World Scientific News

An International Scientific Journal

Modification of Nitinol Biomaterial for Medical Applications

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Review Article

ABSTRACT

In the paper, a review of modification methods which have been applied to Nitinol intermetallic compound used as biomaterial for medical applications, is carried out. A variety of methods used for Nitinol improvement, beginning from its manufacture, covers mechanical treatment, heat treatment, chemical processing including water boiling, electropolishing, plasma ion implantation, coating to improve the corrosion resistance, minimize nickel leaching, improve osseointegration, and/or vascular compatibility, sterilization and disinfection. Nitinol alloying by addition of a third element to replace Ti or Ni has an enormous effect on phase transformation, corrosion resistance and biocompatibility of the newly created ternary Nitinol alloy. Unfortunately, the ternary nitinol alloys – apart from NiTiCu in actuators and NiTiCr in wires used as a pulling-pushing tool in minimally invasive spine operation – have not found a widespread industrial application yet. One of the most effective surface finishing operations used for metallic biomaterials, with a special attention directed to Nitinol, appears to be magnetoelectropolishing (MEP). A uniform magnetic field used in MEP process can be generated by permanent magnets or by electromagnets. MEP leads to refinement of surface chemical composition impossible to achieve by standard electropolishing. During MEP of alloys and intermetallic

compounds, ferromagnetic elements, such as Fe (from stainless steels) or Ni, are primarily removed from the surface so that the passive film on Nitinol is totally composed of titanium oxide. One more unique feature of metal samples after MEP is their de-hydrogenation noticed both in stainless steels, niobium, titanium and Nitinol. In fact, the fatigue resistance of Nitinol after MEP referred to as-received, dependent on the refinement and displacement of inclusions, increases from three to seven times.

1. INTRODUCTION

The main two factors which still prevent the broader usage of nitinol as biomaterial in vascular as well as orthopaedic application are: (1) nickel leaching from implantable devices to surrounding tissue, and (2) unexpected fractures. In spite of various new techniques for preventing nickel release from nitinol which were proposed in recent years and several old processes developed for other biomaterials adapted to treat nitinol, the problem re-appears again and again (US FDA-Public Workshop 2012 [1]). A lot of recently published papers show many discrepancies concerning levels of nickel release from nitinol in the *in vitro* studies. They range from very low in the beginning of exposure to biological fluid until becoming undetectable after short time of exposure [2] to very long lasting with increased concentration up to several months [3, 4]. Those discrepancies are mainly due to a variety of finishing techniques, treatment protocols and final sterilization methods used to treat nitinol.

It is very important to find the best possible way to finish nitinol implantable devices after all production steps (machining, drawing, shape seating and aging and oxide removal, including sterilization), and establish one binding protocol. The tendency to fracture is the main reasons of uncertainty in using nitinol vascular implantable devices. The fractures were reported for nitinol peripheral stents [5, 6] as well as for vena cava filters IVC [7-9].

It must be clearly pointed out that all nitinol surface modifications for medical applications after sterilization should be tested for interaction with living cells (endothelial, platelets, osteoblast, etc.), at least *in vitro* or, if possible *in vivo* environment. The techniques to prevent nickel release from nitinol without compromising other properties – especially thermal shape recovery which makes nitinol unique among other metallic implants – can be broadly divided as follows: mechanical, physical, chemical, electrochemical, and bioactive.

2. MECHANICALLY TREATED NITINOL

In the absence of any mechanical surface treatment protocol, the treatment methods used are of proprietary origin. They include sanding, grinding, high luster-polishing followed by wiping or ultrasonically bathing of residues with water, detergents, organic solvents, etc. Surfaces treated by these methods lack reproducibility in corrosion resistance [10, 11]. Many *in vitro* studies in simulated body fluids were carried out on corrosion resistance on mechanically polished nitinol with very contradictory results. Some researchers reported low localized corrosion resistance [12-15] where pitting potential was usually lower than 500 mV

vs. SCE (Saturated Calomel Electrode). Other studies showed totally opposite results which indicated excellent corrosion resistance after mechanical polishing [2, 16], and in many cases pitting potential was recorded above 1000 mV vs. SCE. Recent work of Bai et al. [17] shows that mechanically sanded nitinol is highly resistant to pitting corrosion when exposed to saline solution at 37 °C. The authors attribute this behavior to passive film of n-type structure which prevents electron transfer from metal to the solution and thus prevents metal dissolution. They point out that surface roughness has no significant effect on pitting corrosion resistance of nitinol.

Some researchers [18-20] have shown biocompatibility inferiority of mechanically finished nitinol surfaces when compared to other treatments. The elemental composition of mechanically polished surface (1µm finish) depends on the sample polishing, cleaning and handling procedures. The total concentration of surface contaminants such as Ca, Na, Mg, Si, P and Cl coming from polishing or cleaning solutions or from calcium powdered gloves varied from 1 to 8%, thus affecting the concentrations of metals on the surface [21-23].

The inconsistency in corrosion resistance and also biological performance could be the results of Beilby layer which was created by grinding and laser cutting and left on the surface due to inadequate post treatment. Also, intermetallic inclusions from the bulk of material which could be exposed by mechanical finishing are responsible for chemical heterogenicity of the surface. The biological performance of mechanically polished nitinol surfaces is compromised by alteration of surface topography due to martensitic relief induced during grinding and polishing [23, 24]). As was shown in the works of Muhonen et al. [25, 26], osteoclast (a type of <u>bone cell</u> that resorbs bone tissue) morphology and activity deteriorate on martensitic phase of nitinol.

Altering the topography by grooving nitinol surface was used by Palmaz et al. [27] to promote fastest endothelialization *in vitro* model. The grooved surface increased the rate of migration of endothelial cells up to 64.6% when compared to smooth control surface. The authors of that research concluded that larger grooves resulted in greater migration rate, cells were aligned in the direction of grooves and were elongated. The impact of different surface roughness of mechanically polished nitinol surface (80, 400 and 2400 grit size) on adhesion and proliferation of human gingival fibroblastic and embryo osteoblastic cells was evaluated by Wirth et al. [28]. Those two types of cells showed totally different response to tested roughness. Fibroblast cells adhesion was significantly reduced on rough nitinol surface (400 grit finish) while osteoblast cells were not affected by roughness increase. The growth and proliferation of fibroblast was compromised by increase in roughness. Osteoblast viability was reduced on smoother surface (2400 grit finish).

3. HEAT TREATMENT

Different ways of improving biocompatibility and corrosion resistance of nitinol through heat treatment in various gaseous environments were explored in order to find a way to create a very stable TiO_2 passive layer [29-33], which theoretically would be able to make nitinol totally immune to body fluids after implantation and thus resolve the problem of nickel release to surrounding tissues. It is well known that corrosion resistance of titanium and its alloys, including nitinol, depends on high corrosion resistance of titanium oxide TiO_2 which originates spontaneously when fresh surface is exposed to air. Using heat treatment oxide on

nitinol can be modified. Its thickness can be controlled by applied temperature and time. Vojtech et al. [34] investigated the formation of oxide when subjected to air at 25 °C, 480 °C and 530 °C for 10 minutes, and the oxide thickness of 10 nm, 70 nm and 140 nm was obtained, respectively. In another study by Vojtech et al. [35], samples of mechanically polished and chemically etched nitinol were thermally oxidized in temperature of 530 °C for 10 minutes and exposed to physiological solution with pH=2 for nickel release evaluation. The results showed that thermal oxidation of mechanically polished samples retarded nickel release slightly, but in the case of chemically etched sample nickel release was strongly accelerated. It is noteworthy that chemical etching without thermal oxidation is one of the best methods to prevent or decrease nickel release from nitinol surfaces. Study by Lutz et al. [36], which tracked non-radioactive markers, ^{60}Ni and ^{46}Ti indicated Ni atoms as diffusing species within immobile Ti matrix during thermal oxidation of nitinol. The diffusion of Ni leads to layered sequence of Ti-oxide-Ni_3Ti-NiTi formed during thermal oxidation.

When thermal oxidation continues further to the point that Ni content is above the particle nucleation threshold in the oxide grains, it is more energetically favorable to form metallic particles within the TiO_y layer than increase the thickness of intermetallic layer [37]. In this case thermal oxidation could lead to Ni free oxide layer with Ni-rich intermetallic sub-layer containing pure nickel particles.

When Ni atoms diffuse in to the matrix to form Ni-rich intermetallic sublayer some of Ni atoms will contribute to a small Ni gradient in the underlying Ni-Ti matrix, possibly yielding an austenite-martensite interface due to the strong composition dependency of the martensitic transformation temperature [37]. The nickel enrichment of sublayer in nickel-rich intermetallics and pure nickel particles, which results from thermal oxidation of nitinol should be avoided, especially in the case where nitinol device is implanted in a living organism. Nickel intermetallics and pure nickel particles become the reservoirs of nickel, which starts to leach after body fluids compromise the protective properties of TiO_2 oxide. It has to be pointed out that exactly the same transformations of nitinol oxides, including nickel accumulation in sublayer, occurs during standard production procedures of nitinol medical devices such as: laser cutting, wire drawing followed by air annealing in temperature above 700 °C and shape setting in temperature between 500-550 °C. For this reason, it is very important to remove nickel accumulated in oxide sublayer and create new nickel depleted or totally nickel free oxide.

4. CHEMICAL ETCHING AND WATER BOILING

Chemical etching is very often used to remove nitinol surface deformed by production operations such as: laser cutting, welding, shape setting, annealing of drawn wire, etc. The standard etching solution consists of $HF/H_2SO_4/H_2O$ in 1:4:5 proportions. These proportions are critical for preventing hydrogen ingress in nitinol, which can lead to hydrogen embrittlement (above 100 ppm) and changes in phases and transition temperatures of NiTi [38]. According to Shabalovskaya et al. [24, 39, 40], oxides on nitinol after etching are a combination of amorphous and nanocrystalline phases about few nanometers thick. Owing to this very low oxide thickness, nitinol etched surfaces did not deteriorate under the strain of up to 6-8% in tension mode [41]. The etched nitinol surfaces are more homogeneous compared to the mechanically polished ones because etchant contains very powerful hydrofluoric acid

which dissolves a lot of intermetallic inclusions which otherwise are retained after mechanical polishing. Water boiling and autoclaving in steam and water under pressure promotes oxidation of etched nitinol surfaces [42]. This gentle treatment assists oxygen diffusion toward the bulk of the alloy and simultaneously Ni release to boiling water. The result is thicker titanium oxide layer (10-20 nm) depleted in nickel atoms.

Some researchers studying effects of chemical etching and electropolishing have come to conclusion about inferiority of corrosion resistance of electropolished surfaces versus etched ones [19-21, 30]. The stated reason behind the inferiority of corrosion resistance of electropolished surfaces was retention of intermetallic inclusions after termination of the process. It is necessary to bear in mind that chemical etchant contains very powerful acid, namely HF. However, most electrolytes used for electropolishing do not contain F^- ions. We can speculate that if electropolishing electrolyte contained HF, the outcome would be totally different and the resulting surface would also be depleted of surface intermetallic inclusions. It is worth to note that electrolyte containing HF was successfully used for electropolishing nitinol [43] with satisfactory results. The corrosion resistance of nitinol electropolished in HF containing electrolyte was improved in comparison to nitinol not subjected to electropolishing and the pitting started approximately at 1500 mV and 1300 mV, correspondingly.

5. ELECTROPOLISHING

Electropolishing is one of basic electrochemical processes used in metallic biomaterial surface finishing [43-48]. First of all, the explanation of applied voltage and current density relationship during the process is necessary. This relationship is best explained by analyzing V-I polarization curve (**Fig. 1**).
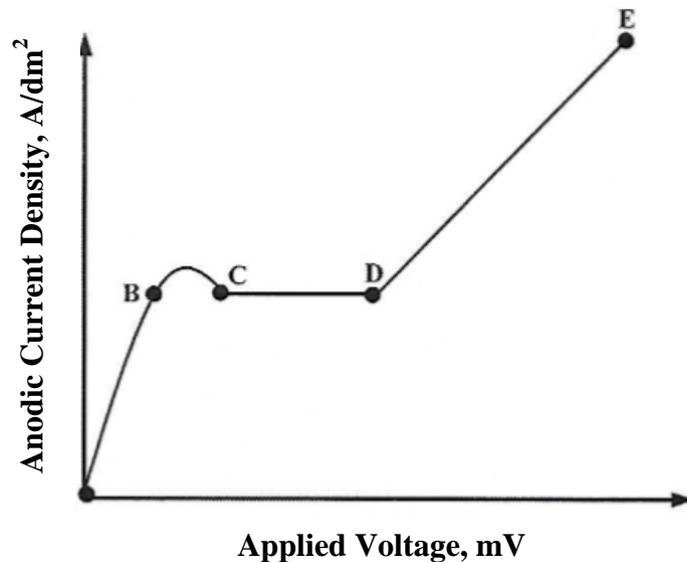

Fig. 1. Electropolishing curve for average electropolishing process

After starting the electropolishing process from point A to point B (Fig. 1) the current density increases linearly with applied voltage. In this region of electropolishing, the surface doesn't change much from its original appearance, however some signs of pitting are visible. No polishing occurs between point B and C. This region is characterized by fluctuation in applied voltage and current density, which results from oxides or salts formation. The polishing effect starts in the region between point C and D. This region is known as the current density plateau [44-47]. Most metals and alloys electropolished in this region show the best electropolishing results. In this region, electropolishing occurs without any signs of oxygen evolution from the anode. In this region, the increase of voltage doesn't increase current densities. In section D-E of the polarization curve the increase of voltage gives rise to current densities. The polishing continues, but the electropolished surface becomes covered with oxygen bubbles. With increased voltage, oxygen evolution increases drastically. This vigorous oxygen evolution in some cases creates severe surface pitting and in others, leads to a very satisfied finish e.g. in austenitic 300 series stainless steels. This region of the curve (D-E) is known as transpassive region [48].

Currently, electropolishing process followed by sterilization is the gold standard of finishing nitinol implantable devices such as: stents, heart frame valves, IVC filters, etc. Electropolishing is a hundred years old electrochemical process which uses electrolysis principles [44-46]. The metal object (in this case nitinol) which has to undergo electropolishing is connected to the positive terminal of DC (direct current) power supply submerged in appropriate electrolyte in electrochemical cell with negatively connected cathode. When current is applied to the cell the anode (metal object) starts to dissolve under controlled conditions. Upon process termination the surface of treated metal object becomes smoother, more corrosion resistant and in case of implantable devices more biocompatible. These new desirable surface properties result from electrolytic dissolution of double layer [44, 47] and creation in its place of a more homogeneous, stable passive film whose content is increased with titanium at the expense of nickel [31]. This new, more improved passive layer can be explained on the basis of Hoar's theory [44], a widely accepted theory of constant formation and dissolution of oxide layer during electropolishing process. This problem was developed in the continuous works by Hryniewicz [45-47]. Our continued works, presented recently by Rokicki and Hryniewicz [48] proposed a new, supplemental "enhanced oxidation-dissolution" theory of electropolishing process which includes nitinol. This new theory eliminates the indispensability of viscous layer, which is postulated in almost all electropolishing theories.

According to American Society of Testing and Materials (ASTM) standard, ASTM F86, electropolishing and nitric acid passivation are two main techniques recommended for surface treatment of medical devices to remove deformed native oxide layers and replace them with more uniform ones [49]. As those techniques are only FDA (Food and Drug Administration – USA) recommendations and not requirements, the electropolishing process found a wide acceptance in medical nitinol device industry and became the gold standard for their finishing. However, nitinol electropolishing process is not standardized and therefore numerous proprietary electropolishing protocols are applied to nitinol with different results [50]. The main differences lay in electrolyte composition and process parameters during the electropolishing: voltage, amperage, temperature, time, electrolyte agitation conditions, cathode material, etc. It must be mentioned that all the differences discussed in literature refer to the electropolishing processes carried out in the plateau region, below oxygen evolution

regime. However, it has to be acknowledged that all electropolishing and magnetoelectropolishing procedures discussed in this paper, and referred to nitinol, were performed in the transpassive region of polarization curve under oxygen evolution regime, unless otherwise marked.

One of the most widely used electrolytes for electropolishing nitinol which gives satisfactory, shiny finish is 3M solution of H_2SO_4 in CH_3OH by Neelakantan et al. [51]. This electrolyte is used in temperature between 0-10 °C. Two different kinds of electrolytes were used in the study of bare nitinol surfaces by Shabolovskaya et al. [19-22]. The electrolyte to electropolish austenitic nitinol consisted of 10% perchloric and 90% acetic acid mixture and was used under constant 20 V potential at room temperature. The martensitic nitinol was electropolished in 70% methanol and 30% nitric acid mixture at –45 °C. Both electropolished surfaces showed satisfactory finish. Simka et al. [54] in their electropolishing-passivation studies of nitinol used electrolyte composed of sulfuric acid/hydrofluoric acid/ethylene glycol. Smoothing and brightening of nitinol surfaces was achieved.

The relatively new electropolishing technology using pulse/pulse reverse waveform carried out in very low viscosity electrolyte (17% sulfuric acid) was recently introduced by Faraday Technology Inc. (Clayton, OH, US) [53]. This technology claims good electropolishing results for spontaneously passivating metals and alloys, including nitinol.

6. PLASMA ION IMPLANTATION

Ion implantation process uses electric field to accelerate ions and introduce them to the solids. This process is used to alter chemical, physical as well as electrical properties of treated object. The ions used in implantation vary widely, from nonmetals such as argon, oxygen, nitrogen to metals such as tantalum, hafnium, etc. Ion implantation technique is employed to improve surfaces of implantable metallic medical devices, including those made of nitinol. The main reasons for applying this process to nitinol are: to decrease nickel surface concentration and thus make nitinol surfaces more haemocompatible, and to improve overall corrosion and wear resistance. The studies by Shen et al. [43], and Yankov et al. [54] have shown corrosion and biocompatibility improvement of nitinol implanted with oxygen and nitrogen. Levintant-Zayonts et al. [55] used nitrogen to implant nitinol surface and thus improved hardness and wear resistance with positive results.

However, Wolle et al. 2009 [56] found no improvement in cyclic fatigue test results on nitinol endodontic rotary files after nitrogen implantation. The argon implanted files showed some degree of improvement and withstood greater number of fatigue cycles before fracture than the untreated samples. In contrast to these results, Rapisarda et al. [57] found improvement in fatigue resistance of implanted nitinol rotary files compared with a control group. Maitz [58] found that implanting oxygen to nitinol is a useful method for decreasing surface nickel concentration. In this case fibrinogen adsorption on oxygen implanted nitinol was decreased but conformation changes were higher than on untreated surface. The implantation did not influence platelets adherence, endothelial cell activity or cytokine release.

Tantalum ion implantation was used by Cheng et al. [59] because of its good biocompatibility and high mass absorption coefficient. Zhao et al. [60] achieved improved wear resistance with simultaneously decreased nono-hardness by implantation of hafmium.

Hf-NiTi exhibited better pseudoelastic behavior and retained surface integrity even after being strained in tension to 10%. In another study, Zhao et al. [61] showed that by implanting hafnium in nitinol surface, nickel release can be decreased and osteoblast-material interactions and haemocompatibility improved. They found suppression of platelets adhesion and activation and explained this by the decreased surface energy and nickel content by hafnium implantation.

Meisner et al. [62] studied influence of implantation of silicon, titanium and zirconium in nitinol surface on proliferation of rat mesenchymal stem cells (MSC's). The study revealed that samples of untreated as well as implanted nitinol did not show any cytotoxic action toward rat MSC's cells. Moreover, the study showed total bioinertness of untreated nitinol on MSC's cells by failing to induce their proliferation. Contrary, ion implanted surface showed signs favorable for proliferation.

7. COATING

Coating is another type of treatment applied to bare nitinol surfaces in order to improve their corrosion resistance, minimize nickel leaching, improve their osseointegration, vascular compatibility and to create substratum capable of drug delivery. One of the most popular and commercially used coating designs to improve the biocompatibility of nitinol stents is DLC (diamond-like carbon). This coating is used alone or in combination with other polymeric coatings. Kim et al. [63] found decrease of neointimal hyperplasia on DLC coated nitinol stents compared to control uncoated group. However, when coated stent was additionally grafted with PEG (polyethylene glycol) more hyperplasia was found compared with either control bare nitinol or DLC coated stent. Although DLC coating can improve biocompatibility of bare nitinol stent, it can also create some problems. The most important is the delamination, which can occur under the cyclic loading of contraction and expansion of vascular stent [64]. The delamination of DLC coating strongly depends on thickness of Si buffer layer. Delamination can be greatly suppressed by increasing the Si buffer layer. Flamini et al. [65] found out that the best thickness of Si buffer layer is about 150 nm. By increasing the layer thickness beyond this number adhesion of DLC can be compromised.

To improve nitinol osseointegration and prevent nickel leaching from skeletal implants many methods of coating nitinol with hydroapatite have been developed in recent years. Katić et al. 2013 [66] studied usefulness of sol-gel derived biphasic calcium phosphate ceramics coating method. The study showed the need for multilayer coating to prevent cracking of single-layer coating by different thermal expansion coefficients of nitinol substrate and CaP coating. This multi-layer coating exhibits good bioresorbility, is biodegradable *in vivo*, and its low content of CaP could be helpful in enhanced osseointegration.

A study of nitinol bare surfaces as compared with TiN (titanium nitride) coated surfaces [61] showed a decreased nickel content in coated nitinol surface. Also TiN coating of nitinol improved hydrophylicity of its surface and contributed to the expression of genes related to cell adhesion and other physiological activities. Zhang et al. [67] studied influence of nano-structured TiN/Ti coating deposited on nitinol cardiac occluders implanted in the ram's heart on its nickel release. The results showed that nickel release was significantly reduced to endocardium compared with control untreated nitinol devices. Other polymeric coatings on nitinol stents are currently studied as drug delivery platforms or solely for improvement of

nitinol's biocompatibility. As drug eluting stents with durable polymers have a tendency to contribute to late stent thrombosis which in many cases can be fatal, some researchers concentrate on developing drug free polymeric coating which is anti-thrombogenic with in situ good endothelialization properties. This goal was achieved by Bakhshi et al. [68] who developed a non-biodegradable, nanocomposite polymer based on polyhedral oligomeric silsesquioxanes and poly (carbonate-urea) urethane coating for nitinol stent.

A different approach is currently taken to the only FDA approved nitinol peripheral drug eluting nitinol ZILVER PTX stent [69]. In this case the stent is directly coated with immunosuppressant and antiproliferative paclitaxel drug. The report by Dake et al. [70] suggests that polymer free drug eluting stent is a promising endovascular therapy considering its overall anatomical and clinical effectiveness.

8. NITINOL ALLOYING

The addition of a third element to nitinol to replace Ti or Ni has an enormous effect on phase transformation, corrosion resistance and biocompatibility of the newly created ternary nitinol alloy. There are two main reasons for adding the third element to nitinol: suppression of transition temperature and martensite stabilization [71]. The martensite suppressant (Fe, Co, V, Mn, Al, Ta, Cr) could be substituted in a small amount for nickel without seriously impairing the shape memory effect but simplifying processing and adding stability into high temperature service. Another group is martensite stabilizers which increase transformation temperature. This group consists of Hf, Zr, Pt, Pd elements. Some other elements were also researched as possible additives to nitinol. Addition of Nb increased corrosion resistance and machinability. Haider [72] and Pulletikurthi et al. [73] studied the influence of adding Cr, Ta, Cu elements on the corrosion resistance and biocompatibility of ternary alloys. The comparative cytotoxicity study indicated that Ni and Cu ions exhibited greater toxicity toward HUVEC cells as compared with Ti or Cr ions.

However, the ternary nitinol alloys have not found a widespread industrial application yet. Only two of ternary alloys known to the authors have found narrow industrial application: NiTiCu in actuators and NiTiCr in wires used as a pulling-pushing tool in minimally invasive spine operation.

9. STERILIZATION

According to the CDCP (Centers for Disease Control and Prevention), "Sterilization means the use of a physical or chemical procedure to destroy all microbial life, including highly resistant bacterial endospores". Every implantable medical device which will contact tissue or the vascular system upon implantation requires sterilization.

Sterilization can be broadly divided in three categories:

(1) high temperature-pressure sterilization (autoclave)
(2) chemical sterilization
(3) radiation sterilization.

9. 1. Steam autoclave and dry heat sterilization

This method is commonly used to sterilize surgical tools. However, this method can change some properties of metallic materials which are sensitive to prolonged heat and moisture. In the case of nitinol implantable devices this method is not used because nitinol implantable devices such as stents, heart valves frames, IVC filters are heat treated for shape setting. The high temperature of steam sterilization would change the already set A_f temperature and cause problems with deployment and proper functionality of device. The same applies to dry heat sterilization. Thierry et al. [13-15] investigated the influence of various sterilization techniques on nitinol surface properties. Dry heat increased oxide thickness and surface roughness. Water contact angle was altered and nickel content in passive layer was increased. Steam autoclaving was found [14, 15] to increase passive oxide thickness together with increased nickel content. Study by Shabalovskaya [42] showed that autoclaved nitinol surface contained 2% of nickel, which did not suppress the rat lymphocyte cell growth. The influence of dry heat and steam sterilization on bending of nitinol wire was investigated by Alavi et al. [74]. Dry-heat sterilization was carried out in oven at 160 °C for 120 minutes. Steam sterilization was performed in autoclave with saturated steam at 103 kPa at 121 °C for 24 minutes. In both cases sterilization resulted in decreased superelasticity.

9. 2. Chemical sterilization

Ethylene oxide (EtO) is a low temperature (50-60 °C) effective sterilization method with 16-18 hours cycle. Ethylene oxide gas kills microorganisms, including spores, by direct contact. It is used to sterilize heat and moisture sensitive material, including nitinol implantable devices. The disadvantage of this technique is that it can leave toxic residue on the sterilized surface. Thierry et al. [13-15] observed some deposits on the nitinol surface after EtO sterilization. The surface became more rougher and was slightly enriched in nickel. Study by Shabalovskaya et al. [29] revealed surface discoloration with black stains of various shapes. Auger analysis of black stains indicated carbon contamination. It is worth to note that in this study EtO sterilized samples showed the same nickel content as mechanically polished samples, but induced no nickel release. This was explained by the difference in chemical state of nickel in passive layer of both nitinol samples. The mechanically polished nitinol surface contains nickel in both oxidized and elemental states. The nickel in nitinol surface which underwent EtO sterilization is bound in more complex chemical compounds, including organic ones.

Hydrogen peroxide plasma (Sterrad) low temperature sterilization process was introduced by Johnson & Johnson Co. to fill the gap between autoclave high temperature sterilization, which unfortunately cannot be used in some cases (nitinol devices), and EtO process which can leave toxic residuals. In this process reactive plasma is created by activation of hydrogen peroxide by radiofrequency (RF) energy. The operating temperature of this process ranges between 45-50 °C and lasts between 45 and 70 minutes. According to Shabalovskaya et al. [30] the hydrogen peroxide sterilization can have negative effect on the biocompatibility of nitinol.

Paracetic acid is an oxidant and disinfectant in liquid form and is used for decontamination. Living cells are destroyed by paracetic acid when it combines with extra oxygen atom – plasma process. Thierry et al. [15] found out that paracetic acid plasma sterilization drastically reduced contact angle, making nitinol surface more wettable. The decontamination process

using only liquid paracetic acid had no influence on wettability change. Except for this, their study did not indicate significant difference between nitinol surface which underwent paracetic plasma or paracetic liquid treatment.

9. 3. Radiation sterilization

Radiation sterilization methods can be divided in two groups: ionizing and non-ionizing radiation sterilization. The first group utilizes beta, gamma, X-rays, E-beam etc. It was found out [28, 75] that gamma irradiation of nitinol samples prior to cytotoxicity evaluation did not create any adverse effects. Groth et al. [76] and Pelton [77] demonstrated no adverse effect of E-beam sterilization on overall performance of nitinol and concluded that this kind of sterilization was safe and effective for medical devices. Smith et al. [78] studied irradiation-assisted stress corrosion cracking (IASCC) of nitinol during E-beam sterilization. From his findings he concluded that nitinol is susceptible to IASCC when in presence of constraining stress, fluorinated polymers, and E-beam irradiation.

Ultraviolet light UV sterilization was used by Shabalovskaya et al. [29, 30] to assess and compare it to EtO sterilization of nitinol on human lymphocyte proliferation. In the case of UV sterilization, nickel content was increased compared with EtO sterilized samples and its release to the medium was also higher. However, stimulation of human lymphocyte cells was similar to that caused by EtO sterilized samples, which induce zero nickel concentration in medium.

10. DISINFECTION

Sodium hypochlorite has broad spectrum antimicrobial activity, however, it is not able to destroy endospores and therefore cannot be classified as sterilization agent. Instead, it is classified as disinfectant. It is widely used as water and laundry disinfectant, cleaner of environmental surfaces and is also used in dentistry to clean and decontaminate endodontic rotary files used in root canal procedures. As almost all rotary endodontic files are made of nitinol, it is very important to research the influence of NaClO on nitinol. It has to be mentioned that NaClO is used not only as cleaning and disinfecting agent but also as lubricant and irrigation agents during the procedure. It appears, however, the literature regarding the influence of NaClO on corrosion and fatigue resistance of nitinol rotary files is very controversial and full of discrepancies.

O'Hoy et al. [79] conducted experiments with nitinol rotary files subjected to several cycles of exposure to dilute sodium hypochlorite solution (1% NaClO) and Milton's disinfectant solution (1% NaClO + 19% NaCl). Every cleaning cycle consisted of scrubbing, rinsing and 10-minute immersion in NaClO, followed by ultrasonic cleaning for five minutes. After ten cycles of cleaning, the files did not show any adverse effect of cleaning on fracture resistance. SEM analysis did not show any signs of corrosion. Other NiTi samples have shown pitting corrosion.

The authors described this corrosion behavior as brand-specific. Barbosa et al. [80] also did not find any adverse results of exposure of nitinol rotary files to NaClO solution on their mechanical properties. Conclusion from this experiment is that the exposure to 5.25% NaClO solution effects neither resistance to flexural fatigue nor torsional resistance of NiTi K3 endodontic files. Shen et al. 2012 [81] have not found any adverse effect of 6% NaClO

solution on nitinol rotary files during 25-minute exposure. The exposure did not reduce cyclic fatigue fracture resistance. The fractographic appearance of files fatigued in NaClO was very similar to those fatigued in air and water. Additionally, no pitting corrosion was found on surface of the instruments. In contrast, Peters et al. [82] found degrading effect of NaClO immersion on rotary files fatigue resistance. It is worth noting that only 28 files out of 160 showed signs of gross corrosion.

11. EFFECT OF MAGNETIC FIELDS

11. 1. Magnetoelectrodissolution

One of the first researchers who experimentally determined influence of external magnetic field on dissolution of metals were Dash & King [83]. They observed that in the absence of magnetic field the dissolution of partially submersed copper anode took place due to air/ electrolyte interference. By applying magnetic field of 0.9 T, a uniform dissolution at one side of the anode was achieved. When magnetic field was reversed, dissolution took place on the opposite side of the anode. The periodic reversal of magnetic field led to uniform dissolution without preferential thinning at air/electrolyte interference. In addition, they found out that the resistance of electrolytic cell was reduced by application of magnetic field. Some electrodissolution systems exhibit current oscillations at constant potential condition (copper in H_3PO_4, niobium in H_2SO_4/HF electrolytes, correspondingly). By applying magnetic field to such a system it is possible to decrease or even totally eliminate oscillation due to increased mass transport or kinetics interactions.

Li et al. [84] researched effects of magnetic field on the anodic dissolution of nickel in $HNO_3 + Cl^-$ solution. They found all types of magnetic effects on nickel dissolution. Magnetic field decreased current in active region, but in the passive region magnetic field had almost no influence. However, they concluded that the effects of the magnetic field are almost the same as those of the stirring. Wang & Chen [85] used holographic microphotography technique to study periodic dissolution of iron in magnetic field. The periodic behavior of iron dissolution was quite sensitive to the strength of magnetic field. At magnetic field of 100 mT current oscillation totally disappeared. This was due to enhanced mass transport by externally applied magnetic field.

11. 2. Magnetoelectropolishing

The word "magnetoelectropolishing" was first used by Rokicki in his US Patent Application number US 11/009,190 filed in US Patent Office on December 10, 2004 which became US Patent Number 7632390 on December 15, 2009 [86]. Magnetoelectropolishing is electropolishing performed in superimposed uniform magnetic field. Magnetic field can be generated by permanent magnets or by electromagnets. **Fig. 2** shows two magnetic fields distribution patterns, one of the flat round magnet and the other of ring magnets stacked together. All magnets are magnetized by their thickness.

As can be seen from the drawings (Fig. 2), magnetic field distribution depends on magnet type. In the case of flat round magnet which is positioned directly under the electrolytic cell magnetic field (Fig. 2a) its strength is greatest directly above the center of round magnet and decreases in peripheral direction (under constant distance from the surface). In the case of ring magnets (Fig. 2b), which are magnetized through thickness and

stacked together, a more uniform magnetic field can be obtained. For that reason, ring magnets as more effective are advised to use for magnetoelectropolishing experiments. **Fig. 3** shows distribution of iron filings above flat round magnet (a) and rings magnet stacked together (b). As can be seen from the pictures, ring magnets create more uniform magnetic field (b).
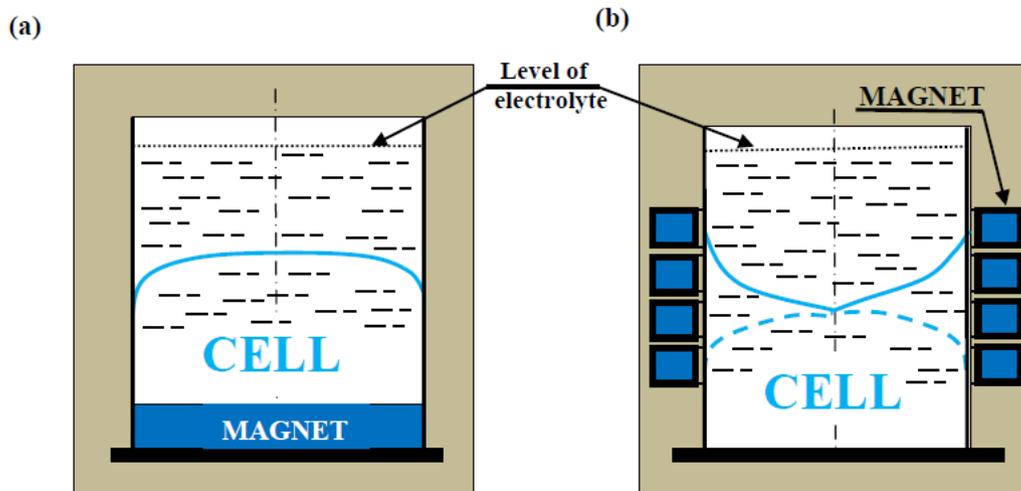

Fig. 2. Magnetic field distribution (light blue) when using (a) flat round magnet, (b) ring magnets

Magnetoelectropolishing process can be defined as controlled dissolution of metal, alloy or intermetallic compound by electropolishing process under the influence of externally applied magnetic field [86-89]. The main reason for utilizing an electropolishing process is to improve the quality of the surface. The imposition of a magnetic field during electropolishing process provides an enhanced opportunity to achieve desirable results. Some examples of magnetoelectropolished nitinol implantable parts and instruments are presented in **Fig. 4**.
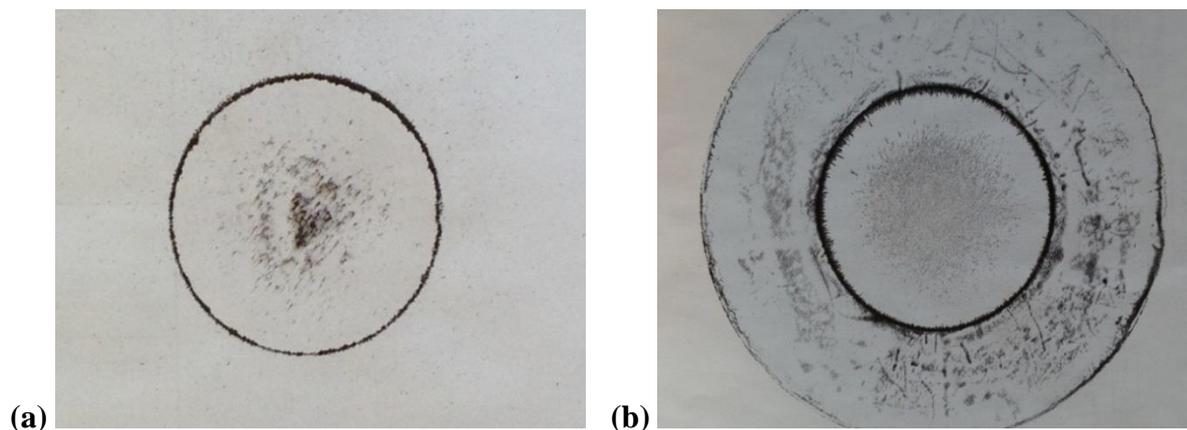

Fig. 3. Magnetic field strength indicated by iron files of **(a)** flat round magnet, **(b)** four rin magnets stacked together
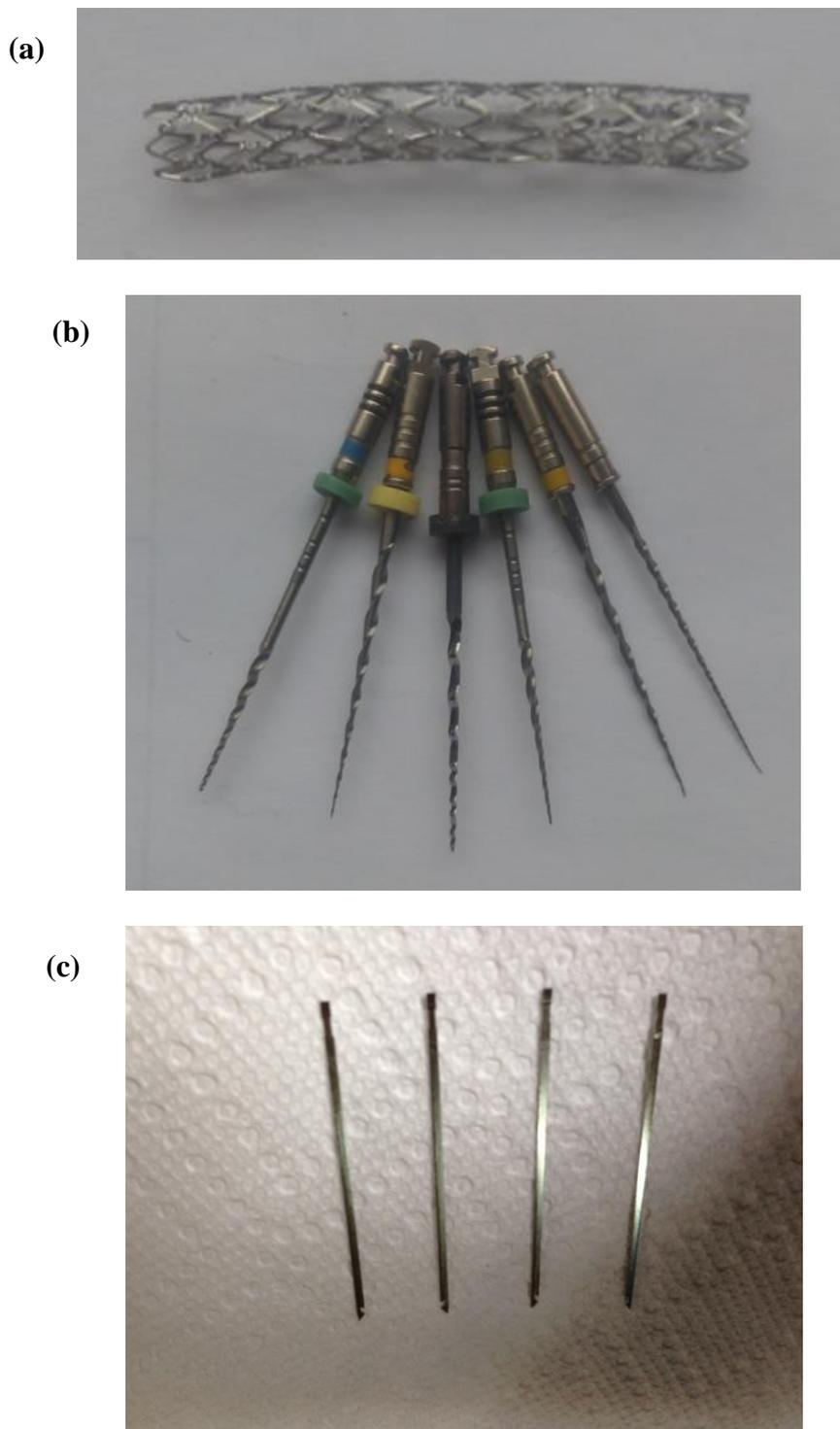
(a)

(b)

(c)

Fig. 4. Nitinol tools and instruments undergoing magnetoelectropolishing (MEP): (a) NiTi stent of OD ϕ 3.3 × 27 mm, (b) NiTi endodontic files of OD about ϕ 1.0 × 23-25 mm, (c) NiTi needles which undergo double bending during surgery. The flat working part of the needle of dimensions 50 × 1.42 × 0.29 mm, connected with cylindrical rod 205 × 1.53 mm (the rod is cut/not visible in the photo)

The electropolishing process performed under externally applied magnetic field leads to refinement of surface chemical composition impossible to achieve by standard electropolishing. As will be shown later, those chemical surface composition changes of metallic materials used to produce implantable medical devices enhance their bio- and haemocompatibility. The addition of the external magnetic field to electropolishing process also drastically minimizes microtopography by lowering microroughness [88-90], and minimizing actual surface area on micro and nano scales of the various metallic materials. In magnetoelectropolishing processes, an externally applied magnetic field works in two distinctive ways, either by enhancing or retarding the rate of the dissolution process. The change in rate or speed of the process does not depend on either the magnetic properties of the material or the composition of the electrolyte. The main factor, which has not been earlier reported as being responsible for the two-way influence of externally applied magnetic fields on the magnetoelectropolishing process, is created by the oxygen regime. When magnetoelectropolishing is performed with a constant potential under oxygen evolution the current density decreases and less material is dissolved. The rate of retarding the process depends upon the strength of the externally applied magnetic field [89-91].

One important fact is that during MEP of alloys and intermetallic compounds, ferromagnetic elements are primarily removed from the surface. The XPS study of magnetoelectropolished 316L stainless steel [90-92] showed increased selective dissolution of ferromagnetic elements (Fe, Ni) under magnetic field influence. The XPS analysis of passive film on nitinol which underwent magnetoelectropolishing under oxygen evolution regime has not detected nickel in any form [93]. The passive film was totally composed of titanium oxide.

12. CONCLUSIONS

The aim of the paper was to present a variety of the available methods used for modification of nitinol biomaterial for medical applications. After decades of crucial trying and different experiments with techniques and technologies offering modifications and improvements of nitinol, magnetoelectropolishing appeared to be the most effective method [86-101]. The works were begun almost two decades ago, with Rokicki's patents on magnetoelectropolishing [86, 87] and the first summary on metallic biomaterials' surface finishing, including magnetoelectropolishing (MEP), was presented in the book [102] by Hryniewicz. A good deal of work on magnetoelectropolishing of stainless steels using a flat magnet was presented by Rokosz in his book [103].

It appears that after magnetoelectropolishinng (MEP) of both, nitinol and other titanium alloys, as well as many other metallic biomaterials studied by the authors, the treated metal surfaces are distinguished with quite new chemical, electrochemical/corrosion, physical and mechanical properties, including much better bio- and haemocompatibility (e.g. removal of nickel from nitinol surface). One of the unique features of metal samples after MEP is their de-hydrogenation investigated and noticed both in stainless steels, titanium and niobium [104-108]. This phenomenon of a considerable reduction in hydrogen content may be also one of the reasons of unusual increase in fatigue resistance of the Nitinol needles studied recently [105]. They are to be the subject of publications under a separate article/s in the near future.

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