speed and held within it for the time required to the whole wetting of the substrate surface and the formation of chemical interactions between the substrate and the sol. After the dwell time in the sol, the substrate is withdrawn vertically to the liquid at a programmed and constant speed in a controlled environment condition of temperature and pressure. The movement of the substrate upward leads to the drainage of the sol and its homogeneous deposition on the substrate surface. At the same time, solvent evaporation takes place from the thin sol layer leading to its gelation. The main parameters affecting film thickness are the sol viscosity and the withdrawal speed. In particular, the slower is the withdrawal speed and the lower is the viscosity, the thinner is the coating thickness. However, film structure and features (e.g., porosity, transparency, opacity, etc.) also depend on size and structure of the particles in the sol, condensation rate, the forces (e.g., shear, capillary, and surface tension) generated during the film deposition, environmental conditions (such as temperature, relative vapor pressure, airflow, humidity, etc.) which, in turn, influence evaporation step, and the eventual heat-treatment carried out on the coating.

Another commonly used deposition technique is the spin-coating. In this process, the substrate surface is wholly covered with the sol. Then, the substrate is spun around an axis perpendicular to the coating area (spin-up step) and accelerated up to a set spinning speed. Its choice is a function of the sol properties and the substrate nature [36]. The centrifugal force leads the liquid to flow radially outward, inducing the sol expulsion from the substrate surface [30–37]. Following the spin-off step, where the substrate is kept in rotation for a set time, the excess liquid flows towards the edge and leaves the surface as droplets and the evaporation of the volatile species from the sol layer leads to the sol gelation and thin film formation [30,38]. The final film thickness depends on angular velocity, sol viscosity, and solvent evaporation rate. Moreover, the coating properties are influenced also by solution features: in addition to its viscosity, the sol species concentration, the drying rate, and sol surface tension have a key role. Besides, the set instrumental parameters also have significant importance, such as final

rotational speed, acceleration [36,39], and ramping rate to achieve the final spin speed. In particular, the higher is the angular speed of spinning and the longer is the time for spin-up stage, the thinner is the film [36].

Therefore, unlike the dip-coating technique, in the spin-coating process, the film thinning occurs mainly by evaporation and centrifugal draining.

When the sol-gel method is coupled with spray-coating, the sol is atomized or nebulized to form a fine mist of droplets by employing compressed air or pressurizing the sol. Then, a nozzle system is used to deposit the fine droplets on the whole substrate. To obtain nebulization, the sol viscosity has to be lower than in the dip and spin coating technique. The coalescence of the fine droplets can take place if the surface is wettable. This technique is widely used in industrial applications because it is faster than the other deposition techniques, it allows an easier application on substrates with irregular shapes, the waste of coating sol is much smaller, and it is suitable for establishing an in-line process. However, the clogging of the nozzle tip can occur over time, due to the solvent evaporation and the resulting sol gelation, and the coating of hydrophobic surfaces can be an issue [40].

3. The Applications of Sol-Gel Coating Technology in Biomedical Field

A variety of metal implants are employed in various disciplines of medical sciences depending on the requirement of a specific application. The surface properties of the implants are crucial factors in determining the rejection or acceptance of a material in the body since the biomaterials meet and interact with the biological environment through the surface. Therefore, an extension of the lifetime of the implants can be achieved by designing suitable surface modifications able to hinder the main processes leading to implant failure. The mechanisms hindering implants integration and tolerance and that induce biofilm formation, wear, and corrosion phenomena are reported below, together with an overview of the sol-gel coatings proposed for modifying the surface of the metallic biomedical devices to avoid such processes that limit implant lifetime.

3.1. Biocompatible Coatings for the Improvement of Implant Integration

The properties of the biomaterials used in the manufacture of implantable devices play a key role in the success of orthopedic and dental surgery [41]. The most used materials for permanent implants in contact with the bone are metals, in particular pure titanium and its alloys [41]. One of the most important reasons for using titanium as an implant is its inertia and safety for human use. However, in recent years, it has been shown that all metals undergo degradation phenomena in the long-term because no metal is completely inert in vivo [7]. Titanium-based materials have a good combination of biocompatibility, mechanical strength, and osseointegration properties.

Brånemark [42] in the early 1950s was the first to use the term “osseointegration” to describe stable fixation between a metal titanium dental implant and bone tissue in a rabbit model. Since then, osseointegration has become a phenomenon of importance not only in dentistry but also in orthopedic and rehabilitation sciences [43]. Osseointegration starts with the activation of an osteogenic process with a tightly regulated cascade of intracellular and extracellular biologic processes [44] and is influenced by chemistry, topography, and other surface features [43].

Whenever an implant is introduced into the body, it will always generate an inflammatory response by the human body. This process allows the activation of the macrophages which induce the fibroblasts to produce collagen molecules forming a capsule around the implant, which results as foreign materials. The fibrous encapsulation is the main limit of many implants because leads to their isolation and hinders their sticking to the bone due to the lack of bioactivity [7]. The capsule thickens as long as the phagocytic activity continues, subsequently leading to implant mobilization which causes its performance reduction and its early failure (aseptic loosening of the implant) [7]. Numerous factors can promote or inhibit this process. In particular, it has been noted that titanium and its alloys show minimal encapsulation while stainless steel and CoCr alloys give rise to a thicker fibrous capsule [45]. The formation of the fibrous capsule around the metal implants is difficult to

avoid and depends on implant design and host bone quality. In particular, the surface properties of the biomaterials have all been implicated in the success and failure of osseointegration.

To avoid encapsulation and to ensure strong bonding between the bone and the implant, several surface modification techniques have been used aiming to make the implant more similar to the body constituents. However, to understand how to modify the surface of materials for mimicking body tissues, and the binding mechanism to the bone, knowledge of the chemistry of the bone is needed. Bone has a composite structure made up of cells, proteins, and minerals. The inorganic mineral phase of the bone constitutes approximately 50% of its weight and is mainly composed of carbonated HA. For this reason, the use of bioactive HA coatings is extensively proposed. Their presence has been shown to promote bone formation, adhesion, and fixing of metal substrates [46]. In the literature, several deposition techniques are reported to obtain bioactive HA as well as other coatings with several chemical compositions: sol-gel immersion coating, electrochemical deposition, plasma spraying, and sputtering coating [47–49]. Among these coating techniques, the sol-gel dip-coating method turns out to be the best one. This technique allows obtaining thin HA films on several substrates, such as porous titanium [29] and its alloys [50–53], alumina [54], or 316L stainless steel [55], with a good chemical homogeneity. The latter is ensured by using the required stoichiometric amount of each pure raw materials to prepare the dip solution. In particular, calcium nitrate hydrate is used as the source of calcium whereas several sources of phosphate groups were proposed, such as triethyl phosphite (after pre-hydrolysis) (see Figure 3) [29], $(C_2H_5O)_3PO$ [51,52], P_2O_5 [53,54], or $(NH_4)_2HPO_4$ [50]. Moreover, the coating amount and layer thickness can also be controlled by adjusting the concentration of suspension and number of dips.

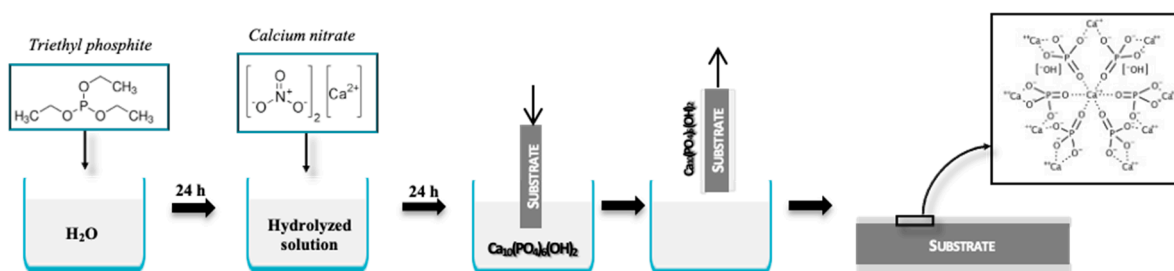


Figure 3. Schematic representation of the sol-gel dip-coating process used by Domínguez-Trujillo [52] to obtain hydroxyapatite sol-gel coating on porous titanium substrates.

Stan and Ferreira [56] used the sol-gel chemical routes to obtain bioactive fluor-hydroxyapatite (FHA) to coat the surface of Ti6Al4V medical-grade alloy. The results show good integration in the bone tissue and duration much longer than conventional HA. The presence of fluoride ions in the HA structure, indeed, stimulates the proliferation of bone cell and decreases the bio-resorption rate of the HA leading to a long-term chemical and mechanical stability. The hydroxyapatite coatings not only provide a mechanism for improving implant osseointegration but also work to seal the interface from wear particles and periprosthetic osteolysis associated with macrophages. Sharifnabi et al. [57] achieved similarly good results synthesizing an Mg-substituted fluorapatite coating on 316L stainless steel. The data reported show that the sol-gel coatings improve the wear and corrosion resistant as well as the biocompatibility of the substrate. To improve the mechanical properties of the HA coatings, Yoruc et al. [58] proposed the synthesis of composites coatings consisting of zirconia (ZrO_2) reinforced-HA.

However, other types of coatings have been studied to improve the osseointegration of metal implants [59]. As osseointegration is also guaranteed by good biocompatibility of the implant, different coatings have been developed to improve the biocompatibility and bioactivity of the implants. The use of coatings consisting of SiO_2 -based materials [60–66], and other alkali metal oxides-based glasses and ceramics (e.g., TiO_2 [67–71], ZrO_2 [11,72], and $ZrTiO_4$ [73]), entirely inorganic or organic–inorganic hybrids (OIHs), has been widely studied due to the known high biocompatibility

of such materials [74–77]. Moreover, such studies show that the use of OIHs coatings is advantageous in term of coating morphology. The presence of a polymer, indeed, leads to a coating elasticity improvement and thus to obtain crack-free layers. In term of biocompatibility, instead, the results are affected by the polymer nature. In particular, poly(ϵ -caprolactone) (PCL) [62,64] or polymethyl methacrylate (PMMA) increase leads to a decrease of biocompatibility due to the hydrophobic nature of these polymers, which can inhibit cell adhesion and, thus, cell viability [78]. On the contrary, polyethylene glycol (PEG) [68] presence leads to a cell viability increase ascribable to the increase of the surface hydrophilicity [79] and mesoporosity [80], which enhance cell adhesion and growth [79,81].

Besides the results obtained *in vitro*, those obtained *in vivo* also prove that the presence of sol-gel coatings improves the proliferation and differentiation of bone cells and, thus, implant osseointegration. Urbanski et al. [82] used sol-gel method to produce titanium dioxide (TiO₂) and silica (SiO₂) films to coat stainless steel 316L (SS) and titanium alloy (Ti6Al4V) [7]. These coated materials were implanted in the rat femur resulting in a lower inflammatory response in both cases, suggesting that the presence of the coatings leads to an improvement in biocompatibility and osseointegration of the substrates [7]. Ballarre et al. [83] improved the *in vivo* performance of AISI 316L stainless steel by the deposition of OIH coatings synthesized using tetraethylorthosilicate (TEOS) and methyltriethoxysilane (MTES) as precursors. The implants were coated with two layers: The former obtained by adding SiO₂ colloidal particles to the TEOS–MTES OIH sol, the latter synthesized starting from the former sol by adding SiO₂–P₂O₅–CaO glass–ceramic particles. The results prove that the layers act as a barrier hindering ions migration from alloy. Moreover, the coatings promote the development of newly formed bone in the periphery of the implant when it is implanted in a rat model. However, the quality of the newly formed bone is affected by the amount of SiO₂ particles. In particular, the coating containing 10% of SiO₂ particles and 10% glass–ceramic particles showed a stiffness similar to the values for old cortex bone and short periods of maturation and mineralization of newly formed bone tissue around the implant [83].

Therefore, sol-gel coating technology for the materials surface modification represents an attractive tool to obtain implants showing outstanding biocompatibility and osseointegration properties. This is a target that has not yet been achieved despite the researchers' efforts.

3.2. Antimicrobial Coatings

Each year, many medical devices are used as surgical implants and, unfortunately, a significant proportion of each type of devices is colonized by bacteria and becomes the focus of an implant-related infection. Implant-related surgical site infection is one of the main reasons for implant failure in orthopedics and trauma following medical implant surgery. It leads to high economic and social costs due to the hospital prolonged to stay of patients and often the need implant replacement with a burden on the health care facilities [84,85]. The prosthetic joint infection affects between 0.5% and 15% of patients undergoing primary or revision joint arthroplasty [1].

The onset of the microbial infection after biomaterials implantation is caused by a competition between the host and the bacteria for surface colonization and can lead to biofilm formation [1]. The hindering of biofilm-associated infections represent a medical and surgical challenge [41].

This process can destroy tissue adjacent to the implant leading to poor vascularization, implant loosening, detachment or even dislocations [41,86]. Bacterial adhesion occurs with the interaction between the proteins of the bacterial cell and functional groups on the material surface [41] (Figure 4). Mature bacterial biofilms are extremely difficult to eliminate with conventional antimicrobial therapies because they are highly resistant to treatment with antibiotics [41].

This is due to bacterial biofilm's ability to impede the infiltration of antibiotics due to the biofilm exopolysaccharide matrix. As a result, patients develop recurrent infections after surgery and inflammation is poorly controlled, leading to failure of the surgery [87].

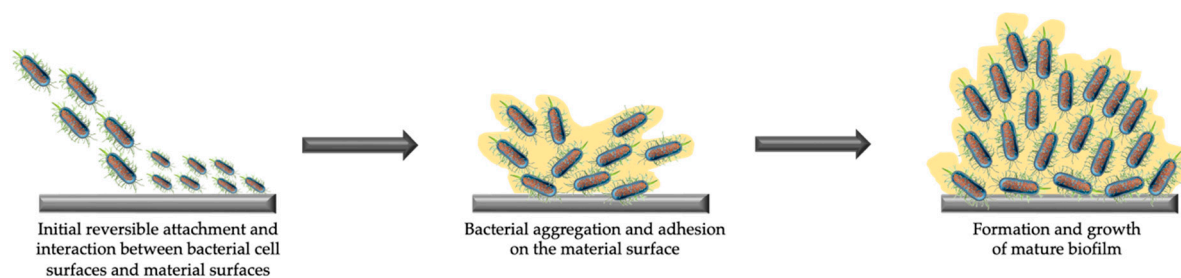


Figure 4. Illustration of the biofilm-associated infections process on the medical device.

In the last decades, the design of new biomaterials incorporating antibiotics has been made, assuming that the antibiotic can be gradually released to give higher local concentrations at the implant site than can be achieved by systemic therapy. Radin et al. [88], for example, produced a coating on titanium plates using silica sol-gels for local vancomycin delivery. Although these new materials can effectively prevent infections, long-term exposure to antibiotics enhances risks for the generation of drug-resistant bacteria strains. Moreover, the concentration of antibiotics released from the prosthesis has a short duration of effect, resulting in an unsatisfactory antimicrobial effect. Tschon et al. reported that some patients may even develop toxic effects and hypersensitivity [89]. To date, no treatment or drugs incorporation can guarantee rapid and complete biofilm destruction or prevent infection recurrence. Therefore, long-term clinical success depends upon the antimicrobial properties of the implanted materials. The research has been focused on the prevention of biofilm formation by implant surface modifications aiming to avoid both the spread of pathogens and material deterioration. Numerous studies reported the ability of coatings to minimize bacterial adhesion and inhibit biofilm formation to protect implanted biomaterials [90–93].

Besides the possibility of obtaining uniform and homogeneous coating thickness and high adherent biocompatible coatings even in complex shapes, the main advantage of using sol-gel coatings technology in antimicrobial coating production is the low processing temperature, which allows easily film integration with a wide variety of thermolabile natural and synthetic antibacterial and/or organic compounds destined to be locally delivered at a controlled rate.

Palla-Rubio et al. [94] prepared sol-gel hybrids loaded with different amounts of chitosan for titanium substrates coating. The reported results show that the addition of chitosan improved the antibacterial activity of the sol-gel coatings. Chitosan is a linear polysaccharide that is considered both bactericidal, able to kill living bacteria, and bacteriostatic, able to hinder the growth of bacteria without necessarily implying their death [94]. The antimicrobial activity of the chitosan is due to the positively-charged amino groups of its chemical structure that interact with the negatively-charged bacterial cell wall, killing the bacteria [95].

García-Arnáez et al. [96] proposed sol-gel silica-based coatings doped with two bactericides: octenidine dihydrochloride (OCT) and chlorhexidine diacetate (CHX). Both tested antibacterial compounds give complete antibacterial protection to the coatings due to their controllable release. Furthermore, they also showed that the presence of the two antibacterial compounds does not affect human osteoblasts vitality. For this reason, they suggested this system as a tool for coating medical devices to prevent implant bacterial colonization.

In the last decade, in addition to the incorporation of the antimicrobial drugs or metals in the sol-gel matrix for the coating of a biomedical implant, natural compounds extracted from plants are widely used. Natural products are today some of the main sources of new drug molecules due to the development of pathogenic bacterial strains that possess resistance to more antibiotics used currently in various diseases. Jaiswal et al. [97] incorporated coumarin in a silane sol-gel coating containing Ag. Sol-gel coatings that had coumarin complexes with Ag were found to be highly effective in inhibiting the growth of *S. aureus* and *Enterobacter cloacae*.

In many studies, titanium implants are coated with sol-gel films containing metal additives, such as Ag [98–100], Cu [101], or Zn [102]. Fu et al. [103] and Massa et al. [104] reported the impact of Ag

on bacteria growth and the biofilm formation. The silver antibacterial activity is ascribable to the interaction between the positive charge of the silver and the negative ones of the cell wall membrane and DNA structure of bacteria [105]. Gouveia et al. [106] developed chitosan–silica class II hybrid materials loaded with AgNPs as coatings for implantable Ti6Al4V surfaces. The antibacterial effects were evaluated demonstrating that the antibacterial activity increases with chitosan content and that the bacteria are markedly more sensitive to coatings loaded with AgNPs in biofilm assays. Heidenau et al. [107] showed that copper ions displayed the best antibacterial activity compared to Ag^+ and Hg^{2+} in the same sol-gel system. Similar results were found by Gollwitzer et al. [108], who showed that the presence of the copper into the final coating significantly reducing adhesion of bacteria on the surface materials with a better compromise between biocompatibility and antibacterial activity. The release of the copper from sol-gel coatings led to its direct contact with bacteria membrane, causing membrane and cell envelope damage and, thus, the bacteria growth inhibition [109]. However, the antibacterial effect of the copper also depends on the bacteria strain and differences between the Gram-positive and Gram-negative cells [110]. Gram-negative bacteria have an outer membrane in addition to the cell wall, while Gram-positive bacteria do not. The outer membrane acts as a barrier generally reducing the transport of metals into the bacteria cytosol. For this reason, copper penetrates rapidly into Gram-positive cells and a serious toxic effect occurs compared to in Gram-negative bacteria [111].

On the contrary, Zinc ions act more effectively on Gram-negative strains. Zinc antibacterial activity is likely to only be bacteriostatic, rather than be bactericidal [112]. The porins embedded in the outer membrane of Gram-negative bacteria permit nonselective passive diffusion of Zn ions across the outer membrane. Afterwards, the Zn ions are transported by inner membrane transport systems into the cytosol; this process is energy-dependent, and, thus the living conditions of the bacteria become worse as the bacteria transport more Zn ions [112]. Gram-positive bacteria lack an outer membrane and the amount of Zn ions they transport, and thus the consumed energy, is less than Gram-negative ones. As a result, the Gram-negative bacteria are more sensitive to the released Zn ions compared to Gram-positive ones. Chung et al. [113] prepared HA coatings modified with Ag^+ and Zn^{2+} ions on Ti6Al4V implants. The obtained data show that the antibacterial activity on a Gram-positive strain is ascribable mainly to Ag ions, whereas the Zn ions lead to an enhancement of biocompatibility. Therefore, sol-gel HA coating containing a suitable amount of Ag and Zn can allow obtaining implants able to efficiently resist microorganisms and with outstanding biocompatibility.

Besides, the hydrophobic surface can inhibit the growth of bacteria. Pradheebha et al. [114] reported the manufacture of superhydrophobic coatings by sol-gel method using MTES, 3-Glycidyloxypropyl trimethoxysilane (GPTMS), and (1H,1H, 2H, 2H perfluorooctyl) triethoxysilane (FTS) as precursors. SiO_2 nanoparticles were added to the obtained sol leading to the production of fluoro silane-based sol-gel nanocomposite coatings. The coatings were applied on AISI Stainless steel 304 substrates physically modified using a nanosecond pulsed laser for creating nano-scaled roughness. The roughness implementation due to the laser textured surface and to the presence of the SiO_2 nanoparticles in the coating contributes to the coating adhesion and hydrophobicity improvement. Moreover, the preliminary test for the antibacterial activity for these surfaces showed a bacterial inhibition rate of $89 \pm 2\%$ even in the absence of additional antibacterial agents. All works incorporating metal ions in the coating demonstrate that the combination of the bactericidal effect of metal ions with the hydrophobicity of the coating surface can provide an antibacterial effect through the synergy of both phenomena. Therefore, the sol-gel coating could be a good strategy to avoid the implant failure providing antibacterial properties to all different type of implants.

3.3. Coating for Corrosion Protection

The main biomaterials used in reconstructive surgery (e.g., orthopedics) are metals and their alloys [115,116]. The increasing clinical use of metal implants highlights the problems related to the preservation of the implant integrity in the long term [116]. Metal biomaterials, indeed, are highly reactive, and none of them is entirely inert in vivo [43]. Furthermore, the environment inside the

human body is physically and chemically more corrosive than the ambient one [116,117]. Consequently, metallic implants easily undergo corrosion in the body [116]. Corrosion phenomenon can decrease the lifetime of an implanted appliance, leading to the necessity of secondary surgery. After initial success, indeed, the implant failure can occur due to the loss of close contact between the bone tissue and the implant. This is caused by the onset of inflammatory processes in periprosthetic tissues induced in turn by the release of wear debris and corrosion products and metal ions from the implanted materials as a consequence of the device use and/or its exposure to the hostile biological environment (Figure 5).

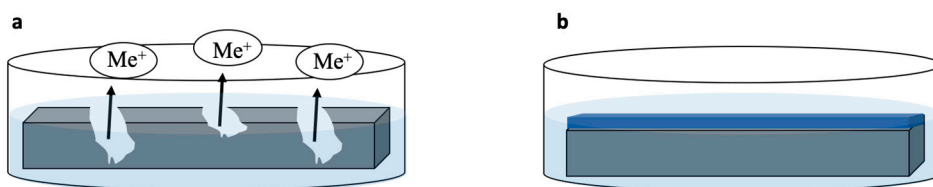


Figure 5. (a) Uncoated; and (b) sol-gel-coated metal substrates exposed to the aggressive bio-environment.

The inflammatory processes and the consequent elevated oxidative stress lead to the formation of granulation tissue and fibrous capsule around the implanted device and induce osteoclast activation. Therefore, an osteolysis process of the periprosthetic tissue takes place which leads to bone resorption, implant mobilization, and aseptic loosening [118]. Several *in vivo* studies report histological evidence of the inflammatory response onset in the tissues of the implant site, as well as the presence of metallic ions and particles [43]. Moreover, Okasaki and Gotoh [119] reported that the corrosion products or dissolved metal ions can either build up in tissues next to the implant or may be transferred to the other body parts entailing a risk for the human life [117].

Titanium and its alloys are widely used in orthopedic and dental fields due to their excellent biocompatibility and corrosion resistance ascribable to the ability of spontaneously developing an oxide layer on the surface which acts as a barrier between the implant and the bio-environment [120]. The main limitation in titanium clinical use is the local mechanical abrasion due to the use of the implant, which can damage the surface oxide film, leading to a decrease of the corrosion resistance and a continuous release of metal ions [117].

Management and control of corrosion is a crucial problem from biological, metallurgical, and cost points of view [43]. Therefore, in the last years, the research has focused on the development of several strategies to extend the prostheses lifetime preventing wear and corrosion phenomena [4]. With this regard, the design of protective coatings able to prevent, mitigate, and delay the corrosion process [121] has been carried out proposing the use of material with specific properties, such as effective corrosion protection, abrasion and cracking resistance, good adhesion to the metallic surface, and long lifespan [121].

Sol-gel coatings are recently attracting more attention as corrosion protective layers for different metallic structures [4], including aluminum and its alloys, carbon steel, stainless steel, and galvanized steel [121].

Figueira et al. [121–123] showed that different OIH coatings have been proposed for corrosion protection on a lot of metallic substrates obtaining excellent results.

Hosseinalipour et al. [124] developed biocompatible OIH coatings on 316L stainless steel using 3-methacryloxypropyltrimethoxysilane (TMSM) and TEOS at different molar ratios as sol precursors. The results show that the coatings improve the corrosion resistance of the substrate and that the better corrosion protection is obtained when TMSM and TEOS are used with a 1:1 molar ratio. Garcia et al. [125] obtained good results in terms of corrosion resistance and bioactivity preparing a OIH sol-gel coating on Ti6Al4V synthesized using MTES and TEOS with molar ratio TEOS:MTES = 2:3 and containing particles of hydroxyapatite, glass, and glass/ceramic $CaO-SiO_2-P_2O_5$. Coatings for delaying corrosion advance in AISI 316L stainless steel were developed by Juan-Díaz et al. [126,127]

starting from MTES and TEOS or MTES and GPTMS combined with different molar ratios. The results of electrochemical analysis reported in these studies reveal the formation of pores and water uptake during the degradation of the coatings and that the degradation kinetics of the coating is mainly influenced by TEOS and GPTMS amount, respectively. Higher TEOS or GPTMS amounts lead to higher wettability and water absorption of the coatings, due to the increase in the number of polar groups. This degradation process can lead to the disbanding of the coating and the onset of corrosion at the interface [126,127]. The increase in corrosive resistance of silica-based OIH sol-gel coatings obtained starting from MTES and TEOS precursors was also observed by Omar et al. [128]. Motalebi et al. [129] achieved the increase of the corrosion and wear resistance of AISI 316L stainless steel for biomedical applications developing an OIH coating with self-healing ability. This is known as the ability of a coating, in a certain environment, to repair damaged areas due to external factors [121]. Motalebi et al. [129] obtained film with such feature using vinyltrimethoxysilane (VTMS) as sol precursor and doping it by the addition of rosemary extract that acts as a green corrosion inhibitor. The main component of rosemary extract is the rosemary acid (a phenolic compound) and other polyphenolic compounds able to readily form complexes with di- and trivalent metal ions (e.g., Fe^{3+} ions) using the phenolic groups. The electrochemical results show that this component by interfering in anodic reactions leads to decrease of reaction rate and thus increase of corrosion resistance [129]. These coatings provide barrier protection between the metal surface and the aggressive bio-environment. The VTMS coating incorporated with 0.05% rosemary extract produced maximum inhibition. The incorporation of rosemary allows an inhibition efficiency higher than 90% [129].

However, entirely inorganic sol-gel coatings are also proposed as protective layers enhancing both cytocompatibility and corrosion resistance of the coated implants. In particular, sol-gel ZrO_2 [130], $\text{ZrO}_2/\text{SiO}_2$ [131], Nb_2O_5 [132], $\text{SrO-SiO}_2\text{-TiO}_2$ [133], or TiO_2 -based coatings [134–140] have been proposed to improve the corrosion resistance of several metal substrates, such as steels [130,137,140], titanium grade 4 [131], Ti6Al4V [134,138], NiTi alloy [133,139], and Mg-based alloy [135,136]. Liu et al. [67], Cheng et al. [141], and Chiu et al. [142] demonstrated that the presence of the sol-gel coatings improves NiTi alloy corrosion resistance reducing Ni release, which can cause allergenic and toxic effects when its concentration exceeds a certain level in the body. Kaur et al. [143] prepared HA coatings on 316L stainless steel by the sol-gel method and found that hydroxyapatite-coated samples showed better corrosion resistance and better implant properties as compared to uncoated 316L stainless steel. Thus, hydroxyapatite coatings are expected to enhance the corrosion resistance of alloys by forming a barrier against the dissolution of metal ions and at the same time promote implant bone-bonding ability [144]. These results are in agreement with the works of Jafari et al. [145] and Rojaee et al. [146]. The former group proved that HA sintered coatings obtained via sol-gel dip-coating improved Ti-14Zr13Nb alloy corrosion resistance and bioactivity [145] while the latter group prepared a sol-gel derived nanostructured hydroxyapatite (n-HAp) coating on AZ91 alloy using dip-coating technique achieving stabilizing alkalization behavior and improving the corrosion resistance of AZ91 alloy. It was concluded that n-HAp coated AZ91 alloy could be a good candidate as a type of biodegradable implant material for biomedical applications [146]. Guo et al. [147] prepared a TiO_2 coating on an HA-coated magnesium alloy to further improve the long-term corrosion resistance of HA-coated magnesium alloy. The obtained results suggest that, beyond effectively enhancing the corrosion resistance, the HA/ TiO_2 composite coatings improve in vitro cytocompatibility and antibacterial properties of Mg alloy and porous HA coating, potentially widening the application of Mg alloys in the biomedical field. Balamurugan et al. [148] and Mohammed and Hussein [149] successfully deposited TiO_2 -reinforced HA composite sol-gel coating on the surface of surgical grade 316L stainless steel and on a new biomedical Ti-Zr-Nb alloy, respectively. They proved that the composite HA/ TiO_2 films can be considered suitable for hard tissue applications as they possess both good biocompatibility and outstanding wear and corrosion properties. Moreover, Balamurugan et al. [150] also evaluated the performance of zirconia reinforced HA sol-gel coating on 316L stainless steel, demonstrating that the reinforced coatings are more corrosion resistant than both uncoated 316L SS and the HA-coated one and that the coatings act

as a barrier for the metal ion release from the metallic substrates without altering the good bioactivity and biocompatibility.

Therefore, the versatility of the sol-gel method can also be used to improve properties, such as wear and corrosion resistance, of different metallic implants. However, more resources and research are needed to turn the dream of developing a biocompatible and corrosion- and wear-resistant implant material, more similar to the human bone, into reality.

4. Conclusions

Several techniques for the surface modification of metallic implant are continuously being investigated. The present review shows that the sol-gel coating technology is among the most promising for achieving the implants' performance improvement and the extension of the biomedical implants' working life. The surface modification using the sol-gel coating technology is building the future of the implants for biomedical applications by solving numerous unanswered questions in terms of improved osseointegration, antibacterial, and anticorrosive properties, to avoid the early implant failure. This coating technology offers the possibility to design the features of the coating as required from the specific applications through an adequate selection of the precursors, the environmental conditions, and the instrumental parameters used. Among all the advantages, sol-gel coating presents a relatively inexpensive approach to the modification of the implants' surface. However, the complexity of the method in terms of selecting the parameters during the different stages of the process and the relative scarcity of information on the sensitivity to the processing conditions represent the challenge to address for further research and development of this promising technology.

Currently, the study of sol-gel coatings in the biomedical field takes place mainly at the laboratory scale. Before translating any laboratory success into a possible commercial product, it is necessary to face a series of challenges in a real scenario, such as the evaluation of the potential risks for the human health due to cell-coating material or tissue-coating material interactions.

Overall, in the field of medicine, the sol-gel coatings have great promise for society by providing a performant biomedical implant in the near future.

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