Chapter 3: Bioactive coatings

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3.1 Introduction

During the last decades numerous implant devices based on various classes of materials for a wide range of clinical applications have been developed to improve patients' life. In the past, the selection of a specific implant material was often made on the basis of its bulk properties, especially its mechanical parameters, and in terms of the biological behaviour. More or less inert materials have been preferred to prevent strong foreign body reactions and implant rejection. In fact, the proper integration of an artificial implant into the surrounding tissue is a key clinical outcome of a successful implantation procedure. As a consequence, all processes initiated by the implant insertion at the host tissue-material interface must occur without inducing adverse reactions like chronic inflammatory response, the formation of undesired fibrous tissue, or the occurrence of implant-related infections. In this view the concept of bioinert implant materials has been successful for many years and is valid for many implants still today. Nevertheless, along with our advanced knowledge of the complex biological reactions at the tissue-material interface and driven by increasing clinical demands and patient expectations, this concept began to shift in the middle of the 1990s toward the development of bioactive implant surfaces to elicit a specific biological response at the material interface. Following this new strategy, micro-structured implants and implants with porous surface structures have been developed, achieving a more stable interlocking between the implant and the surrounding tissue. Thus, the concept of bioactive implant fixation was established resulting in an improved primary fixation of many bone implants and often also in an increased implant lifetime. A key feature of this concept consists in the use of approved and mostly bioinert implant materials with suitable bulk properties for the chosen clinical application combined with a specific surface design and/or surface coating enabling the implant to actively interact in a desired way with the biological environment. This interaction can vary with the implant function and its location in the body. In the case of bone implants an increase in bioactivity is mainly directed to a rapid adhesion and anchorage of bone cells (osteoblasts) to the implant surface to promote mineralization and tight binding of newly formed bone tissue to the implant.

Several approaches have been considered to render originally inert implants bioactive. An already mentioned strategy represents the micro- or nano-structuring of implant surfaces which can be performed by common processes like ablation, etching or blasting. Another versatile approach which has gained growing importance during the last decades is the development of bioactive and optionally degradable coatings.

Bioactive coatings are coatings that have the capability of direct bonding to living tissues, such as soft tissue and bone, forming a strong chemical bond. Osteoconduction on biologically active ceramics is attributed to the formation of bioactive bone-like apatite. The apatite originates from the chemical interaction of the ceramics with the surrounding body fluids. Therefore, the design and development of advanced bioactive and/or biodegradable materials is highly dependent on the control of their chemical reactivity in and with body fluids. However, the current common bioactive coatings based on ceramics and bioglass have yet to show suitability for all required clinical applications. Therefore, the development of novel designs of bioactive materials is necessary. Emerging bioactive coatings, for example those based on bioactive composite coating, polymer-based bioactive and degradable coatings as well as antimicrobial coatings receiving increasing attentions and being exploited for biomedical applications. Novel biologically active materials designed based on chemical reactivity in body fluids are here reviewed.

Coatings offer unique possibilities to control the surface properties of an implant by a variety of features including surface structure, porosity and roughness, chemical composition, hydrophilicity-hydrophobicity balance, the presence of functional groups, the degradation behaviour and last but not least the incorporation of drugs or other bioactive molecules.

Among known bioactive materials, calcium phosphates and resorbable bioglasses have already found widespread applications as coatings for orthopaedic and dental implants. Whereas calcium phosphates closely resemble the composition of the mineral phase of bone displaying osteoconductive, and in some cases also osteoinductive properties, bioglasses are able to form silicate-rich layers promoting deposition of hydroxyapatite and thereby rapid osseointegration.

Bioactive coatings based on natural polymers like collagen or gelatine have also been used to improve cell acceptance of various implants for many years. An overview on common biopolymers and their chemically modified derivatives used as implant coatings and the obtained biological effects, especially in terms of improved implant integration by stimulating cell activity but also protection of implants against microbial infection, will be provided. Special attention will be paid to new advanced coating concepts like the incorporation of peptide

sequences derived from high molecular weight proteins to trigger cell adhesion on implant surfaces or the approach to generate macromolecular assemblies by combining different bio-macromolecule mimicking the natural extracellular matrix and its unique biological functions. Finally, new developments in the field of synthetic polymers designed to show specific biological effects like promotion of cell adhesion or antimicrobial activity are highlighted.

Bioactive coatings have been applied onto various substrates for biomedical applications. These include Ti-alloy, stainless steel, magnesium alloy, bioactive ceramics and polymer composites. Ti-alloy (e.g.Ti-6Al-4V) has been proven to be suitable for load bearing implants such as hip implants (Hench 1991; Geetha et al. 2009). However, it has poor biological activity and weak interface bonding between Ti implant and tissue because of “stress shielding” caused by the mismatch of Young's modulus (Liu et al. 2004).

Stainless steel substrates is an economical alternative for orthopaedic implants (Garcia et al. 2004) to reduce costs in public health services. On the other hand, phosphate coated magnesium alloy implants have shown excellent biological responses, together with outstanding mechanical properties and degradability in the physiological elements, and have been therefore, and have been extensively studied. (Song 2007; Hornberger et al. 2012). However, corrosion of magnesium alloys would occur in human body fluid or blood plasma even though with the presence of phosphate coating.

Bioactive ceramics and bioglass have been used in bone repairing (Liu and Miao 2004) and different applications (Galliano et al. 1998) as they could elicit a specific biological in vivo response at the interface and attach to the tissues.

However, the application of many materials for medical implants is often hindered due to their stiffness, which is generally to be higher than human cortical bone. Composite theory states that, when the stiffness of a ceramic or metallic implant is higher than the bone, there is, according to the load sharing principle (Hull and Clyne 1996), a possibility of bone resorbtion due to a reduced mechanical environment, (Park and Lakes 2007). This is following the ‘‘Wolff’s Law’’, i.e., with the imposed changing stress/strain, bone would remodel such that the stress or strain is retained within particular levels (Wolff 1892). For example in total hip replacement, bone resorption in the proximal femur has led to a common problem of aseptic loosening of the prosthesis attributed to stress and strain in the femoral cortex due to implantation of the metallic femoral hip replacement (Learmonth 2012). Elastic characteristics of the implant play an important role in allowing the femur to attain a physiologically acceptable stress state. In fact, human hard tissues serve as templates, since they are natural composites, for the development of replacement tissue. In order to address the problem of

modulus-mismatch between existing implant materials and bone, and promote good adhesion and bonding between the implant and host tissue, concept of analogue biomaterials has been introduced (Bonfield et al. 1981). Subsequently, a variety of bioactive composite materials has been investigated and developed (Bonfield et al. 1981; Boccaccini et al. 2010a). These composite materials consisting of more than one type of materials (e.g. metallic, ceramic, or polymeric) have been designed as either reinforcement or matrix for biomedical applications.

The non-metallic nature of polymer composite implants would avoid the generation of at least one source of particles or ions formed at metallic implant surfaces (Agins et al. 1988). These polymer composites implants could exhibit isoelastic properties (i.e. similar stiffness to their surrounding host tissues) because of their non-isotropic properties and versatility in design, such feature is increasingly believed to promote bone in-growth and reduce stress shielding (Huiskes et al. 1992; Williams 2000).

Min Wang (Wang 2003) has reviewed some promising composites for tissue replacement and regeneration, as well as the rationale and strategy of developing these composites and the factors influencing the production and performance of bioactive composites have been discussed to meet various clinical requirements.

3.2. Processing/characterisation/ biocompatibility and bioactivity properties of bioactive coatings

3.2.1: Hydroxyapatite coatings

Hydroxyapatite (HA) is a calcium phosphate-based apatite with the chemical formula [$Ca_{10}(PO_4)_6(OH)_2$], which has similar chemical composition and crystal structure as the apatite in the human teeth and bones, as first identified by DeJong in 1926 (De Jong 1926). Thus, HA is a biocompatible material with the desired bioactive and osteoconductive properties (Yamamuro et al. 1990; Corpe et al. 2000). However, synthetic HA was only accepted as a promising biomaterial for use in bone grafts, orthopaedics, and dentistry 40 years ago. The crystallinity between natural hydroxyapatite and synthetic HA coatings has been studied. The crystallinity of the synthetic HA coatings can be controlled to be similar to biological apatites with less crystallinity by controlling the heated treatment of apatitie coatings to a temperature between 400 and 600°C. At higher temperatures (>700°C), the apatite coatings appeared more crystalline, with a mixture of hydroxyapatite, octacalcium phosphate and magnesium phosphate (Assis et al. 2005).

However, HA is brittle with low fracture toughness and poor fatigue resistance and higher Young's modulus than human cortical bone. Therefore, the applications are limited to the use in low load or non weight bearing *in-service* conditions, such as bone fillers, ossicular bone replacement under low loads and materials for maxillofacial reconstruction (Yamamuro et al. 1990).

The combination of the high mechanical strength and load bearing of metals (e.g. Ti-6Al-4V and stainless steel 316L) with the osteoconductive properties of calcium phosphates has overcome the physical limitations of HA and enabled hydroxyapatite coatings on bioinert metal implants to be widely used in hard tissue replacement implants and orthopaedic applications such as femoral stem in a hip replacement device. HA coatings deposited onto metallic alloys have demonstrated the ability to simulate bone formation, to improve the implant to bone bonding and enable a more natural osseointegration of the metallic implants with surrounding tissues, as well as minimising the risk associated with the liberation of metallic wear particles or metallic ions from implants (Agins et al. 1988). Hence HA has been developed as biological fixation of load bearing biomedical implants as an alternative to cemented fixation.

Stoichiometrically, HA has a molar ratio of Ca:P of 1.67. According to the American Society for Testing and Materials (ASTM) F1609 (ASTM 2014) and International Organization of Standardization (ISO) 13779-2 (ISO 2000) the properties of HA coatings and their specifications for biomedical implants applications, crystalline HA content lower than 45% and the ratio of Ca:P should be within the range of 1.67-1.76, with the HA coating adhesion from pull out tests of implants greater than 15MPa. Dumbleton and Manley (Dumbleton and Manley 2004) have summarised a list of commercially available medical implants as shown in Table 1.

Table 1 – Properties of commercially available hydroxyapatite coatings (Dumbleton and Manley 2004).

Manufacturer	**Hydroxyapatite content (%)**	**Crystallinity (%)**	**Thickness (μ)**	**Porosity (%)**	**Location of coating**
Stryker Orthopaedics (Ostenoics)	>90	70	50	Dense	Proximal part of stem

Stryker Orthopaedics (Benoist Girard)	>90	>75	60	<10	Proximal part of stem
Joint Replacement Instrumentation (JRI)			200		Fully coated stem
DePuy, J & J (Landanger)		>50	155±50	<10	Fully coated stem
Biomet		62	55	5	Proximal part of stem
Smith and Nephew			200±50	20	Proximal part of stem
Corin	97	>75	80-120	3-10	Proximal part of stem
Centerpulse (Intermedics)	94	72	55±5	3	Proximal part of stem
Zimmer	70 (and 30% tri-calcium phosphate)		80-130		Proximal part of stem

(i) Coating manufacturing methods

The deposition methods would affect the coating microstructure and properties. Various coating methods have been explored to deposit HA coatings to increase bioactivity and to improve bonding. These include plasma spraying (De Groot et al. 1987; Berndt et al. 1990; Klein et al. 1991), electrophoretic deposition (Ducheyne et al. 1990), sputtering (Ong et al. 1992), sol-gel (Liu et al. 2002), pulsed laser deposition (Lo et al. 2000) and electron beam evaporation combined with ion beam mixing (Mohseni et al. 2014a). To date, only plasma spraying is being used commercially and approved by the US Food and Drug Administration (FDA). The advantages and limitations of these method have been reviewed and discussed (Zhang 2013; Mohseni et al. 2014a).

Thermal spraying such as plasma spraying is a major coating method used to manufacture HA coatings onto metal implants. It involves the melting of ceramic HA powders in a plasma and the molten powders are subsequently spray deposited onto the surface of medical implants. This is a relatively low cost process with a high deposition rate. The effect of process parameters (e.g. particle size and velocity, oxygen pressure, fuel gas type, and spraying power and distance) on the microstructure and properties of HA coatings has been reviewed (De Groot et al. 1987; Berndt et al. 1990; Klein et al. 1991). Earlier investigations have shown that these coatings can successfully enhance clinical success to as little as a 2% failure rate after 10 years. Pure crystalline HA (with Ca:P=1.65) has also been deposited with adequate mechanical adhesion (23MPa) onto non metallic polymer composites (e.g. carbon fiber/polyamide based composite) by plasma spraying that complies with ISO 13779 (Auclair-Daigle et al. 2005). The HA coating also exhibited bioactivity in simulated body fluid which is needed for orthopedic applications.

Despite the capability of plasma sprayed HA coatings to improve bone strength, provide initial osseointegration and their excellent clinical performances, the optimum coating properties required in order to achieve maximum bone response have yet to be realised. This is due to the intrinsic drawbacks of the plasma spraying process. These are attributed to the high temperature melting and/or thermal decomposition during the plasma spraying, which tends to cause variation, non-uniformity and uncontrollability in phases, crystallinity, density and microstructure of HA coatings which would lead to different mechanical properties and behaviours. Typically, partially dehydrated HA is the main constituent in plasma-sprayed HA coatings, together with amorphous CaP and other more soluble phases originating during deposition at high-temperatures, such as tri-calcium phosphate (TCP). The ratio of HA to TCP is crucial for bone regeneration. The crystallinity for plasma-sprayed HA coatings is approximately 65% (Ong et al. 2006). Such high processing temperature may also cause phase transformation, grain growth, and high residual stress in the HA coating and poor controlled stability and reproducibility (Hench 1991). Table 2 shows the thermal effects of HA.

Table 2 – Thermal effects of hydroxyapatite (Hench 1991).

Temperature (°C)	**Reaction (s)**
25-200	Evaporation of absorbed water
200-600	Evaporation of lattice water
600-800	Decarbonation

800-900	Dehydroxylation of HA forming partially or completely dehydroxylated oxyhydroxyapatite
1050-1400	HA decomposes to form β-TCP and tetracalcium phosphate (TTCP)
<1120	β-TCP is stable
1120-1470	β-TCP is converted to α-TCP
1550	Metling temperature of HA
1630	Lemting temperature of TTCP, leaving behind CaO
1730	Melting of TCP

Rapid cooling during plasma sprayed deposition tends to produce amorphous coatings, micro-crack and low porosity. This would lead to poor coating adhesion, limiting the optimum fixation with the implants, interface separation between the coating and the substrate, and the long term durability of the HA coatings. Furthermore, plasma spraying is a line-of-sight coating technique. Difficulties may exist in coating complex 3D implants uniformly and even coatings on porous metal surfaces. Furthermore, this is a relative high deposition process, thus it cannot incorporate growth factors and biologically active agents that stimulate bone healing.

Other deposition techniques have been explored to improve the quality of HA coatings, such as electrophoretic deposition (Ducheyne et al. 1990), pulsed laser deposition (Lo et al. 2000), sputter deposition (Yang et al. 2005), sol–gel (Chai and Ben-Nissan 1999), deposition of apatite coatings from simulated body fluids (Bigi et al. 2002) and Electrostatic Spray Assisted Vapour deposition (Choy 2003; Hou et al. 2007).

The ability of **electrophoretic deposition (EPD)** to form coatings onto complex shapes at low temperatures and at low cost has attracted increasing interests for biomedical applications (Ducheyne et al. 1990; Zhitomirsky and Gal-Or 1997; Wang et al. 2002). During the EPD process, HA powders are deposited from a stable colloidal suspension using a DC electric field (Wang et al. 2002). However, the HA coatings deposited by EPD tend to be porous, which may lead to corrosion and coating spallation due to the penetration of body fluids. The use of post annealing to reduce the coating porosity would lead to coating shrinkage and cracking (Soares et al. 2004). The micron sized grain structure has poor adhesion, fracture toughness and compressive strengths, therefore, this limits the use of EPD HA coatings on metal implants.

Sputtering is also a promising method to produce adherent HA coatings with good bioactivity that could address some of the brittleness of plasma spray deposited HA, that limits its usage in load bearing conditions, whilst exhibiting good bioactivity (Yang et al. 2005; Mohseni et al. 2014a). However, sputtering is also a line-of-sight process and has difficulty to coat the 3D

implants uniformly. Other drawbacks of this technique include the use of expensive and sophisticated reactor and vacuum systems and slow deposition rate. Moreover, the sputtering occurs at low deposition temperatures, hence the deposited HA coatings tend to be amorphous and require subsequent annealing to achieve the desired crystallinity. Otherwise, the low crystallinity would accelerate the dissolution of the film in the body.

Other vacuum deposition techniques such as ion beam assisted deposition (IBAD) have also been explored. This method combines ion beam bombardment and physical vapour deposition, which enable the deposition at low temperature and the close interaction between the coating materials and the substrate at the atomic scale, creating an intermixed zone at the interface of the substrate and the coating that results in adherence, high reproducibility and reliable HA coatings (Cui and Luo 1999; Hamdi and Ide-Ektessabi 2003). However, IBAD is also a direct-line-of-sight deposition process and has similar difficulties in coating the 3D implants uniformly. Furthermore, the HA coatings would tend to crack after heat treatment, likely due to the thermal expansion mismatch between the coating and the substrate which could reduce the coating adhesion (Choi et al. 1998).

Pulsed laser deposition (PLD) involves the use of high power laser energy to vaporize the bulk coating material from a target, which subsequently condense onto a substrate. The process would be repeated to achieve the required coating thickness. Although PLD allows the deposition of thin and adherent stoichiometric HA onto titanium substrate surface (Lo et al. 2000), this is a direct-line-of-sight deposition process and would have similar difficulties in uniformly coating 3D implants. Furthermore, it also has a limited deposition zone.

Sol–gel method tends to use alkoxide based precursors. This method involves the formulation of a homogeneous solution containing all of the component metals in the correct stoichiometry. Therefore, the control of chemical homogeneity and stoichiometry of the synthesised materials at molecular level is made possible. This method has been used to synthesise HA powder and coatings (e.g. via dipping or spin-coating). Nanocrystalline thin film hydroxyapatite coatings have been produced via the sol-gel route where the sol precursor can be applied to the substrate by dipping or spray coating. Coating thickness varied between 70 and 1000nm depending on the number of applied layers. However, the sol-gel produced HA coatings tend to require subsequent heat treatment at high temperatures (e.g. 1000°C) (Chai and Ben-Nissan 1999) and these processes would need to be repeated to achieve the desired thickness which is time consuming and laborious. Furthermore, the removal of solvent and organic residues of sol-gel coating during heat treatment tends to lead to a weak structural integrity.

Apatite coating from simulated body fluids. The bioactivity of hydroxyapatite-coating with the ductility of metallic implants have been used in load-bearing parts, however, they exhibit high elastic modulus and no biodegradability. Whereas, living bone is a composite consisting of 70 weight% inorganic component, hydroxyapatite, and 30 weight% organic component, collagen (Park and Lakes 2007). The organic component acts as a template for the structure of inorganic component and control its deposition to form finely constructed organic–inorganic hybrids of life via biomineralization (Mann 2001). The unique composition and structure of natural bone not only would give high strength and fracture toughness, but also deformability and low elastic modulus.

However, the hydroxyapatite fabricated by plasma-spray technique (as described in earlier section) is different from bone apatite in the point of composition and structure, where bone apatite exhibited a broad X-ray diffraction pattern due to its low crystallinity and small crystallite size (20-40nm) (Kamitakahara et al. 2007).

Kamitakahara (Kamitakahara et al. 2007) reviewed the development of bone-like apatite coating on substrates for bone reconstruction using solutions mimicking body fluid which shows high affinity against bone tissue. The **biomimetic approach** consists of soaking metal implants in simulated body fluids at a physiologic temperature and pH. Apatite coatings have successfully been formed by the immersion of chemically pre-treated substrates such as glasses, metals, and polymers in metastable simulated body fluids (SBF) (Kim et al. 2011, Rezwan et al. 2006). The advantages of such approach include: (a) a low-temperature process, therefore, applicable to any heat-sensitive substrate including polymers; (b) ability to form bone-like apatite crystals having high bioactivity and good resorption characteristics; (c) uniformly deposited onto complex and/or implant geometries; and (d) capable of incorporating stimulating factors for bone-growth. This low temperature process allows bone-like apatite coating to be applied on the surfaces of biodegradable polymers which can be used as scaffolds for bone reconstruction (Chau et al. 2004) or as an adsorbent of organic substances (Kawai et al. 2006) during the biomineralization process.

Although SBF mimics the inorganic composition, pH and temperature of human blood plasma, it is unknown whether these conditions are optimal for a coating process. Other drawbacks include processing times from 7 to14 days requiring daily resupply of SBFs and the need to maintain supersaturation for crystal growth, which requires constant pH. Moreover, local precipitation or formation of heterogeneous coatings due to the low solubility of HA and limited operational range of concentrations for the metastable phase could result from the low solubility of HA and the limited concentration range for the metastable phase. This operation

is extremely difficult and might lead to local precipitation or uneven coatings. Such an intricate and long process can hardly be applicable in the coated prostheses industry (Habibovic et al. 2002).

New and promising coating methods are continuously being developed in order to deposit HA with optimal coating properties. One of these methods is **Electrostatic spray assisted vapor deposition (ESAVD)** (Choy 2003), which is a novel and cost-effective technique that has been used to deposit adherent HA coatings in a single step onto Ti-alloy substrates. Pure and well-crystallized HA coatings with well controlled structure and stoichiometry at molecular level have been successfully deposited at 500°C using the single-step ESAVD method from a sol solution consisting of phosphorus hydroxyl-alkoxide, alkoxy-nitrate, and some remaining calcium nitrate (see Fig. 1). A detailed overview of this deposition technique for the synthesis and deposition of nanostructured oxide materials has been reported by (Hou et al. 2007). The *in vitro* study indicated that the deposited HA coatings were sufficiently stable to maintain their structural integrity in SBF. After 14-day immersion in SBF, the surface of the coating was completely covered by a biomineral particulate layer (particle size less than 100nm) consisting of biologically active bone-like carbonate-containing apatite. The layer resulted from the chemical reaction of the ceramic surface with surrounding body fluid leading to the precipitation of the ions from SBF solution as shown in Figure 2. Thus, the HA coatings deposited by ESAVD method showed osteoconduction.

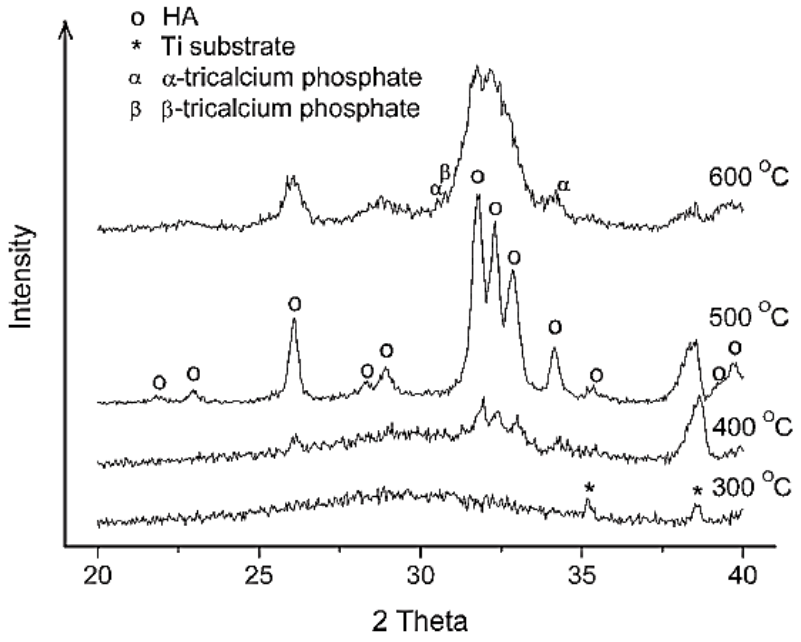


Figure 1 - XRD of HA coatings deposited at different deposition temperatures (Hou et al. 2007).

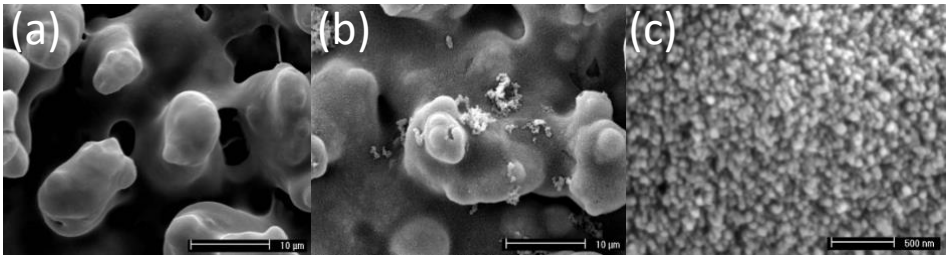


Figure 2 - Surface morphology of the as-deposited and soaked HA coatings. (a) As-deposited HA coating; (b) after 14-day immersion in SBF; (c) a higher magnification of (b) (Hou et al. 2007).

(ii) Coating adhesion

The adhesion and bond strength of HA coating to the metal implant, as well as the similarity of the HA coating composition and biocompatibility with the bone, is crucial in order to make use of the load-bearing ability of the metal alloy implant. Any detachment or coating spalling from the implant in the human body would have adverse effects due to the detached particles (Wang et al. 1996). Fig. 3 shows the comparison of adhesion strength values of HA coatings on Ti-6Al-4V deposited using various techniques.

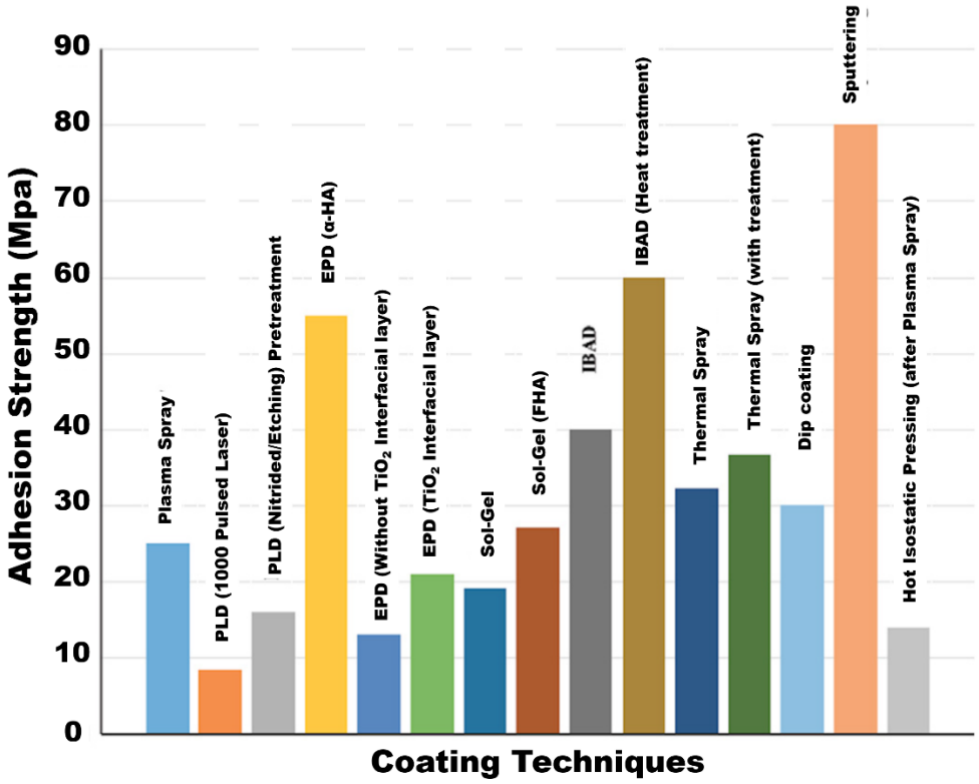


Figure 3 - Quantitative comparison of different coating techniques (Mohseni et al. 2014b).

From Fig. 3, HA coating produced by sputtering has the best adhesion to Ti-6Al-4V substrate. However, due to the drawbacks of HA coatings as described earlier, sputtering is yet to be used widely at a commercial scale for the manufacturing of HA onto medical implants. In general the adhesion of HA onto substrates is rather weak susceptible to fatigue failure. Hence the adhesion of HA coatings needs to be improved for load bearing implants.

(iii) Improvement of coating adhesion

The low coating adhesion has hindered the wide use of HA coated implants. The improvement of the bonding between the ceramic HA coating and the metallic implant is important irrespective of the coating manufacturing methods. In fact, there is an increasing demand for durable and reliable load bearing medical implants, such as hip and knee replacement, going as far as to exceed the lifetime of the patient. HA coated implants experience loss of the biomaterial fixation after the implants have been in the human body for a long time. The failure noted by orthopaedists and dentists tend to occur at the HAP-titanium interface and through dissolution of the coating itself (Geesink et al. 1987). Revision surgeries are needed to re-secure or insert new coated implant. Thus, the interfacial control and improvement βetween

the implant and natural tissue is crucial. Hence surface modification and texturing have been explored to enhance osseointegration as summarised below.

(a) Pretreatment and post treatment

The work by Riedel, for example, has indicated the importance of surface topography on the effect of mesenchymal stem cell and osteoblast response to titanium surface. Polished pre-treated Ti surface outperformed those prepared from the as-received condition. Similarly argon etching, especially with the optimal etching energy of 700eV, also demonstrated positive impact on the cellular interaction of the as-received substrates. Such improvement may be due to the hierarchical texturization of the etching imparted on the surface of the substrates (Riedel 2010). Furthermore, post-anneal etched surface outperformed the annealed hydroxyapatite (deposited by sputtering) surface.

Other surface treatment such as laser surface nitriding and subsequent etching of the substrate has also shown to be an effective pre-treatment method for improving the adhesion strength of HA coated onto Ti-6Al-4V (Man et al. 2009).

In addition, the substrate cleaning method also influences the HA coating adhesion. HA coatings adhered better to ultrasonically cleaned substrates than to high pressure air cleaned substrates tested according to ASTM C-633 (Hsiung et al. 2012). Furthermore, the same authors also found that a combination of ultrasonic cleaning and cryogenic treatments can effectively improve the HA adhesion and coating properties.

(b) Interfacial layer

The deposition of interfacial layer such as TiO_2 (Blind et al. 2005) and TiN (Kummer and Jaffe 1992; Blind et al. 2005) prior to the deposition of HA have been developed to improve the bonding and adhesion of HA to Ti-alloy substrates. Compositionally graded coating has also been explored to improve the adhesion of HA to Ti-alloy substrates (Park and Condrate 1999).

(c) Double-layered porous structures:

Bioactive coatings with double porous structure in micro and macro scales as reported in the literature (Raines et al. 2010; Gittens et al. 2011), for example, could be adapted here as one of the combined approaches to improve the coating adhesion of HA to metal implants. Such structures exploit the benefits of micropores (0.05-10μm in size) in promoting osteoblast attachment and proliferation on Ti implant. Whilst, the macropores (50-400μm in size) on

implant surface could provide mechanical locking to improve the fixation strength between implant and tissue after implantation (Bobyn et al. 1980; Zhou et al. 2014).

(d) Functionalisation of HA

Bosco et al. (Bosco et al. 2015) reported the functionalization of hydroxyapatite nanocrystals with anti-osteoporotic drug (e.g. alendronate) as bioactive components for bone implant coatings to decrease osteoclastic activity to address the unbalance between osteoclasts and osteoblasts in patients, especially with bone metabolic disease. The functionalization assists the coated implants to regain load-bearing functions (i.e. mastication or gait cycle) owing to a locally improved bone quality and help towards a more successful bone implant

(e) Other surface modification

Current medical implants have no signalling interaction at the tissue-implant interface, thus reducing the ultimate efficacy of these devices by forcing biology to treat it as a foreign entity. This limitation needs to be addressed in order to realise the full potential and extend the lifetime of the next generation of devices. Meyers et al. (Meyers and Grinstaff 2012) have reviewed the used of biomimetic approach to modify the device surface, and explored its effectiveness in communicating with the surrounding cells and proteins. Both the covalent and adsorptive strategies for device modification and their advantages and disadvantages have been reviewed. A biomimetic approach that combines non-fouling and bioactive surfaces seems to be promising in this field. Results suggested that natural ECM components might replace other strategies to afford non-fouling enzymatically degradable surfaces, or loosely bound through non covalent methodologies which might allow the cells to remodel up and integration with device surface, and synthetic coatings. However, several questions remain, including the appropriate ratios of “non-fouling” and “signalling” components and the performance of the bioactive coatings in *in vivo* and *in vitro* studies.

Although stringent antiseptic operative procedures, infection rates (0.5-3.0%) of total joint hip arthroplasties still occur during in primary total hip arthroplasty (Antti-Poika et al. 1990; Nasser 1992; Hendriks et al. 2004). This could lead to significant medical costs, increase in morbidity and decrease in patient satisfaction (Nasser 1992). Various surface modification methods have been explored to incorporate antibacterial property to biomaterials in order to minimise infections in implants. These include incorporating chitosan nanoparticles with antimicrobial agents (Schmidmaier et al. 2006), surface functionalization via attaching polycationic group (Cen et al. 2004), coating of silver ions (Ewald et al. 2006) and antibiotic (e.g. minocycline/rifampin) (Bosetti et al. 2002). The increase in antibiotic resistance has becoming

a major medical concern, whereas silver is a promising antibacterial material. A recent approach includes the creation of a multifunctional surface by co-depositing the osteoconductive HA with antibacterial Ag (Bosetti et al. 2002). In this case, the *in vitro* cytotoxicity was observed between HA and Ag-HA surfaces, and anti-bacteria properties of Ag-HA increased.

(iv) Other bioactive ceramic coatings

HA coated implants experience loss of the biomaterial fixation after long-term insertion in the human body. This failure tends to occur at the HAP-titanium interface, with dissolution of the coating itself as described by orthopaedists and dentists (Geesink et al. 1987). Alternative bioactive coating based on calcium titanate (CT) coating has been explored as this is chemically stable and the dissolution of the coating layer in a living body can be prevented (Ohtsu et al. 2004). It has been demonstrated by (Ohtsu et al. 2007) that a crystallized CT coating (ca. 50nm thick) on titanium can activate osteogenesis in hard tissues in rat. Moreover, CT reacts actively with titanium, therefore, it is expected the bonding strength at the coating-substrate interface could be improved.

3.2.2 Bioglass coatings

Bioglass formulations are glasses to which living bone tissue can be bonded. Conventional glass contains at least 65% silicon oxide which is useful to provide resistance to humidity, however, silicon oxide is biologically inactive. The work on bioglass was initiated by Hench et al in the late 1960s (Hench et al. 1971). Hench el al. developed the first bioactive glass based on Na_2O-CaO-SiO_2-P_2O_5 system, demonstrating that glasses consisting of 40-45% of silicon oxide, 20-25% of sodium oxide, and 20-25% of calcium oxide are bioactive (Hench et al. 1971).

Hench et al have investigated the role of glass and the physical, chemical, and biological aspects of the bone-bond formation with the surrounding tissue (Hench and Clark 1982). Dycheyne (Ducheyne 1985) has reviewed structural, mechanical and biological properties of bioreactive glasses, covering: (a) the relationship between the composition and bonding and its influence on the bone bonding mechanism and the rate of bond formation; (b) mechanical properties of these bioglasses, where various degrees of success could be achieved for the use of bioglass in highly stressed applications; and (c) the effect of loading on the glass properties and their bonding characteristics. The author has also established the influence of a critical set of parameters based on the failure analysis of bioactive glasses. Interface of

various glasses and glass ceramics in a bony implantation bed has been reviewed by Gross et al. (Gross and Strunz 1985).

Most of the bioactive glasses contain a relatively large amount of SiO_2. Calcium phosphate glass-ceramics without silica, $(x)CaO\text{-}(90\text{-}x)P_2O_5\text{-}(y)Na_2O\text{-}(10\text{-}y)TiO_2$ (x=45-60, y=0-10) have been reported by Kasuga et al., and the glass composition of (x=60 and y=7) has been explored as a coating on Ti-29Nb-13Ta-4.6Zr alloy by glazing method, i.e. placing the glass powder on the β-Ti alloy substrate and heating at 800°C in air. The glass layer reacted with the oxide layer formed on the alloy to form strongly bonded phosphate reaction layer with tensile bond strength 20-25MPa and *in vitro* bioactivity tests showed that the glass-ceramic coating is bioactive (Kasuga et al. 2003). Like bioceramic HA, bioactive glass has high chemical stability, ability to form strong bonds with metallic substrates, can help to increase the corrosion resistance of the substrate and it is also a biocompatible material. Furthermore, bioactive glass has a higher dissolution rate and higher bioactivity than hydroxyapatite (Xiao and Liu 2006). Moreover the composition of the bioactive glass coating can be tailored to have close thermal expansion coefficient match between the coating and the substrate (Peddi et al. 2008). Additionally, bioactive glass coatings can induce the formation of a thin layer of inorganic component of human bone of hydroxycarbonate apatite (HCA) when placed in biological environment of the body (Hench 1998). Bioactive glasses have been explored for biomedical applications (Vallet-Regí et al. 2003; Balamurugan et al. 2006).

$CaO\text{-}SiO_2\text{-}P_2O_5$ containing bioactive glasses tend to bond directly to soft and hard tissues, for a range of different compositions. These compositions have also been shown, through *in-vivo* tests, to not produce a toxic response, neither local nor global, nor inflammation and foreign-body immune system responses (Sepulveda et al. 2002). It has recently been shown that the cellular response of osteoblasts to bioactive glass is genetically controlled (Hench and Polak 2002).

The key difference between HAP and bioglass is that the bioactivity of glass can be tailored and controlled by varying its chemical composition to be close to the bone. It has been shown (Lopez-Sastre et al. 1998a) that bioglass has better physical and chemical characteristics for spraying at high temperature and would produce bioglass coatings with larger pore size, higher porosity and larger contact area with bones than HA coatings. However, the comparative study performed by Lopez-Sastre et al (Lopez-Sastre et al. 1998a) showed that HAP coating gave a stronger and earlier fixation to the bone than bioglass. The failure of the bioglass coating tends to occur at the interface between bone and coating. The mechanical tests of bioglass indicated that the shearing force was between four and ten times greater for

HAP. With bioglass there was retarded maturation and newly-formed coatings were poorly mineralised. HA coated implants have better integration than those coated with bioglass (GSB formula) which could be due to the presence of an excessive amount of aluminium oxide in bioglass. In addition, HA also demonstrated intense new bone formation with highly mineralised osseous trabeculae near the interface, whereas bioactive glass coatings a showed macrophage reaction with small amounts of new bone. Moreover, bioactive glass coatings were observed to be brittle, which would eventually lead to fractures on the interface that would cause the failure of the implants (Takeshita et al. 1996; Zhang et al. 2001).

In addition, like HA, the drawbacks of bioactive glass include poor mechanical properties, such as low tensile strength, fracture toughness, fatigue resistance and elastic modulus (Rawlings 1993). Therefore, bioactive glasses are mainly used in low or non-load bearing situations or compressive load situations in solid or powder form to make use of their bioactivity, for examples, bone restoration and augmentation, middle ear repair, vertebral and iliac crest replacements (Cao and Hench 1996). In addition, bioactive glass is being investigated as promising coating for prosthetic metallic implants in order to improve the osseointegration of the medical implants, and protect the metallic implants against corrosion from the body fluids and the tissue (Jones 1996).

Sol-gel is the common method used for the synthesis of bioactive glass. It not only has a lower synthesis temperature as compared to traditional melt processed bioactive glass but also achieves higher bioactivity and biodegradability (Fathi and Doostmohammadi 2009b). The bioactive range of bioactivity in the system CaO-SiO_2-P_2O_5 is larger for sol-gel bulk materials than for correspondent glasses obtained by melting (Gallardo et al. 2001). The high surface area of the sol–gel derived nanoporous structure helps to improve the rate of HCA layer formation and the bonding with host tissue (Chen et al. 2010).

Bioactive glass coatings can be deposited using the coating techniques describe in section 3.2.1(i). Garcia et al. have shown that coating of bioactive glass on biomedical grade stainless steel exhibited better corrosion resistance and bioactivity as compared to the uncoated substrates (Garcia et al. 2004). Different techniques have been used to deposit bioactive glasses onto implants. These include plasma spraying (Lopez-Sastre et al. 1998b; Arifin et al. 2014), sol-gel (Kokubo et al. 2003; Liu and Miao 2004; Fathi and Doostmohammadi 2009a), electrophoretic deposition (EPD) (Boccaccini et al. 2007; Moskalewicz et al. 2013; Pishbin et al. 2014), and sputtering techniques (Saino et al. 2009; Stan et al. 2009). The strengths and limitation of each of these processing techniques have been reviewed and presented earlier under section 3.2.1(i).

Bioglass coatings deposited by plasma spray tend to have a weak glass/metal interface which together with rapid dissolution in body fluids when implanted would cause coating failure (Hench and Wilson 1993). Other techniques, such as enamelling, have also failed because the glass crystallized significantly, resulting in lack of adhesion to the substrate (Pazo et al. 1998).

New generation of bioactive glasses with various compositions are being developed and may hold promise as reviewed by Jones (Jones 2013). Solgi et al (Solgi et al. 2015) have developed bioactive SiO_2-CaO-P_2O_5-SrO quaternary glass by incorporating a small amount of strontium (5 mol%). This bioactive glass can stimulate bone cell production of alkaline phosphatase bioactivity and it is a biocompatible material. Strontium is a bone-seeking agent, and could benefit patients suffering from osteoporosis as it can suppress osteoclast activity (Hoppe et al. 2014). Such strontium containing bioactive glass could also be produced in the form of coatings (Gorustovich et al. 2009).

Functionalisation In general, the body tends to respond to a foreign object (e.g. medical implant) by coating readily with plasma proteins (Latour 2005). Living cells, when in contact with the material surface, interact with the molecular structure of the adsorbed protein layer which could lead to conformational changes that influence the protein stability and protein–surface interaction (Roach et al. 2005). It is essential to minimise structural changes in proteins and to increase implant efficacy through surface modifications. Grafting of the surface by appropriate chemical bonding is one of the approaches to minimize structural changes in proteins, without weakening their effectiveness (Verné et al. 2009). Magyari et al. (Magyari et al. 2015) investigated the *in-vitro* bioactivity of the surface modified bioactive glasses of SiO_2-CaO-P_2O_5 by functionalization with aminopropyl-triethoxysilane and/or by fibrinogen in order to understand the influence of the proteins on the apatite-like layer growth and the blood compatibility of these materials. They have found that the fibrinogen adsorbed on the glass surfaces induces a growing of the apatite-like layer and good blood compatibility of the materials after fibrinogen and bovine serum albumin adsorption.

Bioactive glass ceramic coatings based on (Bioverit®I) have been applied on Al_2O_3 in order to improve the osseointegration of Al_2O_3 ceramics for total hip and knee arthroplasty. The 35 µm thick coating consisted of 30.5% SiO_2, 11.4% P_2O_5, 15.9% Al_2O_3, 14% CaO, 14.8% MgO, 5.8% K_2O, 2.3% Na_2O and 4.9% F^- (weight %) and was fabricated by a sintering process at 1000-1300 °C. The coating exhibited advantage under load-bearing conditions with higher interfacial shear strength and formation of mineralized bone directly in contact with the implant. On the other hand, the uncoated Al_2O_3 was found to bind to the bone through a thick

connective tissue layer, which results in low interfacial shear strength (Ignatius et al. 2005). Despite this promising result, further investigations still need to be conducted on the stability of the coating after longer implantation periods and under more critical loading conditions

3.2.2 Polymer-based bioactive and degradable coatings

3.2.2.1 Natural polymer derived coatings

Numerous natural and synthetic polymers have been explored as coatings for surface modification of different biomaterials. Among the natural polymers especially peptides and proteins, but also various polysaccharides and glycosaminoglycans, have been widely used to improve the cell acceptance of a selected implant material.

Immediately after incorporation of a foreign material into the body, extracellular matrix (ECM) proteins like fibronectin and vitronectin are non-specifically adsorbed on the material surface. Cells indirectly interact with the material surface via the adsorbed proteins controlled by cell membrane receptors, so called integrins. Integrins bind to specific domains of adsorbed proteins of which the arginine-glycine-aspartic acid (RGD) tripeptide is the most prominent. Because the availability and accessibility of these specific domains of adsorbed proteins are influenced by the material surface properties, the latter ones also strongly influence the adhesion and further behaviour of cells (Vasitaa et al. 2008).

Several approaches have been explored for the immobilization of proteins like collagen (Geissler et al. 2000, Morra et al. 2009) gelatine (Marois et al. 1995, Liu et al. 2008, Vanderleyden et al. 2014), fibronectin (Cornelissen et al. 2013) and laminin (Oyane et al. 2005, Bougas et al. 2012) onto implant surfaces. Most of these studies report an accelerated tissue healing and an increase in new tissue formation. For bone implants it was stated that the adhesion of mesenchymal stem cells on selected extracellular matrix proteins promotes their differentiation along the osteogenic pathway (Salasznyk et al. 2004). In addition, in many studies, an enhanced osteointegration of implants was observed in different animal models (Morra et al. 2003, Schliephake et al. 2005). Although an extensive literature has been published, especially on collagen coating there are still some mechanistic aspects on the biological activity not yet fully understood. Among these open points (Morra et al. 2009) are:

(i) the role of supramolecular arrangement of collagen (“monomeric” versus “fibrillar”);
(ii) collagen surface chemistry (specifically the role of chemical crosslinking and of covalent attachment to the surface versus simple adsorption);
(iii) optimal collagen surface density; and

(iv) characterization of the collagen coated surfaces.

Covering of biomaterial surfaces with high-molecular weight proteins is often connected with specific problems including immune reactions, denaturation processes caused by substrate surfaces or the procedures of surface immobilization, or also loss of bioactivity during sterilization. A promising approach to engineer the material-tissue biointerface consists in the attachment of short bioadhesive ligands specifically binding to cellular receptors. Currently, the most prominent ligand for integrins, major extracellular matrix receptors, is the already mentioned RGD motif (Ruoslahti and Engvall 1980). The process of integrin-mediated cell adhesion comprises a complex cascade of various overlapping events including cell attachment, cell spreading, organisation of actin cycloskeleton, and formation of focal adhesions (Lebaron and Athanasiou 2000, Hersel et al. 2003).

Normally, stable linkage of adhesion peptides is necessary because the ligands have to withstand both contractile forces of the cells during formation of focal adhesion (Katz et al. 2000) and manual forces resulting from the incorporation of the ligand-containing implants during surgery. In the last years various strategies have been reported to attach RGD or similar peptides either directly to the biomaterial surface by covalent linking via a spacer or via incorporation into a polymeric coating. A variety of functional groups including hydroxyl, carboxyl, amino or thiol functions are principally suitable for the covalent RGD peptide attachment to the spacer or the substrate coating. Special efforts have been undertaken to stimulate cell adhesion on metallic bone and dental implants to achieve rapid ingrowth of those implants into the surrounding tissue. Conventional techniques like plasma or chemical vapour deposition have been used to pre-activate the metallic surfaces for the subsequent coating process.

A family of different RGD motifs (e. g. RGD, RGDS, GRGD, YRGDS, YRGDG, YGRGD, GRGDSP, GRGDSG, GRGDSY, GRGDSPK, CGRGDSY, GCGYGRGDSPG, RGDSPASSKP G_4RGDASSK, CGGNGEPRGDTYRAY) containing further amino acids in the sequence functioning as spacers, binding units for selective coupling and marker groups simplifying the detection of the peptide on the surface have been developed. Cyclic RGD-derived peptide structures with a high integrin affinity have been introduced by Kessler (Aumailley et al. 1991) (Fig. 4).

Besides the RGD sequence, other cell adhesion motifs have been identified which can address other integrins, secondary binding sites of integrins or other cell receptors, mainly the proteoglycans receptor or the 67-kDa laminin receptor (for an overview see Hersel et al. 2003).

A triple-helical, collagen-mimetic GFOGER peptide, selectively promoting β2β1 integrin binding was recently used as bioadhesive coating (Reyes et al. 2007)

Direct immobilization of the RGD motif on titanium, hydroxyapatite or glass surfaces can be performed using conventional silane chemistry as exemplarily shown in Fig. 5 (Olbrich et al. 1996, Porte-Durrieu et al. 2004).

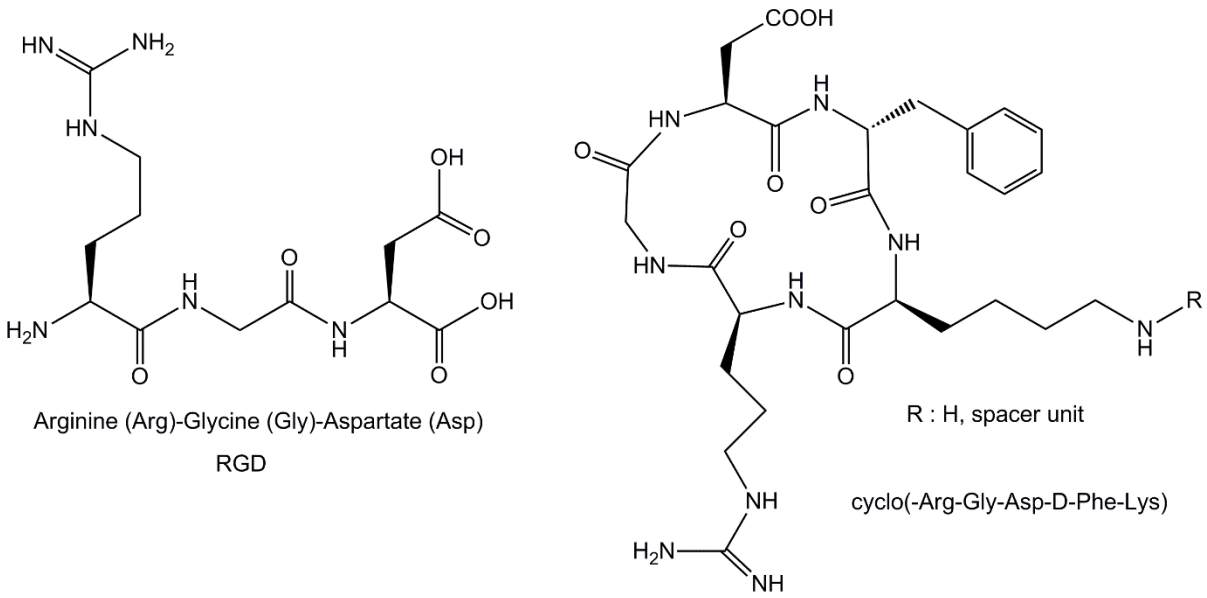


Figure 4 - Linear (left) und cyclic RGD (right) sequence containing cell adhesion motif.

Alternative synthetic routes to attach the RGD peptide to titanium surfaces represent the use of 11-carboxyundecylphosphonic acid (Gawalt et al. 2003) or carboxy-terminated oligo(ethylene glycol)-alkane phosphate as adhesion promoters (Gnauck et al. 2007). In analogy to the silane chemistry also amino-functionalized titanate linkers have been used to link RGD via a dextran layer onto titanium (Dubs et al. 2009).

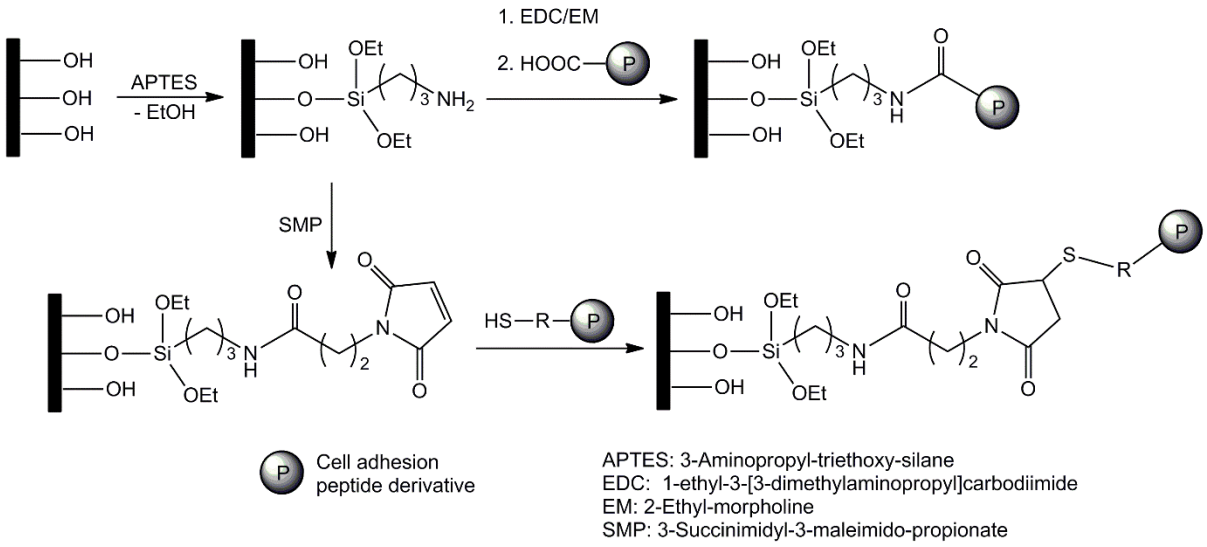


Figure 5 - Direct binding of cell adhesion peptides onto titanium surfaces via different silanization routes.

Cyclic RDG peptides have been bound to titanium surface via specific anchor groups, e. g. phosphonate (Auernheimer et al. 2005) or thiol groups (Elmengaard et al. 2005) introduced into the peptide molecules directly during peptide synthesis.

A variety of natural and synthetic polymers were equipped with RGD-derived peptides using mainly covalent linkages via amide bond formation. For this purpose an activated polymeric carboxyl group was reacted with the nucleophilic N-terminus of the peptide. Common peptide coupling reagent like 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDC) can be used to activate the carboxylic group. Preparing the N-hydroxysuccinimide active ester of the polymer in the first step, the peptide coupling can also be performed in water. Amino groups of polymers can be transformed into carboxyl groups (e. g. by succinic anhydride) prior to attaching the RGD peptide as described above. Similarly, polymeric hydroxyl groups can be pre-activated (e. g. with N,N'-disuccinimidyl carbonate or p-nitrophenyl chlorocarbonate) prior to peptide coupling or the peptide can be coupled to the polymer hydroxyl function using a diisocyanate. Polymers with introduced thiol groups can be linked to cysteine-containing RGD sequences by formation of a disulfide bonding. More recent approaches also use chemoselective ligation to form stable bonds without the need of activating agent and without interfering with other functional groups. A more detailed overview of those reactions is given by Hersel et al. (2003).

It seems to be obvious that the RGD peptide has to stand out from the artificial surface to reach the binding site of the integrin. It is assumed that peptides that extend out 11-46 Å from the surface can reach the majority of receptors (Hersel et al. 2003).

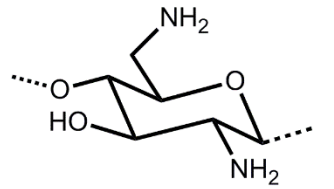
The many years of encouraging results of *in vitro* cell adhesion and proliferation on RGD functionalized biomaterials have led to numerous *in vivo* studies. In these studies to confirm the biological activity and evaluate the clinical applicability more variable results have been obtained. It has been seen that in many cases the effectiveness of RGD-based coatings was not as high as promised by the *in vitro* results. Nevertheless, positive results were achieved for example in bone regeneration. *In vivo* studies with RGD coated titanium bone implants using different animal models have shown a better bone on-growth combined with a reduction in fibrous tissue anchorage, and an improved mechanical fixation of the implant within the surrounding tissue as compared to the uncoated implant samples (Elmengaard et al. 2005, Schliephake et al. 2005, Shannon et al., 2008).

Polysaccharides are polyfunctional biomacromolecules of innate biocompatibility. Whereas some members of this class like cellulose or chitin are more or less stable in the human body others, including dextran or chitosan, PDLA are degraded over time. Polysaccharides offer a diverse set of physicochemical properties based on their sources, monosaccharides, composition and molecular weight. Due to their polyfunctional character there exists a wide range of physical and chemical modifications of native polysaccharides able to meet technological needs (Shelke et al. 2014). Among commercially available polysaccharides chitosan has found considerable interest to develop bioactive coatings for biomaterials.

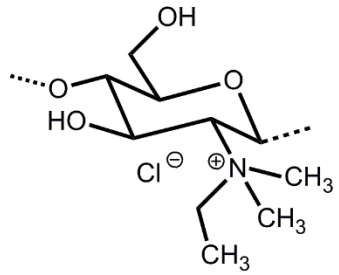
Chitosan obtained by deacetylation of the parent polysaccharide chitin is a linear copolymer of β-(1–4) linked 2-acetamido-2-deoxy-β-d-glucopyranose and 2-amino-2-deoxy-β-d-glycopyranose. The molecular weight is in the range between 50 and 100kDa and common products contain 10-30% of remaining N-acetyl residues. Chitosan is normally insoluble in aqueous solutions at a pH above 7, but is readily soluble in dilute acids at pH<5. As a cationic polymer chitosan is able to interact with negatively charged molecules rendering it a promising candidate in drug delivery systems and gene therapy (Dash et al. 2011, Anitha et al. 2014). Apart from that, chitosan exhibits enhanced wound healing, osteoconductive, and antimicrobial properties (Bumgardner et al. 2003). It was recently shown that the physical adsorption of chitosan on titanium implant surfaces of different roughness improve the surface wettability without modifying the surface roughness. These results suggest that polyelectrolyte surface modification on Ti surfaces could enhance bone formation and increase osseointegration in dental and orthopedic implants (Park et al. 2011). In an *in vivo* study

chitosan-coated pins were implanted in the tibia of adult male New Zealand white rabbits and histologically evaluated for healing and bone formation. After 12 weeks minimal inflammatory response and a typical healing sequence of fibrous, woven bone formation, followed by development of lamellar bone, were observed for the chitosan-coated pins (Bumgardner et al. 2007). Polyelectrolyte multilayer structures containing chitosan have been developed as functional coatings and intensively tested *in vitro*. The formation of multilayers on titanium film surfaces was performed using a layer-by-layer (LBL) self-assembly technique, based on the polyelectrolyte-mediated electrostatic adsorption of chitosan and gelatine. Cell proliferation and cell viability of osteoblasts on those films as well as on control samples exhibited higher values for multilayer-modified titanium films *in vitro* (Cai et al. 2007). A rat tibia model with bilateral placement of titanium alloy implants was employed to analyse the bone response to those polyelectrolyte multilayer chitosan/gelatine and chitosan/hyaluronan surfaces *in vivo*. The results showed that the chitosan/gelatine and chitosan/hyaluronan coatings have a positive effect on mechanical implant anchorage in normal bone (Zankovych et al. 2013).

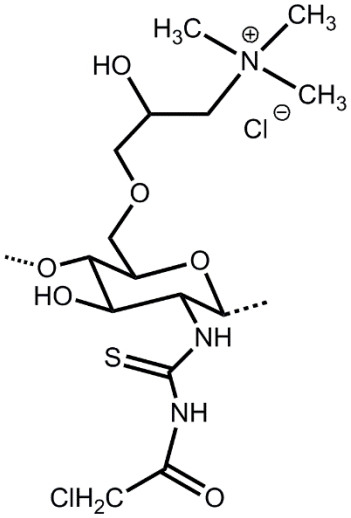
Since the antimicrobial activity of chitosan is rather low, considerable efforts have been undertaken to synthesize more potent antimicrobially active chitosans usable as coatings for biomaterial surfaces. A common approach to increase the antimicrobial activity of chitosan is the improvement of the water solubility and the positive charge density within the molecule. This results in the synthesis of numerous derivatives (Fig 6) like N-1-carboxymethyl-2-(4-methylpiperazinyl)-substituted chitosan (Masson et al. 2008), 6-Amino-6-deoxychitosan (Yang et al. 2012) or O-quaternary ammonium N-acyl thiourea chitosan (Li et al. 2015).



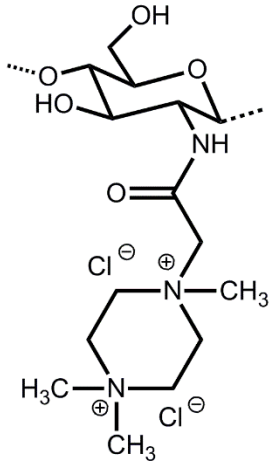
6-amino-6-deoxy chitosan



N-ethyl-N,N-dimethyl chitosan



O-quaternary ammonium
N-acyl thiourea chitosan



di-quaternary N,N,N-trimethyl
piperazine chitosan

Figure 6 - Selected antimicrobially active chitosan derivatives with a higher antimicrobial activity compared to unmodified chitosan

In a recent study structure−activity relationships in terms of the antimicrobial activity and human cell toxicity of different N-alkyl quaternary chitosan derivatives were systematically investigated (Sahariah et al 2015). N-alkyl and N,N-dialkyl chitosan derivatives with ethyl, butyl, and hexyl chains were synthesized and subsequently quaternized to provide the corresponding N,N,N-methy-dialkyl as well as N,N,N-dimethy-alkyl chitosan derivatives. The well-defined derivatives were tested for antibacterial activity against Gram positive (*S. aureus, E. faecalis*) and Gram negative (*E. coli, P. aeruginosa*) bacteria. A correlation with the length of the alkyl chain was found, but the order was dependent on the bacterial strain. With a few exceptions a descending order in antimicrobial activity with increasing hydrophobicity was detected. The most active compound was N,N-dimethyl-N-ethyl chitosan. Toxicity against human red blood cells and human epithelial Caco-2 cells was found to be proportional to the length of the alkyl chain. Shortening the alkyl chain length resulted in lowering of the hemolytic activity and also of the cytoxicity against epithelial cells of the chitosan derivatives. On determining the selectivity toward bacterial cells over human red blood cells which is expressed by the ratio HC50 (50% hemolysis)/MIC (minimal inhibition concentration), again the N,N-dimethyl-N-ethyl chitosan exhibited the highest values. Also the N,N,N-trimethyl chitosan was found to possess a promising selectivity. Overall, highly selective compounds, which were significantly more active against bacteria than human cells could be obtained (Sahariah et al. 2015).

In addition to various proteins further macromolecular constituents like glycosaminoglycans (GAGs) and more complex proteoglycans are present in the ECM. GAGs are complex negatively charged unbranched heteropolysaccharides composed of disaccharide repeating units (for structures see Fig. 7).

In contrast to proteins, GAGs may be less immunogenic and less sensitive to denaturation processes. Due to their anticoagulation properties, heparin coatings have been investigated for years in haemodialysis systems, coronary stents and other blood-contacting medical devices (Kim and Jacobs 1996, van der Giessen et al. 1998, Wendel and Ziemer 1999). In addition, it is known, that both the high-sulfated GAGs heparan sulfate and heparin are able to interact not only with ECM components (collagen, fibronectin) but also with growth factors to sequester the latter ones in their active conformation and protect them against proteolytic attacks. Various growth factors containing heparin-based coatings have been developed to improve the efficiency of the highly active but also very sensitive protein molecules. Among

growth factors used in this approach are basic fibroblast growth factor (bFGF) (Wissing et al. 2000), recombinant human bone morphogenic protein (BMP-2) (Kodama et al. 2013), and vascular endothelial growth factor (VEGF) (Wang et al. 2013).

In contrast to the concept of immobilization of a single biologically active macromolecule onto the biomaterial surface, a relatively new and innovative approach consists in the *in vitro* building of an artificial ECM (aECM) mimicking the microenvironment of the native ECM in its ability to guide morphogenesis in tissue repair and engineering (Bierbaum et al. 2012). In many native ECMs collagen fibrils are the basic constituent. As a consequence, most often collagen, especially collagen type I, is used to generate aECM in combination with typical components of the ECM like glycopeptides, glycosaminoglycans or proteoglycans. Depending on the tissue target and the purpose, aECM with a broad compositional and structural variety is available to tune the cell- and tissue-relevant environmental properties including mechanical stability, bioadhesive character, proteolytic susceptibility, and growth factor binding capacity.

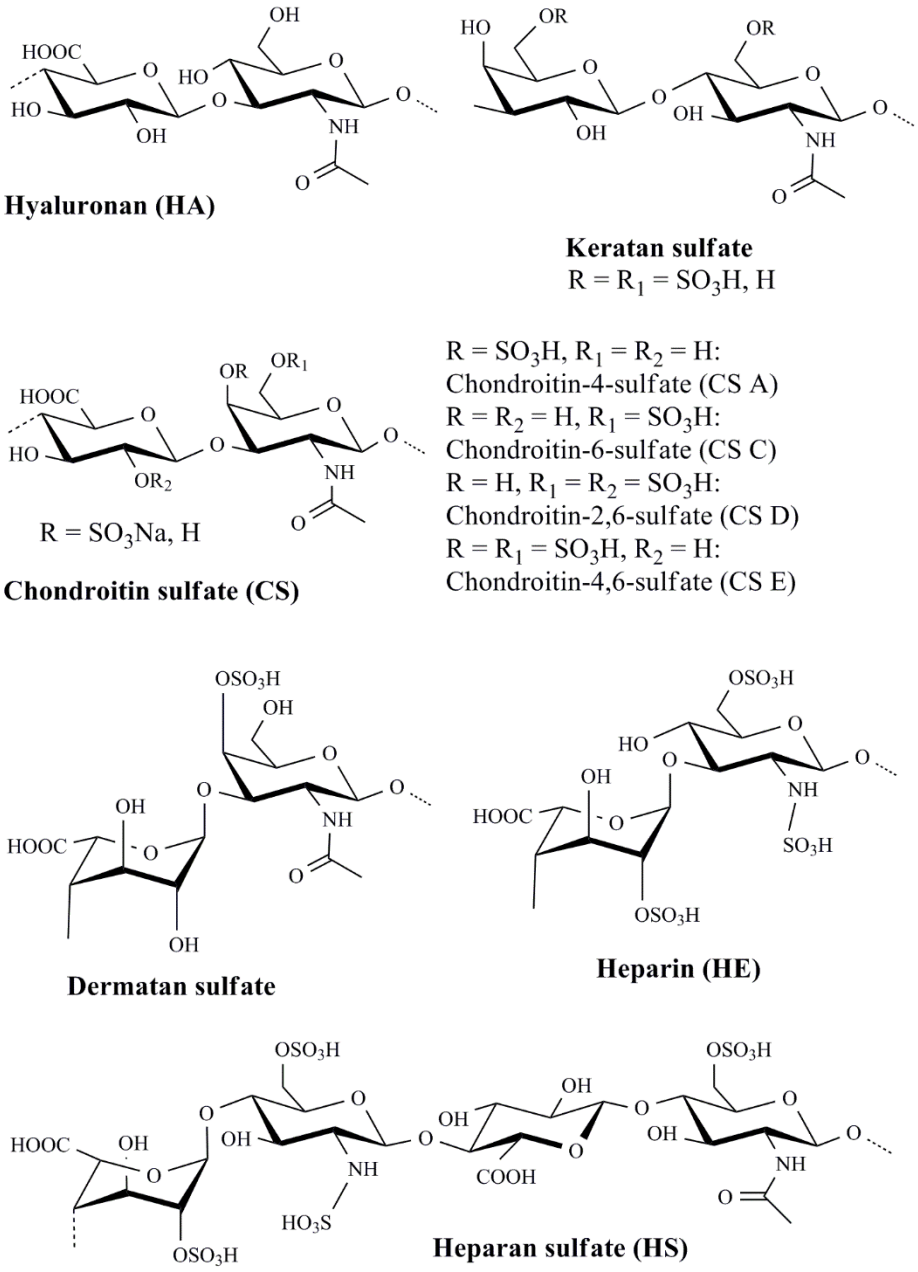


Figure 7 - Repeating units of natural glycosaminoglycans (GAGs)

Collagen-based aECM can be built using either suspensions of insoluble collagen fibers, or solutions of collagen monomers which then are allowed to form fibrils in vitro (Bierbaum et al. 2012). Both the resulting constructs can then be used in similar ways to coat biomaterial surfaces by simple physical adsorption or covalent immobilization.

Various multi-component aECMs have been reported in the literature containing collagen type I as basic structural element in combination with other collagens (type III (Bierbaum et al. 2003) or type V (Birk 2001)), and other proteins (fibronectin (Bierbaum et al. 2003), laminin (Tate et al. 2009)). While proteoglycans can only be included in collagen-based aECM to a

limited degree due to inhibition of the fibril formation, the incorporation of GAGs is possible and results in aECM with interesting properties, especially with regard to growth factor interactions. The GAG-collagen interaction is unspecific and is mainly driven by electrostatic interactions between the negatively charged carboxylate and sulphate groups of the GAGs and positively charged amino acids of the related protein. Furthermore, many mediator proteins (growth factors, interleukins, further chemokines) interacting in vivo with GAGs are of basic nature or have basic amino acids or at least a sequence of basic amino acids. Having this in mind, collagen/GAG-based aECMs represent a promising future tool to modulate growth factor accumulation and release. Hence, aECMs comprising collagen and different sulfated GAGs have been intensively studied during the last decade. The incorporation of heparin into collagen matrices has an impact on the release of VEGF and stimulates angiogenesis (Wolf-Brandstetter et al. 2006). Matrices containing collagen type II and chondroitin sulfate have been shown to increase proliferation of chondrocytes and endothelial cells (Cao and Xu, 2008) *in vitro*. Hyaluronan, the only non-sulfated GAG, does not interact with growth factors and has only a minor effect on cells if included into collagen matrices. This is changed if hyaluronan is chemically sulfated leading to derivatives with degrees of substitution (DS) in a range between 1.0 and 3.0 (the DS values is the average number of introduced substituents per disaccharide repeating unit, i. e. in the case of hyaluronan the DS can range between 0 and 4) (Hintze et al. 2009). It could be demonstrated by biophysical and immunological methods that matrices with sulphated hyaluronans exhibit a stronger binding strength to BMP-2 and TGF-β1 than chondroitin sulfate-containing matrices at a comparable DS of the GAGs (Hintze et al. 2012, Hintze et al. 2014). In a further study poly(lactide-co-glycolide) scaffolds were coated with collagen matrices containing either chrondoitin sulfate or hyaluronan sulfate, and the effect of these coatings on the prolifertation and osteogenic differentiation of human mesenchymal stem cells was investigated in vitro. Whereas only minor differences were found in cell proliferation, osteogenic differentiation, determined by alkaline phosphatase activity and mineral deposition, was strongly enhanced compared to uncoated samples (Wojak-Cwik et al. 2013). Recently, the new sulfated GAG/collagen aECMs have been tested in a mini-pig model as coatings for dental implants to reveal their potential for improving healing processes in vivo. The coated implants supported peri-implant bone formation within a healing period of 8 weeks and showed an increased bone volume density compared to uncoated implants (Korn et al. 2014).

3.2.2.2 Bioactive and degradable coatings based on synthetic polymers

In the literature there exists a variety of coating materials derived from synthetic organic polymers. Unlike many natural macromolecules only very few of them are known to directly

promote cell adhesion, proliferation, and differentiation. One example of a cell adhesion stimulating synthetic polymer is the plasma polymerized polyallylamine (PPAAm) network. The surface coating is performed under vaccum in a microwave plasma reactor in the presence of allylamine monomer (Finke et al. 2007). Different substrates including metals used for bone and dental implants, ceramics and even polymers can be used. As a result of titanium, a thin, homogeneous, highly cross-linked polymeric film is deposited on the substrate. This film is resistant to hydrolysis and delamination and sufficiently equipped with free amino groups. The incubation of human osteoblastic MG-63 cells onto PPAAm-coated titanium discs demonstrated enhanced osteoblastic focal contact formation as vinculin, paxillin and phosphorylated focal adhesion kinase, concerning actin cytoskeleton development. Interestingly, these cell responses on PPAAm are similar to collagen-bonded surfaces (Finke et al. 2007). Comparable results were also obtained depositing the PPAAm coating onto electrospun poly(L-lactide-co-DL-lactide, PLDLL) fiber meshes (Schnabelrauch et al. 2014).

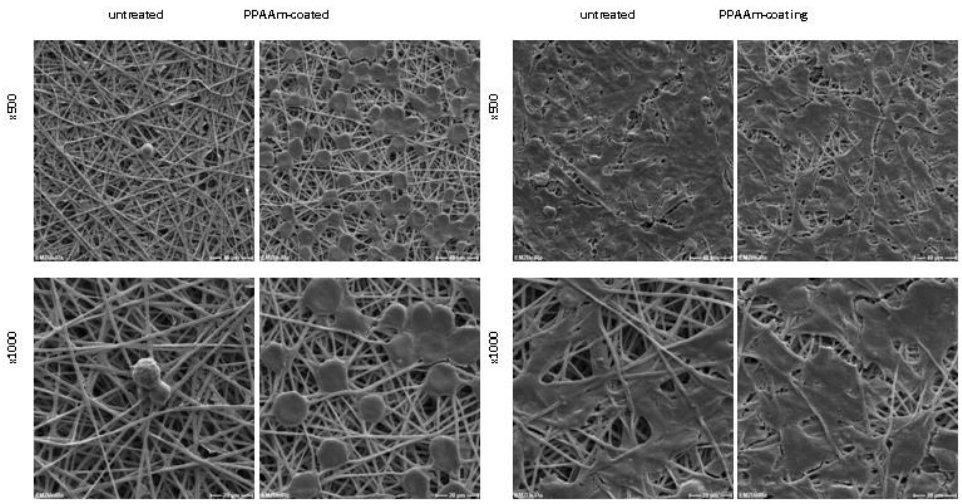


Figure 8 - Scanning electron microscopical images showing spreading of Ca9-22 human gingival epithelial cells on untreated and PPAAm-coated PLDLL fiber meshes after 0.5 and 24h (scale bar = 40µm (upper row) and 20µm (lower row)) (reproduced from Schnabelrauch et al. 2014).

The PPAAm coating did not affect the fragile microstructure of the fibre mesh preserving the advantageous structural properties of these materials with regard to their use in tissue engineering.

In vitro cell experiments using human gingiva epithelial cells, human uroepithelial cells, and MG-63 cells confirmed an improved cell spreading on PPAAm surfaces already after 0.5 h of

incubation (Fig. 8). First *in vivo* data on the biocompatibility of PPAAm-modified polylactide meshes demonstrated that the coating has no influence on the local inflammatory reaction.

Synthetic biodegradable polymers including polyesters (polylactides, polyglycolides, poly(-lactide-co-DL-lactic acid and polyphosphazenes) are normally of hydrophobic nature and lack innate specific cell adhesion and proliferation activity. Coatings derived from these polymers are currently used mainly in controlled drug delivery for local therapies (Malafaya et al. 2005, Seyednejad et al. 2011) and also for growth factor release systems (Schmidmaier et al. 2001), as well as vaccine applications (Andrianov et al. 2009; Ulery et al. 2011).

Poly (lactic acid) has suitable biodegradation behaviour and high mechanical stability (Garlotta 2001) and it tends to be used in the form of thin films for biomedical applications, including tissue engineering and drug delivery therapies (Tsuji and Ikarashi 2004; Garric et al. 2005). A rapid aerosol assisted deposition process has been developed for the preparation of biodegradable poly (D,L-lactic acid) (PDLLA) films with well controlled surface morphology and thickness (Hou et al. 2008). It involves the generation of polymer fine aerosol droplets which are directed towards a heated substrate, with rapid evaporation of solvent, and subsequently deposits a polymer film onto the substrate.

Additionally, polymer coatings are under investigation to increase the corrosion resistance and to control the degradation behaviour e.g. of magnesium and Mg alloy implants (Hornberger et al. 2012; Smith and Lamprou 2014).

The control of interfacial interactions between a biomaterial and its biological environment is a key feature for the design of biomaterial and biosensor surfaces. Resistance to nonspecific protein or cell interactions is a particularly relevant issue in microfluidic, diagnostic, and implantable devices ranging from small-diameter vascular grafts to biochips in medical diagnostics. Despite considerable research efforts, surface coating that completely eliminate protein adsorption onto a medical device over a long time has not been achieved. Nevertheless a variety of coatings have been identified to substantially reduce protein adsorption. Polyethylene glycol (PEG) has great potential to create non-fouling and represents the standard for comparison with newly developed non-fouling materials. A combination of the water retaining mechanism of the polymer chain and its resistance to compression to its extended coil conformation is regarded as the most probably factor in prevention of PEG surfaces protein adsorption (Bridges and Garcia 2008). As a current drawback to the use of PEG, its lack of versatile grafting techniques to stably link PEG molecules to biomaterial surfaces remains the most prominent. To solve this problem several new robust grafting techniques for PEG on metal surfaces have been developed using e. g. potent phosphonate

(Zoulalian et a. 2006), phosphate (Gnauck et al. 2007) or dopamine (Dalsin et al. 2005) linker (see Fig. 9). Other hydrophilic polymers such as poly(2-oxazoline)s (Konradi et al. 2008), poly(glycerols) (Calderon et al. 2010) phosphorylcholine-derived degradable polymers (Nederberg et al. 2004) are also potential candidates to resist protein adsorption. Interestingly, PEG and poly(2-oxazoline)s which are supposed to be non-degradable until now have been found in a recent study to undergo oxidative degradation under biologically relevant conditions (Ulbricht et al. 2014). Under the influence of reactive oxygen species a time and concentration dependent degradation of both polymers occurs suggesting that a mid- and long-term biodegradation *in vivo* appears feasible.

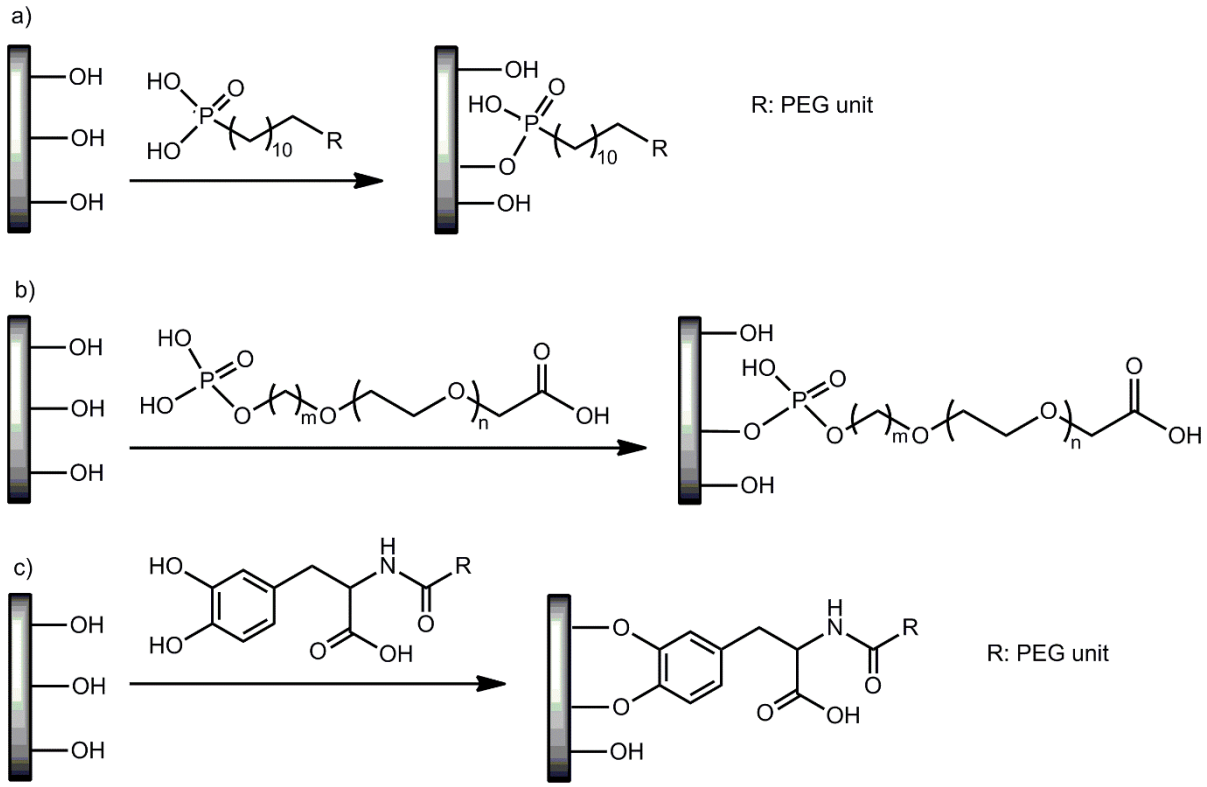


Figure 9 - Immobilization of functionalized PEG structures to titanium surface via (a) phosphonate, (b) phosphate, and (c) dopamine linker

PEGs and other hydrophilic polymers are often applied as molecularly thin self-assembled monolayers (SAMs) on planar surfaces on inorganic substrates. In an aqueous cell-containing medium the stability of those layers are limited. Polymer brushes which are more mechanically robust than SAMs can be generated on non-planar surfaces including colloidal suspensions. Those polymeric coatings can be prepared by surface-initiated polymerizations allowing control over functionality, grafting density, and thickness of the brushes.

Extensive research efforts have focused on hydrogel-based implant coatings of different thicknesses (Hofmann 2002). Hydrogels offer many advantages over traditional surface modification strategies, including nanoscale dimensions with complex architectures, the formation of viscoelastic network structures, the possibility to tune the mechanical strength, swellability, and biodegradability of the hydrogel, the incorporation of multiple chemical functionalities and bioactive molecules, and the ability to deposit onto a variety of material substrates (Bridges and Garcia 2008). Due to the limited biodegradability of many known antimicrobially active synthetic polymers, currently natural polymers derived, for example, from chitosan are often used as hydrogel forming substances. There is an ongoing need to both develop new antimicrobial active and biodegradable hydrogel precursors.

Most antimicrobial polymers have been designed to kill pathogens via a membrane disruption mechanism. That requires macromolecules with a sufficient cationic charge to promote adhesion to the cellular membrane of the microbe. In addition, the polymer should contain a hydrophobic moiety that will attach onto or integrate into the cellular membrane for lysing the membrane. Hydrophilic/hydrophobic balance (amphiphilicity) of an antimicrobial polymer is particularly important because it significantly impacts how the polymer interacts with cellular membranes (Engler et al. 2013). There exist different approaches to control amphiphilicity. In a recent work, cationic biodegradable polycarbonates have been prepared by metal-free organocatalytic ring-opening polymerization of functional cyclic carbonates (Fig. 10, Nederberg et al. 2011).

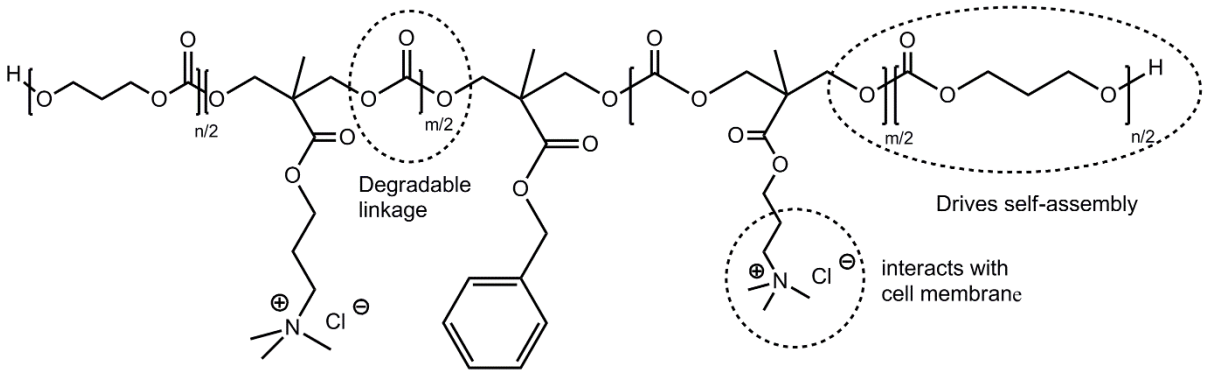


Figure 10 - Cationic, amphiphilic, and biodegradable polycarbonate with antimicrobial activity against Gram-positive bacteria.

Nanoparticles of these polymers are able to disrupt microbial membranes selectively and efficiently thus inhibiting the growth of Gram-positive bacteria, methicillin-resistant *Staphylococcus aureus* (MRSA) and fungi, without inducing significant haemolysis over a wide range of concentrations.

3.2.4: Bioactive composite coatings

Although metallic orthopaedic implants are widely used and there is a strong bonding between the bioactive coating (such as HA) and the bone structure, limitations have been identified. For instance, it has been recognized that there could be an issue with the mechanical stability of the interface between the coating and the metallic substrate during surgical operation, after implantation for a prolonged period and/or post-surgery infections, which have caused the failure of the implants. Various strategies have been explored to address such limitations and one of them is to explore the use of bioactive composite coatings.

Bioactive composites have been shown to successfully overcome the brittleness usually attributed to HA and bioglass coatings, while retaining bioactivity, and also to potentially be used to confer additional properties to the coatings. (Simchi et al. 2011; Mehdipour and Afshar 2012; Venkateswarlu et al. 2012; Gopi et al. 2013; Pishbin et al. 2013; Cordero-Arias et al. 2015). The combination of bioactive glass/ceramic structure with an appropriate biopolymer to form a biocomposite coating has been shown to be able to transform the brittle HA and bioactive glass coating structure into a compliant and soft composite structure (Chen et al. 2006; Kim et al. 2011), while retaining their bioactivity and enable the incorporation of additional functional properties such as corrosion resistance, antibacterial property and release of biomolecules and drugs (Chen et al. 2006; Rezwan et al. 2006; Simchi et al. 2011; Mehdipour and Afshar 2012; Venkateswarlu et al. 2012; Gopi et al. 2013; Pishbin et al. 2013; Cordero-arias et al. 2015), and removing the need to densify glass ceramics at high temperatures. Various bioactive composite coatings have been investigated and some examples are being highlighted here. These bioactive composite coatings have been deposited onto metallic substrates by various processing techniques. These include sol-gel, thermal spray, laser spinning, plasma spray, electrophoretic and electrochemical deposition (Zheng et al. 2000; Jun et al. 2010a; Boccaccini et al. 2010b; Mehdipour and Afshar 2012; Gopi et al. 2013; Pishbin et al. 2013; Cordero-Arias et al. 2014; Pishbin et al. 2014).

Glasses, 6P57 and 6P68, with thermal expansion coefficients that matched Ti-6Al-4V were prepared and used to coat Ti-6Al-4V. Crack free bioactive composite coatings consisting of 20% of hydroxyapatite (HA) and/or Bioglass (BG) particles (45μm) in silicate glass coatings were fabricated by enamelling technique on Ti-6Al-4V substrates. HA and/or BG particles were incorporated into these coatings to increase bioactivity of the silicate coatings while maintaining good adhesion to the substrate. There was no apparent reaction at the glass/HA interface at the temperatures 800-840°C, whereas the BG particles softened and some infiltration of the glass coating occurred during heat treatment. The effectiveness of BG

incorporation would depend on the softening temperature of the glass coating, with higher softening temperatures leading to increased degradation of the BG, whereas this was not the case for HA (Gomez-Vega et al. 2000).

Bioactive glass (SiO_2-CaO-P_2O_5-MgO)/chitosan composite coating was deposited on a 316L stainless steel substrate via electrophoretic deposition from a mixed ethanol-water suspension containing ceramic glass particles and chitosan with the aim to improve corrosion resistance and osseointegration. The water to ethanol ratio of 30% was found to yield a high deposition rate and a uniform, smooth and crack-free coating (7 μm thick) and the current density of the bioactive composite coating tested in artificial saliva was decreased by 52% and corrosion potential shifted toward more noble values as compared to the uncoated samples (Mehdipour and Afshar 2012).

Functionally graded composite coatings are also being considered to enhance interfacial bonding between dissimilar solids in order to minimise thermal stresses, suppress the onset of plastic yielding and to arrest any cracks. HA powder was mixed with titanium oxide (TiO_2) in different weight percentages and spray deposited to produce functionally graded bioactive coatings on Ti-6Al-4V metal substrate. The first layer consisting of TiO_2 particulate coatings was sintered at 900°C for a few minutes followed by subsequent layers of HA-TiO_2 composites of different weight ratios (75% TiO_2 and 25% HA, 50% TiO_2 and 50% HA, 25% TiO_2 and 75% HA, and 100% HA) were performed in sequence and these layers were sintered again at 900°C for a few minutes in order to obtain good adhesion between layers. The hardness and Young modulus values of HA-TiO_2-Ti functionally graded coating were 15.1 and 0.405GPa, respectively (Roop Kumar and Wang 2002).

Gopi (Gopi et al. 2013) reported the use of electrodeposition to deposit carbon nanotubes (CNTs) reinforced hydroxyapatite composite coatings on titanium to exploit the capability of CNTs imparting strength and toughness to brittle hydroxyapatite (HAP). The CNTs/HA composites exhibited efficient corrosion protection of titanium substrate in SBF solution and the enhancement of cell viability of the CNTs-HAP composite coating on titanium.

Multifunctional composite chitosan/Bioglass coatings loaded with gentamicin antibiotic was developed as a potential suitable approach to improve the surface properties of metallic implants by providing both bioactive and anti-bacterial properties for orthopaedic implants. The biocomposite coatings formed bonelike apatite upon immersion in SBF, confirming their bioactivity. The coating released 40% of its gentamicin payload within 5 days of burst release followed by a sustained drug delivery over a period of 8 weeks. It seems the release kinetics could inhibit bacterial growth for the first 2 days and support cellular proliferation for up to 10

days. However, further works are still needed to establish the interfacial bonding of these coatings to the metallic substrate and the optimum gentamicin loading that would provide minimum inhibitory concentration against bacteria as well as supporting cellular attachment and proliferation (Pishbin et al. 2014).

Alternative polymer for bioactive coating is alginate (Cheong and Zhitomirsky 2008) which is a natural polysaccharide. Alginate has been studied for different applications, e.g. biosensors, drug delivery systems and tissue engineering (Joshi et al. 2011; Lee and Mooney 2012). This polymer has a potential binding effect with proteins, growth factors and bone forming cells, and has been explored by Cordero-Arias et al. (Cordero-Arias et al. 2014) to develop nanostructured TiO_2 particles in alginate and TiO_2-bioactive glass/alginate composite coatings on stainless steel coatings for bone contacting materials by electrodeposition from ethanol/water suspensions. Titania has shown to be biocompatible (Nie et al. 2000; Navarro et al. 2008; Bai et al. 2011) and exhibit antibacterial properties (Cui et al. 2005), and enhance implant integration with host tissue when used in bone tissue replacement applications (Navarro et al. 2008). Bioglass particles improved the mechanical properties of the coatings by increasing the adhesion to the substrate and also accelerates the formation of hydroxyapatite after immersion of the coatings in simulated body fluid and the coated substrates shown improved electrochemical behaviour and confirmed the corrosion protection function of the coatings (Cordero-Arias et al. 2014). ZnO/alginate and ZnO-bioactive glass/alginate composite coatings also exhibiting antimicrobial properties and provide corrosion protection (Cordero-arias et al. 2015).

Other composite coating based on a silica xerogel/chitosan (30%) hybrid has been developed as a novel surface treatment for metallic implants. Silica xerogel presents a great bioactivity, with a good chemical bonding to the surrounding tissues, especially bone (Radin et al. 2005; Avnir et al. 2006) while chitosan (>30%) is a biocompatible, non-toxic and biodegradable natural polymer (Bumgardner et al. 2003). Both compounds are excellent candidates for the development of hybrid coating materials on metallic substrates at room temperature, overcoming the cracking problem of the silica xerogel onto Ti-based implants (Jun et al. 2010b).

Osteoblastic cells cultured on the hybrid coatings were more viable than those on a pure chitosan coating and the alkaline phosphate activity of the cells was significantly higher on the hybrid coatings than on a pure chitosan coating (Jun et al. 2010a). These promising results

indicated the potential of silica xerogel/chitosan hybrids as a potentially useful at room temperature processed bioactive coating materials on titanium-based medical implants.

Biologically active molecules can be incorporated using the biomimetic approach during the formation of bone-like apatite layer in SBF. Biocomposite coating based on laminine–apatite has been developed from a metastable calcium phosphate solution containing laminine to give cell-adhesive properties (Uchida et al. 2004). In addition, enzymes and proteins (Leonor et al. 2002) can also be incorporated in the apatite layer during formation in a solution mimicking body fluid (i.e. simulated body fluid) at low synthetic temperature conditions.

Electroactive biocomposite coatings. Liao et al (Liao et al. 2014) have explored conducting polymer as an intelligent electrical implant surface and a bone-mimetic electrophysiological micro-medium as well as citric acid, a small biomolecule found in natural bone, to develop nano-architectured conducting polymer on bone implants via a green fabrication approach in order to improving bioactivity of conducting polypyrrole coating on bone implants (Wallace and Spinks 2007; Liao et al. 2014). In the green approach, citric acid was used to facilitate the template-free electrochemical polymerization for the construction of 1D nano-architectured PPy (NAPPy) on biomedical titanium in PBS. Enhanced bioactivity has been demonstrated in implants modified by 1D NAPPy/citrate from the *in-vitro* biomineralization investigation in simulated body fluid and biological activities (e.g. adhesion, spreading, proliferation and osteogenic differentiation) of osteoblasts. This showed that 1D NAPPy/citrate could be used as a more bionic implant surface and the citrate-assisted green approach could potentially be extended to the construction of other CPs and 1D nano-structures of electroactive materials that are stable, biocompatible, exhibit biomolecule affinity suitable for potential biomedical applications as reviewed by Liao et al. such as biological sensing (Travas-Sejdic et al. 2014), switching biointerface (Liao et al. 2014), neural probes (Abidian et al. 2010), drug delivery (Abidian et al. 2006) and tissue engineering (Balint et al. 2014).

Despite various bioactive composites have been investigated, only a few bioactive composites have been used clinically (Hench 1998). For example, PE/0.4-HA composite has been used as an implant for reconstruction of the orbital floor. The widely use of bioactive coatings is still limited until their long term *in vivo* performance has been established.

3.2.5 Antimicrobial coatings

Microorganisms are omnipresent and represent a crucial factor in the whole living cycle and virtually anywhere human come into contact with them. However, in different areas of life and technical fields, strong hygienic conditions and sterile procedures are absolute requirements

of a modern society. The elimination or extensive reduction of microbes is important for example in food industries, the manufacture of packaging materials, textiles for clothing, air conditioning and ventilation systems as well as in kitchens and sanitary facilities. Particularly, an antimicrobial feature with a high degree of efficiency is essential for general healthcare applications in hospital environments and for medical devices to eliminate pathogenic germs like bacteria and fungi. These microbes compromise the health of the patients especially with immune deficiencies and they might enhance the risk for nosocomial infections leading to serious medical conditions which could cause death in worst case scenarios.

Because of different requirements regarding antimicrobial effects, in recent years, a variety of sophisticated strategies were developed to kill or inhibit the growth of microorganisms. However, the effective removal or combat of microbes is still a scientific challenge especially in view of the worldwide increase of multi-resistant bacteria. The chosen method among those in the antimicrobial arsenal strongly depends on the specific application and sources of microbial contamination.

Particularly for the continued fight of infectious diseases in hospitals the strategy of antimicrobial coating of everyday objects, and especially of medical devices, with novel materials using new technological approaches has been proposed and tested. Thereby coatings based on antibiotics including antimicrobial peptides, antiseptics, antibodies, inorganic components like antimicrobial metal ions, fluorinated compounds, hydrogels, polyelectrolyte multilayers, antibacterial polymers as well as nitrogen monoxide releasing materials and nanostructured surfaces could prevent the adhesion and adsorption of microbes or kill them (Lichter et al. 2009; Wang and Zreiqat 2010; Arora et al. 2013; Gallo et al. 2014). A variety of such coatings are already in use or they are part of clinical studies.

Well known is the application of antibiotics like ciprofloxacin, vancomycin, oxacillin, tobramycin, gentamicin, or rifampicin which are incorporated in polymer matrices to function as a controlled antibiotic release system (McMillan et al. 2011; Brooks 2013). Also film forming antibiotic formulations like gentamicin palmitate can be used for antibacterial coatings showing a suitable retarded drug release (Kittinger et al. 2011; Fölsch et al. 2015).

For the metal ions incorporation approach e.g. of Ag, Cu, or Zn into antibacterial inorganic or organic coatings various methods are applied using chemical and physical processes like sol-gel chemistry, ion beam implantation, or the use of plasma. Metal ions will be released from the surface as the antimicrobial agent whereby the source could be pure metal, colloids, metal or oxide nanoparticles as well as coordinative bound metal ions (Knetsch and Koole 2011; Jaiswal et al. 2012; Gallo et al. 2014).

A relatively new group of coating materials include hydrogels, anti-adhesive polymers and super-hydrophobic surfaces (Ng et al. 2014). These materials exhibit a new mode of action preventing microbial adhesion and adsorption without the risk of drug resistance development. For instance, hydrogels based on natural or synthetic polymers exhibit three-dimensional networks with a very high degree of water content leading to the intrinsic antimicrobial as well as antifouling properties (Ng et al. 2014).

A further promising approach to generate antimicrobial surfaces is the use of polymers with antimicrobial properties (Arora et al. 2013). Thereby the mechanism of action is based on contact killing without releasing antimicrobial substances. It is well known that immobilized quaternary ammonium or phosphonium moieties containing at least one long alkyl chain penetrate and destroy bacterial cell membranes (Xue et al. 2015). Due to these properties permanent antibacterial coatings exhibiting high efficacy even against multi-resistant pathogenic germs without antibiotic resistance threats could be generated.

Over the last decades nitrogen monoxide (NO) also came in focus to develop new NO releasing coating materials due to its strong antibacterial effect (Nablo et al. 2005). It has been demonstrated that the hydrophobic NO penetrates bacterial cell membranes and is able to destroy plated colonies of bacteria. Moreover, NO in low concentrations is an essential mediator of numerous mammalian biological processes and exhibit e.g. an important factor in wound healing (Chen 2005). Consequently a NO releasing coating combines antibacterial with increased wound healing effects (Kim et al. 2015).

4. Future Trends

From the review of the development of bioactive ceramic coatings, despite materialist biocompatible characteristics, it is clear that the adhesion strength of these to medical implants would need to be improved and optimised further in order to increase the durability and long term reliability for load bearing biomedical devices. The mechanical properties of HA components would need to be optimised, ideally offering a Young's modulus less than 20GPa and improved mechanical strength, both in compression and tension (Auclair-Daigle et al. 2005). This can be achieved with a combination of approaches. These include: (i) the continuous development of coating technology that can deposit uniform, reproducible and adherence bioactive coatings onto implants with well controlled structure (e.g. phase stability, crystallinity, thickness, porosity) and composition at nanoscale level; (ii) use of nanotechnology and biomimetic approach; (iii) to develop interlayer and/or composition graded layer; (iv) pre-surface and post-surface treatment to improve the interface control and properties; (v) surface functionalization; and (vi) use of bioactive composites.

Most of the bioactive coatings have been developed for orthopedic applications. Others applications areas in cardiology, neurology, and ophthalmology are underexplored. For examples, coatings that could improve small vascular graft integration while preventing occlusion could have a significant clinical impact, and replacing drug-eluting stent with the use of pro-healing stent that integrates appropriately with both endothelial cells and smooth muscle while preventing platelet and leukocyte adhesion (Meyers and Grinstaff 2011).

In order to achieve long term reliable bioactive coated implants and biomedical devices, in-depth integrated studies on the structure, material surface chemistry, molecular biology, biochemistry, protein absorption, biomimetic, genetic engineering, tissue engineering, surface engineering, nanoscience and technology are needed in order to design, discover and engineer robust, bioactive, biochemical and biomechanical compatible coatings with well controlled structure and composition that are not only be able to replace tissues but also to regenerate them.

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