Periodicals of Engineering and Natural Sciences ISSN 2303-4521
Vol. 8, No. 1, February 2020, pp.33-57

Recent developments of metallic implants for biomedical applications

Fehim Findik [1,2]

[1] Biomedical, Magnetic and Semiconductor Materials Application & Research Center, Sakarya University, Sakarya, Turkey
[2] Metallurgy and Materials Engineering Department, Faculty of Technology, Sakarya Applied Sciences University, Sakarya, Turkey

ABSTRACT

Medical implants have undoubtedly made an indelible mark on our world during the last century. More than 100 million humans carry at least one major internal medical device. The prosthesis industry has topped 50 billion US$ in annual sales, with approximately 150 universities throughout the world proposing an undergraduate program in bioengineering or biomedical engineering. Despite that, however, most medical devices have been constructed using a significantly restricted number of conventional metallic, ceramic, polymeric, and composite biomaterials. In this study, recent developments of metallic implants are summarized for biomedical applications. To do this, first desired properties for biomaterials are defined. Then, types of metallic biomaterials are classified as stainless steel, Mg, Co, Ti, nobble and biodegradable ones. After that, surface modifications are defined for corrugation, topographies and chemical modification. Finally, future perspective is outlined for the sake of development new materials as well as production point of view.

Keywords: Implant; Biomaterials; Application, Metallic Alloys; Surface Modification

Corresponding Author:

Fehim Findik
Metallurgy and Materials Engineering Department, Faculty of Technology, Sakarya Applied Sciences University, Sakarya, Turkey
E-mail: findik@sakarya.edu.tr; Tel: +90-264-616 0260

1. Introduction

A biomedical implant is defined as an artificial organ designed to restore the functionality of a damaged natural organ or body tissue. This requires several requirements that must be met before the material used for artificial organs or artificial organ construction can be evaluated for application. The main requirement of artificial organ or tissue substitution is that it acts as a functional substitute for the original body part. Additional requirements include biocompatibility or biodegradability of the material used in the artificial organ, so that the surrounding tissue accommodates without any immune rejection response or inflammatory reaction.

Metals, ceramics, polymers and natural materials are used in biomedical implants. The need to avoid toxic substances rarely uses aluminum or its alloys, while plain steel corrodes too fast to use on the body. High quality metal titanium, vanadium and chromium alloys are used in orthopedic prostheses (artificial joints) or for fixing plates to fix fractures. Engineering ceramics such as aluminum oxide have been found to provide a hard, low-friction surface that is also suitable for orthopedic prostheses. In many cases, hard aluminum oxide is paired with Ultra High Molecular Weight Polyethylene to produce a very durable container for the hip joint prosthesis and a softer yet wear-resistant polymer to produce a ball joint.

Composite materials attracted attention as biomedical materials. Carbon fiber braids were examined as reinforcing materials for the bodies of orthopedic implants. Surface coatings have been developed to coat a metal into a more acceptable coating by the human body. Metals in basic form are essentially foreign to the human body. When a metal implant is inserted into the tissue, most metals are encapsulated with a thin layer in which human cells are almost empty. Adhesion between the metal implant and the surrounding tissue is relatively weak. Bones contain hydroxyapatite (a form of calcium phosphate) as a structural matrix. When a metal implant is covered with hydroxyapatite, bone cells adhere to the surface of the apatite coating without any interference layer. The hydroxyapatite matrix of bone cells then integrates with the hydroxyapatite coating and adheres perfectly to the coated implant bone.

The range of biomedical materials is expanding very quickly; There is a rapidly expanding range of polymer materials recommended as biomaterials. Biocomposites, that is, composite materials intended for use as biomaterials also contribute to the potential material range. Composite materials develop beyond the relatively simple structure of two, perhaps three, materials for systems with a nanometer scale engineering structure. Vacuum-based surface coating technologies such as Physical Vapor Deposition are used to form regular polysaccharide molecule sequences on a supporting polymer membrane. The purpose of this composite biomedical material is to adsorb selective proteins and reject other proteins. This material can be attached to the electrodes to form a sensor for individual proteins [1].

The basic function of biomedical material varies. The original form of the biomedical implant was a separate material, such as a plate that connects broken bones. Although this type of implant is likely to be in use in the foreseeable future, a new form of implant is rapidly emerging. Highly porous implants, often referred to as 'scaffolds', act as matrices to support cell growth or regrowth when the original tissue is defective. The vital material properties for these 'scaffolds' are flexibility and permeability, so that the cells inside are not protected from mechanical stresses applied to tissues and are not removed from the natural flow of cellular nutrients. It has been found that mechanical stress is required for cell growth in tissues such as arterial and vein walls. If the scaffold is made of natural material, it can even function as a food for cells. Effectively designed scaffolds can provide tissue regeneration in orthopedic joints, intestines and artery walls [2]. Regenerated tissue is more acceptable for the patient than having to live with an artificial material implant that is completely different from the tissues. This article briefly reviews various metal biomaterials, including stainless steel, Mg, Co and Ti based alloys, as well as biodegradable alloys that have the potential to face the challenges of biomedical engineering. In addition, the surface modifications of the implants are outlined and the future perspective is reflected for possible improvements.

2. Preferred properties of biomaterials

A biomaterial must meet the following criteria:

Mechanical properties: By matching the flexibility module of biomaterials with bone ranging from 4 to 30 GPa, stress protection can be avoided [3]. In addition, the material must have a low modulus combined with high strength to prolong the service life of the implant and prevent loosening, so revision surgery is not required.

Biocompatibility: The material developed should be compatible with living systems and should not cause bodily harm, including all the negative effects of a substance on the components of the biological substance (bone, extracellular tissues and the ionic composition of the plasma) [4].

High abrasion resistance: The material should have high abrasion resistance and show a low coefficient of friction when sliding into body tissues. Increased friction coefficient or decreased wear resistance may cause the implant to relax [5]. In addition, wear now can cause inflammation that damages the bone that supports the implant.

High corrosion resistance: An implant made of a biomaterial with low corrosion resistance can release metal ions in the body, causing toxic reactions [6].

Osseointegration: Osseointegration was first described as "a direct structural and functional link between the surface of an organized, live bone and a load-bearing implant" [7]. Surface roughness, chemistry and topography play an important role in good osseointegration [8]. Implant relaxation results from the integration of the implant surface into the adjacent bone [9]. Few researchers say that osseointegration is undesirable because of the risk of not being able to remove the implant after use [10]. However, a few have also shown that the implant can be safely removed [10]. Therefore, osseointegration is a desirable feature in some applications, such as implants, for a biomaterial that is required to ensure the proper integration of the implant with bone and other tissues [11].

Non-toxic: The material should be neither genotoxic (can alter the DNA of the genome) nor cytotoxic (damaging cells).

Long fatigue life: The material should show high resistance to fatigue and failure to prevent implant failure and stress protection from fatigue fracture. Implants have been reported to fail with fatigue in hip prostheses [12].

3. Types of biomaterials

The materials used in the construction of biomedical devices (orthopedic, dental, bone cements, etc.) can be classified as metallic materials, ceramics, polymers and composites. Metallic materials in these four categories are widely used due to their high strength, toughness and good biocompatibility, despite some deficiencies such as release of metallic ions and wear residues. Therefore, only metallic materials will be summarized below as biomaterial.

3.1. Metallic alloys

The high reliability of metallic biomaterials in terms of mechanical performance has resulted in the use of "mainly for the production of medical devices for the replacement of hard tissues such as arterial hip joints, bone plates and dental implants" [13]. Various properties and properties of a wide variety of materials and alloys have been investigated in the medical field [14]. Different alloy systems have been developed for use in the medical field, including stainless steels, Co alloys and Ti alloys. Table 1-3 summarizes the chemical composition of alloys registered in the ASTM Standard and developed for biomedical applications [15]. A brief description of each material is given below.

Table 1. Titanium-based biomedical alloys [16]

Alloy	Microstructure
1. Pure Ti	(ASTM F67-89)
2. Ti-6Al-4V ELI (ASTM F136-84, F620-87)	α+β type
3. Ti-6Al-4V (ASTM F1108-88)	α+β type
4. Ti-6Al-7Nb (ASTM F1295-92, ISO5832-11)	α+β type(Swiss)
5. Ti-5Al-2.5Fe (ISO5832-10)	α+β type (Germany)
6. Ti-5Al-3Mo-4Zr	α+β type (Japan)
7. Ti-15Sn-4Nb-2Ta-0.2Pd	α+β type (Japan)
8. Ti-15Zr-4Nb-2Ta-0.2Pd	α+β type (Japan)
9. Ti-13Nb-13Zr (ASTM F1713-96)	near β type (U.S.A.), Low modulus
10. Ti-12Mo-6Zr-2Fe (ASTM F1813-97	β type (U.S.A.), Low modulus
11. Ti-15Mo	β type (U.S.A.), Low modulus
12. Ti-16Nb-10Hf	β type (U.S.A.), Low modulus
13. Ti-15Mo-5Zr-3Al	β type (Japan), Low modulus
14. Ti-15Mo-2.8Nb-0.2Si-0.26O	β type (U.S.A.), Low modulus
15. Ti-35Nb-7Zr-5Ta	β type (U.S.A.), Low modulus
16. Ti-29Nb-13Ta-4.6Zr	β type (Japan), Low modulus
17. Ti-40Ta, Ti-50Ta	β type (U.S.A), High corrosion resistance

Table 2. Chemical compositions of stainless steels-based biomedical alloys (ASTM) [16]

ASTM designation	Alloy	Cr	Ni	Mo	N	Mn	C	P	S	Si	Cu	Fe
(F138-92)	Bar and Wire											
	Grade 1	17.00–19.00	13.00–15.50	2.00–3.00	−0.1	−2.0	−0.08	−0.025	−0.01	−0.75	−0.5	balance
	Grade 2	17.00–19.00	13.00–15.50	2.00–3.00	−0.1	−2.0	−0.03	−0.025	−0.01	−0.75	−0.5	balance
(F139-96)	18Cr-14Ni-2.5Mo	17.00–19.00	13.00–15.00	2.25–3.00	−0.1	−2.0	−0.03	−0.025	−0.01	−0.75	−0.5	balance
(F621-92)	Sheet and Strip	Same chemical composition as specified in Specification F138, grade 1 and 2										
(F1314-95)	Forgings Nitrogen strengthened 22Cr-12.5Ni-5Mn-2.5Mo	20.5–23.5	11.5–13.5	2.0–3.0	0.2–0.4	4.0–6.0	−0.03	−0.025	−0.01	−0.75	−0.5	balance
		(0.10 < Nb < 0.30, 0.10 < V < 0.30)										
(F1586-95)	Bar and Wire Nitrogen strengthened 21Cr-10Ni-3Mn-2.5Mo	19.5–22.0	9.0–11.0	2.0–3.0	0.25–0.5	2.00–4.25	−0.08	−0.025	−0.01	−0.75	−0.25	balance
		0.25 < Nb < 0.80										

Table 3. Chemical compositions of Co alloys registered in ASTM standard for biomedical applications [16]

ASTM designation	Alloy	Cr	Mo	Ni	W	Fe	Ti	C	Si	P	S	Mn	Co
(F75-92)	Co-Cr-Mo Cast alloy	27.0–30.0	5.0–7.0	−1.0		−0.75		−0.35	−1.0			−1.0	balance
(F90-96)	Co-20Cr-15W-10Ni Wrought alloy	19.0–21.0		9.0–11.0	14.0–16.0	−3.0		0.05–0.15	−0.4	−0.03	−0.03	1–2	balance
(F562-95)	Co-35Ni-20Cr-10Mo Wrought alloy	19.0–21.0	9–10.5	33.0–37		−1.0	−1.0 (B < 0.0015)	0.025	−0.15	−0.015	−0.01	−0.15	balance
(F563-95)	Co-Ni-Cr-Mo-W-Fe Wrought alloy	18-22	3–4	15-25	3-4	4-6	0.5-3.5	0.05	0.5		0.01	1.0	balance
(F799-96)	Co-28Cr-6Mo forgings	26.0-30.0	5–7	−1.0		−0.75		−0.35	-1.0			−1.0	balance
(F1058-91)	Co-Cr-Ni-Mo-Fe Wrought alloy Grade 1	19.0–21.0	6.0–8.0	14.0–16.0		balance		0.15 (Be < 0.01)	−1.2	−0.015	−0.015	1.5–2.5	39.0–41
	Grade 2	18.5–21.5	6.5–7.5	15.0–18.0		balance		0.15 (Be < 0.001)	−1.2	−0.015	−0.015	1.0–2.0	39.0–42
(F1537-94)	Co-28Cr-6Mo Wrought alloy	26.0–30.0	5.0–7.0	−1.0		−0.75		0.35 (N < 0.25)	−1.0			1.0	balance

3.1.1. Stainless steel

In the 1920s, 316L stainless steel became a candidate implant material with good mechanical properties and many applications such as healthcare products. Now studies have revealed that 70% of Orthinox stainless steel is used for hip substitutions in the USA [16]. It is an iron-based alloy containing 11-30% by weight of chromium and unspecified nickel [17]. Stainless steel metals are basically divided into four main categories: Martensitic (BCT-hardest crystalline structure), ferrite (BCC crystalline structure), austenite (FCC crystalline structure) and duplex (austenitic (FCC) plusferrite (BCC) phase). The three stainless steel categories confirm the importance in medical equipment and are widely used for implantation applications. The utility of stainless steel depends on (a) availability (b) low cost, (c) excellent production (d) good biocompatibility (e) toughness, and (f) excellent corrosion resistance [17]. However, the main limitation of stainless steel is associated with crack and abrasion corrosion due to damage to the defensive chrome oxide surface film [18]. When proper surface treatment is not performed, it is often seen that stainless steel causes unwanted biological reactions in the human body [19]. Unlike surface treatment of metals such as titanium, aluminum, gold, silicon-based materials and polymers, research on surface modification of stainless steel is less [20]. It is therefore important to analyze the surface moderation of stainless steel to achieve improved surface engineering through chemical stability, mechanical properties, corrosion resistance, blood interface and longevity [21]. Liu et al. [22] used the water-based sol-gel technique to deposit thin hydroxyapatite film on a coarse 316L stainless steel sample. The presence of microcracks has been shown to reduce the interfacial bond strength of the film, however, it was observed that the adhesion of this coating was 40% more apparent than plasma spray coatings.

Table 4. Categorizations of stainless steels medical alloys [23]

Material type	Application grade	Examples
Martensitic	Dental and surgical instruments	Bone curettes, chisels and gouges, dental burs, dental chisels, curettes, explorers, root elevators and scalers, forceps, haemostats, retractors, orthodontic pliers, and scalpels
Ferritic	Very limited surgical instruments	Solid handles for instruments, guide pins, and fasteners
Austenitic	Large number of non-implantable medical devices. Many short-term implants Total hip replacements	Canulae, dental impression trays, guide pins, hollowware, hypodermic needles, steam sterilisers, storage cabinets and work surfaces, and thoracic retractors
Duplex	Not yet applied in the biomedical field	

3.1.2. Mg-based alloys

Sir Humphry Davy discovered the element magnesium in 1808 and then began researching a biodegradable, biodegradable magnesium implant for biomedical purposes. In the late nineteenth century, magnesium wires and implants began to be used in clinical applications such as cardiovascular, drainage, musculoskeletal, and general surgery [24]. The density and modulus of elasticity of magnesium implants and natural bones are almost the same compared to other commonly used implants made of stainless steel, cobalt-based alloys and titanium alloys. This significantly reduces the stress-protective effect of bone restoration [25]. The need for secondary surgery to remove the magnesium implant is inevitable because magnesium is broken down and removed from the urine in vivo [26]. It is also known that Mg2 + contaminants support the growth of new navicular bone tissue and shorten the cracking time [27]. A related study showed that the human body consumes 250-500 mg of magnesium particles per day with physiological functions. The presence of Mg in an average of 70 kg of human body is about 20 g; the harmful amount is still uncertain [28]. The advantage of magnesium is based on natural properties such as (a) a higher weight-to-weight ratio, (b) good electrical thermal conductivity, (c) excellent vibration and damping, (d) higher damping capacity and (e) an efficiency of electromagnetic shielding. [29].

The main limitation when using magnesium components as implants is the presence of an unprotected or faulty oxide film on the sample surface, which causes increased component corrosion [30]. Another problem is the growth of uncontrolled hydrogen bubbles during corrosion; If the formation of hydrogen gas is too rapid, an obstruction to the blood flow can lead to swelling [28]. There are two possible approaches to increasing the corrosion resistance of Mg and Mg amalgams: (i) change in composition and microstructure containing the grain size [31] and (ii) surface treatment or structural coatings [32].

To increase the corrosion resistance and in vitro bioactivity of magnesium alloys, Razavi et al. [33] used the microarchoxidation method with an electrophoretic deposition process to develop a nanostructured coating made of acermanite and diopside ($CaMgSi_2O_6$) on a biodegradable magnesium alloy. To prevent the initial breakdown of magnesium, Chen et al. [34] proposed a strontium phosphate (SrP) conversion coating process. The coating solution containing 0.1 M Sr and 0.06 M PO43 is reported to produce a strontium apatite (SrAP) surface coating at 80 ° C in a minimal basic environment (MEM) which increases the corrosion resistance of the magnesium sample. As a result, the formation of hydrogen gas delayed the toxic effects of magnesium implants on the surrounding cells and tissues.

The performance of the calcium phosphate film on a magnesium alloy was analyzed by an electrochemical method [35]. Impact and constant potential techniques were used to coat the magnesium sample, and the results showed that the alloy coated with impact potential had better corrosion resistance and three times higher polarization resistance than the constant potential coated alloy.

The Lu team [36] also used the β-tricalcium phosphate (CaP P) coating by chemical reaction of Mg in simulated Hank solution. The Ca-P coating has been found to improve the bioactivity, rate of deterioration and corrosion resistance of the sample. In the following research study, they changed the Ca-P coating by introducing strontium (Ca-Sr-P) and left the electrolyte solution in a pure magnesium sample [37]. (Ca-Sr-P) mixture gave a very smooth, thin and improved microstructure layer on the surface. However, it also helped

protect the magnesium substrate from degradation. Nanostructured self-assembled monolayers (SAM) for surface modification of Mg and its alloys were developed by Mahapatro et al. [38] They conclude that SAMs are a promising technique to change the surface of biodegradable Mg substrates and to improve their performance and response to biological interfaces.

3.1.3. Co-based alloys

The wear resistance of Co alloys is higher than the wear resistance of Ti alloys and stainless steel alloys [15]. In artificial hip joints, the head of the joint is subject to wear. Thus, hip joints are made of Co alloys, such as Co-Cr-Mo alloys that exhibit high strength and ductility. Carbide dispersed in Co alloys has been reported to increase the wear resistance of these alloys [13]. In addition, the conversion of the metastable γ phase to the ens martensitic phase (through a deformational transformation) has been found to increase the wear resistance of the Co alloys [13]. Compared to cast Co-Cr alloys, machined Co-Cr alloys can be used for implant devices with high strength requirements. However, the Ni content in forged Co-Cr alloys causes allergic reactions [15]. Some of the mechanical properties of metallic biomaterials are compared in Table 5. Examples, advantages and disadvantages of metallic alloys used in biomedical applications are summarized in Table 6. As seen in Table 5, Young's Co-Cr alloys module and 10 times more steel than stainless steel can cause strain. However, Young's titanium and alloys module is about 0.5 times higher than that of stainless steel, and therefore the risk of stress protection is lower in Titanium and its alloys compared to Co-Cr alloys and stainless steel.

Table 5. Evaluation of mechanical properties of bone with metallic biomaterials [39]

Material	Young's Modulus, E (GPa)	Yield Strength, (MPa)	Tensile Strength (MPa)	Fatigue Limit, (MPa)
Stainless steel	190	221–1213	586–1351	241–820
Co-Cr alloys	210–253	448–1606	655–1896	207–950
Titanium (Ti)	110	485	760	300
Ti-6Al-4V	116	896–1034	965–1103	620
Cortical bone	15–30	30–70	70–150	

Table 6. Evaluation of metallic biomaterials used in the human body [39].

Metals and alloys	Selected examples	Advantages	Disadvantages	Principal applications [29]
Titanium-based Alloys	CP-Ti, Ti-Al-V, Ti-Al-Nb, Ti- 13Nb-13Zr, Ti-Mo-Zr-Fe	High biocompatibility [24–26]. Low Young's modulus excellent corrosion resistance, low density	Poor tribological properties [27], Toxic effect of Al and V on long term	Bone and joint replacement, fracture fixation, dental implants, pacemaker encapsulation
Cobalt and Cr alloys	Co-Cr-Mo, Cr-Ni-Cr-Mo	High wear resistance [20]	Allergy consideration with Ni, Cr and Co [2] much higher modulus than bone	Bone and joint replacement, dental implants, dental restorations, heart valves
Stainless steels	316L stainless steel	High wear resistance [23]	Allergy consideration with Ni, Cr and Co [2] much higher modulus than bone	Fracture fixation, stents, surgical instruments
Others	Ni-Ti	Low Young's modulus	Ni cause allergy [2]	Bone plates, stents, orthodontic wires
	Platinum and Pt-Ir	High corrosion resistant under extreme voltage potential and charge transfer conditions [30]		Electrodes
	Hg-Ag-Sn amalgam	Easy *in situ* formability to a desired shape susceptible to corrosion in the oral environment [30]	Concerns related to Hg toxicity [30]	Dental restorations

3.1.4. Ti-based alloys

More than 1000 tons of titanium-based materials and devices are implanted to patients worldwide every year [40]. Initial efforts to implant Ti-based biomaterials date back to the 1930s when Ti was seen to be adequately accepted by femoral bone tissues in felines, similar to stainless steel and Co-Cr-Mo. The biomedical use of Ti is due to the relative lightness of the metal compared to conventional steel and Co-Cr alloys, characterized by relevant densities of 4.5, 7.9 and 8.3 g / cm3. Ti is also superior in terms of biocompatibility, biocorrosion resistance, specific strength and elastic modulus.

Depending on their chemical composition, commercially pure Ti is divided into four degrees, where the% by weight of inclusions increase from grade I to grade IV and reach a maximum of 0.7%. O (0.18-0.4% by weight), N (0.03-0.05% by weight) and Fe (0.20-0.50% by weight) have been shown to significantly affect the ductility and strength of Ti. Allotropism in Ti means that the allotropic transformation temperature of 885 ° C is defined by a hexagonal sealed α structure of the material under TAT, at higher temperatures Ti takes on a body-centered cubic β structure. The addition of Al, Sn, C, O or N has been shown to stabilize the a-structure by increasing TAT; however, Mo, Nb, V, Cr and Fe reduce TAT, thus contributing to the β - structure. Unlike form B, a-phase materials exhibit excellent heat and oxidation resistance and weldability (due to single-phase microstructure), but less workability and strength.

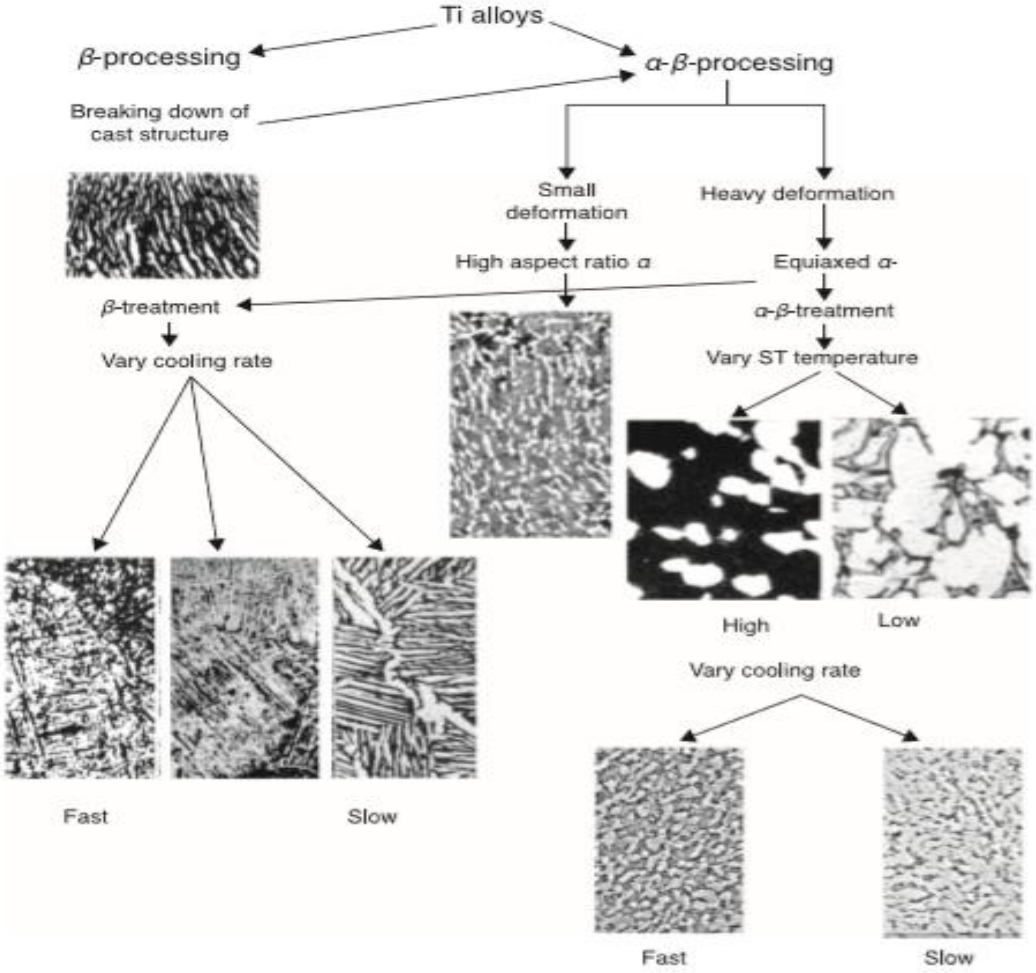

Figure 1. Influence of thermomechanical processing on development of various microstructures in α – β titanium alloys [21]. ST (solution treatment)

Commercially pure Ti is an α -type alloy. Hardening via heat treatment is not used for these single- phase alloys, as increased strength is generally attributed to the precipitation of one phase in the multi-phase system. Using specific amounts of β - stabilizing elements, a two-phase structure comprising both α and β phases can

be attained. The most popular Ti- based biomedical alloy, Ti6Al14V, is comprised of Al (5.5–6.5 %wt) and V (3.5–4.5 %wt), and is a good example of a two- phase structure where the β - phase is dispersed within the α - phase. The precipitation is achieved by means of annealing, followed by rapid cooling (quenching) and subsequent thermal ageing. The latter prompts the metastable β -phase to precipitate in a form of small particles, with the resultant structure showing improved strength compared to an α - β alloy that has been subjected to heat treatment only. In Ti-13V11Cr-3Al alloys, a relatively large concentration of V imparts a clearly β - type microstructure and thus annealing can significantly increase the strength of the material while reducing its ductility. Figure 1 shows the effect of thermomechanical processing on microstructure of Ti alloys [8].

Medical use of Ti-12.5Mo, Ti-8Al-7Nb, Ti-13Nb-13Zr, Ti-29Nb-13Ta4.6Zr and Ti-121Mo-6Zr-2Fe has also been proposed [41-43]. The excellent mechanical properties, anti-corrosion ability, cytocompatibility and biocompatibility of Ti15Nb4Ta4Zr alloys make them suitable for orthopedic implants [44]. Compared to Ti6Al4V, this alloy improved new bone formation and bone mineral density, which is equal to or higher than Ti6Al4V [44]. It has been reported that increasing the Nb content, especially by means of an oxidation process, increases the wear resistance of the alloy due to the hardness and lubricity of the Nb2O5 layer [45]. Since Ti-NbTa-Zr alloys cannot form apatite on their surface under conventional chemical and heat treatment processes, another surface modification method is required [46].

As with other metallic biomaterials, the mechanical properties of Ti and Ti-based alloys vary depending on the type and weight% of the alloy impurities and the processing methodology. The elastic modulus of Ti-based materials at 100 GPa is relatively low compared to steel and Co-Cr alloys, whereas the strength profile is similar among these materials [47]. A biomaterial with a lower Young's modulus can transfer stress between itself and bone homogeneously; however, as the module approaches a bone, the probability of failure will increase under high shear deformation in vivo [48]. Since the fatigue test, which is sufficiently replicated in vivo, is complex, it is difficult to predict exactly how the material will behave under stress after implantation [49].

The standardized in vitro fatigue test includes the Ti-6Al-4V alloy used as a standard material for comparing the results and tension / compression, bending, torsion, and rotating bending fatigue studies [50]. Compared to their specific strengths, Ti-based materials are superior to other implantable metals. For commercially pure Ti, tensile strength values of 240 to 550 MPa are expected to be between 170 and 485 MPa, 15 to 24% elongation and 25 to 30% reduction in area. The tensile strength of Ti-6Al-4V alloys is about 860 MPa, regardless of whether the alloy is poured or poured. Other parameters differ from 758 and 795 MPa yield strengths, a minimum elongation of 8 and 10%, and a minimum reduction of 14 and 20% for cast and forged alloys. The pure strength of Ti biomaterials, ie against a force that can produce slip errors on a material parallel to the direction of the force, is relatively low.

In addition, Ti materials are susceptible to tribocorrosion in the applications that entail a sliding contact between the device components in physiological fluids, such as between the femoral and the tibial or acetabular elements of the hip joint replacement implant [42]. Tribocorrosion is influenced by the electro-chemical and mechanical conditions of the contact, and generally results in the increased rate of biomaterial degradation [41]. Certain Ti alloys, such as Ti-29Nb-13Ta-4.6Zr, have been demonstrated to recover their passive surface configurations under both sliding and fretting contacts [43]. Wear and corrosion resistance of martensitic Ti 6Al 4V ELI alloys was significantly better compared to Ti-6Al-4V ELI alloys with an α - β microstructure [41]. Other studies have suggested the relationship between the microstructure of the material and the rate of its wear is not straightforward [51]. Plasma nitriding of the Ti surfaces has also been shown to improve the wear properties of the material through the formation of a hard compound layer of TiN and Ti 2 N [52]. Plasma assisted chemical vapor deposition of hydrogenated amorphous carbon (a-C:H) onto the surface of the Ti-6Al-4V alloy was also suggested as a method to improve corrosion and wear resistance of the material [53]. Although beneficial at low applied load, the coatings failed prematurely under higher load.

Otherwise, in vivo biocompatibility and corrosion resistance of highly reactive Ti and Ti based alloys results from the presence of a robust passive oxide Ti fim on their surface [40]. In general, the corrosion process causes a rapid reaction on the surface of all metals, from reactive Ti to noble Au. Under certain environmental conditions, for example in the absence of low solubility and defects, such a reaction lm will be characterized by strong adhesion to the substrate and protect the underlying bulk material from deterioration. Typically, these passive oxide layers are 1 to 5 nm thick, optically transparent, and amorphous in nature. The amorphous structure of the layer with the minimum grain boundary and the self-healing feature of fi lm provide low sensitivity to corrosion. In the case of Ti, the oxide layer has been shown to contain amorphous and slightly crystalline TiO2, Ti2O3 and TiO have also been identified [54]. The passive pl formed on the surface of the Ti-6Al-4V alloy was similar in its chemical composition to commercially pure Ti, excluding some Al203 and hydroxyl moieties detected in the alloy. Similarly, titanium dioxide formed primarily on the surface of the Ti-Ni alloy with limited amounts of NiO, metallic Ni and -OH functionality. In contrast, the surface oxide layer on the surface of the Ti-Zr alloy has been shown to consist of titanium and zircon oxides in the bulk material, affecting the relative concentration ratio of Ti to Zr. Higher Zr concentrations resulted in a thicker, more stable protective coating.

In 2017, Eren et al studied about the "characterization of biomedical TiNbSn alloys produced by PIM" [55]. They prepared the alloys by means of PIM method and then they observed that Sn addition had negative effect on the sintered density of the alloy when sintering process conducted at lower temperatures (1250-1400 ^{o}C) but it had no or minimum effect when sintering temperature increased to 1550 ^{o}C (96% TD).

In 2018, BIMAS-RC group published four papers about the biomedical materials. In the first one, they examined "TiNbZr alloys produced via PIM for implant applications" [56]. In this paper they detected by XRD and SEM that Zr behaved as a β stabilizer and according to DTA, and it decreased α to β transition temperature approximately 30 ^{o}C, and elastic modulus remained approximately steady between 103 and 110 GPa (Figure 2). They concluded that TiNbZr alloys can be used as an alternative to known metallic implant materials.

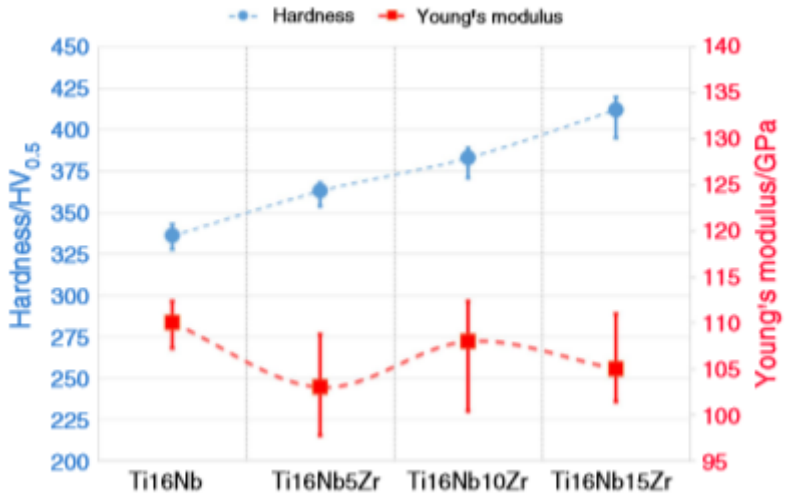

Figure 2. Mechanical properties of the produced PIM Ti–Nb–Zr alloys [56]

In the second paper, they worked on the "metallurgical properties and biomimetics HA deposition performance of TiNb PIM alloys" [57]. The aim was to investigate the effect of the Nb amount on the microstructure, mechanical properties, corrosion behavior and HA formation ability of Ti-Nb alloys in this paper and they used XRD, optical and SEM imaging (Figure 3) for microstructural characterization and hardness measurements and transverse rupture strength for mechanical properties. They concluded that with the increment of Nb content, β phase stability increased in the α+β phases. Also, they observed that Nb content had significant effects on the mechanical properties of the considered alloys, and they observed

lowered elastic modulus (100-115 GPa) than that of the titanium (132-140 GPa). Also, they concluded that the addition of Nb contributed to the improvement of corrosion resistance and induced to increase of HA formation ability.

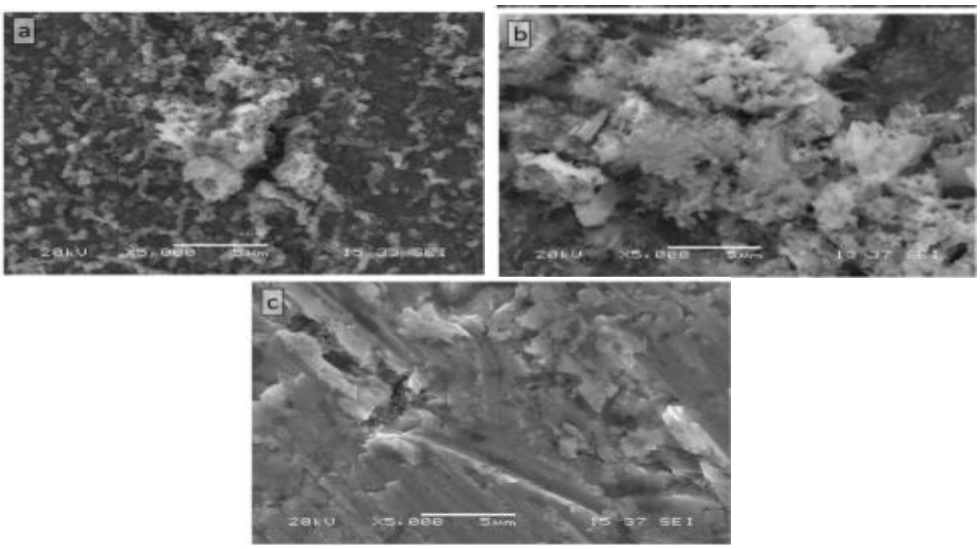

Figure 3. Surface morphology of the alkali-treated a) Ti, b) Ti-40Nb c) non-treated Ti40Nb. (After soaking in SBF for 7 days) [57]

In the third paper, "mechanical properties and electrochemical behavior of porous Ti-Nb biomaterials" were reported by the same group [58]. In this study, Ti16Nb alloys containing porosity between 4 to 60 % were produced by powder metallurgy using different amount of space holder materials (Figure 4). The specimens were sintered at 1200 ^{o}C for 3 h in a high-level vacuum. The effects of space holder content were investigated. It is seen that the addition of 70 vol% space holder materials to the Ti16Nb alloy leads to a decrease in the density value from 4.7 g/cm^3 to 1.9 g/cm^3. Also, it is observed that by producing Ti16Nb with 70 vol% space holder, elastic modulus decreased from 96 GPa to 15 GPa (Figure 5).

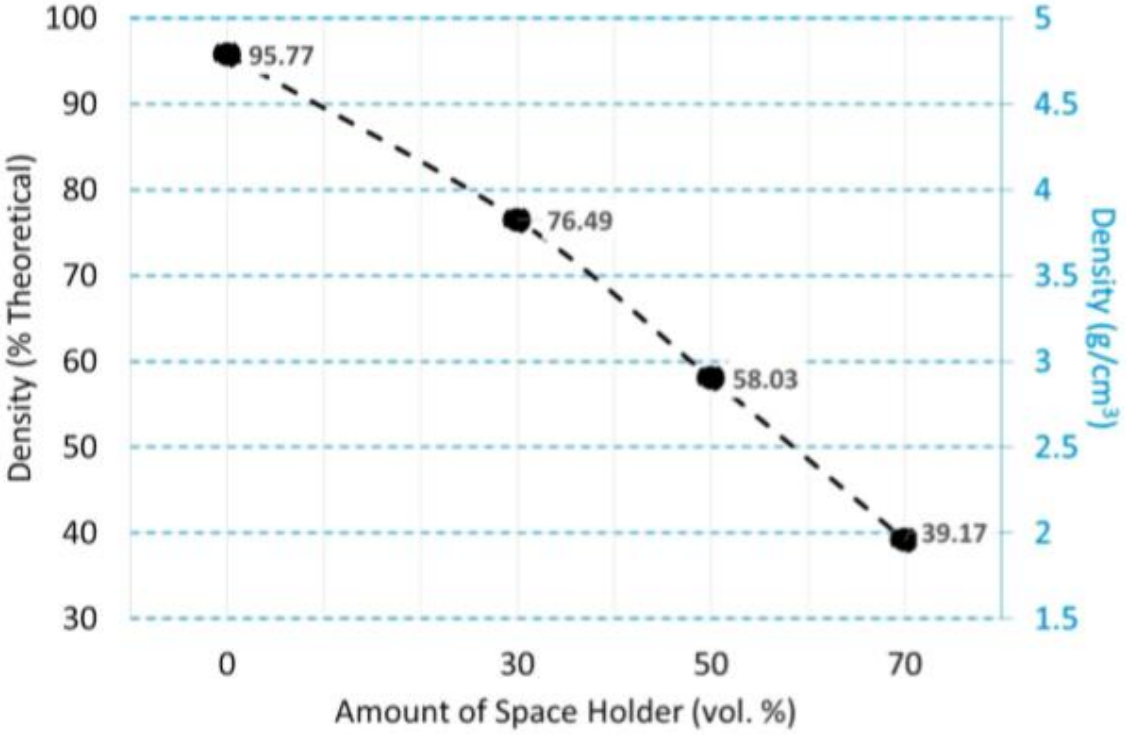

Figure 4. Densities of the samples with different space holder content [58]

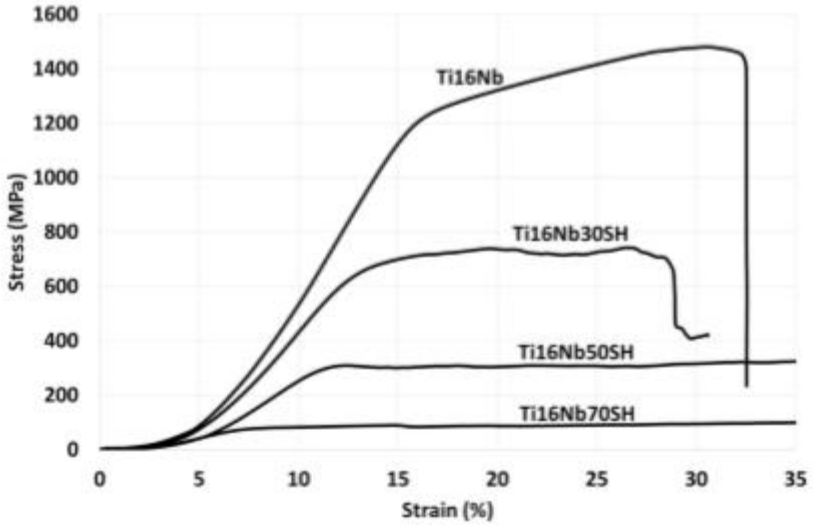

Figure 5. Compressive stress-strain curves of the porous Ti-16Nb alloy with addition of different amounts of NH_4HCO_3 [58]

In their last article published in 2018, they worked on "powder metallurgy processing of TiNb-based biomedical alloys" [59]. They reported that Sn content (2% and 4% by weight) was added to Ti16NbXSn sintered alloys consisting of alpha + beta phases. Hardness and Young's modulus of alloys measured by nanoindentation technique. These results show that there is a relationship between mechanical properties and Nb-Sn content. It was concluded that adding Nb to cp-Ti caused a decrease in Young's modulus.

3.1.5. Nobble alloys

As a result of high durability, stability and excellent corrosion resistance, noble materials and their alloys are widely used in restorative dentistry [60,61]. Gold fillings can be produced by casting or mallet with Au alloys preferred to pure Au for the casting method. The mechanical performance of Au is lower compared to alloy-based materials, and foreign materials such as Cu and Pt (<4%) are known to strengthen Au-based alloys. However, a high concentration of noble material (> 75%) provides their anti-corrosion performance. If the Au level exceeds 83%, the alloy becomes too soft to use in stress-bearing applications such as cups and crowns. Pure gold foil is used for hammer restorations where soft layers are installed in the cavity and are combined with thermal diffusion of atoms between layers under applied pressure. Elemental Ag is introduced into the alloy to improve the color of the product obtained. Higher Pt concentrations (> 4%) have been shown to increase the melting point of the alloy, so small amounts of Zn are added to reduce the melting point while making the process more complex. The surfaces of Au alloys such as Ag-Cu-Au, Pd-Ag-In-Sn and Ag-Pd-Cu-Au are encapsulated by Cu and Ag oxides [62]. There were no significant differences in the mechanical yield strength between Au-Pd, Pd-Ag, Pd-Ag-Au and Au-Ag-Pd alloys; however, their percent elongation varied greatly with the Pd-Ag and Pd-Ag-Au alloys characterized by the highest elongation values [63]. Silver-based amalgam is a mercury-containing alloy that is widely used as dental coating material. The dental benefit is due to its unique feature for the basic Hg to remain in a liquid phase at room temperature and to produce a plastic material that can be easily deformed by reacting with other metals such as Ag and Sn. The use of amalgam is preferred over composite large and complex restorations. There are margins in dentin or cement where isolation is difficult [64]. In practice, the dry Ag-Sn alloy is mixed with Hg, resulting in the reaction: Ag 3 Sn + Hg ↔ Ag 3 Sn + Ag 2 Hg 3 + Sn 7 Hg. Typical dry alloys consist of more than 65% by weight Ag, less than 29% by weight Sn, less than 6% by weight Cu, less than 2% by weight An and less than 3% by weight Hg. Plasticity makes it easy to pack the alloy into the dental cavity and then hardens over time. Generally, the alloy is expected to reach 2% of its final strength after 60 minutes and almost all of its final strength after 24 hours of curing. Once completely hardened, the alloy should contain 45 to 55% Hg, 35 to 45% Ag and 15% Sn. Tin oxide forms the protective oxide layer on the surface of the material.

Dental amalgams have been used for more than 150 years for dental restoration and minimum technological requirements for amalgam setup, compared to gold or composite dental materials, due to their malleability, durability and affordability [65]. However, there has been much debate about the potential toxicity of these substances in vivo. Indeed, even at minute levels, Hg0 is thought to be neurotoxic and nephrotoxic [66]. It is therefore possible that Hg0 may leak from amalgam, thereby exposing the patient's body to increased mercury burden [67]. Over the years, amalgams have been claimed to contribute to a number of diseases, from multiple sclerosis to chronic fatigue, Alzheimer's or Parkinson's disease [68]. However, only a few relevant epidemiological studies have been conducted, and even then, data from dental exposure has been compared to occupational hazardous mercury exposures. Full-scale clinical trials of the population with amalgam exposure are complicated by inadequate longitudinal exposure assessment and negative mixing because higher socioeconomic groups will have access to restorative dental care. Some recent clinical studies have found that neurobehavioral and neuropsychological performance does not differ significantly between children with and without amalgam obstruction [69]. All studies have reported increased urinary total mercury levels, higher mean urinary albumin concentration and increased micro-albuminuria in amalgam patients.

3.1.6. Biodegradable alloys

Biodegradable metals such as magnesium are particularly promising in applications that promote tissue regeneration and healing, especially where load bearing function is required [70]. Magnesium is highly biocompatible and nontoxic, Mg ions are essential for human metabolism [71]. Highly suitable for producing fully absorbable intravascular stents for the treatment of arterial disease minimizes the risk of chronic inflammation and late thrombosis associated with permanent metallic stent implantation. Mg and its alloys for osteosynthesis offer high primary stability, high tensile strength and fracture resistance.

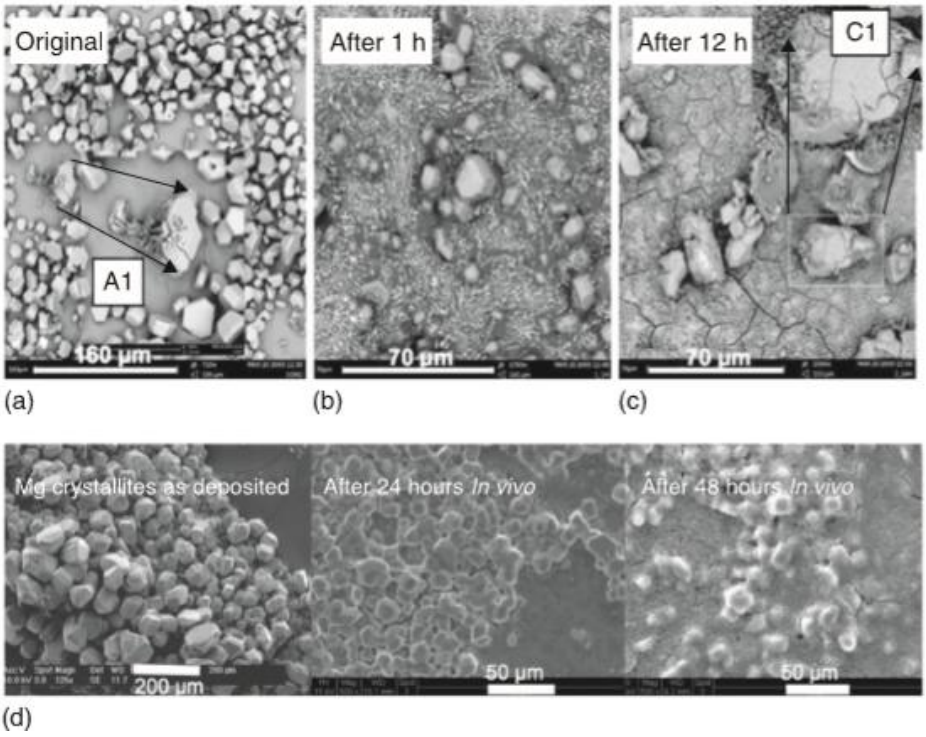

Figure 6. Stability of Mg coating deposited by means of physical vapor deposition onto silicon substrate and tested under in vitro and in vivo conditions. SEM images of Mg coating consisted of micro grains before (a) and after exposure to cell culture (b) and (c). The Mg grains can still be seen after 12 h in the media, a promising result considering most Mg alloys corrode after 1 h; (d) SEM images of Mg coating implanted subcutaneously in mouse, showed the coating to be well preserved and intact after the in vivo conditions, with the thickness of the fibrous capsule in the same range as for titanium control samples suggesting good biocompatibility of the Mg grains [72]

It is also lightweight, has a density of 1.74 g / cm^3, which is 1.6 and 4.5 times less intense than aluminum and steel, respectively [25]. The specific gravity and elastic modulus of Mg is very close to the human cortical bone and reduces anti-stress effects on bone tissue associated with implant integration. In addition, Mg bivalent ions play a close role in the formation of biological apatites, thereby determining the extent of bone fragility, bone healing and regeneration [24].

In spite of its favorable mechanical and biological properties, the clinical applications of Mg are limited by its rapid corrosion rate in vivo (Fig. 6), especially in a physiological environment with pH values between 7.4 and 7.6 and biological fluid being present with chloride ions at levels of 150 mmol/L. Such rapid degradation may lead to the release of large amounts of Mg^{2+}, localized hydrogen gas (H_2) accumulation and alkalization, and to an untimely loss of mechanical strength of the implanted material [24]. For instance, intravascular ultrasound imaging of absorbable Mg stents in human coronary arteries indicated the loss of the radial force and consequent early recoil as a main contributor for restenosis at 4 months [72]. Thus, to meet clinical requirements, precise understanding of degradation kinetics and control over in vivo degradation of implants based on biodegradable metals and alloys are essential, especially at the early stages of implantation where degradation may be most pronounced.

It is important to understand that the environment greatly affects the biodegradation behavior of the absorbable material. The biological environment directly affects the properties and behavior of the implant material through different physico-chemical parameters (eg PH, ion concentrations, oxygen). Simultaneously, as an inserted foreign body, the implant evokes an immunological response and affects the surrounding tissues due to direct and close contact. For example, the Mg alloy (AZ31) screws implanted in a sheep hip bone differed in biodegradation, corrosion morphology and dynamics; screw threads in the bone, upper muscle / connective tissue [73]. Similarly, Mg wires have been shown to undergo extensive biocorrosion when placed in the rat arterial wall, whereas for Mg wires exposed to blood in the arterial lumen for 3 weeks, very little corrosion has been observed [74]. Therefore, in order to adequately predict the long-term behavior of biodegradable metals such as Mg and Mg alloys, an in vitro assessment must be supported by evaluating the degree of biocorrosion that takes place under complementary in vivo conditions.

As with many other metals, the physico-chemical properties of Mg can be adjusted by introducing other elements into the alloy [75]. Changes in the chemical composition as a result of the addition of ligands combined with a selected processing methodology potentially improve the mechanical and corrosion behavior of the material, resulting in the resulting microstructure of the alloy. It has been reported that rare earth metals such as Gadolinium added to the alloy in small quantities have the deepest effect on the corrosion sensitivity of Mg alloys [25].

The above results clearly support the viability of Mg-based biomaterials as biocompatible, fully degradable, lightweight and potentially osteo-inductive materials. However, in order to truly facilitate the clinical application of Mg-based bioabsorbable devices, more extensive in vitro and in vivo studies are required to precisely verify the safety of such devices [25].

Also, some Fe and Fe based alloys are biodegradable. A patent has been recently registered on biodegradable FeMn alloys [76]. The present invention is a method for producing a permeable tubular metal alloy stent inserted into the container and then expanded to a certain extent to maintain the flow in the container as required; - Production using 3D printer, - Using 200-400 W laser source during production, - Spreading alloy forming powders on the tray in the production pool.

4. Surface modifications

The field of implantology is constantly evolving as more is learned about the specific biological relationships of the implant and the environment. Important factors in terms of surface engineering are the effect of surface chemistry, topography at micro and nanometer level, physicochemical effects and biochemical mediated cell differentiation, inevitable bacterial colonization of biological implants, biological dimensions and histology of environmental structures. Suitable surface modification

techniques not only maintain the desired volume properties of biomedical materials, but also improve the specific surface properties required by different clinical applications [77,78].

The focus in the following paragraph is focused on the surfaces of implant materials reserved for hard tissue replacements. Surface modification techniques will be discussed topographically and chemically. Bioactive surface modifications and physicochemical parameters such as crystallinity and wettability will be studied, along with existing trends to optimize topography at the nanometer level, starting with surface grooves at the micrometer level.

4.1. Surface corrugation

The effect of surface roughness on osseointegration rate and biomechanical fixation of hard tissue implants has been identified as a key factor. Essentially, micron-level surface topographies have been reported as important and various surface modification techniques have been developed that operate at this length scale. In particular, observation of faster and increased bone contact with micron-scale rough surfaces produced by scraping and subsequent acid etching stimulated considerable activities. This observation also leads to the conclusion that hard tissue implants based on alloys, mainly titanium, are not only fully bio-inert or biocompatible, but also appropriate surface conditioning may result in protein adsorption, cellular activity or tissue response. higher level of osseointegration. Various studies have shown that morphological features at the micro level control the rate and quality of new tissue formation at the interface [79-80]. Kieswetter et al. It suggests that the complement of autocrine and paracrine factors produced by cells at the bone-implant interface can be guided by changing the implant surface roughness, as reported by the effect of surface roughness on titanium to influence the production of local factors involved in bone formation by osteoblasts. and directly affect the type of interface that occurs in the implant site [81].

Numberless other investigations resulted in the finding that an optimal roughness for hard tissue implants is in the range of 1–10 lm. It was concluded that this range of roughness shows the ability to maximize the interlocking between mineralized bone and the surface of the implant [82]. Be- sides the experimental driven results from in vitro and in vivo investigations, theoretical calculations suggested that the ideal surface structure should consist of hemispherical pits of approximately 1.5 lm in depth and 4 lm in diameter [83] that could be supported by numerous in vivo studies on implant topography effects [84].

In order to obtain well-accepted and integrated implants, the implants must be optimally mechanically locked into the host tissue. Not only the geometric requirements and stress distribution factors of the host tissue direct the topographic demands on the implant surface, but also the thought that the bone adapts to the mechanical loading of osteocytes acting as mechanosensors [85].

Various methods are used to create and construct such microstructural surface properties to meet the demands for increased bone implant contact formation. These methods include blasting, etching, anodization and plasma spraying.

In 2019, the BIMAS-RC research group published three articles on biomedical materials. In the first they published a paper on “biomedical porous TiNbZrTa alloys” [86]. In this article, they produced the alloys by the gap holding method using an ammonium hydrogen carbonate spacer. The pore size distribution, porosity ratio and mechanical properties of the porous alloys obtained were investigated. Sintered porous TiNbZrTa alloys have been found to have suitable mechanical properties (elastic modulus: 36-38 GPa, transverse tensile strength: 154-281 MPa) for hard tissue implants. In the second article [87], “The effect of Zr addition on the corrosion behavior of biomedical PIM Ti-16Nb alloys in SBF”. They first prepared the alloys with the PIM technique and then carried out electrochemical corrosion tests using simulated body fluid using

electrochemical impedance spectroscopy and polarization curve analysis. The addition of Zr has been observed to be effective in increasing the corrosion resistance of the Ti16Nb alloy.

Finally, they published an article on "New HA / graphene oxide / collagen bioactive composite coating with electrodeposition on Ti16Nb alloy" [88]. In this article, a new implant coating material, including grapheme oxide (GO) and collegen (COL) and hydroxyapatite (HA), was manufactured with the aid of tannic acid by electro-precipitation (Fig. 7). The surface of the Ti16Nb alloy was subjected to anodic oxidation and then HA-GO coating was applied to the Ti16Nb surface by the cathodic method (Figure 8). Then, COL was left on the surface of the HA-GO coating by biomimetic method. HA, HA-GO, HA-GO-COL coatings on the surface of the Ti16Nb alloy have increased the corrosion resistance by creating a barrier layer on the surface. For HA-GO-COL coating, the highest corrosion resistance is achieved due to the compactness and homogeneity of the coating structure (Fig. 9). The hardness and elastic modulus of the coatings were measured by the nanoindentation test, and the addition of GO and collagen to the HA coating caused an increase in strength. Adding GO to the HA coating reduces the viability of 3 T3 fibroblast cells, while adding collagen to the HA-GO coating increased cell adhesion and viability.

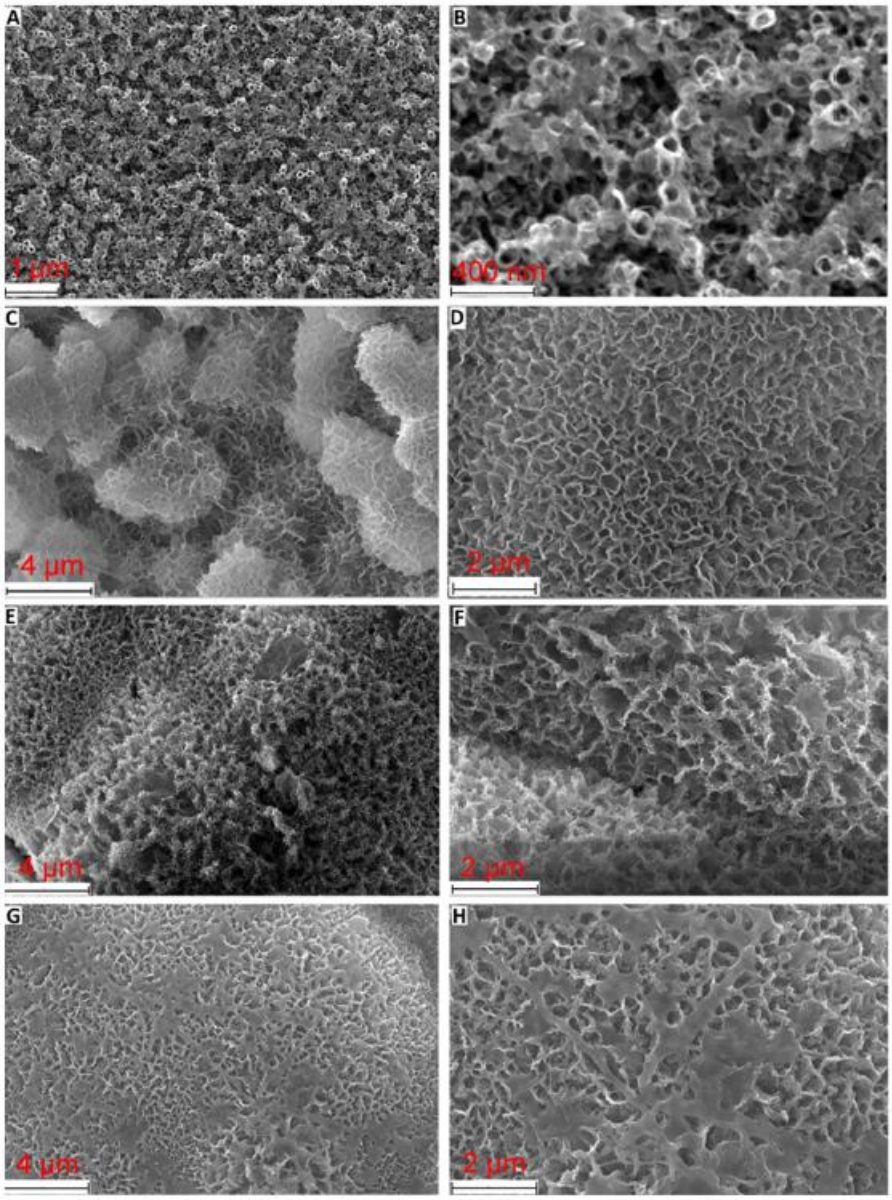

Figure 7. FESEM images of TiO2 NTs formed on the pretreated Ti16Nb alloy surface [A) 50.000x, B) 200.000x] and microstructures of HA [C) 20,000x, D) 40,000x], HA-GO [E) 20,000x, F) 40,000x], HA-GO-COL [G) 20,000x, H) 40,000x] coatings [88]

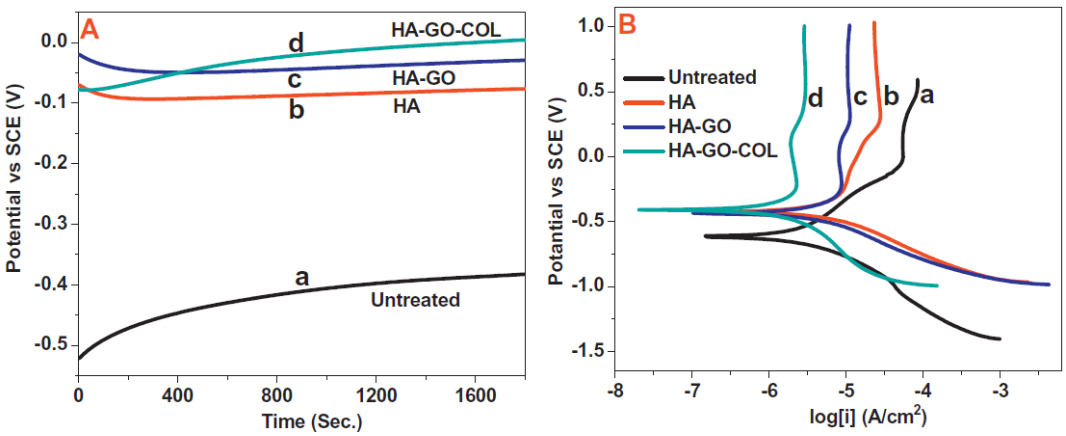

Figure 8. OCP curves of a. uncoated Ti16Nb alloy, b. HA, c. HA-GO, d. HA-GO-COL coatings in SBF (A), Potentiodynamic polarization curves of a. uncoated Ti16Nb alloy, b. HA, c. HA-GO, d. HA-GO-COL coatings in SBF (B) [88]

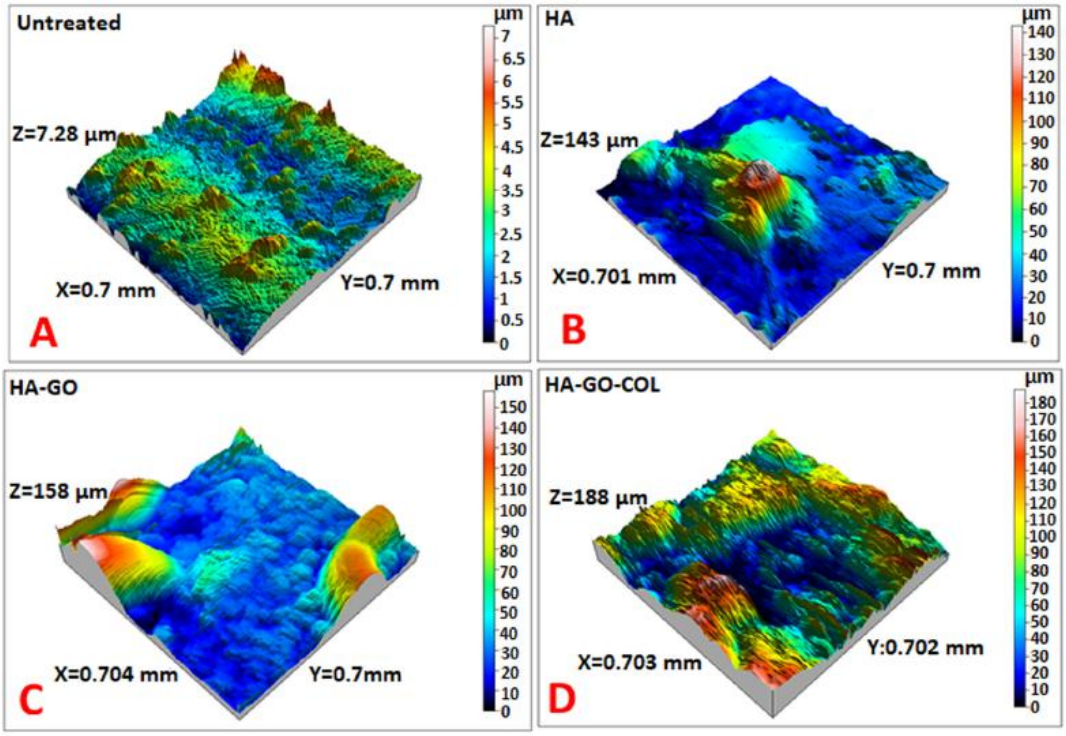

Figure 9. Surface spectroscopy analysis of uncoated Ti16Nb alloy (A) and HA (B), HA-GO (C), HA-GO-COL (D) coatings [88].

4.2. Surface topographies

In the previous paragraph, techniques to change the surface topography on a micron scale are introduced. These surfaces often show random topographies with surface structures ranging from nanometers to millimeters. Zinger et al. Showed that the combination of surface modeling techniques with the next blasting and etching at the sub-micrometer level leads to surface roughness with combined micrometer and nanometer structures and therefore shows improved osteoblast activity [89]. It has been found from such studies that in vitro cell attachment and in vivo bone implant interface can be affected by both nano-scale and micro-scale parameters of topography, in which osteoblasts exhibit an improved bond on submicron-scale structures [90]. The role of surface roughness on both length scales at the micron or nanometer level requires that molecular interactions with the surface occur and, as a direct consequence, the cell adhesion phenomenon and local biomechanical properties of the built-in interface are directly affected by this length scale. Modifications of nano scale surfaces will affect the chemical reactivity of a

biomedical material, thereby affecting the ionic or biomolecular interactions of the surface with the host tissue. Such changes in surface properties modified by nano-scale modifications can alter wetting properties, lead to a different protein adsorption, or have an impact on the mineralization of de novo bone formation. The importance of topography on the nanography scale is emphasized, where an interpretation of the sensitive reaction to nanotopography occurs because there are minor differences in chemistry between one part of the topography and the other. The opposite approach is that there is a small difference in topography, even with small local differences in chemistry with techniques such as nanoprinting [91].

Until now, there is no precise information about the impact of such properties on the biological environment due to the absence of standardized surfaces with high controllable lateral resolution and nano-scale repetitive topography. Increased availability of a well understood and standardized surface structures below 100 nm will help to understand interactions between specific proteins and cells.

In recent years, reports have been published on the special adjustment of surface properties at the nanometer level to investigate possible effects of surface structures in the region below 100 nm. The most promising approaches and the surface chemistries below will be discussed for reproducing the surface roughness in the desired structural sub-100 nm region with reproducibly sufficient lateral resolution at the nanometer scale as well as comparable surface chemistry.

4.3. Chemical modification

Biological tissue mainly interacts with the outermost atomic layers of an implant. Although secondary and other byproduct reactions occur, the primary interaction site is usually defined by the first atomic layers. Various efforts are therefore made to alter the surface of existing biomaterials to achieve desired biological responses [78]. In addition to the morphological modifications of the surface roughness of biomedical implant materials, various chemical modifications of the implant surfaces have been explored to achieve an optimized tissue interaction. The ideal rigid implant should provide a desired feature in any case, regardless of a surface that will induce osseointegration, the implantation site, the amount of bone, or bone quality. Therefore, physicochemical treatments are designed to directly cause surface interactions with the chemical nature of bone to increase and affect de novo bone formation. In principle, physicochemical approaches are either based on control of surface composition, surface free energy, wettability or electrical charges. These treatments can transform a commonly bioinert surface of an implant material, such as metals, into a bioactive character.

5. Future perspective

Surface modification of biomaterials is a broad topic that is considered in a wide range to improve implant performance and service life in a human body. Stainless steel, titanium, magnesium and chrome-cobalt are the leading implant materials in orthopedic applications. The in-depth sophisticated analysis of the published work on surface modification of biomaterials emphasizes that the surface modification process increases biocompatibility, chemical laziness, lubricity, sterility, asepsis, thrombogenicity and hydrophilicity of the biomaterial. Besides, it also improves superior mechanical properties. corrosion resistance, surface hardness, Young's modulus and wear resistance. Surface engineering with the non-traditional processing of biomaterials is the modernist method for the synthesis of biomaterials. With the EDM process, the surface modification path, the composition of the tool electrodes and the intelligent selection of machining parameters ensure the accumulation of minerals compatible with the human body environment, open porous structure and metallic residues. The combined selection of EDM process parameters improves key component properties. In addition, the method can develop replacement bone close to natural bone architecture at all scales and plays an important role in biological systems [4].

From the first appearance of the 1980s to the present, PIII & D has become a popular physical technique suitable for surface modification of various materials. PIII & D can offer versatile processing capabilities to adapt the surface properties of many biomaterials by adding numerous different types of elements and functional groups to the materials. This study reviewed the improvement of the mechanical and bio-logical properties of biomaterials (Ti, Ti alloys and biopolymers) and recent progress with the PIII & D method in China.

Besides composition and physical and chemical properties, the nano and microstructure of the surfaces have been identified as an important factor affecting a number of cellular responses such as cell morphology, adhesion and differentiation. However, the creation of versatile nano- or microstructures cannot be accomplished only with PIII & D technology. Combination of PIII & D with other manufacturing methods may be required to ensure optimum performance of biomedical implants and to be compatible with the specific requirements of biological molecules. In addition, interdisciplinary approaches will be critical for the design of biomaterial surfaces. Ultimately, advances in emerging biomedical applications with fully controlled physical, chemical and biological properties remain a major opportunity for future research [29].

It is well known that corrosion fatigue impairs the performance of biomedical metallic alloys, and these components are still responsible for most disastrous failures despite the evolution of both material quality and design over the years. Therefore, it can be expected that the development of new materials and the development of existing materials will result from this issue. Indeed, there is a lot of information about the isolated aspects of this problem, namely studies on the corrosion or fatigue of metallic biomaterials. Many authors have reported the combined action of the corrosion and fatigue of biomedical alloys in physiological solutions and faced the difficulty of understanding the synergy between them. However, the cumulative fatigue design is very noticeable, while fatigue crack propagation is virtually unexplored. Therefore, there is a strong need to investigate the crack growth behavior of metallic biomaterials in corrosive physiological environments, which are made up of not only saline types but also proteins and enzymes. While the studies linking the corrosion fatigue crack growth mechanisms of biomedical alloys with microstructural features such as grain size, crystal phase composition and distribution are very few, experimental studies including different heat treatments and mechanical processing operations are not found in the literature. everything.

Reliable estimation of the fatigue life of metallic biomaterials will only be possible with the development of precise models based on extensive experimental data. As can be understood from the literature examined in this study, this research area has the potential to expand to all typical metallic materials used for biomedical applications.

The same shortage of systematic research occurs through methods of preventing and reducing corrosion fatigue failure. Even for traditional techniques such as sandblasting and hard thin coatings, corrosion fatigue studies are inadequate. This deficiency is more evident with the most up-to-date methods that produce UFG or surface nanocrystalline materials. More than an efficient research area, corrosion fatigue of biomedical metallic materials is a phenomenon that requires full understanding and prevention of important technological developments [30].

The demand for safe and effective materials in biomedical engineering is greatly increased due to the annual increase in the world population, the increasing number of the elderly and the high functional demands of young people. The basic condition for a biomaterial is that the material and the surrounding physiological environment must coexist without having an undesirable effect on each other. Since the surface is an interface where biomaterials meet and interact with the biological medium (i.e. bone, soft tissue, blood), surface properties are the main factors that ultimately determine the rejection or acceptance of a biomaterial in the body. Biological events that regulate host responses to materials such as protein adsorption and cell adhesion occur at the

biomaterial-tissue interface and are modulated by the physicochemical properties of the material [6].

Many studies have been conducted on biomaterials and implants so far and these studies are still ongoing. In addition to the work carried out, additional studies may be proposed on the following special topics:

a) Recently a lot of metallic materials (Fe, Mg, Ni and Co-based alloys as well as stainless steel) used as biomaterials and implants in the body. However, some more research need to be done about the other metallic materials such as Zr, Nb, Ru, Ag, Ta, Au, Al, Zn, Sn etc for the sake of biocompatibility, toxicity, allergenic and corrosion resistance.

b) For hard tissue replacement, titanium and its alloys are widely used owing to their high corrosion resistance, low density, good biocompatibility, comparatively low elastic modulus, and high strength. Up to now, many researchers have done about the Ti-based biomaterials and implants. Nevertheless, to replace the conventional Ti6Al4V alloys, some more Ti-based implant alloys can be developed adding Zr, Ta, Sn, Hf, Re, Ag etc into Ti-Nb based alloys to eliminate the long-term ignition and carcinogenic effects due to release of toxic elements ions.

c) Iron is a metal suitable for the manufacture of a biodegradable stent. However, implantation of some iron stents has shown that the stents are completely corroded in recorded time, and therefore the faster rate of deterioration for iron is of interest, and further investigation is needed for the degradation procedure.

d) Pure Mg and Fe are not used directly in stent production due to their low mechanical, reliability and bio-reactivity properties. However, some elements can be added to Mg and Fe to produce biodegradable stents. For example, “Zn, Y, Ca, Mn and Ag” elements are added to Mg and “Co, Al, W, Sn, B, C, S” elements are added to Fe to produce better stents.

e) Non-metal implants and biomaterials can be studied; such as polymeric materials (polyacetal, polysulfone and polycarbonate) can be used in the applications of heart/lung assist devices and hard tissue replacements. Also ceramic implants (aluminum oxide, hydroxyapatite, calcium phosphates and carbon) and composites (carbon-carbon, ceramic polymer, epoxy-glass, epoxy-carbon and epoxy-aramide) can also be attractive for the implant applications in the body.

f) The elastic modulus of Ti and its alloys is much higher than the bone and damages the bone. Therefore, porous alloys are prepared and matched with the mechanical properties of the bone.

g) Modification of the Ti alloy surface can provide additional work on the ability to form apatite and increase corrosion resistance.

h) Bioactive coating studies can be performed to increase the corrosion resistance and biofunctional properties of titanium alloys. For this purpose, HA, HA-GO and HA-GO-COL coatings can be applied to Titanium alloy surface by pre-treatment and post-anodization electroaccumulation method.

i) Metallic biodegradable stents were produced in the first generation by casting, forging, machining and thermomechanical methods. Then, powder metallurgy and electro-forming method were used for the production of second generation stents. New modern methods such as 3D printing can be used in manufacturing methods of implants.

6. Conclusions

Recent developments of metallic implants for biomedical applications

The biomedical implant is simply defined as an artificial organ that is used to restore the functionality of a damaged natural organ or tissue of the body. In other words, it is expected to perform the functions of natural organs or tissues without adverse effects on other parts of the body. This requires that various requirements are met by the material used for artificial organs or artificial organ construction before being considered for application. The main requirement of artificial organ or tissue replacement is that it should act as a functional

replacement for the original body part. Additional requirements include Biocompatibility or Biodegradability of the material used in the artificial organ to accommodate the surrounding tissue without any immune rejection response or inflammatory reaction. The following conclusions can be drawn from this study:

a) A biomaterial must meet the suitable mechanical properties; such as a low elastic modulus combined with high strength to extend the service life of the implant and to prevent loosening. Also, it has to be biocompatible, high abrasion and corrosion resistance, osseointegration, non-toxic and long fatigue life.
b) The materials that are used to build biomedical devices (orthopedic, dental, bone cements, etc.) can be classified into metallic materials, ceramics, polymers, and composites. Metallic materials in these four categories are widely used due to their high strength, toughness and good biocompatibility, despite some deficiencies such as the release of metallic ions and wear residues.
c) Biodegradable metals, such as magnesium, hold great promise in applications that support tissue regeneration and healing, particularly where a load- bearing function is required, and also iron based alloys can be used as biodegradable metals within the body.
d) The field of implantology is constantly evolving, as more is learned about specific biological interactions with and around the implant. Important factors for surface engineering include surface chemistry, micro- and nanometer-level topography, physicochemical effects and biological factors.
e) There have been many studies on biomaterials and implants so far and these studies are still ongoing. In addition to the studies carried out, additional studies may be proposed on some more research need to be done about the other metallic materials, to replace the conventional Ti6Al4V alloys, some more Ti-based implant alloys can be developed, further investigation is needed for the degradation procedure in metallic implants.
f) Some more porous alloys are prepared and matched with the mechanical properties of the bone and modification of the Ti alloy surface can provide additional work on the ability to form apatite and increase corrosion resistance.
g) Metallic biodegradable stents were produced in the first generation by casting, forging, machining and thermomechanical methods. Then, powder metallurgy and electro-forming method were used for the production of second generation stents. New modern methods such as 3D printing can be used in manufacturing methods of implants.

Acknowledgements

Thanks to SUBU and BIMAS-RC due to provision of laboratory facilities and SAU due to partial financial support within international bilateral Mevlana project (Project Number: MEV-2018-644) between Pakistan and Turkey.

References

[1] Shi H, Tsai W-B, Garrison MD, S. Ferrari and Ratner BD, Template imprinted nanostructured surfaces for protein recognition, Nature, 15 April 1999, Vol. 398, No. 6728, pp. 593-597.
[2] Senior K. Artificial implants: making the marriage work, The Lancet, 14th August 1999, Vol. 354, No. 9178.
[3] Lawrence, K.J. Anisotropy of Young's modulus of bone. Nature 1980, 283, 106–107.
[4] Black, J.; Hastings, G.W. Handbook of Biomaterials Properties; Chapman and Hall: London, UK, 1998.
[5] Alvarado, J.; Maldonado, R.; Marxuach, J.; Otero, R. Biomechanics of hip and knee prostheses. Appl. Eng. Mechan. Med. GED–Univ. Puerto Rico Mayaguez 2003, 6, 22.
[6] Hallab, N.J.; Anderson, S.; Stafford, T.; Glant, T.; Jacobs, J.J. Lymphocyte responses in patients with total hip arthroplasty. J. Orthop. Res. 2005, 23, 384–391.
[7] Branemark, P.I. Osseointegration and its experimental background. J. Pros. Dent. 1983, 50, 399–410.

[8] Geetha, M.; Singh, A.K.; Asokamani, R.; Gogia, A.K. Ti based biomaterials, the ultimate choice for orthopaedic implants—A review. Progr. Mater. Sci. 2009, 54, 397–425.
[9] Viceconti, M.; Muccini, R.; Bernakiewicz, M.; Baleani, M.; Cristofolini, L. Large-sliding contact elements accurately predict levels of bone–implant micromotion relevant to osseointegration. J. Biomech. 2000, 33, 1611–1618.
[10] Wennerberg, A.; Albrektsson, T.; Jimbo, R. Implant Surfaces and Their Biological and Clinical Impact, 1st ed.; Springer-Verlag: Berlin/Heidelberg, Germany, 2015; p. 168.
[11] Barfeie, A.; Wilson, J.; Rees, J. Implant surface characteristics and their effect on osseointegration. Br. Dental J. 2015, 218, 1–9.
[12] Teoh, S.H. Fatigue of biomaterials: A review. Int. J. Fatigue 2000, 22, 825–837.
[13] Park, J.; Lakes, R.S. Biomaterials an Introduction, 3rd ed.; Springer: Berlin/Heidelberg, Germany, 2007.
[14] Niinomi, M. Metallic biomaterials. J. Artif. Organs 2008, 11, 105–110.
[15] Niinomi, M. Recent metallic materials for biomedical applications. Metall. Mater. Trans. A 2002, 33, 477–486.
[16] Rokkum M, Bye K, Hetland KR, et al. Stem fracture with the exeter prosthesis 3 of 27 hips followed for 10 years. Acta Orthop Scand. 1995; 66:435–439.
[17] Davis JR. Handbook of materials for medical devices. 1st ed. Geauga: ASM international; 2003. Chapter 3, Metallic materials; p. 22–30.
[18] Piehler HR. Pluralistic medical device risk management: standards, regulation, and litigation. In: Fraker AC, Griffin CD, editors. Corrosion and degradation of implant materials: second symposium. Pennsylvania: ASTM International; 1985. p. 1–10.
[19] Zhang F, Kang ET, Neoh KG, et al. Surface modification of stainless steel by grafting of poly (ethylene glycol) for reduction in protein adsorption. Biomaterials 2001; 22:1541–1548.
[20] Kang CK, Lee YS. The surface modification of stainless steel and the correlation between the surface properties and protein adsorption. J Mater Sci Mater Med. 2007; 18:1389–1398.
[21] Thomann UI, Uggowitzer PJ. Wear–corrosion behavior of biocompatible austenitic stainless steels. Wear 2000; 239:48–58.
[22] Liu DM, Yang Q, Troczynski T. Sol–gel hydroxyapatite coatings on stainless steel substrates. Biomaterials 2002; 23:691–698.
[23] Chen Q, Thouas GA. Metallic implant biomaterials. Mater Sci Eng R. 2015; 87:1–57.
[24] Witte F. The history of biodegradable magnesium implants: a review. Acta Biomater. 2010; 6:1680–1692.
[25] Staiger MP, Pietak AM, Huadmai J, et al. Magnesium and its alloys as orthopedic biomaterials: a review. Biomaterials 2006; 27:1728–1734.
[26] Hermawan H, Dube D, Mantovani D. Developments in metallic biodegradable stents. Acta Biomater. 2010; 6:1693–1697.
[27] Rude RK. Magnesium deficiency: a cause of heterogenous disease in humans. J Bone Miner Res. 1998; 13:749–758.
[28] Hornberger H, Virtanen S, Boccaccini AR. Biomedical coatings on magnesium alloys – a review. Acta Biomater. 2012; 8:2442–2455.
[29] Eliezer D, Aghion E, Froes FS. Magnesium science, technology and applications. Adv Perform Mater. 1998; 5:201–212.
[30] Liu N, Huang WM. DSC study on temperature memory effect of NiTi shape memory alloy. Trans Nonferrous Met Soc China. 2006; 16:s37–s41.
[31] Wang H, Estrin Y, Zuberova Z. Bio-corrosion of a magnesium alloy with different processing histories. Mater Lett. 2008; 62:2476–2479.

[32] Gray JE, Luan B. Protective coatings on magnesium and its alloys – a critical review. J alloys compd. 2002; 336:88–113.
[33] Razavi M, Fathi M, Savabi O, et al. Controlling the degradation rate of bioactive magnesium implants by electrophoretic deposition of akermanite coating. Ceram Int. 2014; 40:3865–3872.
[34] Chen XB, Nisbet DR, Li RW, et al. Controlling initial biodegradation of magnesium by a biocompatible strontium phosphate conversion coating. Acta Biomater. 2014; 10:1463–1474.
[35] Kannan MB. Enhancing the performance of calcium phosphate coating on magnesium alloy for bioimplant applications. Mater Lett. 2012; 76:109–112.
[36] Lu Y, Tan L, Xiang H, et al. Fabrication and characterization of Ca–Mg–P containing coating on pure magnesium. J Mater Sci Technol. 2012; 28:636– 641.
[37] Lu Y, Tan L, Zhang B, et al. Synthesis and characterization of Ca–Sr–P coating on pure magnesium for biomedical application. Ceram Int. 2014; 40:4559–4565.
[38] Mahapatro A, Matos Negron TD, Gomes AS. Nanostructured self-assembled monolayers on magnesium for improved biological performance. Mater Technol. 2016; 31:818–827
[39] Ratner, J.B.B.D.; Hoffman, A.S.; Shoen, F.J.; Lemons, J.E. Biomaterials Science: An Introduction to Materials in Medicine; Academic Press: Waltham, MA, USA, 1996; pp. 37–50.
[40] 40. Addison, O., Davenport, A. J., Newport, R. J., Kalra, S., Monir, M. et al. (2012) Do 'passive' medical titanium surfaces deteriorate in service in the absence of wear? Journal of The Royal Society Interface, 7, 3161 – 4.
[41] Cvijović-Alagić, I., Cvijović, Z., Mitrović, S., Panić , V. and Rakin, M. (2011) Wear and corrosion behavior of Ti-13Nb-13Zr and Ti-6Al-4V alloys in simulated physiological solution, Corrosion Science, 53, 796 – 808
[42] Diomidis, N., Mischler, S., More, N. S. and Roy, M. (2012) Tribo- electrochemical characterization of metallic biomaterials for total joint replacement, Acta Biomaterialia, 8, 852 – 9.
[43] More, N. S., Diomidis, N., Paul, S. N., Roy, M. and Mischler, S. (2011) Tribocorrosion behavior of β -titanium alloys in physiological solutions containing synovial components, Materials Science and Engineering: C, 31, 400 – 8.
[44] Nakada, H., Numata, Y., Sakae, T., Okazaki, Y., Tanimoto, Y. et al. (2008) Comparison of bone mineral density and area of newly formed bone around Ti-15%Zr-4%Nb-4%Ta alloy and Ti-6%A1-4%V alloy implants, Journal of Hard Tissue Biology, 17, 99 – 108 .
[45] Li, S. J., Yang, R., Li, S., Hao, Y. L., Cui, Y. Y. et al. (2004) Wear characteristics of Ti-NbTa-Zr and Ti-6Al-4V alloys for biomedical applications, Wear, 257, 869 – 76 .
[46] Fukuda, A., Takemoto, M., Saito, T., Fujibayashi, S., Neo, M. et al. (2011) Bone bonding bioactivity of Ti metal and Ti-Zr-Nb-Ta alloys with Ca ions incorporated on their surfaces by simple chemical and heat treatments, Acta Biomaterialia, 7, 1379 – 86 .
[47] Niinomi, M. and Hattori, T. (2010) Effect of Young's modulus in metallic implants on atrophy and bone remodeling. In: Sasano, T. and Suzuki, O. eds), Interface Oral Health Science 2009, Osaka, Japan, Springer Japan.
[48] Minagar, S., Berndt, C. C., Wang, J., Ivanova, E. and Wen, C. (2012) A review of the application of anodization for the fabrication of nanotubes on metal implant surfaces, Acta Biomaterialia, 8, 2875 – 88.
[49] Niinomi, M. (2008) Mechanical biocompatibilities of titanium alloys for biomedical applications, Journal of the Mechanical Behavior of Biomedical Materials, 1, 30 – 42.
[50] Long, M. and Rack, H. J. (1998) Titanium alloys in total joint replacement: A materials science perspective, Biomaterials, 19, 1621 – 39.
[51] Majumdar, P., Singh, S. B. and Chakraborty, M. (2011) The influence of heat treatment and role of boron on sliding wear behavior of type Ti-35Nb-7.2Zr-5.7Ta alloy in dry condition and in simulated body fluids, Journal of the Mechanical Behavior of Biomedical Materials, 4, 284 – 97.

[52] Manhabosco, T. M., Tamborim, S. M., Dos Santos, C. B. and Müller, I. L. (2011) Tribological, electrochemical and tribo-electrochemical characterization of bare and nitrided Ti6Al4V in simulated body fluid solution, Corrosion Science, 53, 1786 – 93.

[53] Martini, C., Ceschini, L., Casadei, B., Boromei, I. and Guion, J. B. (2011) Dry sliding behavior of hydrogenated amorphous carbon (a-C:H) coatings on Ti-6Al-4V, Wear, 271, 2025 – 36.

[54] Lausmaa, J. (1996) Surface spectroscopic characterization of titanium implant materials, Journal of Electron Spectroscopy and Related Phenomena, 81, 343 – 61

[55] Yılmaz E, Gökçe A, Findik F, Gulsoy O. "Characterization of biomedical Ti-16Nb-(0–4)Sn alloys produced by Powder Injection Molding", Vacuum, Vol. 142, August 2017, pp. 164-174.

[56] Yılmaz E, Gökçe A, Findik F, Gulsoy O. "Assessment of Ti–16Nb–xZr alloys produced via PIM for implant applications", Journal of Thermal, Analysis and Calorimetry, Vol: 134, issue: 1, pp. 7-14, Oct. 2018.

[57] Yılmaz E, Gökçe A, Findik F, Gulsoy O. "Metallurgical properties and biomimetic HA deposition performance of Ti-Nb PIM alloys", Journal of Alloys and Componds, Vol. 746, pp. 301-313, May 2018.

[58] Yılmaz E, Gökçe A, Findik F, Gulsoy O, Iyibilgin O. "Mechanical properties And electrochemical behavior of porous Ti-Nb biomaterials", J. of the Mechanical Behavior of Biomedical Materials", Vol. 87, pp. 59-67, November 2018.

[59] Yılmaz E, Gökçe A, Findik F, Gulsoy O. "Powder Metallurgy Processing of Ti-Nb Based Biomedical Alloys", Acta Physica Polonica A, Vol. 134, Issue 1, pp. 278-280, July 2018.

[60] Mehl, C., Lang, B., Kappert, H. and Kern, M. (2011) Microstructure analysis of dental castings used in fixed dental prostheses: A simple method for quality control, Clinical Oral Investigations, 15, 383 – 91

[61] Ucar, Y., Brantley, W. A., Johnston, W. M., Iijima, M., Han, D. S. and Dasgupta, T. (2011) Microstructure, elemental composition, hardness and crystal structure study of the interface between a noble implant component and cast noble alloys, The Journal of Prosthetic Dentistry, 106, 170 – 8.

[62] Guo, W. H., Brantley, W. A., Clark, W. A.T., Monaghan, P. and Mills, M. J. (2003) Transmission electron microscopic investigation of a Pd-Ag-In-Sn dental alloy, Biomaterials, 24, 1705 – 12.

[63] Ucar, Y., Brantley, W. A., Johnston, W. M. and Dasgupta, T. (2011) Mechanical properties, fracture surface characterization, and microstructural analysis of six noble dental casting alloys, The Journal of Prosthetic Dentistry, 105, 394 – 402.

[64] Soares, A. C. and Cavalheiro, A. (2010) A review of amalgam and composite longevity of posterior restorations, Revista Portuguesa de Estomatologia, Medicina Dentária e Cirurgia Maxilofacial, 51, 155 – 64.

[65] Ye, X., Qian, H., Xu, P., Zhu, L., Longnecker, M. P. and Fu, H. (2009) Nephrotoxicity, neurotoxicity, and mercury exposure among children with and without dental amalgam fillings, International Journal of Hygiene and Environmental Health, 212, 378 – 86.

[66] Clarkson, T. W. and Magos, L. (2006) The toxicology of mercury and its chemical compounds, Critical Reviews in Toxicology, 36, 609 – 62.

[67] Scholtanus, J. D., Özcan, M. and Huysmans, M. C., (2009) Penetration of amalgam constituents into dentine, Journal of Dentistry, 37, 366 – 73.

[68] Bates, M. N. (2006) Mercury amalgam dental fillings: An epidemiologic assessment, International Journal of Hygiene and Environmental Health, 209, 309 – 16.

[69] Bellinger, D. C., Trachtenberg, F., Zhang, A., Tavares, M., Daniel, D. and Mckinlay, S. (2008) Dental amalgam and psychosocial status: The New England Children's Amalgam Trial, Journal of Dental Research, 87, 470 – 4.

[70] Shimizu, Y., Yamamoto, A., Mukai, T., Shirai, Y., Kano, M. et al. (2010) Medical application of magnesium and its alloys as degradable biomaterials. In: Sasano, T. and Suzuki, O. (eds), Interface Oral Health Science 2009, Osaka, Japan, Springer Japan.

[71] Xin, Y., Hu, T. and Chu, P. K. (2011) In vitro studies of biomedical magnesium alloys in a simulated physiological environment: A review, Acta Biomaterialia , 7, 1452 – 9.

[72] Waksman, R., Erbel, R., Di Mario, C., Bartunek, J., De Bruyne, B. et al. (2009) Early- and long-term intravascular ultrasound and angiographic findings after bioabsorbable magnesium stent implantation in human coronary arteries, JACC: Cardiovascular Interventions, 2, 312 – 20.

[73] Willbold, E., Kaya, A. A., Kaya, R. A., Beckmann, F. and Witte, F. (2011) Corrosion of magnesium alloy AZ31 screws is dependent on the implantation site, Materials Science and Engineering: B, 176, 1835 – 40.

[74] Pierson, D., Edick, J., Tauscher, A., Pokorney, E., Bowen, P. et al. (2012) A simplified in vivo approach for evaluating the bioabsorbable behavior of candidate stent materials, Journal of Biomedical Materials Research Part B: Applied Biomaterials, 100B, 58 – 67.

[75] Seitz, J. M., Eifler, R., Stahl, J., Kietzmann, M. and Bach, F. W. (2012) Characterization of MgNd 2 alloy for potential applications in bioresorbable implantable devices, Acta Biomaterialia, 8, 3852 – 64.

[76] Findik F, Iyibilgin O et al. (2016) "Metal Alloy Stent Placed Into Vein And A New Method For Production of This Stent", Turk Patent Institute, Record No: 2016 05339

[77] Schwartz Zvi, Boyan BD. Underlying mechanisms at the bone-bomaterial interface. J Cell Biochem 1994; 56: 340-7.

[78] Puleo DA, Nanci A. Understanding and controlling the bone-implant interface. Biomaterials 1999; 20: 2311-2.

[79] Buser D, Schenk RK et al. Influence of surface characteristics on bone integration of Ti implants J Biomed Mater Res 1991; 25: 889-902.

[80] Gotfredsen K, Hjorting-Nansen E, Budtz-Jorgensen E. Clinical and radiographic evaluation of submerged and nonsubmerged implants in monkeys. In J Prosthodont 1990; 3: 4639.

[81] Kieswetter K et al. Surface roughness modulates the local production of growth factors and cytokines by osteoblast-like MG-63 cells J Biomed Mater Res 1996; 32: 55-63.

[82] Wennerberg A, Hallgren C et al. A histomorphometric evaluation of screw-shaped implants each prepared with two surface roughness. Clin Oral Implants Res 1998; 9: 119.

[83] Hannson S, orton M. The relation between surface roughness and interfacial shear strength for one-anchored implants. A mathematical model. J Biomech 1999; 32: 829-36.

[84] Albrektsson T, Wennerberg A. Oral implant surfaces. Int J Prosth 2004; 17: 536-43.

[85] Wennerberg A et al. A 1-year follow-up of implants of differing surface roughness placed in rabbit bone. Int J Oral Maxillo Implants 1997; 12: 486-94.

[86] Yılmaz E, Gökçe A, Findik F, Gulsoy O. "Biomedical porous Ti-16Nb-10Zr-(0-15)Ta alloys", International Journal of Materials Research Vol: 110 Issue: 4 pp: 375-378 APR 2019

[87] Yılmaz E, Gökçe A, Findik F, Gulsoy O. "Influence of Zr addition on the corrosion behavior of biomedical PIM Ti-16Nb alloy in SBF", International Journal of Materials Research Volume: 110 Issue: 4 Pages: 379-381 Published: APR

[88] Yılmaz, E., Çakıroğlu, B., Gökçe, A., Findik, F., Gulsoy, H.O., Gulsoy, N., Mutlu, Ö., Özacar, M. "Novel hydroxyapatite/graphene oxide/collagen bioactive composite coating on Ti16Nb alloys by electrodeposition", Materials Science and Engineering C, Volume 101, August 2019, Pages 292-305

[89] Landolt D, Chauvy PF, Zinger O. Electrochemical micromachining, polishing and surface structuring of metals: fundamental aspects and new developments. Electrochim Acta 2003; 48: 3185–201.

[90] Anselme K, Bigerelle M, Noel B, Iost A, Hardouin P. Effect of grooved titanium substratum on human osteoblastic cell growth. J Biomed Mater Res 2002; 60: 529–40.
[91] Flemming RG, Murphy CJ, Abrams GA, Goodman SL, Nealey PF. Effects of synthetic micro- and nano-structured surfaces on cell behavior. Biomaterials 1999; 20: 573–88.