

Review

Customized Therapeutic Surface Coatings for Dental Implants

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Abstract: Dental implants are frequently used to support fixed or removable dental prostheses to replace missing teeth. The clinical success of titanium dental implants is owed to the exceptional biocompatibility and osseointegration with the bone. Therefore, the enhanced therapeutic effectiveness of dental implants had always been preferred. Several concepts for implant coating and local drug delivery had been developed during the last decades. A drug is generally released by diffusion-controlled, solvent-controlled, and chemical controlled methods. Although a range of surface modifications and coatings (antimicrobial, bioactive, therapeutic drugs) have been explored for dental implants, it is still a long way from designing sophisticated therapeutic implant surfaces to achieve the specific needs of dental patients. The present article reviews various interdisciplinary aspects of surface coatings on dental implants from the perspectives of biomaterials, coatings, drug release, and related therapeutic effects. Additionally, the various types of implant coatings, localized drug release from coatings, and how released agents influence the bone–implant surface interface characteristics are discussed. This paper also highlights several strategies for local drug delivery and their limitations in dental implant coatings as some of these concepts are yet to be applied in clinical settings due to the specific requirements of individual patients.

Keywords: coating; dental implant; drug delivery; leaching; surface treatment; topography; prosthodontics; therapeutic agents

1. Introduction

Natural teeth are commonly lost due to oral diseases such as tooth decay, periodontal diseases, and trauma [1–3] that affect appearance, speech, and the masticatory system. Aiming to improve patients' quality of life by restoring lost teeth, function, and esthetics, dental implants are commonly used [3–8]. Dental implants are fixtures that are surgically embedded in the jaw bone to substitute the

root part of the tooth [3]. Although intraosseous dental implants are usually cylindrically shaped, there are wide variations in terms of their dimensions and surface morphologies [9]. Dental implants are used to support fixed or removable dental prostheses following satisfactory osseointegration [10–13]. The term “osseointegration” was first devised by Brånemark, a Swedish orthopedic surgeon and a scientist who explored the growth and regeneration behavior of bone on titanium (Ti) implants [4]. Osseointegration was defined as a process of the formation of an effective and functional interface between the implant surface and bone [14]. The osseointegration of dental implants is essential for the long-term prognosis [14–18]. Osseointegration may be affected by a number of factors including the implant’s material properties, surface topography, and geometrical features [16,19]. Therefore, enhancement of the osseointegration of dental implants is always desired to achieve clinical success.

In terms of biomaterials, a variety of materials including metals [20–23], polymers [17,24–28], and ceramics [29–33] have been explored for dental implant applications. However, all materials have their own limitations; for example, metals have high-elastic-modulus and corrosion issues [34,35], polymers absorb water and usually have poor mechanical (wear, strength) properties [36], while ceramics are hard and brittle [36]. In the current scenario, Ti and its alloys are considered as the gold standard and material of choice for dental implants due to their excellent biocompatibility and osseointegration [37]. Commercially pure titanium (CpTi) has high strength, excellent biocompatibility, and corrosion resistance [23,34]. In addition, an oxide layer is formed upon air exposure that facilitates the material–bone interface through the apposition of bone matrix [38,39]. The commonly used titanium alloy included Ti-6 aluminum-4 vanadium (Ti6Al4V) that is preferred due to its better mechanical properties and excellent biocompatibility [36]. However, toxic effects from the release of vanadium and aluminum remain the main concern for these alloys [40]. Although the Young’s modulus of elasticity of Ti and its alloys (~110 GPa) is lower than that of cobalt chrome alloys, it is still remarkably greater than the Young’s modulus of elasticity of bone (10–30 GPa) [41]. Such a gross mismatch in the elastic moduli results in an uneven transfer of stresses (stress shielding), and atrophy of bone, leading to the loosening and failure of implants [42]. On the other hand, using an implant material with lower elastic moduli enhanced the homogeneous stress distribution at the implant–bone interface, thus reducing the bone atrophy [43]. To overcome such issues and to improve the implant material–bone interface, various surface treatment and coating options have been explored for the last few years. As a result, a few surface-modified dental implants are commercially available for clinical use [44].

Considering that the biological tissues establish an interface with the materials’ surface, the surface modifications (etching, sandblasting, and anodizing) enhance the materials’ biological response and osseointegration without affecting the bulk properties [45–48]. In addition to surface modifications, surface coatings of dental implants using a variety of materials and biomolecules have been explored in recent decades [49–53] to achieve certain beneficial effects. For example, the coating of bioactive materials (calcium phosphates and hydroxyapatite (HA)) enhances the surface bioactivity, leading to an improved bone–implant interface [54]. Similarly, coating implants with various pharmacological agents such as bisphosphonates [50,55–57], antibiotics [49,58], antimicrobial peptides, and biomolecules [59–61] has been reported with promising outcomes in terms of surface properties and therapeutic effects. Additionally, the release of medicaments from implant coatings may have certain therapeutic effects for a certain period of time depending on sustained or controlled release. Therefore, to achieve the targeted drug delivery and beneficial therapeutic effects (such as reduced bacterial activity, and enhanced osteoblastic proliferation and activity), drug elution is desired for a prolonged period of time. The present article reviews various interdisciplinary aspects of surface coatings on dental implants from the perspectives of materials, coatings, and drug release. Furthermore, the various types of implant coatings, localized drug release from coatings, and how released agents influence the bone–implant surface interface characteristics are discussed.

2. Mode of Action of Drug-Releasing Coatings

Drug release from implant coatings has attracted the attention of the scientific community around the globe. Classification of implantable drug-releasing devices is not straightforward, due to the presence of many complex implants belonging to hybrid categories [62]. Nevertheless, based on the release potential, drug releasing can be categorized as active or passive. Examples of the structures of different kinds of carrier-based drug delivery systems are shown (Figure 1). Generally, in passive implants, the drug-releasing characteristics are uncontrollable once installed clinically. In passive implants, the drug-releasing potential is eventually governed by the nature of the implant material and drug formulation. Biodegradable and non-biodegradable implants are two subtypes of passive implants. An encapsulated drug in a biocompatible polymeric matrix is a typical example of passive implants. In such implants, modification of numerous key parameters such as the nature of the polymer backbone, drug type or its concentration, implant design, and surface characteristics are varied to control the drug-release kinetics. However, implants are normally metallic in nature where the elution of therapeutic agent is activated by external stimuli targeting the optimal regulation of drug dosage according to the patients' requirement and therapeutic effects [63].

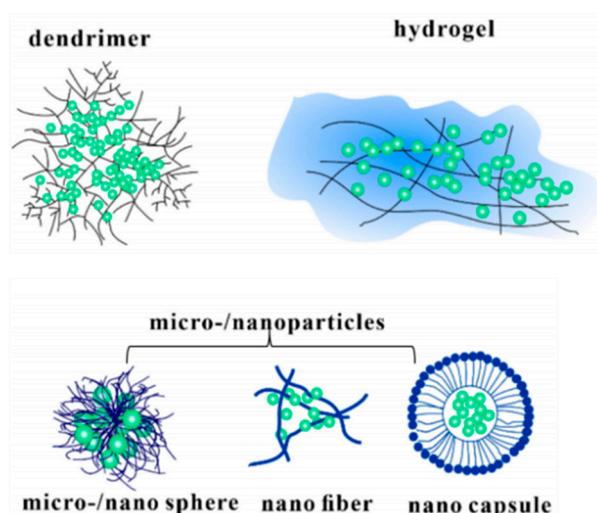


Figure 1. Drug release from implantable biomaterials and description of various types of carrier-based drug-releasing biomaterials [64].

Drug-eluting implants impart healing in addition to their regular task of support. For example, healing therapy is facilitated by controlled release of drug molecules from the implants into the surrounding environment. Drug release is a well-known research area of drug delivery. Due to the recent technological advancement, a plethora of new materials with improved functions and applications have been investigated and incorporated into the development of drug delivery biomaterials. Many macromolecules having natural or synthetic origin have shown excellent potential in controlled drug-release platforms. Most common platforms for sustained drug release include polymer coatings, the drug itself, or a ceramic material. Controlled drug release can be attained by coatings of pH-responsive, as well as enzymatically degradable, soluble polymers [65,66]. Controlled drug release plays a crucial role in maximization of the bio-efficacy and improvement in the quality of life. Drug elution is a process that involves the transfer of drug molecules (the solutes) from the original position to the matrix (biomaterials) to the external surface and then releases in the medium in a controlled or desired manner [67].

A drug carrier implant consists of active molecules (drugs) either on its surface or within the bulk structure, designed in such a manner that it should both retain the activity of the drug for a specific time period and control the release rate as well. Typically, the release of therapeutic agents around the local environment of an implant is governed by diffusion or osmotic pressure and via matrix

degradation [68]. Generally, a drug is released through four main mechanisms: (1) Diffusion-controlled, (2) solvent-controlled, (3) chemically controlled (such as polymer degradation), and (4) pH-sensitive. Diffusion-controlled drug-eluting systems are of two types: (a) Reservoirs and (b) matrices. Similarly, chemically controlled drug release is achieved by two main routes: (a) Material biodegradation, and (b) chemical cleavage of the drug moiety from a biomaterial. On the other hand, solvent activation phenomena comprise either osmotic effects or swelling [67]. Many mechanisms have been investigated that describe how drug release behavior of a drug from a particular matrix is controlled (Figure 2).

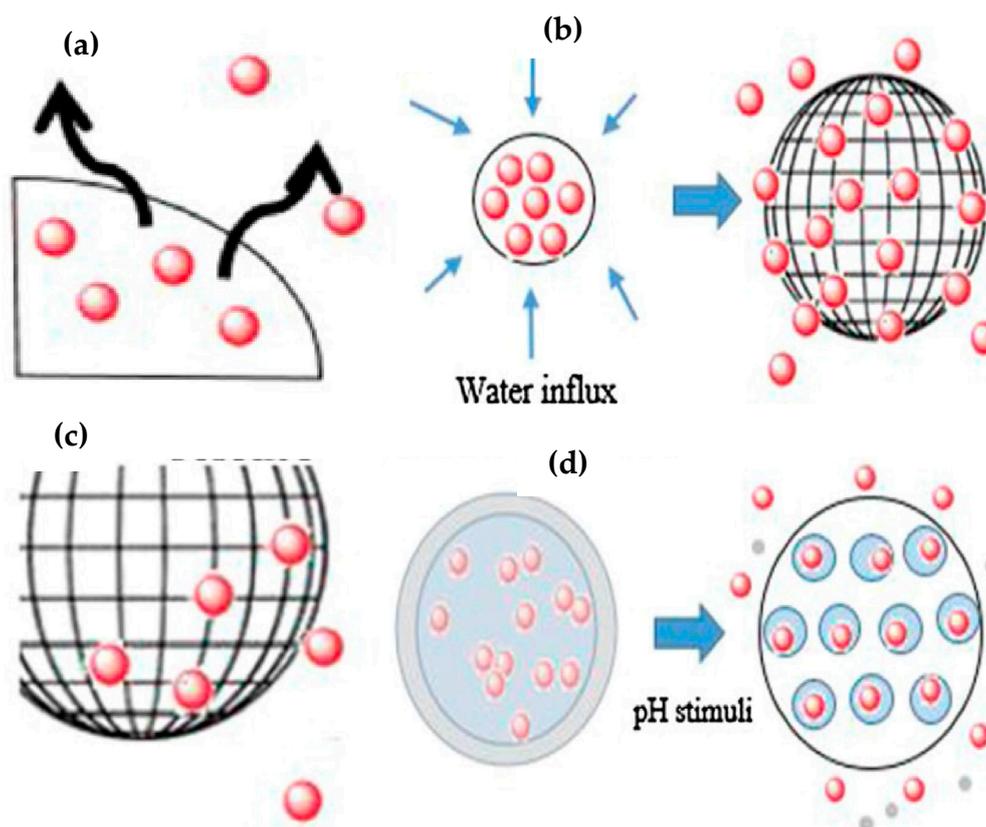


Figure 2. Different drug release mechanisms from nano-carriers have been presented schematically: (a) Diffusion-controlled; (b) solvent-controlled; (c) polymer-degraded; (d) pH-sensitive; (from Son et al. [69]); Reprinted with permission from [69]. Copyright 2017 Springer.

Physiochemical and biological mechanisms such as dissolution, diffusion, portioning, erosion, osmosis, swelling, targeting, and molecular interactions between the matrix and drug are frequently involved in controlling the drug release [70–72]. A drug-eluting implant can exhibit either one or a combination of more than one mechanistic model for an effective controlled drug release. During a drug release process in targeted applications, these mechanisms either exhibit their role at different stages or in a simultaneous fashion. Therefore, the classification of controlled drug-releasing models pertaining to drug release is based on the main mechanisms [73,74]. The major aim of the drug-eluting models is to permit an effective, benign, and reliable supply of the drug to the target site during therapy, and to obtain an anticipated therapeutic response. To this end, the controlled drug release phenomenon is considered critical to keep the drug concentration in the blood (or in a localized area in the case of dental implants) within the therapeutic range [75].

3. Controlling the Drug Release from Coatings

The elution time period of the drug molecule strictly depends upon the technical topographies integrated in implant coatings and the drug load. A range of nanomaterials including polymeric

systems [76,77], hydrogel-based models [78–80], and nanoporous materials [81,82] have been explored for the manufacturing of drug-eluting dental implants. A novel drug delivery model should ensure drug safeguard from a hostile environment, plausible controlled release (in response to environmental stimuli like temperature or pH), and selectivity of a drug to specific organs, cells, or tissues in order to show improved pharmacodynamic parameters of the drug [83,84]. Multiple factors influence drug release kinetics during therapy. A brief summary of these driving factors is shown in Figure 3.

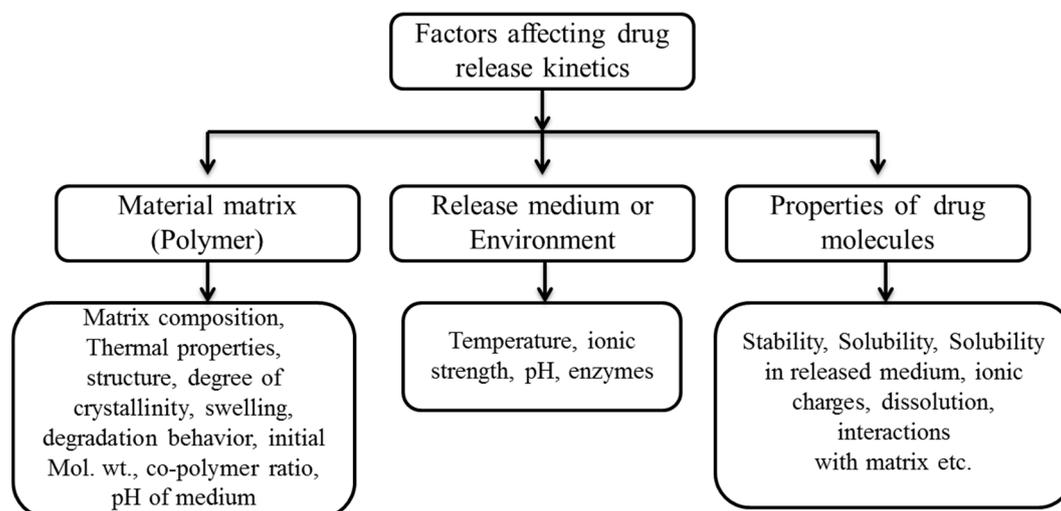


Figure 3. A summary of main factors influencing drug release kinetics.

Many drug-embedding approaches such as incorporation of the drug in the surface coatings, soaking, and chemical bonding have been used, but the burst release of drug molecules provides less control upon drug elution kinetics. Potential drug release around the local environment of an implant is directly related to molecule size, drug solubility in the released medium, ionic charges, and the molecular weight of drugs [85]. Therefore, fundamental characteristics of drug molecules have a strong association with the plausible release of the drug from the matrix for optimal therapeutics. Creel et al. showed that drug hydrophobicity and hydrophilicity have a strong association with drug release. The nature of the drug affects its aqueous solubility, protein binding, local drug concentrations, and tissue retention characteristics [86]. The physicochemical properties of the drug molecules are important in governing their transportation mechanism and binding potential with tissues during the course of drug delivery. Although hydrophilic drugs exhibit free distribution but rapid clearance remains the major concern. The hydrophilic nature of drugs encapsulated in a matrix is not adequate to control the drug release mechanisms, so nanogels have also been reported to delay release kinetics (rates) and offer multiple release kinetics, unlike the pure-Fickian mechanism [87,88]. However, hydrophobic drugs show insoluble behavior in aqueous media, binding potential with fixed tissue elements, and more tissue residence and biological effects [86]. Kamath et al. showed that diffusion or dissolution characteristics of drug molecules affect their release kinetics [89]. Drug release, if governed by the pure diffusion mechanism, is very quick due to the high in vivo clearance [78,79]. To attenuate the diffusional drug release of molecules, biorthogonal strategies were introduced to develop an affinity bond between the polymeric network and peptide (an affinity-based approach) that covalently links a small protein receptor and the observed tunable release rates [90]. Many other investigators have shown similar approaches but developed different functionalization methods for linking drug molecules to the polymeric network [78,91,92].

Venkatraman et al. [93] demonstrated that solubility in the polymer (matrix) also affects the release kinetics of drug molecules. The study inferred that in multilayered coating implants, the drug release was diffusion and degradation-controlled (dominant under high water intake), and the drug load did not affect the release kinetics [93,94]. Too fast a drug release before reaching the target site may

lead to the toxicity and decrease in the drug's concentration, while too slow a release can hamper the drug efficacy at the target site. Likewise, Ranade et al. found that the higher solubility of the drug molecule in release media showed a higher drug release rate, which is not required for optimal controlled release [95].

As the properties of rate controlling may influence the release kinetics of drug molecules, several characteristics such as initial molecular weight of the polymer, co-polymer ratio, pH of the medium, absorption rate, and time period significantly influence the degradation behavior and drug release time period in the case of biodegradable materials [96,97]. A number of studies have shown that thermal properties such as glass transition temperature and crystalline melting temperature of rate-controlling polymers also affect the degradation of the matrix, hydrophobicity, drug release, and solubility in the case of biodegradable materials [98,99]. For drug release from matrix systems, the degree of crystallinity is another factor that affects water diffusion and drug solubility, and influences biodegradation and drug-release biomaterials [99–101].

Processing parameters also play a crucial role in drug delivery and influence the drug release kinetics. Several studies have shown that a selection of coating methods such as air brush, ultrasonic atomization, and dip coating can affect coated film characteristics and drug release [102–105]. Furthermore, solvent properties such as the boiling point, and evaporation kinetics also significantly influence the residual solvent, merging of coatings, and release kinetics [106].

The coating design further influences the release kinetics of drug molecules. Kamath et al. found that the drug-to-matrix ratio influenced the drug loading capacity of matrix and drug elution [89]. A careful optimization of the drug-to-matrix ratio [89], drug density [107], compatibility between drug and matrix [108], physical dimensions of coatings or the coated device, and processing parameters can provide adequate control over the rate of drug release. Raval et al. [109] investigated that coating layer features such as composition and topography further influence the diffusion of the drug through the coating. An adequate control over drug release was achieved by coating the matrix and can be explained by an initial burst release and dissolution. Additionally, a process was recently reported in which a drug moves within the device in multiple layers to provide different drug release rates [109]. Balakrishnan et al. [110] showed that drug concentration and distribution within complex polymeric coatings can be comprehended by a simple Fickian's diffusion model [89,110]. Furthermore, the microstructure of the coating can exhibit processing conditions and eventually affect drug release kinetics. The thickness of the surface layer of the coating and hydrophobicity of the biomaterial also control drug release kinetics by lowering the diffusion process [111]. Otsuka et al. found that mechanical properties of the coated film also affect coating integrity [112].

4. Desired Properties for Drug-Releasing Dental Implants

The main aim of the drug-eluting implant is to achieve a favorable host response and beneficial effects through the effectively controlled, benevolent, and reliable release of the active drug at the localized site. It is critical for eluting implants to release a drug in a controlled manner, maintain a therapeutic concentration at the local site for a feasible period of time [75], and a sustained release of the therapeutic drug [113]. Therefore, an ideal drug-eluting implant coating should release active agents in such a manner that it maintains the drug concentration for a specific period of time, which is required for the targeted therapeutic action. The implant coating should be biocompatible; the eluting active drug or the matrix biodegradation should not have any toxicity or harmful effects both locally and systemically. In addition to excellent biocompatibility, the dental implant coating is desired to improve the tissue–biomaterial interface and to enhance osseointegration. Consequently, bioactive material coatings are known to encourage bone formation and are preferred over bioinert and biotolerant coatings (Figure 4).

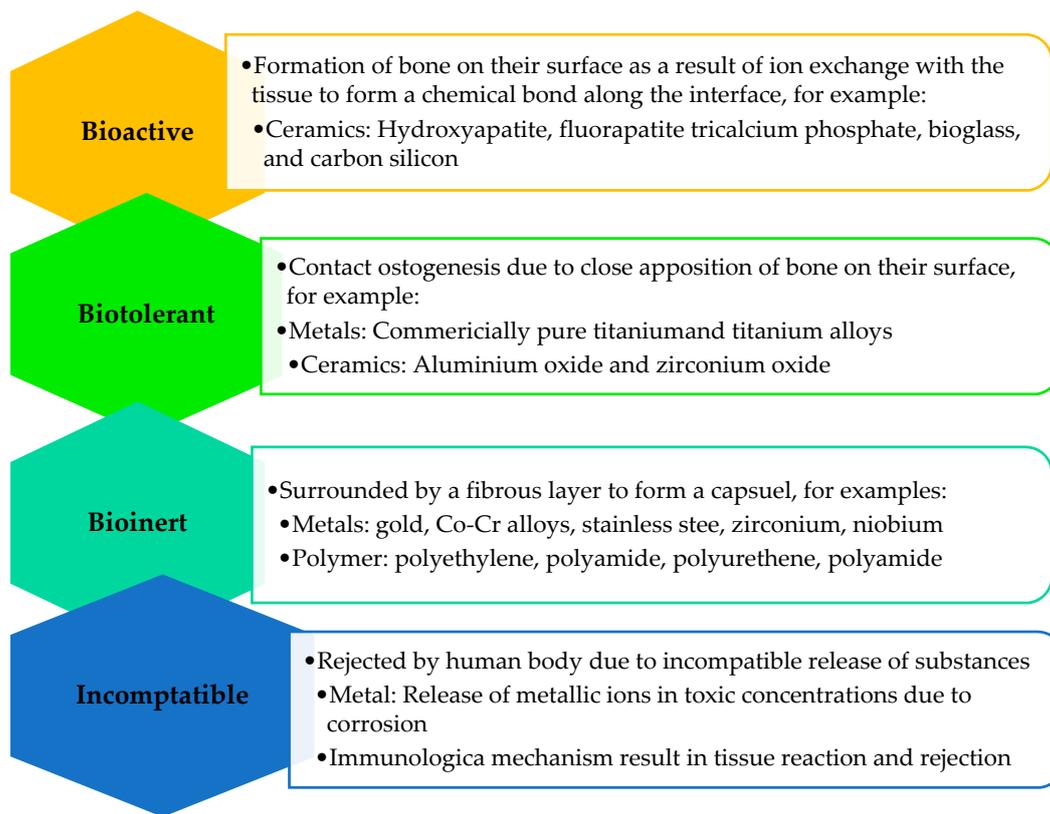


Figure 4. Possible biological responses to different materials when placed in human body.

As discussed earlier, osseointegration is essential for the stability and clinical success of implants. According to the original definition, osseointegration is the direct contact between bone and a loaded implant surface at the microscopic level [14]; however, more recently, it is described as an immune-driven demarcation response (type IV hypersensitivity) to a foreign body Ti implant that is immovable (ankylose) in bone [114]. This biotolerant nature of commercially pure Ti encourages contact osteogenesis [115] due to close apposition of the bone on their surface (Figure 4). It is well established that Ti is stable in a biological environment and does not trigger a foreign body reaction. Several *in vivo* and *in vitro* studies have successfully demonstrated that the clinical success of a dental implant and the resultant osseointegration is directly linked to the implant surface properties such as chemical composition, micro/nano-structured surface topography, and hydrophilicity [37,116,117]. By contrast, failure to osseointegrate results in alveolar bone resorption, loosening, and, ultimately, failure of the implant [118].

The main reasons for failure to establish osseointegration include patient-related factors (poor bone quality and volume, presence of periodontitis, poor systematic health, and smoking) [119,120] and implant characteristics (such as surface texture, shape, and biomaterial) [17,121]. Accordingly, the current research [48,122–124] focused on improving the bone–implant interface and osseointegration while studying various surface treatments for dental implants. To further improve the osseointegration of dental implants, a number of surface modifications had been considered; the hydrophilic surfaces promote cellular adhesion by means of various surface modifications and coatings. Additionally, surface coatings of osseoconductive materials (calcium phosphate (CaP) and HA) promoted the surface properties [125,126].

Immobilization of bioactive materials, osseoconductive biomolecules, and growth factors has been reported to enhance the osseointegration [127]. Additional features (such as bactericidal activity, enhancement of cellular attachment, and inhibition of bacterial film formation) can be added to the implant coatings that are also beneficial in improving the implant–tissue interface and clinical success.

In terms of mechanical properties, the implant material is required to have properties approximating the tissues to be replaced. For example, a gross mismatch of Young's modulus of elasticity and compressive strength of the implant material and bone is likely to generate areas of stress concentration, bone atrophy, loosening, and failure of the implant [42]. Therefore, the implant surface should have a modulus of elasticity, strength, wear, and fracture resistance [128,129] approximating that of alveolar bone [36].

5. Methods of Drugs Coating on Dental Implants

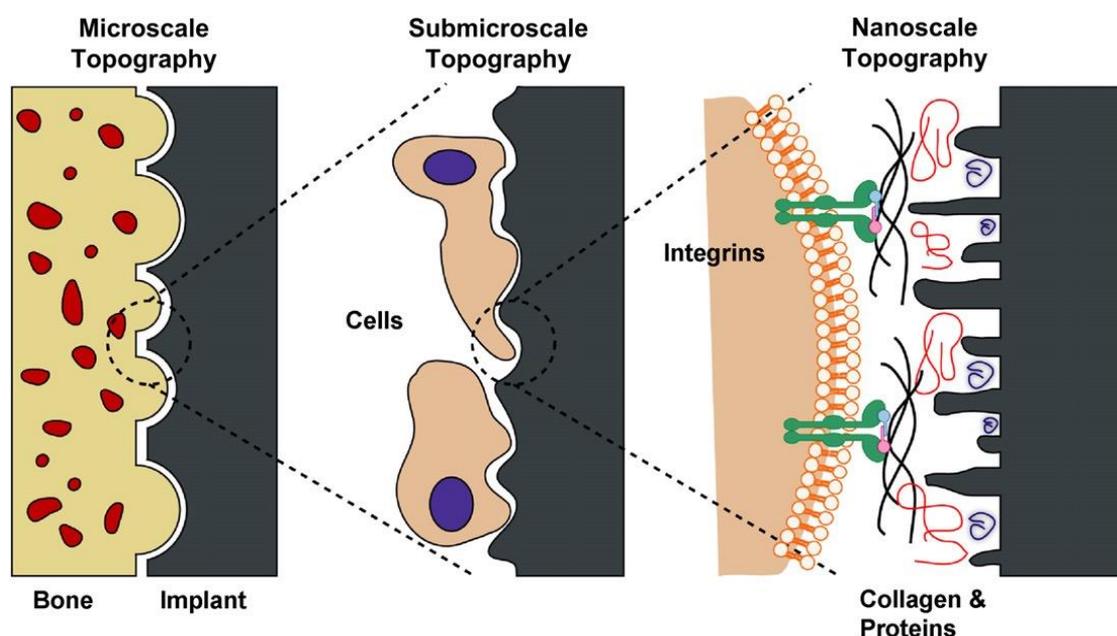
The purpose of implant modification with drugs and biomolecules is not only to retain the bioactivity but also to minimize complications linked to uncontrolled drug delivery dose. Soon after the insertion of the dental implant in the bone, it is covered with a biofilm containing blood cells, proteins, extra cellular bone matrix ions, cytokines, and growth factors that influence migration, growth, adhesion, and differentiation of the bone cell [130,131]. Three main methods including physisorption, covalent binding, and carrier systems [132] are reported in the literature to describe the modification of implant surfaces with proteins, enzymes, and peptides immobilization (Table 1). Moreover, desirable results are obtained by immobilizing growth factors on a nano-coating surface having a higher surface area and affinity. A simple dipping method is used for the adsorption of biomolecules, but this has the drawback of a limited control over the release kinetics and drug delivery, resulting in a disturbance in the retention of the adsorbed molecules, which depends only on weak van der Waals forces (physisorption) [132,133]. Similarly, a controlled drug release is achieved by the physical entrapment of biomolecules in the carrier system, which is attached by a barrier but not chemically bound [134]. The covalent binding of biomolecules to surfaces is a more complex but alternate method of therapeutic agent delivery, which is covalently bonded to the implant surface and releases a lower amount of drug but has a higher loading potential [36,135,136].

The clinical use of localized drug delivery via dental implant surface coatings is still under research and development and not yet well established. In several experimental models, a variety of implant surface modifications to carry different therapeutic agents have effectively been studied. The most common methods for localized drug delivery include the surface treatment or surface modification of implants [58,137,138], microsphere loading [139,140], therapeutic agent loading via scaffolds with a miniature [141,142], loading a hollow cylindrical implant with growth factors and biological molecules [139,143], and photodynamic therapy of implants to drug delivery [144]. However, local pharmacokinetics and predictable quantitative drug elution to an individual targeted dental implant in the peri-implant space site are still at the experimental stage. A sufficient amount of drug delivery into the healthy/inflamed soft tissue around dental implants is also limited by the thickness of the gingival epithelium, and mucosal permeability [145,146]. Therefore, implant surface modifications offering controlled and effective drug elution over a control time due to biodegradable or non-degradable polymers at the nanoscale are possible via structural modification of implant coatings [145].

As discussed, the biochemical methods of implant surface modifications offer a good alternative to physicochemical treatment and topographical alterations of the dental implant (Table 1). These biochemical functionalization approaches study the interaction of host tissue cells (peptides and extracellular proteins) and the implant interface. A good review of in-vitro and in-vivo studies of surface modification by peptides or extracellular matrix proteins on the Ti implant surface reported that these physicochemical interactions of immobilized biological agents is an effective way to stimulate the bone regeneration and enhance cell adhesion remarkably [36,147]. For example, the increase in surface roughness from micron to sub-micron scales (Figure 5) resulted in enhanced differentiation of osteoblast and tissue regeneration, especially when a combination of both micro- and nano-sized surface roughness topographies are employed together [148,149].

Table 1. Methods of biochemical modification and immobilization approaches for bioactive molecules on dental implant surface.

Description	Problems/Benefits	Consequences	Examples
Physisorption or Adsorption [130,133,136,150,151]			
Depending on the implant surface features (roughness, chemistry, surface energy, and wettability), which results in spontaneous adsorption of drugs and therapeutic agents on Ti implant surface via weaker van der Waals forces.	Lack of control over the delivery of molecules. Several parameters such as micro movement of the implant, pH, temperature, and solvent conditions	It is achieved by dipping method Uncontrolled adsorption from the surface	A burst release system, (80%–90%) in 1 h of adsorbed molecule Superficially adsorbed BMP-2 released rapidly in higher concentration
Covalent Binding [134,152–155]			
Cellular adhesion of proteins via covalent bond to prevent systemic effects of drugs	Immobilization of molecules promote mineralization	Proteins bond to the implant surface directly or through a spacer such as hydroxyl (–OH) or amine (–NH) groups	Cell-adhesive proteins (collagen, osteopontin, fibronectin, or vitronectin)
Carrier Systems or Self-Organized Nanoporous Surfaces on Silicon, Aluminum, and Titanium [132,136,156,157]			
Direct integration of drug into the coating material via carrier molecules (polylactide, polyglycolic acid, hydrogels, polypyrrole, and CaP/HA coating)	Growth factors or antibiotics are incorporated into a HA coating; can be delivered in a physiologic-like manner	Antibiotics, proteins, and growth factors are entrapped in crystals formed by precipitation of CaP/HA solution	A slow-release system, protein loaded into the carrier can be 10 times higher than adsorption

**Figure 5.** The interaction of bone and implant surface compared at different scales (Gittens et al. [149]); Reprinted with permission from [149]. Copyright 2011 Elsevier.

More recently, there has been interesting developments related to the use of porous titanium-based implant materials. There are two common methods to produce porous implant surface modifications with highly defined external dimensions: Selective laser melting (SLM) and atomic layer deposition (ALD). In the SLM process, a selective consolidation of melted titanium powders coating layers generated a complex 3D personalized implant surface using focused thermal energy of a computer-controlled laser beam to produce an optimum surface [158,159]. Liu et al. compared surface coatings produced by SLM and sandblasted-large-grit-acid-etched (SLA) methods on dental implants and reported the higher mineral apposition rate of the SLM implant and enhanced osseointegration to the surrounding bone tissue after 12 weeks [160]. Moreover, coating of the SLM-fabricated porous Ti implant surface with CaP and magnesium to encourage bone formation is an attractive development [161]. Recently, investigators have reported a novel ALD method of CaCO₃ films on the Ti6Al4V to coat HA and TiO₂ nanotubes (TNT) to produce a bioactive Ti6Al4V/TNT/HA coating surface with optimal biocompatibility, antibacterial activity, topography, and mechanical properties. In

addition, it was claimed that the ALD system has resulted in enhanced fibroblast cell adhesion and proliferation along with good antibacterial activity [162,163].

6. Understanding Coating–Implant Adhesion Interface

The interaction of the implant coating surface and the host tissues is considered one of the main factors for the long-term clinical survival of dental implants [164]. This implant–bone interface is determined using bone formation on the implant surface toward the bone (contact osteogenesis) and bone formation from the old bone toward the implant (distance osteogenesis) [115]. There is an influence of topographical and wetting characteristics on coating–implant adhesion. Surface modifications of the dental implant are important for the clinical outcome and implant–bone interface success and is achieved by a variety of coating procedures, as shown Figure 6 [37,115].

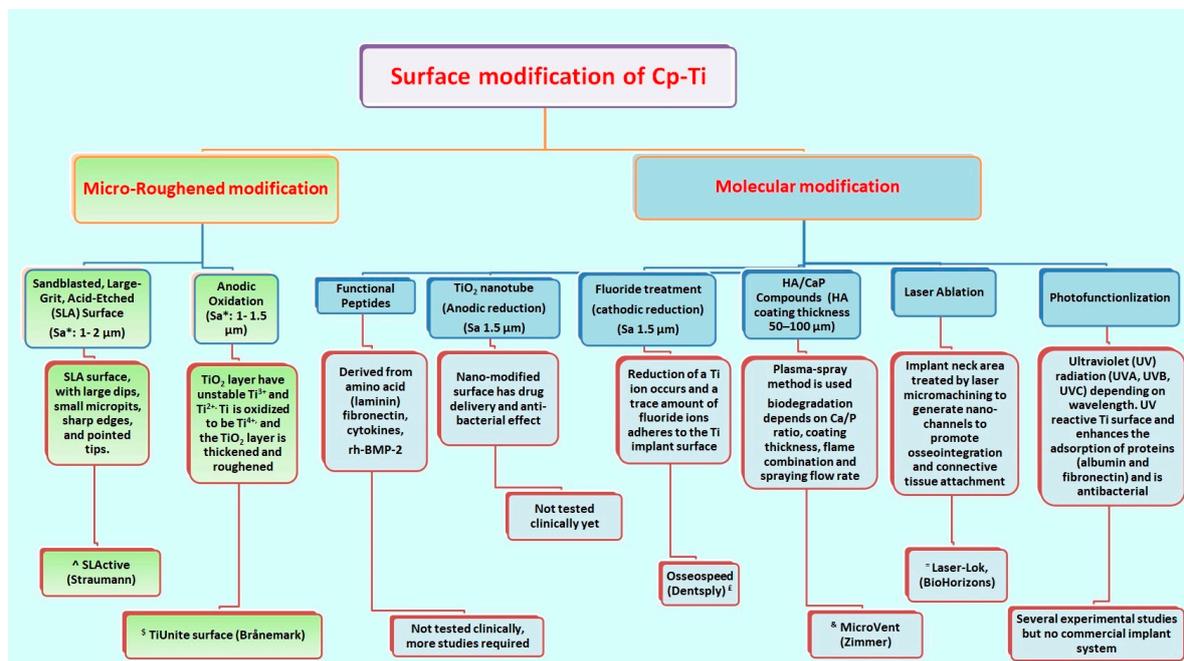


Figure 6. Schematic presentation of surface modification of grade IV commercially pure titanium (cp-Ti). * Sa (the arithmetic mean height of the surface), ^ SLActive (Straumann Institute AG, Basel, Switzerland), § TiUnite surface (Brånemark System, Nobel Biocare, Göteborg, Sweden), § Osseospeed (Astra Tech, Dentsply, Waltham, MA, USA), & MicroVent (Zimmer Dental, Carlsbad, CA, USA), = Laser-Lok (BioHorizons, Birmingham, AL, USA).

The influence of surface roughness, topographic characteristics, and wetting behavior of submicron- and nanocoatings on the differentiation of cells and tissues around dental implants is well-documented. To accelerate the osseointegration, the contact osteogenesis is largely dependent upon the modification of implant coating surfaces [115,165]. Therefore, several techniques have been reported regarding implant surface modification at submicron (1–10 micron)-level topographical modification and the addition of nanotechnological chemical features to the implant surface [165]. The fundamental coating principle of commercially pure titanium (cp-Ti) implant modification was intended to improve the early biological response (growth factors release from the bone matrix) to dental implants that commenced at the surgical osteotomy sites [166]. Additionally, the long-standing clinical survival of dental implants demands that the bone remodeling process should be harmonized with the modified implant surface to achieve predictable success. It is believed that the chemical and physical nature of the implant coating surface improves the quality and speed of the healing process [167]. Figure 6 describes two types of implant modifications of grade 4 CpTi, namely micro-roughened modification (sandblasted-large-grit-acid-etched (SLA) surface and anodic oxidation) and molecular modification

(TiO₂ nanotube, functional peptides, fluoride treatment, HA/CaP compounds, photo-functionalization, and laser ablation). However, some of the recent nano-level modifications presented in Figure 6 have not yet been clinically tested in humans, but these nanoscale surface-modification techniques have shown excellent in vitro and in vivo data; thus, they have promising potential for future clinical use. Nonetheless, biomechanical, micro-radiographic, histological, and drug-elution studies should be conducted in a controlled environment before such experimental coated implants are placed in humans.

7. Therapeutic Dental Implant Coatings

Current biomimetic approaches regarding dental implant coatings encompass the fabrication of biocompatible nanomaterials to effectively control the processes of tissue regeneration, cell adhesion, proliferation, and differentiation. A variety of organic and inorganic nanocoating agents have been studied to achieve optimum therapeutic outcomes from dental implant-coating materials (Table 2). Therefore, there is potential to improve osseointegration along with therapeutic effects by immobilization of bioactive agents, osseoconductive drugs, and growth factors on implant coatings via several possible surface treatments and coating agents [168].

Table 2. List of various materials and biomolecules studied as potential therapeutic dental implant coating agents.

Type	Subgroup	Substance/Biomolecule	References
Inorganic	Elemental	Nano-diamond	[169–171]
		Graphene	[172,173]
		Carbon nanotube	[174–177]
		Silver	[178,179]
		Ca-P	[180–183]
		Titanium	[117,184]
Organic	Protein	Fibronectin	[185]
		Elastin	[186]
		Laminin	[187,188]
		Collagen	[131,185,189]
		Bone sialoprotein	[185,189]
		Osteopontin	[190]
	Growth factors	Bone morphogenetic proteins	[133,191–193]
	Peptides	Arginylglycylaspartic acid	[131]
		Parathyroid hormone	[194–196]
		Antimicrobial GL13K	[197,198]
Polysaccharides		Hyaluronic acid	[193,199]
	Chondroitin 4-sulfate	[131]	
	Chitosan	[58,200,201]	
	Pectin	[179,202,203]	
Drugs	Bisphosphonate	[50,57,204,205]	
	Simvastatin	[194,206,207]	
	Strontium ranelate	[208]	
	Gentamycin	[191,209]	
	Tetracycline	[58]	
	Vancomycin	[210–212]	
	Doxycycline	[213,214]	
	Norfloxacin	[215].	
Chlorhexidine	[58,216]		

7.1. Biomimetic and Bioactive Coatings

To improve the osteoconductivity and osseointegration of dental implants, the biomimetic layers of calcium phosphate (CaP) and hydroxyapatite (HA) coatings had been deposited on implants. One

of the most successful current clinical therapeutic coatings of dental implants employed to achieve biocompatibility and enhanced peri-implant bone formation is CaP and HA [48,217,218]. Earlier, the plasma-sprayed HA coating was thick and rough, which resulted in clinical failures and cracking; however, new physical deposition and chemical techniques facilitated the deposition of thinner (100 nm) CaP/HA coatings having an accelerated and increased bone formation [37,219]. Similarly, organic implant nanocoatings comprising proteins, growth factors, polysaccharides, and drugs were incorporated into the latticework of CaP and HA for numerous therapeutic properties [173,215,217].

An accelerated osseointegration during the early healing phases can be obtained using implant coatings having a composition similar to the human bone [220]. For example, the CaP apatite composition is similar to the mineral bone phase and activates osteoblast cells to initiate bone tissue formation [221]. In addition, bioactive implant surfaces significantly reduced the time required for osseointegration of Ti implants due to improved wettability and better protein adsorption capacity. The bioactive implant coating is characterized by stimulation of the biological activity of surrounding bone tissues (Figure 1). Mostly, nanocoatings, where the coating thickness ranges from 1 to 100 nm, are bioactive [222,223]. Several organic and inorganic molecules have been reported to provide enhanced bioactive nanocoating bonds on the implant and bone interface (Table 2). It is well documented in the literature that the micron/submicron-scale surface roughness enhances osseointegration through osteoblast differentiation [58,115,173]. Moreover, Gittens et al. suggested that the combination of micro-/submicron-scale roughness along with nanoscale structures in vivo improves osteoblast differentiation to indicate the potential for improved implant osseointegration [149]. Bioactive interactions lead to a close adhesion and interconnection along the interface of the implant and surrounding tissues [224].

Following implantation of the CaP-coated implant, Ca and P are released into the surrounding tissues and stimulate precipitation of apatite on the implant surface [180,181]. The stimulation of new bone formation in the case of CaP-coated implants enhances the healing and the clinical success rate [225]. The biomimetic CaP-coated implants establish a greater bone-to-implant contact area compared to uncoated implants [226,227]. These findings and long-term success rate advocated an improved interface and osseointegration in the case of CaP-coated implants.

7.2. Antibacterial Coatings

Infections associated with dental implants are often very complex, multifactorial, and challenging to manage. The most common bacterial infections related to dental implants are Gram-positive bacteria, i.e., *Staphylococcus epidermidis*, *Staphylococcus aureus*, and *Enterococcus* spp., and Gram-negative bacteria, for example, *Pseudomonas aeruginosa* [191,228,229]. The implant surface provides a medium for bacterial adhesion by forming a physical defensive biofilm and diminishes the systemic antibiotic diffusion, resulting in relatively limited drug availability at the infection site [230]. Therefore, scientists are constantly making efforts to develop and optimize antibiotic-loaded therapeutic coatings for dental implants to treat chronic peri-implant infections [164,231,232]. Several therapeutic modifications of implant coatings treating localized implant–bone infections have been proposed by incorporating antibiotics, antimicrobial peptides, and disinfectants. In order to avoid and treat a potential infection adjacent to the implant–bone (host–device) interface, the following should always be considered regarding drug-loaded implant coatings [232,233]:

- (a) As acute infections occur immediately after implant surgery, short-term antimicrobial drug delivery coatings to the host tissues and device interface would help to prevent bacterial colonization, thus preventing the infection.
- (b) Similarly, long-term bacteria can colonize the implant surface; therefore, consistent antimicrobial drug delivery coatings are required to inhibit microbial colonization on the surface over time.
- (c) It is important that, while maintaining both long and short-term drug elution from implant coatings, there should be no alteration in the surface materials' properties; otherwise, it may deteriorate the implant's osseointegration.

A number of studies [58,228,231,234–236] have investigated the incorporation of antimicrobial agents to the implants' coating using dip or spray coating methods. However, it is very challenging to meet the desired requirements during production of implant coatings. A controlled and sustained local drug delivery from dental implants has a substantial potential to replace the use of systematic drugs due to the adequate physiological stability and availability at the local implant site, thus reducing the toxicity risks and higher cost [233,237]. Antimicrobial agents are generally adsorbed on the surface via dip or spray coating methods, but the adsorption of antimicrobial molecules to the implant surface is very weak, which may precipitously cause damage in physiological situations. Due to this reason, the release of antimicrobial agents may either have a relatively short-term potency or result in rapid desorption of the antimicrobial from the implant surface [229].

Consequently, the antibiotic-loaded (gentamycin, amoxicillin, and vancomycin) bioactive coating on dental implants is an attractive possibility to treat the localized infection site by increasing infection prophylaxis confined at the implant site. Various antibacterial implant coatings showing antimicrobial activity to the implant–bone junction have been investigated (Table 2).

Gentamycin is a widely used broad-spectrum antibiotic for coating the implant surface along with the layer of HA to act as a local prophylactic agent [191,209]. Previously, a biodegradable gentamicin-poly(lactic acid)-coated implant was investigated using a rat model. It was reported that adding 10% gentamicin to the poly(lactic acid) coating remarkably decreased implant-related infections [209]. An in vitro study investigated titania nanotubes loaded with gentamicin and reported therapeutic release of the drug, reduction in bacterial adhesion, and enhanced osteoblastic activity [238]. Elution of therapeutic drugs significantly reduced the bacterial adhesion and enhanced osteoblastic differentiation [191,231,239]. Similarly, tetracycline coatings enhanced the attachment and retention of blood clots on the surface during an earlier phase of healing, thereby promoting osseointegration [58].

Vancomycin loaded silica sol–gel film on the implant demonstrated a slow release of vancomycin [210–212], resulting in a lower adherence of bacteria such as *Staphylococcus aureus* to the Ti implant. Vancomycin was covalently attached to the implant surface to make an antibacterial surface to prevent the bacteria attachment for a long time [240]. Ferreira et al. incorporated nanotubes loaded with doxycycline on the dental implant surface to deliver the antibiotic locally and reported that *P. gingivalis* growth was suppressed in the experimental media during a 28 day time interval [214]. Likewise, it was reported recently that an implant surface coated with doxycycline prevented bacterial colonization to control peri-implant mucositis and peri-implantitis [213].

Norfloxacin-biocompatible antibacterial nanocoatings for dental implants containing norfloxacin have been reported using the novel method of nano-spray drying technology along with nanocoatings of poly(lactic-co-glycolic acid) as a biodegradable polymer and norfloxacin as a model antibiotic [215]. The adsorption of the norfloxacin antibiotic was carried out on the nanoparticles obtained from CaP, demonstrating a controlled drug delivery from these nanorod-like structures with an antibacterial potential [241].

Chlorhexidine (CHX) is a broad-spectrum organic antimicrobial and antifungal agent, which is well known in the treatment of several periodontal pathogens [242]. It was absorbed on the Ti implant by inducing surface mineralization with the HA coating [58,216]; however, the resultant CHX-coated surface helped to reduce the bacterial load for a limited time due to short-term antibacterial properties. The CHX-hexametaphosphate nanoparticle was used to fabricate a porous coating on the Ti implant surface having a concentration equivalent to 5 mM of CHX for dental implant coatings [243]. Moreover, CHX delivery from the CHX-polybenzyl acrylate Ti implant coating resulted in inhibition of *streptococci* adhesion, particularly useful to control bacterial infection around the dental implant during the early phase of implant placement [244].

7.3. Antimicrobial Metallic/Metalloid Coatings

A range of metallic biomaterials with antimicrobial properties have been investigated for implant coatings (Table 2). Silver, zinc, and copper are the most widely used biocidal, bactericidal and

bacteriostatic metallic agents having higher efficiency against broad spectrum pathogens [165] and no toxic effects when used in a controlled concentration. The antibacterial activity of silver electrodeposited on tricalcium phosphate (TCP)-coated titanium implants showed the desired bactericidal activity without toxicity in the optimal silver concentration [245,246]. Similarly, the cold-spray coating technique utilized polyether ether ketone (PEEK), silver-doped HA powder, and the chitosan–copper composite for creating antimicrobial implant coatings [247,248].

Recently, different types of graphene implant coatings (reduced graphene oxide and graphene oxide) have been explored as an attractive option for an implant surface coating material due to their higher biocompatibility and antibacterial effects. Several in vivo and in vitro studies have reported a very high surface area and improved osseointegration of a graphene-based implant coating [172,249]. Zeng et al. reported that a graphene/HA coating deposited on the Ti implant showed better biocompatibility, higher bond strength, and better bioactivity compared to only a HA coating or only CpTi [250]. Moreover, the antibacterial activity of graphene is due to the damaging of cell membranes through oxidative stress against multi-resistant bacteria and fungi species [251]. Although a very limited amount of research has been conducted for graphene application-coated dental implants, this material has created new horizons in drug delivery and tissue engineering applications in the near future. In addition, nano-diamonds have been reported for their bioactive and bactericidal potential for implant coatings, thereby enhancing osseointegration and reducing the incidence of peri-implantitis [50,178]. The nano-diamonds surface contains oxygen-carrying groups and charges that are responsible for antimicrobial properties [252]. Silver and nano-diamond implant coatings showed antimicrobial properties against *Escherichia coli* [169]. Biocompatibility of potential coating materials is essential. Vaitkuvienė et al. [253,254] comprehensively investigated the biocompatibility of nano-diamond materials using neural cells. It was reported that the thin coating of oxygenated and boron-doped nanocrystalline diamond (BDD) significantly improves the cellular adhesion and proliferation of neural cells. These findings demonstrated the nano-diamond coatings' good biocompatibility and potential for maintaining the cell viability and proliferation [253]. Another in vivo study [255] investigated the biocompatibility of BDD using an animal-based implantation model. Although the formation of a thin fibrous capsule and mild inflammation was observed, there were no significant differences comparing BDD and the control titanium alloy [255]. The biocompatibility of the nano-diamonds may vary depending on the materials' properties and target tissues. The larger diamond particles (100 nm or more) showed better biocompatibility than smaller particles [256,257]. However, further studies are required to evaluate the nano-diamonds' biocompatibility using various types of cells and materials' parameters. In addition, the current literature determining the mechanical properties and bond strength of nano-diamond coatings on dental implants is scarce and requires further research.

7.4. Antimicrobial Peptides (AMPs) Coatings

Antimicrobial peptides (AMPs) are covalently bonded or physically adsorbed on the implant surface after being derived from human proteins. The broad spectrum capability of AMPs has an effect of antimicrobial activity; therefore, they are particularly useful due to the low host cytotoxicity and bacterial resistance [191,258]. Lee et al. reported that the dual-drug-eluting (gentamicin and bone morphogenetic proteins) Ti implant system can reduce infections and improve osteointegration [191]. In the last two decades, the resistance of antibiotics and microbial agents combating was compromised due to superbugs [259]. This problem is the main hurdle in the successful osseointegration of dental implants and has compromised the oral health in adult, as well as in geriatric, patients [260]. For this reason, new antimicrobial drug approaches are being investigated such as coatings of the antibiotics, laser treatments of the surface, and peptides binding with bioactive ingredients [261,262]. The human body is made up of millions of proteins and peptides and play their role in maintaining body defense, repair, and regeneration. Proteins are genetically coded for their specific functions. Therefore, studying the structures of these proteins and synthetically designing for specific functions can be very futuristic.

The antimicrobial peptides (AMPs) are a natural weapon for the defense against microbes [263]. These AMPs are present in the human body epithelial and non-epithelial surfaces, maintaining natural barriers and fighting against microbial invasions. The oral cavity has a dynamic environment and is lined by specialized mucosa and secretory glands, helping in expressing the defensins, cathelicidins, histatins, statherin, adrenomedullin, and neuropeptides [264]. All these antimicrobial peptides have different roles in the defense of the oral cavity against microbes, viruses, and fungi. In addition, the composition of human saliva is full of bioactive ingredients with potential diagnostic and monitoring capability. There are many proteins and peptides identified from human saliva such as the statherin family, which helps in the remineralization of the dental hard tissues. Table 3 enlisted various AMPs commonly found in the oral cavity.

Table 3. List of key antimicrobial peptides (AMPs) present in the oral cavity [264].

Antimicrobial Peptides	Type	Site of Expression
α -Defensins	HNP-1	Neutrophils (azurophilic granules), gingival crevicular fluid, and bone marrow
	HNP-2	
	HNP-3	Neutrophils
	HNP-4	
β -Defensins	hBD-1	Saliva and suprabasal layer of stratified epithelium
	hBD-2	Gingival epithelium and saliva
	hBD-3	Skin and salivary gland
Histatin	1	Saliva (parotid and submandibular)
	3	
	5	
Adrenomedullin	-	Epithelium
Cathelicidins	LL-37	Neutrophils, inflamed epithelia, and saliva and submandibular glands

The AMPs act against oral microbes by various approaches including the barrel-stave model, carpet model, and toroidal model (Figure 7). It is not proven which is more dominant, but in the last few decades, many experiments have been reported on the basis of the proposed models. In the barrel-stave model, peptides can position themselves to attach to the microbes' cell membranes, leading to the aggregation process of peptides and bilayer formation (Figure 7a) [264]. A prolonged or carpet-like layer formation by the disruption of the cell membranes by peptides is known as the carpet model (Figure 7b). In the toroidal model, all the attached peptides begin to aggregate and bind to the lipid monolayer through pores (Figure 7c).

The use of AMPs in dentistry and medicine has been increasing in the last few decades due to the dynamic combating outcomes. In the past, extensive literature reported on the role of histatins, cathelicidins, and oral defensins peptides in dentistry such as dental implants coatings, and in periodontal tissue regeneration, reducing dental caries and remineralization of dental hard tissue [265–267]. Solid-phase peptide synthesis (SPPS) and recombinant DNA technology have been used to encounter the need for AMPs [268,269]. It has been observed by the coating of AMPs on the dental implant surface that it can actively reduce bacterial infection during the healing period.

The most common dental implant materials of titanium, zirconia, polyetheretherketone (PEEK), and polyetherketoneketone (PEKK) are available on the market [26,262]. All these materials have pros and cons according to their chemistry, biomechanics, physics, surface, and esthetic properties [262,270]. In the past, titanium was coated with antibiotics such as cephalothin, amoxicillin, and gentamycin [154] as discussed above. All these approaches can be applied onto three different dental implant surface biofunctionalization levels, as shown in Figure 8 [271]. The use of peptides in combination with the bioactive ingredients has proven to be a promising futuristic coating for the dental implants for better osseointegration, improved implant and soft tissue sealing, and reducing microbial attacks

during healing time. A protocol was reported by Rodriguez et al. on the binding of KKLPDA and EEEEEEEE peptides on the Ti6Al4V and hydroxyapatite surfaces for reducing the bacterial infection, as well as bringing a new drug delivery system for the orthopedic and dental implant surface functionalization [59].

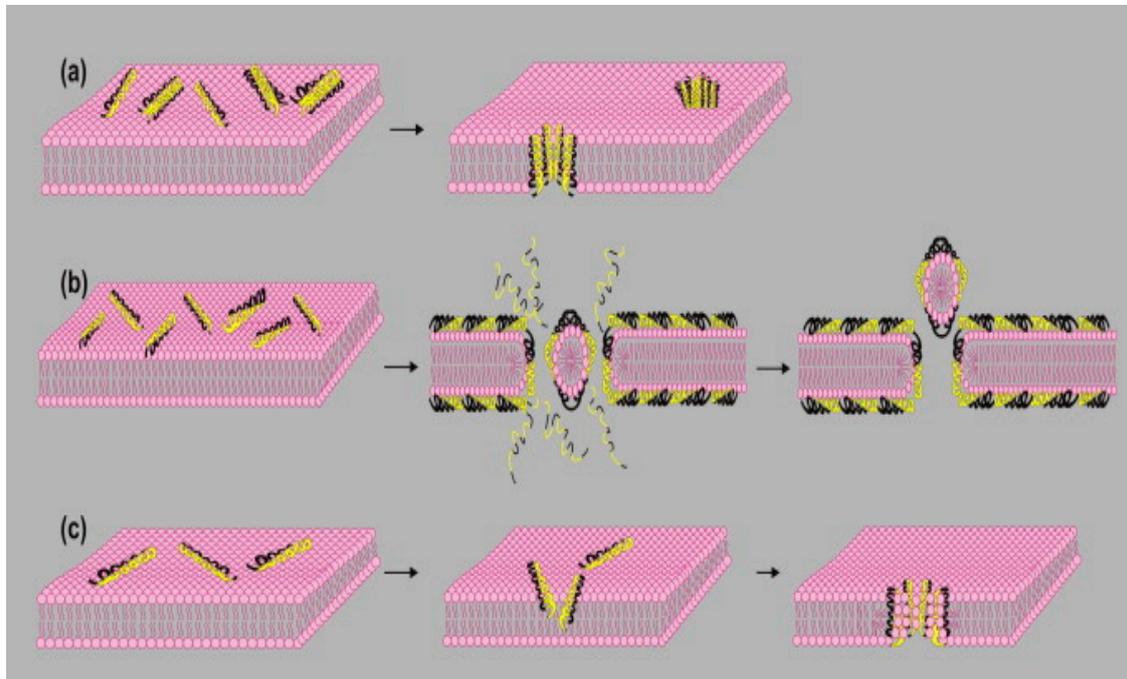


Figure 7. Presentation of various models showing antimicrobial activity of AMP: (a) Barrel-stave model, (b) carpet model, and (c) toroidal model [264]. Reprinted with permission from [264]. Copyright 2016 Elsevier.

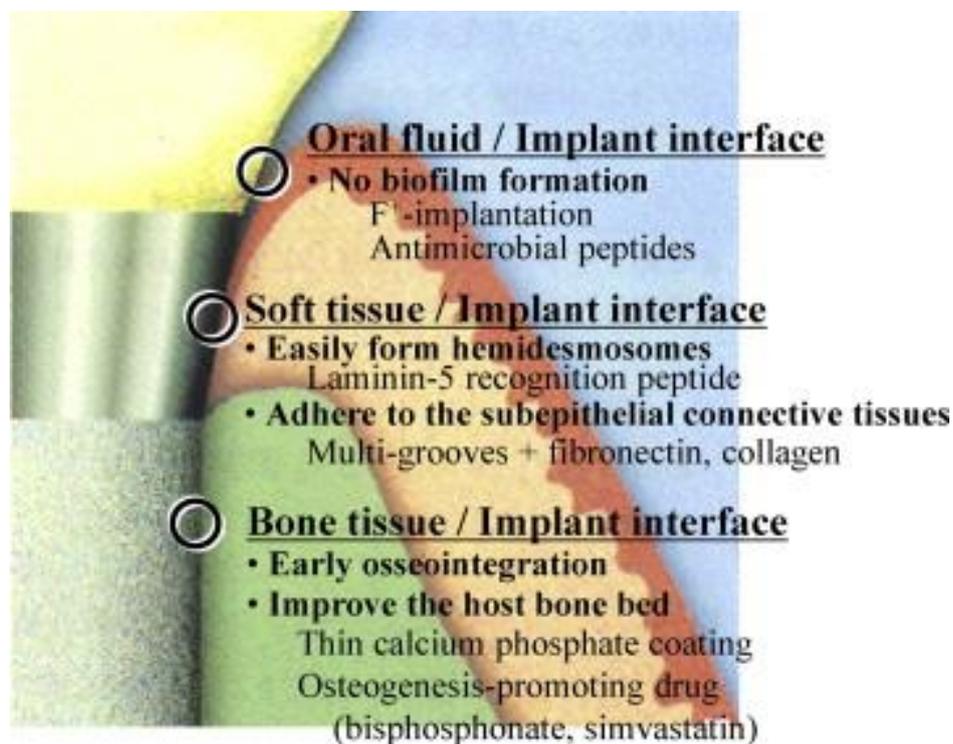


Figure 8. Bio-functionalization of dental implants with surface modification and various interfaces [271]. Reprinted with permission from [271]. Copyright 2011 Elsevier.

Another study reported on the biomodification of new zirconia-based implants with short-motif arginylglycylaspartic acid oligopeptides tailored on the surface and observed rapid osseointegration and improved peri-mucosal sealing, and AMPs reduced the chance of peri-implant infection [272]. With the help of GL13K, a cationic antimicrobial peptide that reduces the *Porphyromonas gingivalis* growth also inhibits its adhesion [273]. In this in vitro study, the GL13K peptides conjugation onto the titanium microgroove proved the improved antibacterial cytocompatibility and promoted the cell growth in the microgrooves [273]. In the in vitro study against the two oral stains of *Streptococcus sanguinis* and *Lactobacillus salivarius* with the titanium surface immobilized with the lactoferrin-derived hLf1-11 antibacterial peptide, it showed an outstanding reduction in the bacterial growth [274]. With the help of human lactoferrin-derived (hLf1-11) peptide, bacterial adhesion on the Ti surface was reduced, inhibited the formation of biofilm, and showed good compatibility with the human fibroblast [275]. Oral defensins peptides are another family member of AMPs found in the oral cavity. The six short motifs of defensins peptides were synthesized by SPPS and characterized against *Streptococcus epidermidis* and *Pseudomonas aeruginosa* [276]. In this study, DLAMP-3 (CRVRGGRCA) showed inhibitory effects against the *S. epidermidis* at 4.37 mg/mL. This DLAMP-3 showed an effect against *P. aeruginosa* at 35 mg/mL [276]. Human beta defensins peptides have an immuno-modulatory effect that promotes bone remodeling [267]. Similarly, Righino et al. reported the new approach for mimicking human antiviral salivary proline-rich peptide (PRP) for medical purposes [277]. Warnke et al. reported a recombinant human beta defensin-2 coating for biocompatibility assessment with the human mesenchymal stem cells (hMSCs) and human osteoblasts, and found no toxicity [278]. Bifunctional peptide binding (BPB) on the titanium discs were engineered in this study to combat the *S. mutans* bacteria, and the results were promising for the coating on dental implants due to antibacterial and antibiofouling activity over the four fouling/cleaning cycles [279]. Human saliva contains many antimicrobial proteins and peptides (defensins, cathelicidins, histatins, statherins, and proline-rich peptides), which are useful for oral health. In the previous discussion, we found that most of them are synthetically engineered and bonded to orthopedic and dental implant surface modifications [264].

7.5. Bisphosphonates Coatings

Bisphosphonates drugs are used to treat patients with resorptive bone disorders including hypercalcemia, osteoporosis, multiple myeloma, and Paget's disease [280]. Commonly used bisphosphonate drugs (alendronate, etidronate, tiludronate, and zoledronate) act by stimulating osteoblasts and bone formation [281], as well as by inhibiting the osteoclastic activity and bone resorption [282]. In patients suffering from the resorptive bone disorders (such as osteoporosis), the altered metabolism and quality of bone may compromise the implant–bone interface and osseointegration [283,284]. Although bisphosphonate therapy may improve the bone metabolism, the long-term systemic administration may lead to bisphosphonate-related osteonecrosis of the jaws (BRONJ) [285] that can be prevented by localized delivery of such drugs. The localized application of bisphosphonates showed promising results for a range of conditions affecting the jaw bone specifically; for instance, improved periodontal healing following mechanical debridement [286], regeneration of the alveolar ridge following extraction [287], and prevention of root resorption [288,289]. Localized bisphosphonates delivery around dental implants reduced the postoperative marginal bone loss and improved the osseointegration [57,290].

A recent systematic review by Najeeb et al. [50] comprehensively analyzed the bisphosphonate-releasing dental implant in terms of osseointegration and advocated the positive effects on dental implant osseointegration. It was further reported that various bisphosphonate drugs (alendronate, pamidronate, and ibandronate) investigated for implant coatings in combination with other compounds (collagen, calcium phosphate, and chondroitin sulphate) showed a significant improvement in the bone formation [50]. Considering the promising benefits of bisphosphonate-coated dental implants, various researchers have further investigated the use of a variety of coating techniques and compositional variables [204,291,292]. For example, plasma spraying was used to apply biomimetic

coatings of calcium phosphates and hydroxyapatite combined with bisphosphonates [291,292]. Similarly, techniques such as heat treatment, anodization [293], and immobilization on a porous surface [294] have been used to coat the Ti implants. Additional surface treatments such as surface anodization enhances surface porosity and the area of titania, hence facilitating the loading and delivery of coated bisphosphonates to the bone [20,293,294]. Similarly, using fibrinogen, an intermediate layer between the Ti implant and bisphosphonate coating may enhance the osseointegration [280]. Although, the clinical studies by Abtahi et al. [57,280] reported a reduction in the marginal bone loss while using the bisphosphonate-coated implants when patients were followed-up for a short period of time.

Currently, there is no consensus in terms of dosage and release of drugs from the bisphosphonate coatings. Increased bisphosphonates release (from 8 to 80 $\mu\text{g/mL}$) in an animal study promoted bone formation; however, no remarkable effects were observed on bone–implant contact [292]. By contrast, Abtahi et al. [57,280] used a bisphosphonate concentration (less than 1 $\mu\text{g/cm}^2$), but the effects of varying dose or concentration on human subjects were not investigated. Although, the preliminary and experimental research has shown promising results in terms of new bone formation and osseointegration around bisphosphonate-coated dental implants. However, information regarding the long-term prognosis and effects of variables such as drug concentration is scarce. The systemic and localized effects of bisphosphonate release on peri-implant tissues have not been addressed adequately. Therefore, further clinical trials with a longer follow-up period are essential to validate the current evidence and clinical efficacy for using the bisphosphonate-coated dental implants.

7.6. Zirconia Coatings

In 1789, a German chemist, Martin Klaproth, discovered zirconium dioxide (ZrO_2) during analysis of the mineral zircon (ZrSiO_4). However, it was Swedish chemist, Jöns Jacob Berzelius, who isolated the zirconium/zirconia (Zr/ZrO_2) in the pure form in 1914 [295,296]. There are three crystalline phases of ZrO_2 (monoclinic, cubic, and tetragonal phases). The tetragonal phase is used for dental applications. However, in later years, due to research efforts, a combination of Zr-yttria was developed and named yttria-stabilized tetragonal ZrO_2 polycrystals (Y-TZP) [297]. This was made available for usage and was considered the material of choice for hip implants in the late 1990s [296,298]. Use of ZrO_2 as a biomaterial in orthopedics first started in 1984, mainly in the United States and Australia. This rapid shift toward Y-TZP in the late 1980s and 1990s was due to a much better strength and lower grain size, resulting in better wear properties and technical advantages in terms of sintering [299].

Today, due to excellent esthetics, biocompatibility, and physical properties, Y-TZP became the material of choice for all-ceramic-material indirect dental restorations [298,300]. Its use in dentistry started in the 1990s first for root canal posts and later for prosthetic abutments. The development of its use in the dental prosthetics started with the opportunity for manufacturing ceramic posterior-fixed partial prostheses [301] followed by its use as an intraosseous dental implant in late 1990s [302]. During the last decade, ZrO_2 dental implants have emerged as a viable alternative to Ti dental implants due to its potential osseointegration and bioinert properties, in addition to its esthetic superiority [303–305]. Its radiopacity is similar to that of Ti and can be visualized radiographically [306]. Other advantages of ZrO_2 over Ti are less bacterial colonization on ZrO_2 and the absence of corrosion as Ti is reported to produce corrosion products at the site of dental implants [307,308].

Zirconia is known for excellent mechanical and physical properties [309]. Apart from superiority in the physical properties, research studies show better performance for ZrO_2 implants over the Ti implants in terms of biocompatibility due to the non-release of ions and creation of an excellent osteoblast attachment and cellular proliferation that are essential for fast growth of the bone around the implant surface [308,310]. By contrast, Ti implants compromise cell viability, inducing apoptosis, with a decrease in active osteoblasts and compromising the quality of bone [311]. Evaluation of periodontal integration showed improved adhesion of fibroblasts on the ZrO_2 surface and stronger attachment, respectively [312,313]. Despite possessing several advantages, current literature reported a limited number of long-term studies involving ZrO_2 implants [29]. To date, although the Ti dental implant

is still considered the gold standard for dental implant applications, some studies have reported allergic reactions related to Ti [314]. Besides, the generation of galvanic effects after contacting saliva intraorally [308] and wear particles leading to inflammatory responses are also reported due to Ti implants [315]. Therefore, more clinical studies are required to further explore the potential of ZrO₂ implants without having adverse reactions [19]. In order to combine the advantages of both the commonly used dental implant materials, i.e., ZrO₂ and Ti, a combination of Ti implants coated with ZrO₂ particles seems a viable option to explore [19].

The quality of osseointegration mainly depends on the surface properties of dental implants [316]. It is logical to combine the superior osseointegration, biosecurity, and esthetic abilities of ZrO₂ with the better fracture resistance of Ti [317]. A number of surface modifications to improve the surface chemistry/topography of coated ZrO₂ interacting with biological tissues were studied. Mainly, these can be classified into three groups of physical (e.g., plasma spraying), chemical (acid etching), and biological (e.g., protein absorption) [124,317]. The methods used successfully for the surface modifications on Ti with ZrO₂ includes sandblasting with or without acid etching (SLA), dip-coating, and plasma spraying [311,318]. Among these methods, plasma-sprayed coating can be considered a powerful tool due to the significant improvements in the physical/chemical properties of substrate materials. In addition, by manipulation of some parameters, the physical properties such as surface topography, roughness, porosity, and crystallization can be controlled [319,320].

In a recent study, Huang et al. [321] compared the plasma-sprayed nanostructured ZrO₂-coated Ti implants and reported the superior osseointegration of plasma-sprayed ZrO₂ implant coatings in all quantified parameters [321]. They also claimed an increased number of osteoblastic attachments on ZrO₂-coated implants in the early stages. After two weeks, the histological analysis revealed increased osteoblasts attached on the ZrO₂-coated implants, and this was further confirmed by micro-CT images, which showed an abundance of bone formation around the ZrO₂-coated implants. The plasma-sprayed ZrO₂ coating produces an ordered microscale surface layer that improved the osteoblastic attachment, proliferation, and differentiation [322]. These results validated the theory that a higher free-energy surface promotes the attachment of osteoblasts [323]. The difference in the osseointegration between the Zr-coated Ti implants and the Ti implants decreased at four weeks, whereas, at 12 weeks, an almost similar bone trabeculae thickness, a space indicating similar trabeculae arrangement, and the quality of bone were found [324]. The initial and better osseointegration exhibited by the Zr implants and similar osseointegration to that of Ti implants later in the healing period are reported in several research studies [310,322–326]. Though this finding may be non-significant in terms of final osseointegration outcome, the initial rapid and fast osseointegration shown by the Zr-coated implants can be useful in some clinical scenarios to achieve improved stability of the implants to enhance the osseointegration and prognosis [327,328]. Plasma-sprayed nanostructured Zr-coated Ti implants emerged as a promising alternative to commercially pure Ti implants, due to excellent biocompatibility, better esthetics, soft-tissue response, increased osteoblastic activity, and osseointegration at the early stages of healing. Further studies in different clinical scenarios at longer follow-up times are mandatory to validate these findings.

8. Limitations and Future Challenges for Coated Dental Implants

In the recent decades, although plenty of research studies have investigated various coating materials, drugs, and techniques, there are currently very few coated dental implants available for clinical applications. In order to translate implant coatings for clinical applications and to obtain benefits from the controlled targeted therapeutic release, additional clinical studies overcoming various obstacles are a prerequisite. Clinical failure of dental implants is still observed despite the promising outcomes from the outgoing research [118,329,330]. The peri-implant infections and malfunction of the bioactive surface coating are associated with implant failure [329,330]. For example, poorly bonded or undermined coatings may chip off under the mechanical stress of screwing or may laminate prematurely, resulting in an inadequate osseointegration and failure of dental implants [121].

Generally, mechanical properties (such as modulus, tensile, and fatigue strength) of coating materials are remarkably weaker compared to the underlying metal or alloy [331]. The poor mechanical characteristics of therapeutic coating materials resulted in the formation of surface microcracks, leading to fracture and failure [332]. Considering the complex dynamic stresses applied at the implant surface following fixation, further improvements in the mechanical properties of implant coatings are essential for long-term clinical success.

Plasma spraying is commonly used to coat HA on the implant surface [123,333–335]. However, there are certain limitations such as a thicker coating (few microns) and the need of substrate surface pretreatment such as grit blasting [121]. In addition, unfavorable porosity, crystallinity, and residual stresses at the implant–CaP coating interface remained the main concerns [331]. In the clinical prospects, the most important is delamination, that is, failure of the coating layer at the interface due to poor bond strength and residual stresses at the implant–CaP coating interface. Such delamination and release of coating particles may lead to implant failure [336,337]. The shortcomings of plasma-sprayed coatings can be overcome using simulated body fluid biomimetic biomineralization approaches to deposit a layer of CaP apatite [121]. In addition, a roughened substrate surface as a result of surface treatment enhanced the mechanical stability of the CaP coatings. Therefore, the coating–implant interface bond strength and mechanical properties are crucial, and there is need of future research to improve these properties.

The biocompatibility of coated dental implants needs special attention as current literature reporting long-term clinical studies about the biocompatibility of therapeutic coated implants is scarce. During the active release of drug molecules by diffusion or osmotic pressure, the coating matrix degrades [68]. The coating material and its dissolved agents and byproducts must be biocompatible to prevent any localized or systemic toxic effects. Although the main purpose of the drug-eluting coating is to permit an effective and reliable supply of the drug to the target site for an anticipated therapeutic effect, it is not a straightforward phenomenon. Nonetheless, controlling the drug release involves a number of factors including the materials' chemical interaction and physical properties such as dissolution, diffusion, erosion, and osmosis [70–72]. The initial burst release of the drug upon implantation leads to poor control over drug elution kinetics and also compromises the sustained release required to achieve the therapeutic effects for a longer time. Therefore, it is important to control the drug release rate; drug elution at a faster rate may have unwanted toxic effects, while a slower release rate compromises the therapeutic efficacy. Significant research including *in vitro* experiments, animal models, and clinical studies has been conducted with promising outcomes; yet, the aforementioned limitations are the main obstacles for translating various coated implants from the laboratory bench to the market. Currently, a number of researchers are focusing on addressing the limitations and improving the properties of implant coatings. As a result, more therapeutic coated dental implants are expected to be available for clinical applications in the near future.

9. Conclusions and Future Trends

The present article reviewed various aspects of therapeutic surface coatings on dental implants from the perspectives of materials, coatings, drug release, and related beneficial effects. Various types of eluting implant coatings targeted to improve the surface properties, implant–bone interface, and osseointegration were reviewed. Currently, scientists are actively exploring the preclinical characteristics of a variety of medicaments, and inorganics and organic biomolecules including peptides and growth. Available data have indicated that the therapeutic coatings on dental implants effectively improved the surface properties and implant–bone interface by delivering various drug molecules or bioactive components locally without exerting any systemic side effects. Furthermore, the bioactive implant coating strategies clearly suggested the improvement in the osseointegration by mimicking bone remodeling characteristics at the submicron/nanoscale level and enhancing osteoblasts differentiation and bone regeneration. In addition, bioactive materials, bisphosphonates, and antibacterial and antimicrobial implant coatings effectively achieved the respective therapeutic

actions. However, only a few of the coated implants are commercially available, while the majority of therapeutic coated dental implant research is at preclinical stage. Although plenty of in vitro and animal studies have been conducted to explore a variety of coating materials, drugs, and techniques, an inadequate number of clinical studies have investigated the long-term performance of coated implants under the complex dynamic conditions of the oral cavity. Future research should focus on bridging the gap between current evidence and clinical applications. To this end, additional clinical studies involving longer follow-up are essential. Additionally, extensive supplemental research is required to address the limitation of the coated implants, such as the poor coating–implant bonds; related mechanical properties need gross improvement to avoid chipping and biocompatibility issues; and biodegradation products should be focused on in the clinical settings. In terms of drug release kinetics, the controlled release of active biomolecules maintaining the required drug concentration for an optimal period of time at the target site is challenging and requires further investigations. Further developments and translating various coated dental implants to clinical applications have vital significance as the demand of dental implants is increasing sharply due to multiple factors such as population growth, increased life expectancy (aging population), and improved quality of life. In the coming decade, we hope that more therapeutic coated dental implants with improved physical/chemical/mechanical properties, biocompatibility, and controlled drug release will be available at a lower cost for clinical use and to benefit the enormous number of dental patients.

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