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Shape Memory Implants
(ed.) L'H. Yahia
pp. 35-45

2000

Corrosion Resistance and Biocompatibility of Passivated NiTi

Christine Trepanier, Ramakrishna Venugopalan, Alan R. Pelton

1 Introduction

Equiatomic nickel-titanium (NiTi) or Nitinol possess a unique combination of properties, including superelasticity and shape memory, which are very attractive for biomedical applications. NiTi has been used in orthopedic and orthodontic implants for several decades and has contributed to significant improvements in these fields [1, 2]. This alloy is rapidly becoming the material of choice for self-expanding stents, graft support systems, filters, baskets and various other devices for minimally invasive interventional procedures (Fig. 1) [1, 3]. While the superior performance of NiTi over conventional engineering materials for implants is well documented [1, 4, 5], the high nickel content of the alloy (55 weight % Ni) and its

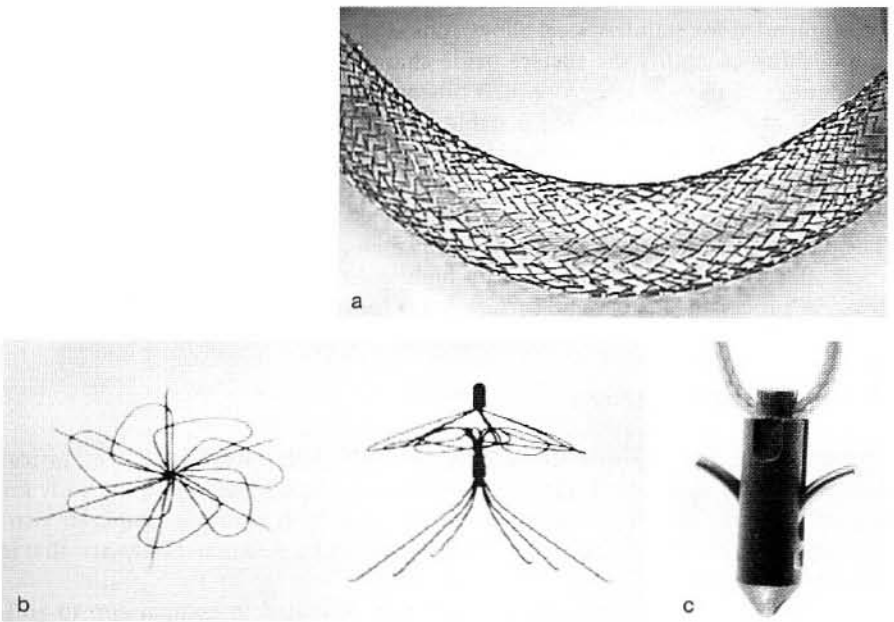


Fig. 1. Various types of minimally invasive interventional NiTi devices. **a** Cordis SMART stent. **b** Simon filter. **c** Mitek bone anchor

possible influence on biocompatibility continues to be an issue of concern. This concern is further complicated by the conflicting literature on corrosion resistance.

Human tissue contains approximately 0.1 ppm of nickel, which is essential in nutrition for biological functionality of the human body [6, 7]. The potential for higher nickel concentration release from implant material may generate harmful allergic, toxic or carcinogenic reactions [7–9]. Besides NiTi and 316L stainless steel, another high nickel containing alloy, MP35N (35 weight % Ni), exhibits good biocompatibility and is used for implants in orthodontics, orthopedics and cardiovascular applications [10–12]. Furthermore, the atomic bonding forces between Ni and Ti in intermetallic NiTi are considerably higher than in a Ti alloy with a small amount of Ni [13], and will not produce the same reactions as pure metals. Thus, it is important to recognize the synergistic effect of alloying elements when evaluating the biocompatibility of any alloy.

The limitation in the use of NiTi for medical implants is due to literature references that report moderate corrosion resistance and cell culture compatibility. However, a careful study of these references reveal that NiTi material processing history and surface conditions are generally not well documented. It is now well known that NiTi requires controlled processing to achieve optimal mechanical and thermal properties. Optimization of the thermo-mechanical processing provides good fatigue life and general mechanical properties to meet the stringent structural requirements of medical implants. Similarly, surface processing is required in order to promote optimal corrosion resistance and biocompatibility of the material. In fact, ASTM F86 [14] standard recommends an appropriate chemical treatment of metallic implants to ensure passive surface condition. The treatments recommended for stainless steel alloys consist of a nitric acid passivation or electropolishing to modify the surface oxide characteristics, increase their corrosion resistance and therefore improve their biocompatibility. NiTi is a passive alloy like titanium and stainless steel and a stable surface oxide protects the base material from general corrosion. The surface is predominantly composed of titanium oxide and thus its passivity may be further enhanced by modifying the thickness, topography and chemical composition of the surface by selective treatments [15–17]. The purpose of this chapter is to focus on the bio-corrosion properties of NiTi, and their effect on biocompatibility and to highlight the importance of documenting material processing history and surface finish for such evaluations.

2 Active Corrosion Testing

Our understanding of corrosion behavior of a new material is based on empirical comparisons with materials that we know already to perform well in the body for a particular application. Thus, any corrosion test is in reality a simple in vitro comparison of limited electrochemical properties of a new material to one that is already in clinical use.

The active corrosion behavior of NiTi was evaluated in comparison to 316L stainless steel discs passivated and sterilized according to ASTM F86 standard practices for metallic implants. Potentiodynamic polarization testing was con-

ducted per ASTM G5 [18] in de-aerated Hank's physiological solution at 37°C. Tafel extrapolation and Stern-Geary currents were used to calculate the corrosion current density (I_{corr}) in ampere/cm² at the corrosion potential (E_{corr}). The breakdown potential (E_{bd}) was determined from the y-axis co-ordinate corresponding to the intersection of a line fit extrapolation of the passive and transpassive regions. The protection potential (E_{prot}) was the y-axis co-ordinate of the point where the reverse polarizations scan crossed over the forward scan.

Overlaid polarization plots of NiTi and 316L stainless steel are presented in Figure 2. The E_{corr} values for NiTi were more active compared to 316L stainless steel. The I_{corr} values were in the nA/cm² range for both NiTi and 316L stainless steel. The E_{bd} values for NiTi were almost three times greater than 316L stainless steel. The NiTi samples exhibited instantaneous repassivation (no hysteresis) on scan reversal at the vertex potential compared to the significant hysteresis exhibited by the 316L stainless steel. The approximately 150 mV region between the E_{prot} and E_{bd} of the 316L stainless steel makes it more susceptible to propagation of existing surface damage than NiTi. It should be noted that these results are valid only for conditions where no surface damage is involved. Similar results were presented by Venugopalan et al. [19] in their testing on small diameter NiTi and 316L stainless steel stents. Nevertheless, most minimally invasive devices may be susceptible to scratch damage due to the nature of their deployment. Thus, it is imperative that the corrosion behavior of scratched NiTi be fully characterized and understood.

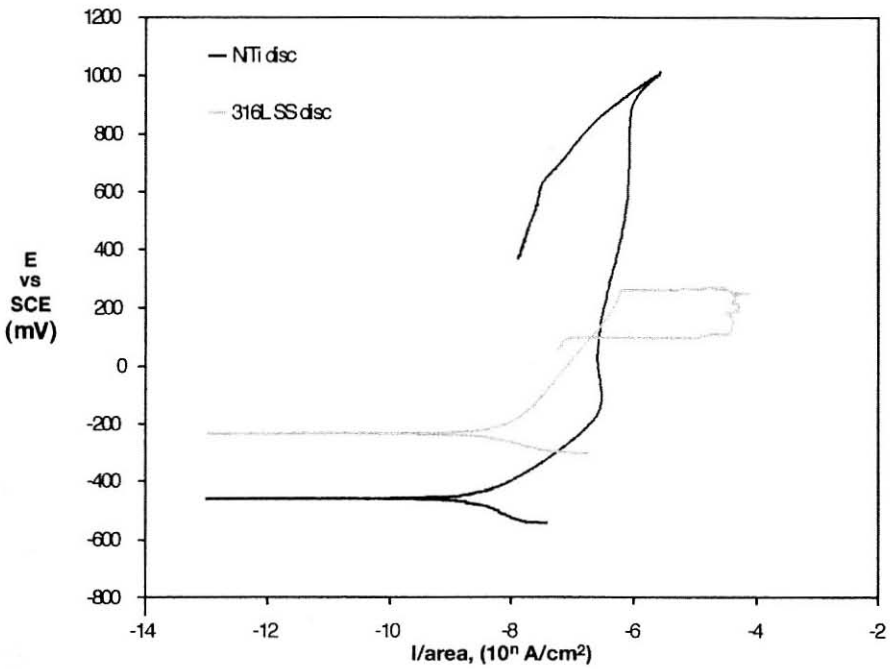


Fig. 2. Potentiodynamic polarization curves for NiTi and 316L stainless steel in de-aerated Hank's physiological solution at 37°C

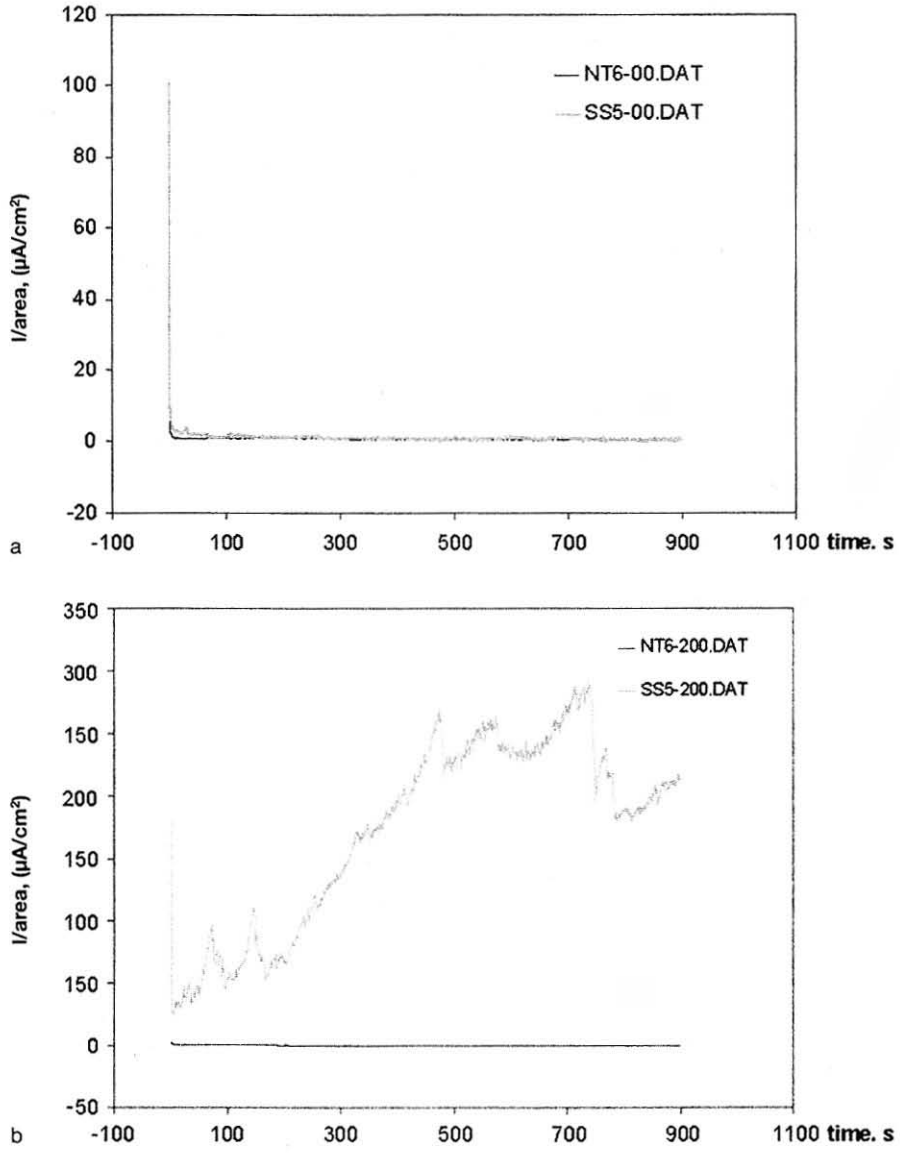
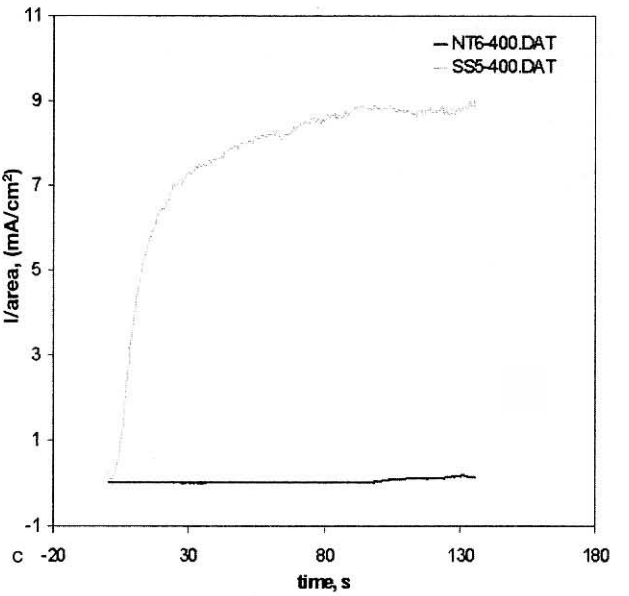
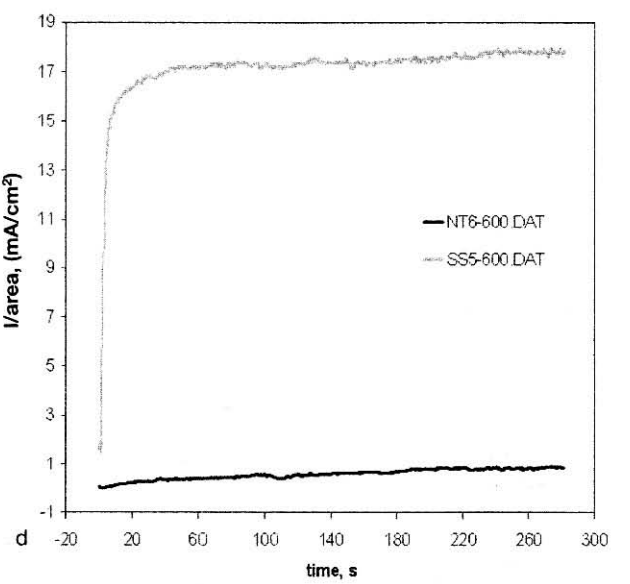


Fig. 3. Current density profiles after scratch tests at specific potentiostatic holds in de-aerated Hank's physiological solution at 37°C: **a** 0 mV, **b** 200 mV, **c** 400 mV and **d** 600 mV. All potentials are expressed with reference to a standard calomel electrode

NiTi and 316L stainless steel samples were subject to step polarization experiments in de-aerated Hank's physiological solution at 37°C [20]. The samples underwent physical scratch damage using a diamond stylus as opposed to the potentiostatic surface rupture method described in ASTM F746 [21]. The samples





were scratched before the potentiostatic holds (P-Hold) at 0 mV, 200 mV, 400 mV and 600 mV with reference to a saturated calomel electrode (SCE) and the current density profiles were monitored. A decreasing current density trend indicated that the material was able to repassivate the surface damage while an increasing current density trend indicated that the sample was not able to repassivate the damage at that P-hold. Current density >500 nA/cm² was used as a threshold to define total loss of ability to repassivate scratch damage.

Representative overlaid current density plots at each potentiostatic hold are presented in Figure 3. The NiTi discs and the 316L stainless steel samples exhibited decreasing current densities and hence complete repassivation after scratch damage at the 0 mV potentiostatic hold. At the 200 mV potentiostatic hold, the NiTi samples exhibited decreasing current densities compared to the increasing current densities exhibited by the 316L stainless steel samples, indicating the 316L stainless steels alloy's inability to achieve total repassivation. However, the 316L stainless steel current densities did not exceed 500 nA/cm^2, a threshold value for total lack of repassivation ability. At 400 mV and 600 mV potentiostatic holds, the current densities for NiTi and the 316L stainless steel samples exceeded 500 nA/cm^2. It should be noted that the 316L stainless steel samples exhibited a faster current density transient to the 500 nA/cm^2 current density benchmark value. In conclusion, the region of repassivation capability after scratch damage for the NiTi was approximately 200 mV potential range greater than the 316L stainless steel.

3
Passive Corrosion Behavior

Passive dissolution studies in simulated physiological environments allow us to track a corrosion process through its initiation and propagation and to discriminate between the two. The effect of the environment on the device can be ascertained by visual inspection or scanning electron microscopy of the device removed from the environment at predetermined time segments of the study. The effect of the device on the environment can be determined by analyzing the media for ionic by-products using inductively coupled plasma (ICP) or atomic absorption spectroscopy (AAS).

NiTi, MP35N, 316L stainless steel alloy, and commercially pure nickel were obtained in the form of discs (surface area approximately 4.5 cm^2) and polished to 1200 grit surface finish. The alloys were passivated based on ASTM F86 standard and all samples were sterilized under UV light. The samples were placed in tissue culture plates and the plates were filled with 4 mL of Hank's physiological solution using aseptic procedure. The samples were then placed in a water-jacketed incubator with humidity, temperature and multiplex gas control. The tests were conducted under a mixed-gas environment (20.9% O_2, 5.0% CO_2, and air) at 37°C. The samples were removed 1, 6, 12, 24, 48, 72, 96 and 120 h, and 7, 14 and 21 days after placing in the incubator. Three samples of each group were removed per time period. The media was extracted, made up to 4 ml to normalize concentration effects resulting from evaporation, and analyzed using AAS to determine the ionic content of Ni.

A semi-log plot format was used to overlay the results (Fig. 4) as they spanned over multiple orders of magnitude. The 316L SS and NiTi alloy exhibited the least (tens of ppb) Ni ion release into the media. The MP35N exhibited an order of magnitude increase (hundreds of ppb) in Ni ion release into the media compared to the NiTi and 316L SS alloys. The negative control, commercially pure nickel, exhibited the highest amount (thousands of ppb) of Ni ion release into the media (as expected).

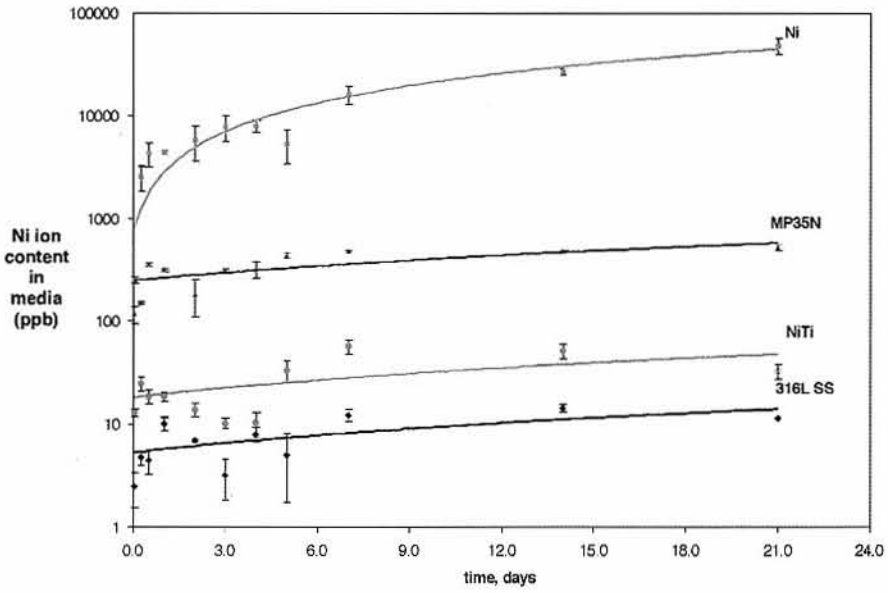


Fig. 4. Ni-ion concentrations released by Ni, MP35N, 316L stainless steel, and NiTi in Hank's physiological solution at various time periods of removal during dissolution study. The dissolution study was conducted in mixed-gas atmosphere at 37°C

4
Effect of Surface Layer on Corrosion Resistance

Several studies have demonstrated that passivated NiTi surface layers consist predominantly of a titanium oxide layer (TiO_2) [15–17, 22] similar to that found on Ti alloys [23]. This is in agreement with theoretical thermodynamics, which specify that the free energy of formation of TiO_2 is favored over other nickel or other titanium oxides [22]. This oxide layer serves two purposes:

1. Increases the stability of the surface layers by protecting the bulk material from corrosion
2. Creates a physical and chemical barrier against Ni oxidation by modifying the oxidation pathways of Ni [24]

The stability of the surface layer on NiTi and its ability to protect the material from corrosion have been investigated in several studies by electrochemical experiments.

Early studies performed by Kimura and Sohmura [25] showed that passivation promotes the growth of an oxide layer on NiTi and resulted in its improved corrosion resistance in 1% saline solution at 37°C. More recently, Trepanier et al. [16] investigated the effects of electropolishing and heat treatments of NiTi stents on their corrosion resistance in Hank's physiological solution at 37°C. These results indicated a significant improvement in the corrosion resistance of NiTi stents that was attributed to the formation of a thin and very uniform Ti-based oxide

layer. The authors concluded that uniformity rather than thickness of the oxide was most important to the improved corrosion resistance for this kind of devices. Furthermore, as was shown by Kimura and Sohmura [25], a thin oxide layer is preferable to maintain the integrity of the surface layer to sustain the large deformation induced by the shape memory effect.

A comparative study of the corrosion resistance of passivated Ti-6Al-4V, 316L stainless steel and NiTi was performed in Hank's physiological solution by Wever et al. [15]. Their results show that while Ti-6Al-4V was the most corrosion resistant, NiTi samples were more resistant to chemical breakdown of their passive film than 316L stainless steel samples. Our results are in agreement with Wever et al. regarding the corrosion behavior of NiTi in comparison to stainless steel. These results highlight the importance of a well-controlled and optimal surface preparation process to achieve good and reproducible corrosion resistance for both materials. Furthermore, our scratch test investigations demonstrated that both NiTi and stainless steel exhibit a decreased resistance to pitting once their surface is severely damaged. Nevertheless, in the event of a similar surface damage, NiTi is still characterized by a higher resistance to localized corrosion compared to stainless steel.

5
Nickel Release and Biocompatibility

Since nickel release during the bio-degradation of NiTi is an important concern for its use as an implant, several studies have been undertaken to measure this value. For example, Barret et al. [26] and Bishara et al. [27] investigated nickel release from NiTi arch wires (processed by the manufacturer) in saliva. During an in vitro dissolution study, they found that NiTi and stainless steel appliances released a similar total amount of Ni around 18 ppm after a 28 days dissolution study. In a second study, orthodontic patients with NiTi appliances had Ni-concentration in their blood measured for a period of 5 months. Results show no significant increase in the nickel blood level throughout this study.

A comparative in vitro cell culture study was undertaken by Ryhanen et al. [28] in which they measured Ni released from NiTi and 316L stainless steel in a fibroblast and osteoblast cell culture media. In both media, Ni levels were higher in the NiTi group the first day and decreased rapidly as a function of time to achieve similar levels as 316L after 8 days. It is important to note that even though Ni release was higher in the NiTi group, it did not reach toxic values and cell proliferation or cell growth near the implant surface was not affected. Furthermore, NiTi was only mechanically polished without additional passivation treatments, whereas the stainless steel was electropolished according to the guidelines of the manufacturer. Ryhanen et al. [28] hypothesized a further decrease in Ni release if additional passivation treatments, such as electropolishing, are performed on NiTi. Wever et al. [15] conducted a similar comparative study with passivated NiTi and 316L stainless steel in Hank's solution. Ni release from NiTi was maximum the first day (14.5×10^{-7} $\mu g/cm^2/s$) and reached undetectable levels similar to 316L stainless steel after 10 days.

More recently, Jia et al. published their results on Ni release from NiTi and stainless steel orthodontic appliances [29]. Their study showed that NiTi released more Ni (maximum of 4.1 ppb) than stainless steel arch wires in a period of 24 hours. Furthermore, in agreement with several studies, they have shown that a threshold value of 30 ppm is needed to trigger a cytotoxic response during in vitro experiments. Our results on electropolished NiTi and 316L show that this Ni release threshold is far from being reached, even after 21 days of immersion in Hank's physiological solution.

Biocompatibility of a material may be simply defined as its ability to be well accepted by the body. Since every material will generate a "foreign body reaction" when implanted in the body, the degree of biocompatibility is related to the extent of this reaction. In order to study this phenomenon, in vitro testing with cell cultures allows isolation of the reaction from each cell and physiological media, whereas, in vivo testing provides a more complete response involving the biological environment and immune system. Both types of tests have been undertaken to better understand the biological response to NiTi.

A recent in vitro study revealed no significant differences between the cell growth behavior near the surfaces of different implant materials (mechanically polished Ti and NiTi, electropolished 316L stainless steel) [28]. A microscopy analyses also showed that the cells had grown very near to Ti and NiTi alloys while they were less close to the stainless steel samples. The authors concluded that NiTi showed very good biocompatibility and that it had an excellent potential for clinical applications. Also, passivated NiTi showed no cytotoxic, allergic or genotoxic activity based on a MEM extract cytotoxicity test, a guinea-pig sensitization test and genotoxicity testing, respectively [30]. Similar results were obtained for the control group composed of passivated 316L stainless steel samples. In a different study that addressed only the genocompatibility of the material, NiTi exhibited a good biocompatibility behavior similar to Ti and 316L stainless steel on cellular chromatin [31].

Cutright et al. [32] have studied the tissue response to subcutaneous implantation of NiTi wire sutures in rats for a period of 9 weeks. The inflammatory response was minimal starting 3 days after implantation and the healing process initiated after 1–2 weeks consisted of a fibrous capsule formation around the implant. This reaction was similar to the one generated by similar stainless steel wires. In addition, Castleman et al. [33] evaluated the biocompatibility of chemically passivated NiTi by inserting plates into beagle femurs for periods ranging from 3 months to 17 months. The histological analysis of muscular tissue surrounding the implantation site showed no significant difference between NiTi and Cr–Co plates. Neutron activation analyses near the NiTi implants have indicated that there was no significant presence of metallic Ni in the muscle. Based on their observations, they concluded that the material was safe to conduct further testing.

More recently, Trepanier et al. [34] performed an in vivo study on passivated NiTi stents. Implantation of the material in rabbit paravertebral muscles and study of the inflammatory reaction for periods ranging from 3 weeks to 12 weeks demonstrated good biological response to NiTi. Analysis of the fibrous capsule surrounding NiTi stents revealed a decrease in thickness with time. A compara-

tive 26-week follow-up study was conducted on rats to assess the effect of different materials on soft tissues [35]. In this study, short-term biocompatibility of polished NiTi was similar to polished Ti-6Al-4V and electropolished stainless steel when in contact with muscle and perineural tissue. These results indicate promising soft tissue compatibility of NiTi.

6 Conclusions

Based on the abundance of literature reports, passivated NiTi has improved corrosion resistance compared to stainless steel. NiTi is protected from corrosion by a highly stable and biocompatible Ti-based oxide layer. This good corrosion behavior will prevent degradation of the material in the physiological environment and therefore will promote biocompatibility. Ni release from NiTi has been shown to be minimal in every study. The Ni dissolution rapidly decreases from a maximum (well below cytotoxic levels) to nearly non-detectable levels few days following NiTi immersion in a physiological media. Corrosion resistance of NiTi can be further enhanced by different surface treatments such as electropolishing which promote a very uniform oxide layer. In vitro and in vivo studies show that NiTi exhibits good biocompatibility and does not promote toxic or genotoxic reactions when in contact with a physiological environment. Therefore, passivated or properly treated NiTi can be considered a biologically safe implant material with unique mechanical properties.

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