

Review

A Review of In-Situ Grown Nanocomposite Coatings for Titanium Alloy Implants

Urvashi F. Gunpath *  and Huirong Le 

College of Engineering and Technology, University of Derby, Derby DE1 3HD, UK; h.le@derby.ac.uk

* Correspondence: u.gunpath@derby.ac.uk; Tel.: +44-01332593286

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Abstract: Composite coatings are commonly applied to medical metal implants in order to improve biocompatibility and/or bioactivity. In this context, two types of titanium-based composite coatings have been reviewed as biocompatible and anti-bacterial coatings. The different composites can be synthesised on the surface of titanium using various methods, which have their own advantages and disadvantages. Moving with the smart and nanotechnology, multifunctional nanocomposite coatings have been introduced on implants and scaffolds for tissue engineering with the aim of providing more than one properties when required. In this context, titanium dioxide (TiO₂) nanotubes have been shown to enhance the properties of titanium-based implants as part of nanocomposite coatings.

Keywords: implants; tissue engineering; scaffolds; orthopaedics; composite; nanotechnology; smart technology; anti-wear; biocompatible; anti-bacterial

1. Introduction

An implant is a manmade material inserted in the human body with the aim of repairing or replacing the previously damaged tissue [1]. Composite coatings are widely used on different types of materials to enhance the compatibility and durability of implants. Metallic materials are still the main biomaterial for dental or skeletal implants owing to their exceptional mechanical properties [2–5]. Cobalt-based alloys, stainless steel and titanium and its alloys are known metallic materials, which have been used as implants. However, due to the lowest Young's modulus and corrosion resistance of titanium and its alloys, they are considered to be the best option for metallic implants even though the modulus is still higher than natural bone [6]. The factor that contributes to the corrosion resistance of titanium is the presence of the inert surface of a naturally formed oxide layer on the latter [7]. Nonetheless, since titanium alloy is preferred over pure titanium in the medical field due to the higher mechanical strength, the naturally formed oxide layer on the alloy is not always stable, and alloy metal species are released from the surface, which can be toxic [8,9]. Modifying the oxide layer under certain conditions can prevent such leaching and even add enhancing properties to the implant [8,10]. Further emphasis has been placed on the modification of surface topography and/or surface chemistry of biomaterials with the aim of functionalising the surface and making the implant last longer [11]. Roughening the oxide layer on titanium or its alloy is one of the modification processes, which make the surface more biocompatible. This can be achieved through plasma spraying, sandblasting, acid etching or anodisation [12,13]. Since the surface of the bone is nano-structured, nano-modification of surface topography has attracted significant interest [11,14]. Growing titanium dioxide (TiO₂) nanotubes on the surface of Ti alloy is an effective way of providing the required roughness with a high surface to volume ratio and hence high reactivity [15]. Anodisation is an electrochemical process whereby TiO₂ nanotubes can be grown in-situ on the surface of titanium/titanium alloy. This fabrication process is desirable as it allows the formation of uniform nanotubes arrays and a controllable pore size [16]. TiO₂ nanotubes on titanium are known to improve the ability of apatite formation and cell activity in

the surrounding [17]. Due to their tubular structure and the increased surface area to volume ratio, the nanotubes can be used as scaffolds for other nanomaterials to provide additional properties to the implant.

In the case of orthopaedic implants, the materials need to mechanically attach to the bone and integrate into the body environment as well [18]. In this context, implants have been made in such a way that they provide the mechanical properties required while being able to act as a scaffold for tissue engineering and provide local drug delivery as well. This paper aimed to shed light on the different types of composite coatings available (Section 2) and the methods used to fabricate them (Section 3). Last but not least, Section 4 concentrates on the development in multifunctional composite coatings in the field of implants.

2. Types of Composite Coatings

Composite coatings are used on different biomaterials. In this paper, Ti-6Al-4V was chosen as the biomaterial in question as a base for the composite coatings owing to the vast usage in the orthopaedic world. They are widely used as implant or fixation materials, and their surface can be modified to act as a scaffold for tissue engineering. In this context, ceramics and biomolecules are the two main types of composite coatings that are commonly used on Ti-6Al-4V-based implants depending on the purpose of the latter [19,20].

In the world of orthopaedics, there is always the risk of infection due to the involvement of foreign material inside a human body. Infection is a common cause of malfunction and failure [21–23]. Depending on the location where a biomaterial is used, it can be made anti-infective with the aim of combatting infections or as prophylaxis [22,24]. Anti-infective agents can be coated on or embedded in biomaterials to provide the necessary properties [22,24]. Section 2.1 concentrates on anti-bacterial coating. Silver or zinc oxide nanoparticles, acting as anti-bacterial agents, can be embedded in TiO₂ nanotubes on Ti-6Al-4V, which have been studied as composite coatings. The coatings for an implant also have to be biocompatible, which means they are not toxic to the surrounding biological tissues [25]. Furthermore, the concept behind tissue engineering itself depends on the ability of materials to promote cell adhesion and proliferation in order to facilitate tissue regeneration [26,27]. Section 2.2 is dedicated to biocompatible composite coatings and concentrates on ceramic grown on titanium-based material.

2.1. Anti-Bacterial Coatings

Combatting infections in implants is of great significance. Composite coatings could be the solution. Local anti-bacterial agent delivery is one such example that has been researched extensively for use as composite coatings on implants. This method has been shown to be more efficient with low toxicity [28]. TiO₂ nanotubes have nanotubular structures, which can act as a carrier of anti-bacterial nanoparticles aiming at local delivery [29,30]. Antibiotics have been used as a bactericidal agent on nanotubes. However, implant-related infections are often caused by more than one bacterium, and they occasionally develop resistance to antibiotics [31]. This is where metallic anti-bacterial feature becomes the alternative solution. Silver, copper and zinc nanoparticles have been used positively on TiO₂ nanotubes due to their anti-bacterial property and nanostructures [32–39]. Nonetheless, the silver nanoparticle is considered the best owing to the better anti-bacterial properties and the better resistance to bacteria [40–42]. Thus, integrating silver nanoparticles to TiO₂ nanotubes grown on titanium alloy is an excellent example of an anti-bacterial composite coating for implants. The nanostructured morphology of the embedded silver nanoparticles on the nanotubes attracts human cells to grow on the surface, hence acting as a scaffold for tissue engineering [43,44]. However, silver nanoparticles are toxic if released in high amounts at one time. Most studies analysing the behaviour of silver nanoparticles in the presence of human cells have shown different levels of toxicity, depending on the release rate and size of the nanoparticles [37,45]. For this reason, the size and attachment of the nanoparticles to the nanotubes' wall and the control of silver release from the coatings are the main factors to be considered when growing the latter as composite coatings.

Different methods have been employed to fabricate silver nanoparticles on the surface of TiO₂ nanotubes grown on titanium or its alloy. One method of assembling uniformly distributed silver nanoparticles on the nanotubes is electron beam evaporation [44,46]. The latter method has successfully produced uniformly distributed silver nanoparticles on the surface of nanotubes coating on titanium. In the study by Lan et al., 2013, the distribution of the nanoparticles was uniform with different sites of attachments, depending on the diameter of the nanotubes on which they were attached [44]. Figure 1 shows the SEM images of the attached Ag nanoparticles on titania nanotubes of diameter 25, 50 and 100 nm. The size of the nanoparticles remained the same, even though the diameter of the nanotubes increased. The nanoparticles were attached to the inside of the nanotubes wall when the diameter was 100 nm, as seen in Figure 1F, while Figure 1D shows that when the diameter of the nanotube was 25 nm, the Ag particles were on the surface of the nanotubes layer, affecting the nano-topology of the coating on titanium [44]. However, Figure 1G shows that the release of silver from the composite coating over 2 weeks was the same in both cases. The silver release was a steady release over the 14 days in both cases.

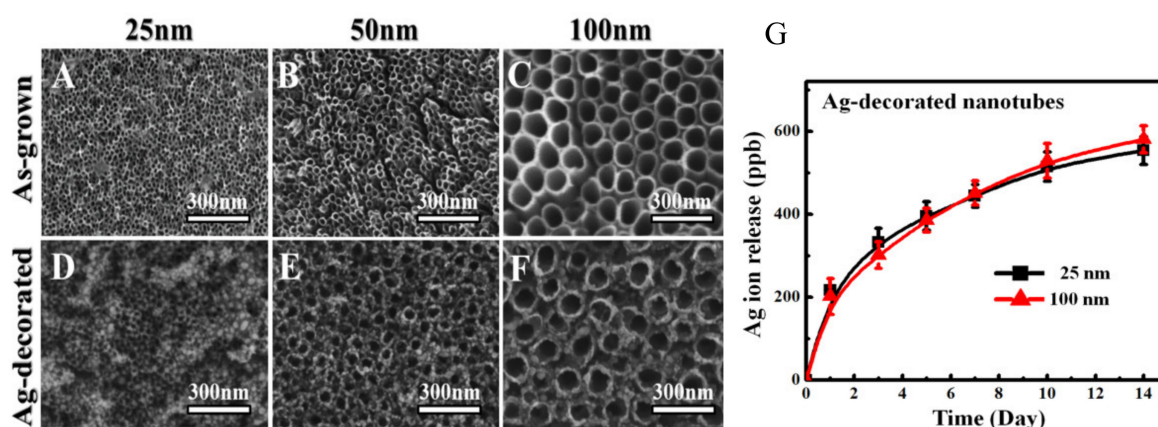


Figure 1. (A–F): SEM images of self-organized TiO₂ nanotubes with different diameters. The as-grown (A–C) and Ag-decorated (D–F) nanotubes with diameters of 25, 50 and 100 nm, respectively. **G:** Cumulative Ag release profiles from the 25- and 100-nm-diameter Ag-decorated nanotubes into phosphate buffered saline, PBS. There were no statistical differences among the Ag-decorated samples with regards to the nanotube diameter (SEM \pm SE, One-way ANOVA, $p > 0.05$, $n = 3$). (Reproduced with permission from Lan et al., Both Enhanced Biocompatibility and Antibacterial Activity in Ag-Decorated TiO₂ Nanotubes; published by PLOS ONE, 2013, CC BY 4.0 [44]).

The anti-bacterial property of the composite coatings containing silver nanoparticles on TiO₂ nanotubes was tested in the presence of *Staphylococcus aureus* grown in tryptic soy broth [44]. Figure 2 shows the composite coatings after 4 h of exposure to *S. aureus*. The coatings with Ag nanoparticles on 100 nm diameter nanotubes had the least bacteria present on the surface after the exposure (Figure 2F) as compared to the coatings involving 25 nm diameter nanotubes (Figure 2D).

After confirming the anti-bacterial property of the composite coatings on titanium, there was a need to make sure that the surface was not toxic to human cells. As such, the coated surfaces with silver nanoparticles on TiO₂ nanotubes with diameters ranging from 25 nm to 100 nm were exposed to human fibroblast cells grown in Eagle's minimum essential medium. It was observed that the cells grew better on the 25 nm diameter nanotubes both in the presence and absence of silver nanoparticles, as shown in Figure 3A,D.

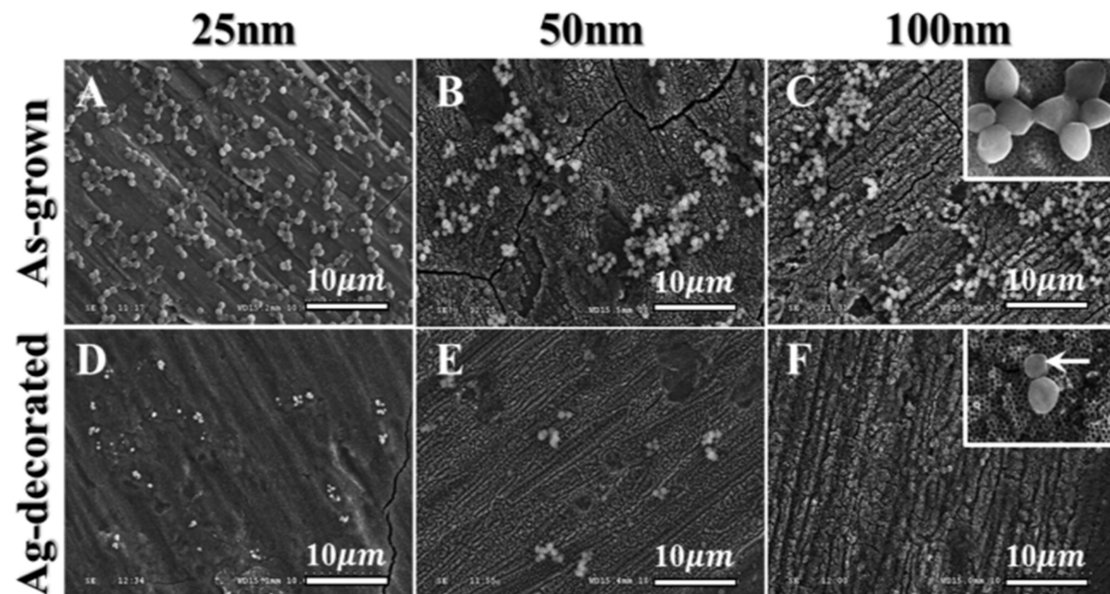


Figure 2. SEM images of *S. aureus* grown on as-grown or Ag-decorated TiO₂ nanotubes of different diameters. Numerous bacteria colonies on the as-grown nanotubes (A–C), while only a few bacteria could be seen on the Ag-decorated series (D–F) (Reproduced with permission from Lan et al., Both Enhanced Biocompatibility and Antibacterial Activity in Ag-Decorated TiO₂ Nanotubes; published by PLOS ONE, 2013, CC BY 4.0 [44]).

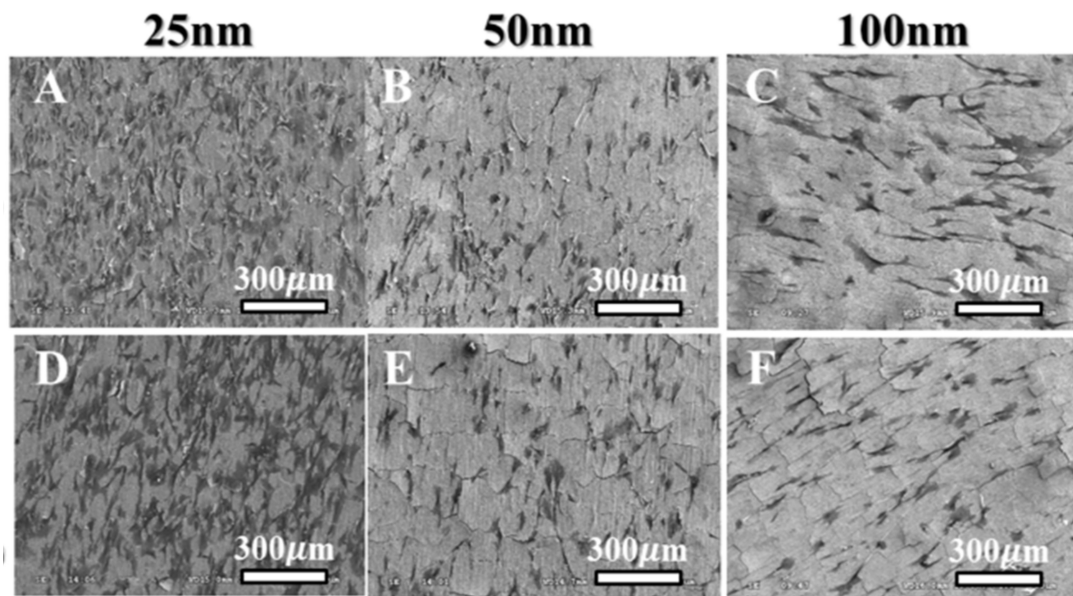


Figure 3. SEM images, showing the cell adhesion and proliferation of human fibroblast cells on the as-grown (A–C) and Ag-decorated (D–F) TiO₂ nanotubes with the diameters of 25, 50 and 100 nm, respectively. The fibroblasts cultured on the 25-nm-diameter nanotubes revealed good cell adhesion with the development of an elongated cytoskeleton, while those on the 50-nm-diameter or larger nanotubes showed rounded cell morphology with a lack of cell spread in both the as-grown and Ag-decorated samples. (Reproduced with permission from Lan et al., Both Enhanced Biocompatibility and Antibacterial Activity in Ag-Decorated TiO₂ Nanotubes; published by PLOS ONE, 2013, CC BY 4.0 [44]).

In the study by Lan et al., a composite coating on titanium was successfully synthesised [44]. The coating provided the necessary anti-bacterial property against one of the main cause of infection in implants, *S. aureus* [47]. It was also shown that human fibroblast cells could grow on the silver-containing

surface as they would grow on just TiO₂ nanotubes. Therefore, it could be concluded that the silver nanoparticles added to titania nanotubes by e-beam are anti-bacterial while enhancing the biocompatibility of the titanium. The low level of toxicity could be due to the steady release of silver from the composite coatings, as seen in Figure 1G, over 14 days as the release of a large amount of silver in the first 24 h have been shown to be toxic to cells. Several more similar coatings have been synthesised throughout the last few years [46,48]. These types of anti-bacterial composite coatings prevent infection as soon as they come in contact with bodily fluid. More research is still being done with respect to growing silver nanoparticles on TiO₂ nanotubes to provide anti-bacterial effect for as long as possible [45]. This implies a slower release of silver from the composite coating and/or a release of the anti-bacterial agent only when the infection is present. This is where smart coatings could enhance the characteristics of composite coatings [49].

2.2. Biocompatible Coatings

With metallic orthopaedic implants, osseointegration is an issue when used on its own in the human body; hence, there is a need for surface modification [50,51]. The main aim is to allow the implant to integrate successfully in the human body while being able to deliver the necessary functions. Increasing the surface roughness of titanium alloy is one option, which has gained enormous interest over the last few years. Grit blasting and chemical etching are examples of such methods, but the roughness and morphology of the resulting surface cannot be fully controlled [50,51]. In-situ grown TiO₂ nanotubes on the surface of Ti alloy is one way of providing a controllable nano roughness to the surface, whereby the nanotubes provide the necessary scaffold for bone cells to grow [52–54]. Stress shielding remains an issue with surface modification [55]. In this context, composite coatings with lower modulus can help relieve the effect of stress shielding [55,56].

Hydroxyapatite (HA) is a bioceramic material that has a similar structure to the bone, but it does not have the mechanical strength required to work in load-bearing application [57–59]. Nonetheless, when used as a coating for titanium alloy, HA adds to the bioactivity of the alloy, hence increasing the osseointegration of the alloy in the body [59,60]. Several techniques have been used to grow or add HA on the surface of metals and alloys, such as sol-gel technique, plasma-spraying, biomimetic deposition, electrodeposition, laser ablation, and so on [58,61].

To improve the adhesion and stability of HA coating on titanium (Ti), Liu et al. [62] investigated the behaviour of osteoblast cells grown on HA-coated Ti. After having polished the titanium (PT), it was acid-etched (labelled ET) with the aim of roughening the surface. The etched surface was then exposed to 10 M NaOH in a high-pressure kettle at 100 °C for 24 h, hence labelled NT. Subsequently, HA was deposited biomimetically on the alkali-treated surface by dipping NT in simulated body fluid (SBF), hence forming HAp/NT. The surfaces of PT, ET, NT and HAp/NT were then viewed under high-resolution scanning electron microscopy (SEM, Hitachi S-4800), and the elements present were analysed using energy dispersive X-ray spectrum (EDX). Afterwards, they were exposed to mouse osteoblastic MC3T3-E1 subclone 14 cell line in a-MEM (Minimum essential media) media. 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2-H-tetrazolium bromide (MTT) and alkaline phosphatase (ALP) assays were then performed on the cells grown on the coated and uncoated titanium after 2, 4, 6 and 8 days of exposure [63].

The SEM images of the PT, ET, NT and HAp/NT are shown in Figure 4A–D. Figure 4C shows a flowery nano-structure from the sodium titanate formed from the alkali treatment, and Figure 4D illustrates nano-needles' structures formed on the surface of the anodised titanium, whereby a layer of HA was present. Figure 4E confirms the presence of HA after exposure to SBF with the ratio of calcium to phosphorus being 1.67. Further details on the chemistry involved in the growth of HA would be discussed further in Section 3.4. The calculations from MTT assay by Liu et al. is expressed in Figure 5A, whereby it could be observed that the cell growth during day 2 and 4 was not significantly different on PT, NT and HAp/NT [62]. But as from day 6, both NT and HAp/NT showed a higher number of cells. The ALP assay showed similar observations (Figure 5B). The change in morphology

and the presence of HA did increase the biocompatibility of the titanium successfully. As mentioned before, the nanostructure did mimic the nano-morphology of bone, allowing the coating to blend in. Also, since HA have similar mineral phase to bone, osteoblast cells attachment was favourable, thereby preventing rejection [64]. This study is one example where HA was used as a coating, which enhanced the biocompatibility of the implant material [62].

Several more types of composite coatings containing organic molecules, nanoparticles and many more are used on metals with the aim of providing biocompatibility to the material so that they can integrate successfully in the body, hence reducing the risk of malfunction and/or rejection [65]. Nonetheless, biocompatibility in different parts of the body would require different composite coatings. However, implants aiming at being in the heart or eye or any other part of the body would require composite coatings made of biomaterials, promoting their integration in the respective organs.

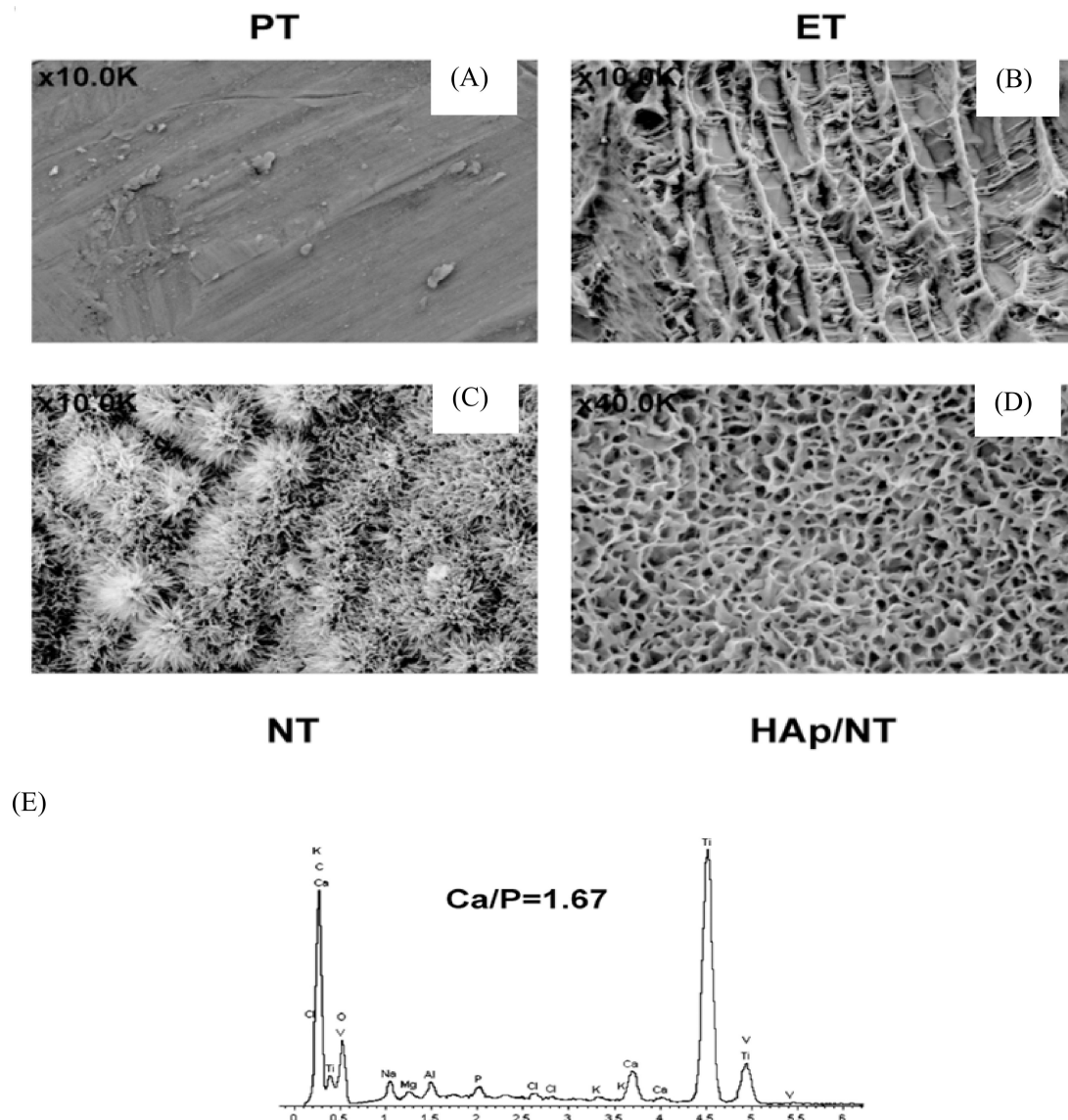


Figure 4. Scanning electron microscopic image of (A) polished titanium, PT, (B) Acid-Etched, ET, (C) Etched titanium exposed to sodium hydroxide, NT and (D) hydroxyapatite deposited on NT, HAp/NT. (E) EDS analysis of the surface of HAp/NT, highlighting the ratio of calcium (Ca) to phosphorus (P). (Reproduced with permission from Liu et al., Rapamycin/sodium hyaluronate binding on nano-hydroxyapatite coated titanium surface improves MC3T3-E1 osteogenesis; published by PLOS ONE, 2017, CC BY 4.0 [62]).

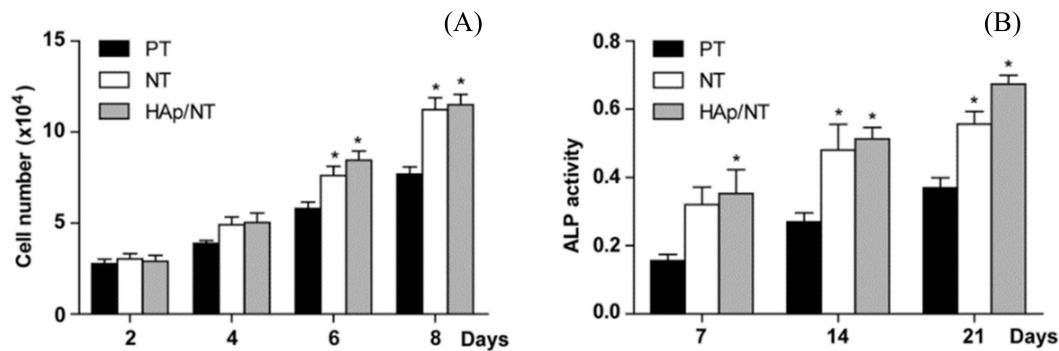


Figure 5. (A) Cell vitality and (B) Alkaline phosphatase (ALP) activity of MC3T3-E1 cells after 2, 4, 6 and 8 days of exposure to PT, NT and HAp/NT (Reproduced with permission from Liu et al., Rapamycin/sodium hyaluronate binding on nano-hydroxyapatite coated titanium surface improves MC3T3-E1 osteogenesis; published by PLOS ONE, 2017, CC BY 4.0 [62]).

3. Synthesis of Composite Coatings

There are different methods through which composite coatings can be synthesised, some of which have been discussed in the previous section. Section 3 gives more details on the chemical/electrochemical methods employed. This segment divides the different techniques that have been used to synthesise composite coatings successfully in the past into four categories, namely, chemical deposition Section 3.1, electrophoretic deposition Section 3.2, electrochemical deposition (anodising, electroplating) Section 3.3, biomimetic deposition Section 3.4. The remaining techniques, such as plasma spraying, ion beam, laser deposition, are described in Section 3.5.

3.1. Chemical Deposition

Composite coatings on implants usually involve various chemical components, so manipulating the chemistry involved is the main concept behind the synthesis of the coatings for different materials. A chemical deposition is one fabrication technique, allowing specific reactions to take place on the surface of the material to be coated so that the coating sticks to the substrate. Chemical deposition can vary in different ways, and examples of chemical deposition include the surface chemical conversion, chemical vapour deposition, sol-gel deposition and dip coating. Examples of the complex version of chemical deposition are electrochemical deposition and biomimetic deposition, which will be described later [66]. The sol-gel technique is a method whereby a chemical solution is used to produce a network of particles after the solvent from the solution has been evaporated, which is used very often in the fabrication of composite coatings because of its ability to produce multicomponent coatings of various size, shape and format [67–69]. This technique is effective while being cost-effective and simple [69–71]. Issues with the sol-gel method are that it is the most time consuming, and the adhesive strength between the composite coating and the material is not that strong [72,73]. Chemical vapour deposition (CVD) is a widely used chemical deposition method whereby the substrate to be coated is exposed to the precursor of the material to be coated, which reacts on the substrate forming the required coating. It has many advantages as being a low cost and low maintenance procedure, which can produce a uniform coating with structural control at the nanometer level [74–77]. CVD has been selected as it is low-cost, low maintenance and effective process for depositing uniform films, exhibiting good adhesion to the growing substrate; moreover, the easiness in controlling the growth rate allows a high reproducibility of the samples. However, CVD requires high vacuum and specific precursor material, which can be evaporated [78–80]. Chemical conversion is a process whereby the required coating is produced on the substrate from a source in the solution. It is a method widely used for the synthesis of graphene oxide [81] and silver nanoparticles. As part of bone implants, AgNp/TiO₂ composite coating on titanium has been used successfully, as mentioned in Section 2.1. There are issues with toxicity, which have been overcome by ongoing research by the researchers mentioned in the latter section, but

the anti-bacterial properties of the latter coating triumphed over the toxicity issue (Section 2.1). There are several methods of synthesis, among which chemical reduction is one of the simplest and most commonly used [82,83]. The commonly used reducing agents for this reaction are sodium borohydride, sodium dodecyl sulphate, citrate, ascorbate and elemental hydrogen [82–84]. The reason behind its vast use is the fact that nanoparticles of different morphology and dimensions can be fabricated using this method [82,85]. In previous work, silver nanoparticles have been successfully synthesised on the surface of TiO₂ nanotubes. In this section, the chemical reduction of silver nanoparticles on the nanotubes has been discussed, while Section 3.3 has analysed the electrochemical method of synthesising the underlying nanotubes.

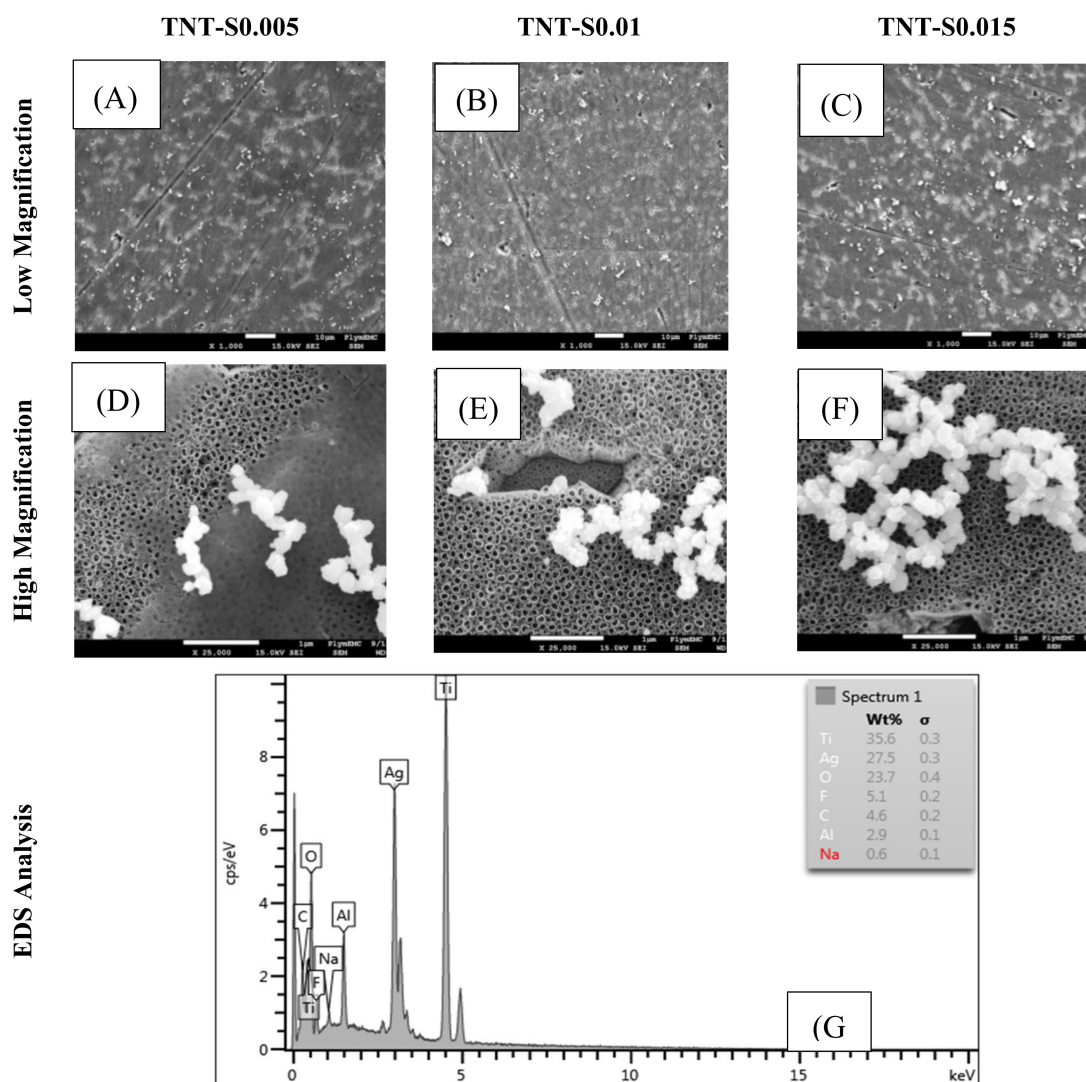


Figure 6. SEM images of silver nanoparticles forming micro-clusters on titanium dioxide nanotubes, TNT grown using (A) 0.005 M, (B) 0.01 M and (C) 0.015 M of silver ammonia solution and 0.002 M δ -gluconolactone as a mixture at low magnification. (D–F) show the higher magnification of (A), (B) and (C). (G) EDS analysis of the silver nanoparticles grown on TNT, showing the distribution of the different components on the surface. (Reproduced with permission from Gunputh et al., Anodised TiO₂ nanotubes as a scaffold for antibacterial silver nanoparticles on titanium implants; published by Elsevier, 2018, [39]).

In the study by Gunputh et al. [39], delta-gluconolactone was used as a reducing agent for silver ammonia with the aim of forming silver nanoparticles of diameter less than 100 nm which were formed in clusters of varied dimensions. In the latter study, the concentration of the δ -gluconolactone used was

maintained at 0.002 M throughout. Initially, in method 1, the TiO₂-coated Ti-6Al-4V alloy was exposed to the mixture of the silver source, silver ammonia and gluconolactone for 10 min. The concentration of the silver ammonia (S) was varied from 0.005 M to 0.015 M, and the resulting clusters formed on the surface of the nanotubes (TNT) are illustrated in Figure 6. TNT-S was used as a labelling aid, whereby TNT represented the nanotubes, and S represented silver ammonia used followed by the respective concentration in number. As such TNT-S 0.005 represented a silver nanoparticles-coated titanium dioxide nanotubes, whereby a concentration of 0.005 M silver ammonia was used. Panels A–C show a low magnification of the TNT-S coating, and D–F show a higher magnification of the respective figures TNT-S0.005, TNT-S0.01 and TNT-S0.015, whereby micro-clustering was observed with an increase in the size of the clusters with an increase in the concentration of silver source. The low magnification showed the coverage of the coating, while the higher magnification zoomed in to have a closer look at the morphology of the clusters.

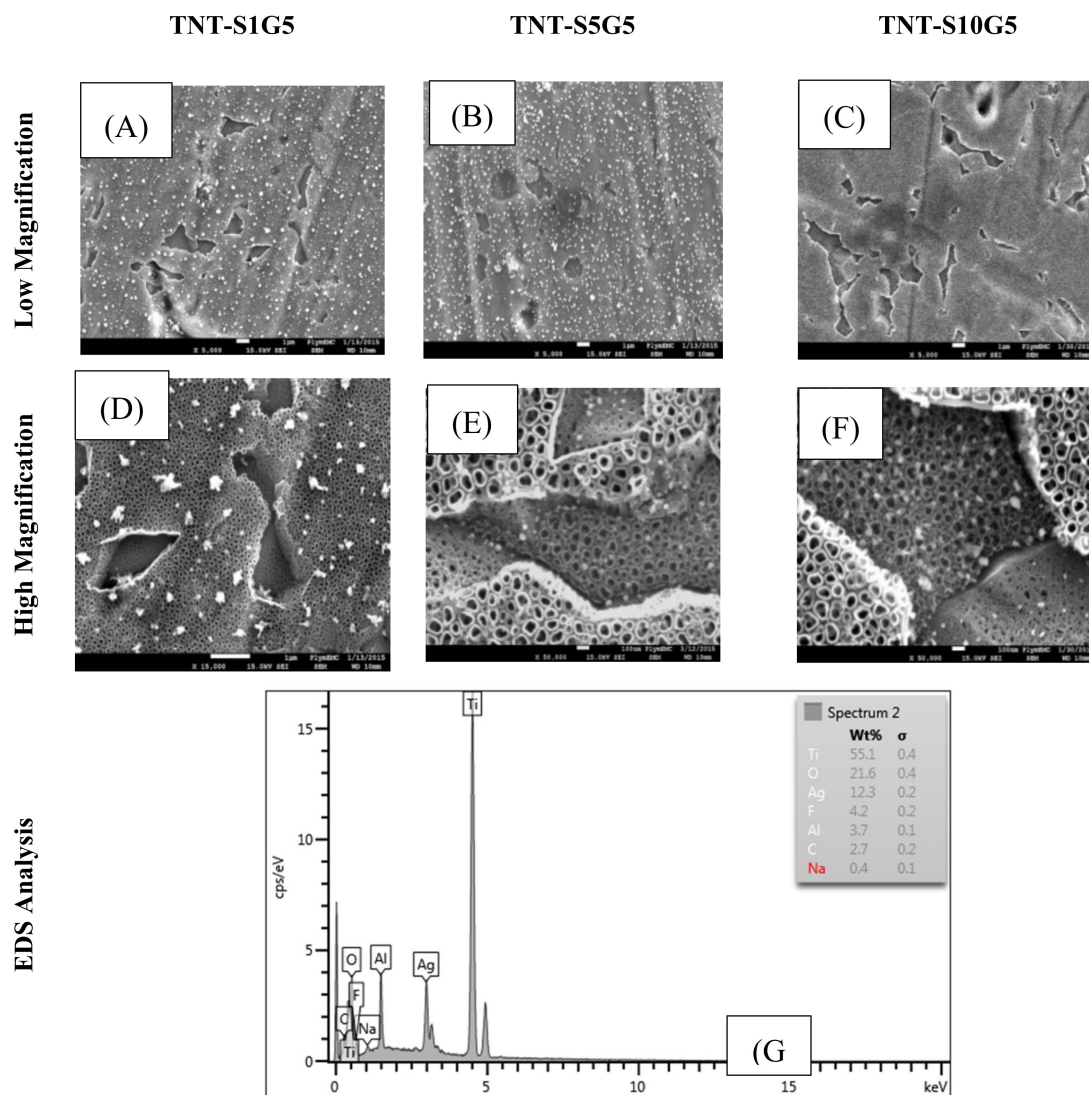


Figure 7. SEM images of nanoclusters of silver nanoparticles grown by using 0.015 M Silver Ammonia and 0.002 M δ -gluconolactone and the exposure time to silver ammonia being (A) 1 min, (B) 5 min and (C) 10 min and exposure to G being 5 min. (D–F) Higher magnification SEM images of TNT-S1G5, S5G5 and S10G5, respectively. (G) EDS analysis of the silver nanoparticles-coated TNT. (Reproduced with permission from Gunpath et al., Anodised TiO₂ nanotubes as a scaffold for antibacterial silver nanoparticles on titanium implants; published by Elsevier, 2018, [39]).

Using the same chemical reduction method, in method 2, TNT was exposed to 0.015 M silver ammonia for 1–10 min followed by exposure to 0.002 M gluconolactone for 5 min. Panels A–C of Figure 7 show the low magnification image of the coated surfaces of S1G5, S5G5 and S10G5, respectively, with the number being the duration for which the samples were left in the latter solution. Panels D–F show the same coatings at a higher magnification, whereby the size of the nano-clusters was seen reducing with increasing duration of exposure to silver ammonia. In both Figures 6 and 7, G represents the EDS analysis, which confirms the nanoparticles to be silver.

The clustering was assumed to happen because of the large size of the gluconolactone molecule reducing silver ammonia. The latter molecule had several –OH, and, as such, for each molecule of reducing agent, four silver components were reduced, and they would attach to each other. After each coating was synthesised, the coated material was ultrasonicated in deionised water for 10 min to remove the excessive silver attached to the surface. Then, they were exposed to simulated body fluid in triplicates ($n = 3$) with the aim of measuring the amount of silver released from the coating after 24 h. The micro-clustering was seen to release a significantly larger amount of silver as measured by ICP-MS as compared to the nano-clustering (Figure 8). After analysing the distribution and release of silver from the coating, coating from method 2, TNT-S10G5 was found to be the best to be used as a coating on implants as it had a uniform distribution of nanoclusters of silver nanoparticles fully covering TNT while releasing the least amount of silver from the coating after 24 h exposure to SBF. In the human body, too much silver can be toxic, as mentioned in Section 6.2.3; as such, an ideal implant needs to release enough silver to be bactericidal while being biocompatible.

To summarise, in general, chemical deposition is a cheap and simple method of synthesising composite coating, whereby huge effort is not needed, and the resulting nano-structure and distribution of the coating can be manipulated by modifying the involved parameters, such as the concentration of chemicals, temperature or duration of exposure to the substrate.

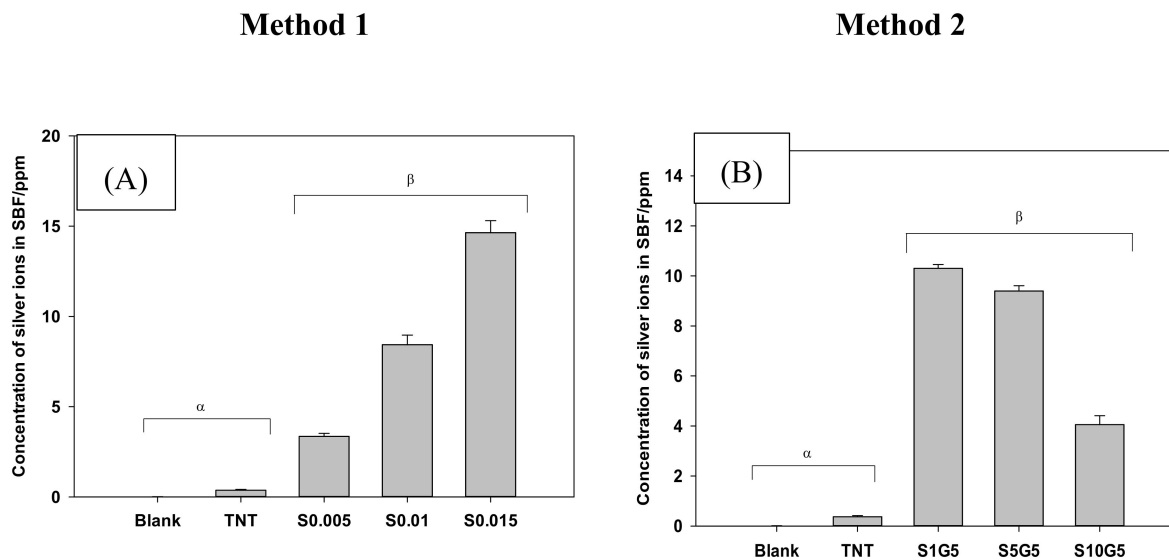


Figure 8. ICP analysis of acidified simulated body fluid (SBF) after 24 h exposure of samples from (A) method 1 and (B) method 2 of silver nanoparticles synthesis, showing the silver release in both cases. In both cases, TNT and Blank (α) expressed a similar presence of ions in the SBF ($p > 0.05$). In (A), TNT-S0.005, TNT-S0.01 and TNT-S0.015 had significantly different amount of silver in the SBF from each other (β) and were significantly different from the controls ($p < 0.05$). In (B), similar observations were obtained with TNT-S1G5, TNT-S5G5 and TNT-S10G5, having a significantly different amount of silver in SBF from each other and the controls with a p -value less than 0.05. (Reproduced with permission from Gunpath et al., Anodised TiO₂ nanotubes as a scaffold for antibacterial silver nanoparticles on titanium implants; published by Elsevier, 2018, [39]).

3.2. Electrophoretic Deposition

Electrophoretic deposition is an electrodeposition method, whereby an electric field is applied between two electrodes in a suspension, whereby the particles move towards the oppositely charged electrode, which is the substrate to be coated [72,86,87]. It has been successfully used to fabricate composite coatings for biomedical devices [88,89]. Examples of such coatings are HA, reinforced HA, polymers, bioglass, graphene-containing material and many more [90–92]. The electrophoretic method also allows the co-deposition of polymers and ceramics, which make this method favourable when it comes to composite coating [86]. However, sometimes pre-treatment and/or post-treatment is required in order to stabilise or strengthen the coating [72,92]. Even though sometimes the electrophoretic deposition is used as a 2-step procedure, it is still widely used in the synthesis of composite coatings because of its efficiency, homogeneity, high deposition rate, ability to produce controllable thickness, inexpensiveness and versatility [88,89,93]. It has been successfully used to coat surfaces of bulk objects and to infiltrate porous substrates.

Several researchers have successfully coated biomaterials with composite coatings, which, in turn, has provided the required biological properties as hypothesized in their work. Seuss et al. were able to use alternating current-electrophoretic deposition (AC-EPD) to produce composite coatings made of chitosan and Bioglass on Ti-6Al-4V. The latter coatings were shown to be bioactive and anti-bacterial while being robust [87]. Chen et al. fabricated a polyvinyl alcohol-reinforced alginate-Bioglass composite coating on 316L stainless steel with excellent adhesive strength [94]. Xiong et al. synthesised an HA composite coating on Mg alloy using micro-arc oxidation followed by EPD [95]. The latter composite coating was shown to have good anti-corrosion properties [95]. Similar observations have been made when a ceramic/organic composite-coated Mg alloy has been shown to be corrosion-resistant [96].

Electrophoretic deposition on its own or used in collaboration with another technique has been shown to give rise to robust, corrosion-resistant, biocompatible and even anti-bacterial composite coating. Several types of research have been done on the latter, and more is being done with the aim of combining all the required properties in one composite coating. The whole aim is to be able to coat implants successfully while acting as a platform for successful tissue engineering.

3.3. Electrochemical Deposition

Electrochemical deposition, as per its name, is a deposition method, whereby chemical deposition is assisted by a current. During this process, an electric field is applied in a liquid-containing dispersed charged particles between the substrate to be coated and another electrode so that a thin layer of the coating is formed [97–99]. Similar to chemical deposition, an electrochemical deposition involves no high temperature or pressure and no high cost, and the technique is easily portable [50,97,98]. An electrochemical deposition allows the synthesis of homogeneous coating of micro to nanoparticles [72,99]. The most important reason for its use in composite coatings is the fact that this method allows deposition of more than one material on a substrate [58,98]. Several composite coatings have been successfully synthesised on the surface of the metal with respect to using it on implants and for tissue engineering. Examples of such coatings are the different chemical phase of calcium phosphates, including hydroxyapatite and hydroxyapatite-reinforced with carbon nanotubes (CNTs), TiO₂, ZrO₂ and chitosan [100–102]. The hydroxyapatite formed using this method has been shown to have higher wear and corrosion resistance and a higher adhesive strength when reinforced with other materials. There are several factors that influence the characteristics of the coatings, such as the structure, coverage, morphology and associated properties. The influencing parameters of the electrochemical reaction are the current or voltage applied and the composition and pH of an electrolytic bath [75,98].

An example of an electrochemical method is the anodisation method, whereby the substrate to be coated is made the anode [72]. Anodisation is one of the main methods of synthesising TiO₂ nanotubes, which can be embedded with other nanoparticles for the use as a drug-carrying composite coating on titanium alloy, as mentioned in Section 3.1. Among the various electrolytes that have been used

in the latter synthesis, aqueous electrolytes are considered to produce strongly adhered nanotubes due to the rougher exterior nanotube walls [103,104]. A previous study by Danookdharree et al. shed light on the influencing factors of the process, such as pH and initial voltage ramp. The 0.2–0.5 wt% NH_4F and 0.5–1 M $\text{NH}_4\text{H}_2\text{PO}_4$ were used as electrolytes, which provided the necessary ions for the redox reaction, as shown in Figure 9A [105]. The reaction led to the formation of uniformly distributed TiO_2 nanotubes with 116.2 ± 6.4 nm (mean \pm S.E.M., $n = 6$) diameter on the majority of the surface of Ti-6Al-4V disc, as shown in Figure 9B,C, whereby Figure 9C zooms on the β -phase of the alloy, which had smaller nanotubes than the α -phase (104.4 ± 4.7 nm).

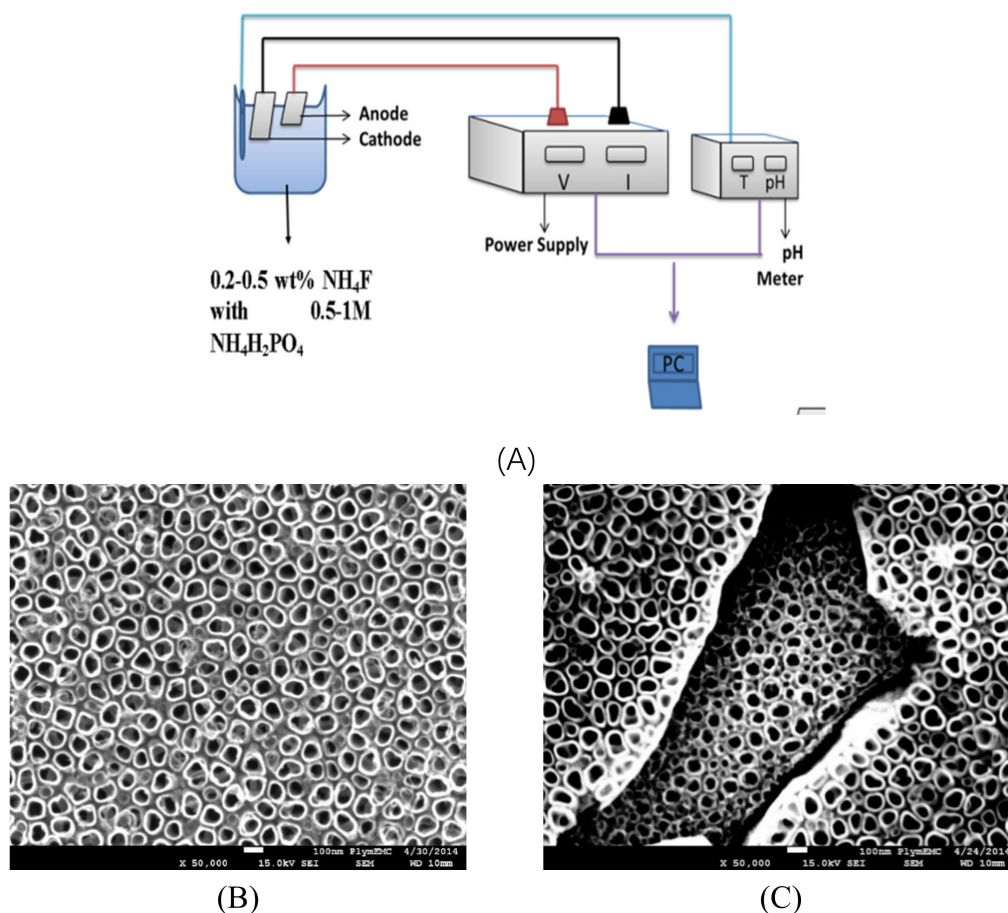


Figure 9. (A) Anodisation process using NH_4F and $\text{NH}_4\text{H}_2\text{PO}_4$ as electrolytes, (B) an example of the resulting nanotubes formed on the majority of the Ti-6Al-4V alloy disc and (C) the difference in the nanotubes in the α and β phase of the alloy, as viewed under the SEM at $\times 50,000$ magnification. (Reproduced with permission from Danookdharree et al., The Effect of Initial Etching Sites on the Morphology of TiO_2 Nanotubes on Ti-6Al-4V Alloy; published by IOP, 2015, [105]).

The pH did not have any effect on the diameter of the nanotubes, as seen in Figure 10A, but the increase in the initial sweep rate from 0.2 to 1.5 V/s led to a decrease in the diameter of the nanotubes, as shown in Figure 10B. Nonetheless, when there is an increase in the actual voltage used for anodisation, the nanotubes' diameter is known to increase [65].

The electrochemical technique can be simple, but every single aspect of the experiment does affect the resulting coating and has to be carefully considered [106–108]. This is what makes the latter method one of the best deposition techniques for composite coating, especially at a nano-level.

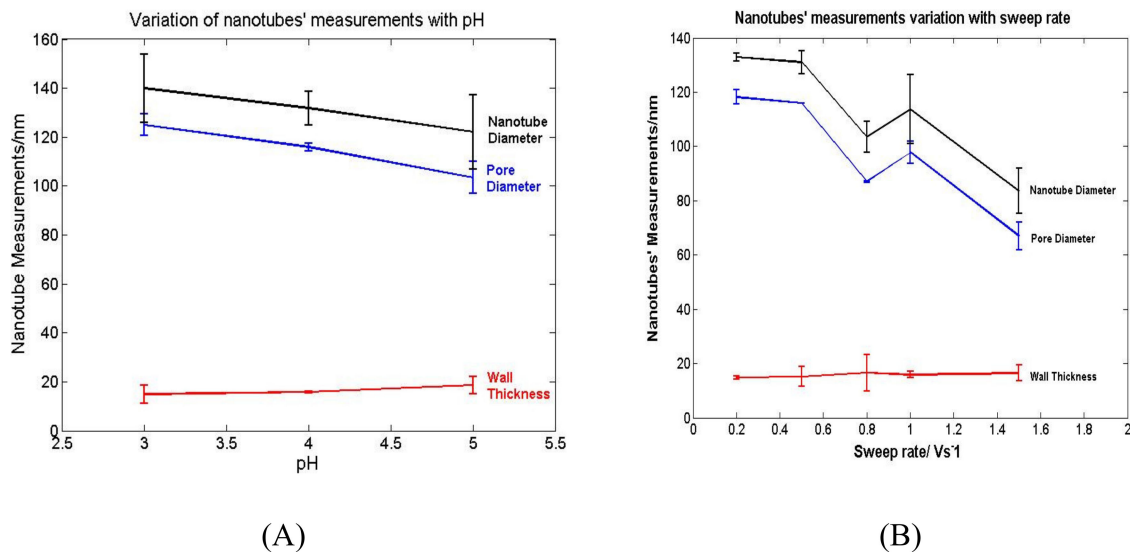


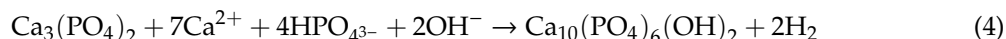
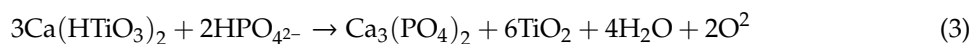
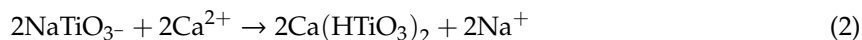
Figure 10. Variation of nanotubes dimensions with respect to (A) pH and (B) sweep rate. Reproduced with permission from Danookdharree et al., The Effect of Initial Etching Sites on the Morphology of TiO₂ Nanotubes on Ti-6Al-4V Alloy; published by IOP, 2015, [105]).

3.4. Biomimetic Deposition

Biomimetic deposition, as per its name, is a deposition method, whereby a synthetic deposition is made by mimicking a biochemical reaction. Among the different methods of synthesis of composite coatings, the biomimetic deposition method takes place on its own and does not require any reducing agent or external voltage for the process [109,110]. It is also considered to be environmentally friendly and inexpensive [111]. Different types of materials, such as metals and metal oxides, like Au, Ag, SiO₂, TiO₂, ZrO₂, can be synthesised using the biomimetic method [112,113]. In the world of orthopaedics, there is a bigger interest in the biomimetic synthesis of hydroxyapatite on metals with the aim of increasing biocompatibility and promoting osseointegration, as mentioned in Section 2.2. The biomimetic growth of HA on metals started with the work of Kokubo when the author grew TiO₂ nanotubes on the surface of titanium followed by the exposure of the latter coated surface to simulated body fluid with pH (7.4) and ion concentrations (Na⁺ 142.0, K⁺ 5.0, Mg²⁺ 1.5, Ca²⁺ 2.5, HCO₃³⁻ 4.2, Cl⁻ 147.8, HPO₄³⁻ 1.0, SO₄²⁻ 0.5 mM), which are nearly equal to those of human blood plasma at 36.5 °C for 10 days [114]. Hydroxyapatite having 10CaO·3P₂O₅·H₂O as a chemical formula has a calcium to phosphorus ratio (Ca/P) of 1.67 [115,116]. As such, when growing the latter on metal, several parameters have to be considered to make sure that the resulting coating does have the specific Ca/P ratio.

An example of an HA coating formed using this method is shown in Figure 4D. The latter figure illustrates the uniformly distributed nanostructure of HA on the surface of titanium foil. The EDS analysis also confirmed the calcium to phosphorus ratio of 1.67 (Figure 4E). The original method used by Kokubo (1997) took 10 days for HA to successfully grow on the surface of metal [114]. A quicker method of fabricating the coating using biomimetic deposition would be to use a concentrated version of the SBF while making sure that the pH and temperature are maintained with continuous replenishment of the concentrated SBF so that the appropriate ratio of Ca/P is obtained [109,117]. The concept around the synthesis of hydroxyapatite revolves around the initial nucleation stage, whereby calcium is attached on the surface of the material before crystallising to HA crystals [114,118–120]. With the aim of growing hydroxyapatite at a nano-level, in order for nucleation to happen, a rough base is required. In the case of the study of the growth on titanium, the metal was initially etched in concentrated alkali, hence creating a rough TiO₂ surface [62]. The following alkali treatment with NaOH then creates sodium hydrogen titanate layer, which converts to sodium titanate as per Equation (1) [114,118]. Then, the titanate acts as a base for the nucleation to start once exposed to SBF. As a result, calcium titanate is

formed according to Equation (2), after which, calcium phosphate (Equation (3)) is formed, which allows the apatite crystals to successfully form as per Equation (4) [118,120]. The concept behind the growth of the HA on the titanium foil is summarised in Figure 11, whereby the effect of the different steps on the surface morphology is demonstrated.



The biomimetic method is already time-consuming and difficult to get it perfectly right. In such a situation, adding other material to the base material allows a better bond between the HA and the base. Examples of such materials are graphene oxide, collagen, gelatin, carbon nanotubes and many more [109,111,117].

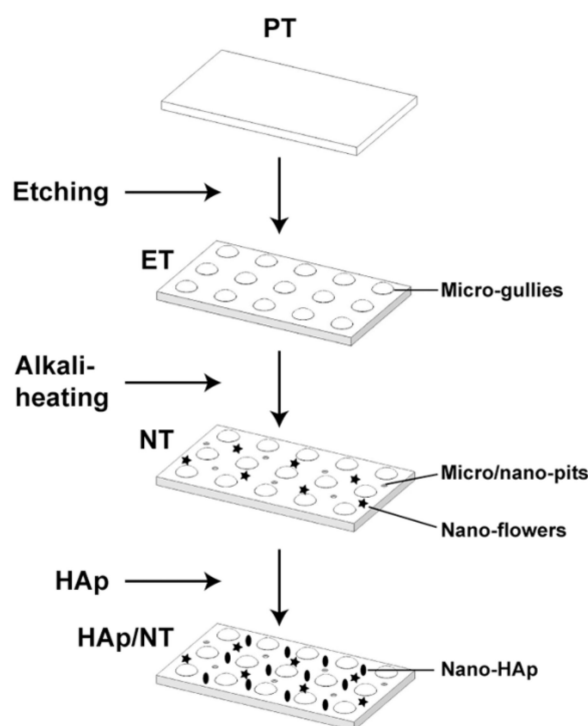


Figure 11. Surface topographical changes during the pre-treatment of the titanium foil surface before and after the addition of hydroxyapatite (HA). (Reproduced with permission from Liu et al., Rapamycin/sodium hyaluronate binding on nano-hydroxyapatite coated titanium surface improves MC3T3-E1 osteogenesis; published by PLOS ONE, 2017, CC BY 4.0 [62]).

3.5. Other Deposition Methods

There are many more deposition methods which are used and are being continuously researched about. Examples of such methods are the layer by layer coating, plasma spraying, physical vapour deposition, ion beam deposition, laser deposition and many more.

The layer-by-layer deposition method involves the deposition of oppositely charged particles layer by layer and is mainly used when it comes to producing a coating involving more than one component hence the research in relation to composite coating [121,122]. It is an easy, versatile and efficient deposition method that has attracted attention in biomaterials synthesis [19,123]. In the world of composite coatings, the latter deposition method has been used with the aim of functionalising the

surface of inert material, synthesising drug-carrying coating for fast and slow release and fabricating thin coatings with high strength [121,123,124]. The materials involved in the synthesis of composite coatings by this method include polymers, peptides, nanoparticles, ceramic and metals.

Plasma spraying is a method that has been used to coat medical implants in the past and is still being used. The process involved is the use of high temperature from an ionised inert gas to melt ceramic or metal powders, which are sprayed on the substrate to be coated [66,125]. It is very common to coat medical implants with HA using this method with the aim of increasing biocompatibility and preventing corrosion [57,125]. However due to the brittleness and low adhesion force of the HA formed from this method, plasma spraying could be combined with other techniques, such as isostatic pressing, or the HA being fabricated could be reinforced with other materials, such as carbon nanotubes [57,125,126]. As a whole, plasma spraying is considered to be cost-effective, and the method has the ability to control the microstructure of coatings and make them have good properties [57,127]. Nonetheless, it has drawbacks, such as low adhesive strength, non-uniform coating and the induction of changes in the microstructure of the coating.

Physical vapour deposition is an environmentally friendly coating technique, which is used to deposit inorganic material of variable thickness and good adhesion strength on the required substrate with the aim of providing good corrosion resistance [80,125,128]. The technique involves the deposition of plasma metal ions on the substrate to be coated with the help of an electric field [80,129]. With respect to the resulting coating, physical vapour deposition, PVD has been used in the synthesis of composite coating for orthopaedics implants. Examples of such coatings are HA, diamond-like coating, TiO₂ and nano-silicon [80,128]. The weak link in this context is the low crystallinity of the resulting coating and the high cost of the procedure [130].

The above-mentioned deposition techniques are continuously being researched, and many more are being investigated with the aim of having the appropriate composite coating for the respective implant or the required tissue engineering. This is a long process as so many aspects have to be taken into consideration, ranging from mechanical properties to biological properties. Other aspects to be considered are the feasibility, accessibility and economic aspects.

4. Future Trend

Various composite coatings have been magnificently put together by so many researchers in the past. Trying to combat all possible problems from implants and in relation to tissue engineering has been the centre of attraction. However, getting the recipe for the perfect biomaterial or composite coating right is not simple and would require more extensive work. One of the solutions to addressing this issue is the use of smart coatings. It is a coating that has at least one property that can be modified when induced by stimuli generated by intrinsic or extrinsic factors, such as pH, stress, temperature, electric and magnetic fields [113,131,132]. Smart composite coatings are being constantly studied about in the medical world with different aims. Examples are drug-carrying coating and self-healing coating [132,133].

In the field of drug delivery, TiO₂ nanotubes have been considered to carry drugs for implants and tissue engineering in different medical needs and deliver them when required by different types of external stimuli, but some drawbacks need to be taken into consideration as well just in case, the external stimuli do not reach the coating adequately, or the coating is not biocompatible [36,133,134]. Nanoparticle-involved composite coatings have been reviewed with the aim of acting as a scaffold for smart tissue regeneration/repair, and, with respect to this review, composite materials like chondroitin sulfate-reinforced collagen scaffolds, fibrin gel incorporating transforming growth factor beta-1 and porous HA scaffolds combined with biodegradable poly(lactic-co-glycolic acid), PLGA microspheres loading dexamethasone have been investigated [135].

The above-mentioned properties and materials are examples of where smart composite coatings are heading. With the world heading towards smart technology, the smart coating could be considered

as the solution to the issues faced by implants in the human body. The aim is to provide the necessary properties as soon as contact is made while being able to combat expected problems as time goes by.

5. Summary

Composite coatings have significant importance in the world of orthopaedics both on the surface of implants and scaffolds for tissue engineering. The components of the latter composite coatings are selected, depending on the location where needed and the function they are expected to perform. The fabrication methods are selected, depending on the characteristic of the coatings required. Since the biological reactions occur at a nano-level in the human body, nano-composite coatings have gained more attention recently, and smart coatings have also been considered to be important in this field.

Author Contributions: For research articles with several authors, a short paragraph specifying their individual contributions must be provided. The following statements should be used “Conceptualization, H.L and U.F.G.; methodology, H.L and U.F.G.; software, U.F.G.; validation H.L and U.F.G.; formal analysis, U.F.G.; investigation, U.F.G.; resources, U.F.G.; data curation, U.F.G.; writing—original draft preparation, U.F.G.; writing—review and editing, H.L and U.F.G.; visualization H.L and U.F.G.; supervision, H.L.; project administration, H.L and U.F.G.; funding acquisition, H.L., All authors have read and agreed to the published version of the manuscript.”, please turn to the CRediT taxonomy for the term explanation. Authorship must be limited to those who have contributed substantially to the work reported.

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