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Stent' in Vitro Degradation Rate and Toxic Degradation Products

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Abstract

Medical stents are tubes made of a metal or plastic wire mesh. They are inserted into a hollow structure of a body part to keep an anatomic vessel or passageway open. Stents placed in the body can cause toxic effects by releasing metal ions into the body, and can also cause harmful effects on the body by creating corrosion products. In this study, the decomposition rate and release of corrosion products in artificial body fluid (PBS) of a stent sample with a nitinol structure produced for medical purposes were examined. If any metal decomposes in the body, it can endanger human life and can damage the body via heavy metal residues and toxic radical products that accumulate over long periods in the body. An in vitro degradation test was performed according to the standard 10993-13 and metal release values were found after short periods (one month) for nitinol. In the present study, the release values and possible toxic effects of nickel and titanium within the body with long-term intra-body use were examined. By calculating the mass loss caused by degradation, its relationship to heavy metal release inside the body and the possible side effects on human health of heavy metal residues were evaluated. Low metal ion release values of heavy metals resulting from degradation were determined by the ICP-OES device. Physical changes (diameter) in the surface of stent parts were also measured to compare and evaluate with the degradation rates. When the nitinol stent' toxicological distribution of released heavy elements were investigated; after one month of degradation the 191 ppm release level of tungsten was in toxic range, while the levels of nickel and titanium were in a acceptable range in the scopes of literature. Also it has been found that after approximately 12 years the whole nitinol stent wire would be dissolved and released into the body.

Key Words

"*nitinol, degradation, tungsten, toxic elements, coil stent*"

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1. Introduction

Stents are specially made of corrosion resistant materials. These materials include titanium, nickel, tungsten, nitinol, and stainless steel. Tungsten, which is found in soil and rocks in nature, is not found in a pure form but found together with other mineral structures. It increases the strength, flexibility, and durability of metals when included in metal alloys. In addition, it has a high melting temperature (3422 degrees). This advantageous property allows its use in bulb filaments and X-ray tubes. Because of the hard structure of tungsten carbide, tungsten is also widely used in abrasive, insert grinding, and cutting tools in industry [Knowles et all., 2021]. It has been determined that the limit for tungsten as a volatile component in industrial plants should be <10 ng/m^3, while this limit should be in the range 1.82-6.04 µg/L when it is in drinking water [Haddad & Zikovsky., 1985]. For tungsten, the Occupational Safety and Health Administration (OSHA) has set the allowed 8-hour average exposure limit as 5 mg/m^3 (5 ppb). When metal particles are in dissolved form an exposure limit of 11 mg/m^3 has been determined for the construction and shipbuilding industries [Keith., 2005]. As a result of exposure to tungsten components, low sperm mobility has been observed along with other side effects such as increased embryotoxicity and cancer [Keith., 2005, Wild et all., 2000]. It has also been found to cause localized irritation to the mouth and eyes when those areas are exposed to it. Moreover, an implanted tungsten alloy (91.1% tungsten, 6.0% nickel, and 2.9% cobalt) was found to cause aggressive tumors in rats [Keith., 2005, Wild et all., 2000, Nyren et all., 1995]. According to these studies, nickel and cobalt alloys are known to cause tumors.

After low dose nickel was implanted in mice, histopathological and immunohistochemical studies showed rapid metastasis in the liver. Histological lesions in the heart were observed as a result of exposure to 62.5 and 125 mg/kg/day soluble sodium tungstate via oral gavage in rats. There were also behavioral disruptions affecting motor activity [McInturf et all., 2011].

In a clinical study on an endobronchial nitinol coil stent, this product was used in 155 patients and not used in 157 other patients. Comparison of the results showed a 20% increase in mortality in those who underwent the endobronchial coil treatment [Sciurba et all., 2016]. Corrosion studies on these stents have also been carried out. In a corrosion simulation performed with stents in accordance with the scope of "ASTM G61-78 Standard Practice for corrosion resistance measurements" in Ringer's solution, it was predicted that there would be melting and loss of 275 µm/year. Moreover, polyurethane coatings (5-30 µm) were applied to the stents to extend the life cycle of these medical materials and reduce their metal release into the body. When this coating was applied, the melting rate (degradation rate) decreased from 275 µm/year to 13 µm/year [Mazumder et all., 2003].

In the present study, the degradation of nitinol samples in phosphate-buffered saline (PBS) was examined within the scope of the standard 10993-13:2010 (Biological evaluation of medical devices - Part 13: Identification and quantification of degradation products from polymeric medical devices) and the percentage of degradation was also calculated. In addition, the possible toxic metal ions released and their amounts that could occur within the scope of the standard *10993-15:2019 (Biological evaluation of medical devices - Part 15: Identification and quantification of degradation products from metals and alloys*) were calculated using an ICP-OES device and their damage to the human body was evaluated

2. Materials and Methods

A commercially used nitinol sample (endobronchial nitinol coil stent) was used for this experimental process. The diameter of the nickel–titanium wire was about 297 µm. Around this nitinol wire there was a tungsten wire 58 µm in diameter wrapped in a spiral. All around the entire wire was a 75-µm-thick coating of polypropylene to decelerate the effect of degradation. The ICP-OES device was calibrated for nickel, tungsten, and titanium. The operating conditions for the ICP-OES are given in Table 1. Nickel, tungsten, and titanium are the main known elements in the stent. For these metals, ICP-OES calibration curves are given in Figure 1, Figure 2, and Figure 3.

The structure of the nitinol wire was visually inspected under a Leica DM5000B stereomicroscope with 100× magnification. A Dasqua model (4210-2105 part number) digital micrometer (±0.001 mm) was used to measure the diameter of the nitinol wire's components in the micrometre range before and after the degradation experiment. In addition, the percentages of the elements in the nitinol wire were measured using an X-ray fluorescent (XRF) spectrometer (SPECTRO X-LAB 2000, AMETEK, Germany). XRF technology provided the determination of the chemical composition of the nitinol samples in this system. The XRF system has a 50 W/60 kV X-ray tube for excitation and TurboQuant II software accurately analyzes unknown liquid, powder, or solid samples. Degradation experiments were conducted according to the standard 10993-13: 2010 (Biological assessment of medical devices — Part 13: identification and quantification of degradation products from polymeric medical devices).

3. Results and Discussion

The effects of degradation on the nitinol stent will occur initially, but slowly; after several years of implantation, these effects will become accelerated. At the tissue contact interface, the released ions will "burst-out" at higher levels locally. Over time, metal ion accumulation will occur and after long periods accumulated ions are taken up by the adjacent cells. Determining the released nitinol's heavy element level is of critical importance. In vitro experiments involve simulations of body environments outside the living being. Every piece of laboratory equipment is a device with upper and lower measuring limits. To measure a value and obtain a reliable result, the data obtained must be between these limits. A piece of laboratory equipment has lower limit of detection (LOD) and low limit of quantification (LOQ) values. To obtain reliable results these limits must be defined before the experiment

Every measurement device must be calibrated for the related measurement region and the LOD and LOQ must be defined to have a reliable and meaningful result [Doğan., 2020]. Otherwise data measured under the LOD values would be invalid. The ICP-OES is a highly sensitive piece of chromatography equipment. LOD and LOQ values for the ICP-OES are defined in Table 2. The LOD was defined for tungsten as 1 ppb, for titanium as 1 ppb, and for nickel as 0.5 ppb. The LOQ was defined as 3 ppb for tungsten, as 24 ppb for titanium, and as 1.5 ppb for nickel with the device program. Values measured below these LOQ values would be invalid; this is the measurement limit for this device.

All the ionic metal release experiments were performed in PBS. PBS simulates the body liquid. This buffer solution is commonly used in biological research experiments. PBS is also recommended by the standard TS-EN ISO 10993-13. The pH of this water-based salt solution was set to 7.4 to simulate blood pH level. The buffer solution contains disodium hydrogen phosphate, sodium chloride, potassium chloride, and potassium dihydrogen phosphate. The related metallic ion values in the blank PBS, before the metal ion release experiment, were also measured and considered. Blank PBS's related metal element levels were as follows: tungsten 50 ppb, titanium <8 ppb, and nickel <0 ppb (Table 2). When degradation occurs the pH level must be monitored. pH is another parameter used to assess the degradation level. pH level decreased from 7.4 to 6.99 value after degradation. This change was calculated with the formula pH = -log[H+]. To achieve this pH value (6.99), the equivalent of 1.5×10^6 million positive ionic compounds [H+ or positive metalic ions] must be released into the PBS solution by the degraded material.

A stent is made up of two main compounds (Figure 5, Figure 6). The main backbone wire consists of nickel and titanium (Figure 5, labeled B1). This backbone, named "nitinol", is coiled with tungsten wire (Figure 6, labeled A). Degradation decreased the diameters of the A and B wires' parts separately and decreased the whole nitinol's diameter (Figure 5, labeled B1) after the degradation (Table 3). XRF measurements were recorded before and after the degradation experiments and the results are given in Table 4.

Accelerated degradation experiments were done at 70 degree celcius. Three days accelerated degradation of sample at 70 degree celcius corresponds to 1 month degredation at 37 degree celcius. Long term intra body temperature 37 degree celcius exposure in PBS was simulated by the accelerated degradation experiments. Experiments conducted in accordance with TS EN ISO 10993-13 calculated the percentage of degradation in samples according to equation 1. WL: amount of degradation; W0: initial weight; Wr: dry weight. The degradation percentage and derived data are summarized in Table 5.

$$WL\% = (W0 - Wr)/W0 \times 100 \quad (1)$$

Investigation of the degradation revealed that it accelerated logarithmically with time (Figure 4). After one month of degradation 191 ppm tungsten was released into 40 mL of PBS liquid. The level of released titanium was <8 ppm and the level of released nickel was 252 ppb (Table 2). When these values are evaluated over one year approximately, it is estimated that 2292 ppm tungsten, 96 ppm titanium, and 3 ppm nickel would be released.

In a previous study, it was reported that released nickel ion levels of around 7500-30000 ppm are carcinogenic and negatively affect the growth of cultured 3T6 embryo mouse fibroblast cells [Shih et all., 2000]. Within the scope of the present study a released nickel ion level of 3 ppm seems negligible after 1 year. Titanium is a well-known and frequently used heavy metal. There is no known toxic effect of this biomedical material but it has some long-term negative effects via its corrosion product (TiO2) [Kim et all., 2019]. In an experimental study performed with pure titanium and a titanium alloy (Ti-6Al-4V), the results did not show any significant increases in lactate dehydrogenase (LDH) or morphological change [Rae., 1981]. LDH is an enzyme involved in energy production and this enzyme's value increases as a marker when tumors, cancers, infections, anemia, muscle trauma, cell toxicity, and bone fractures occur.

A release level of the heavy metal tungsten larger than 5 mg/L (5000ppm) would be lethal [Van der voet., 2007] after only 1 month, and so when the level of tungsten released in the present study (191 ppm) is considered, it is far below this harmful limit. Moreover, in a study performed with degraded embolization coils by in situ evaluation, an average tungsten level in the blood of 8.4 µg/L (8.4 ppb) was not showed toxic affects [Butler et all., 2000].

However, in the present study the stent's nitinol and tungsten wire diameters decreased differently. The outer layer consists of coiled tungsten and it degraded more than the inner nitinol core wire. The diameter of A, the tungsten part, decreased from 58 µm to 51 µm after one month of degradation (Figure 5, Figure 6). The diameter of the nitinol (B1) wire decreased from 297 µm to 295 µm after one month of degradation. A tungsten coil covers the inside nitinol wire and this coil mostly dissolves before the nitinol inner core wire with degradation (Figure 5). The outer tungsten coil (A) covers the inner nitinol core wire (B1) and decelerates the inner wire's degradation. This affected the XRF results before and after degradation. XRF results gave the nitinol wire composition. The maximum percentage was for tungsten. Titanium and nickel levels were around 50-60% after the degradation (Table 5).

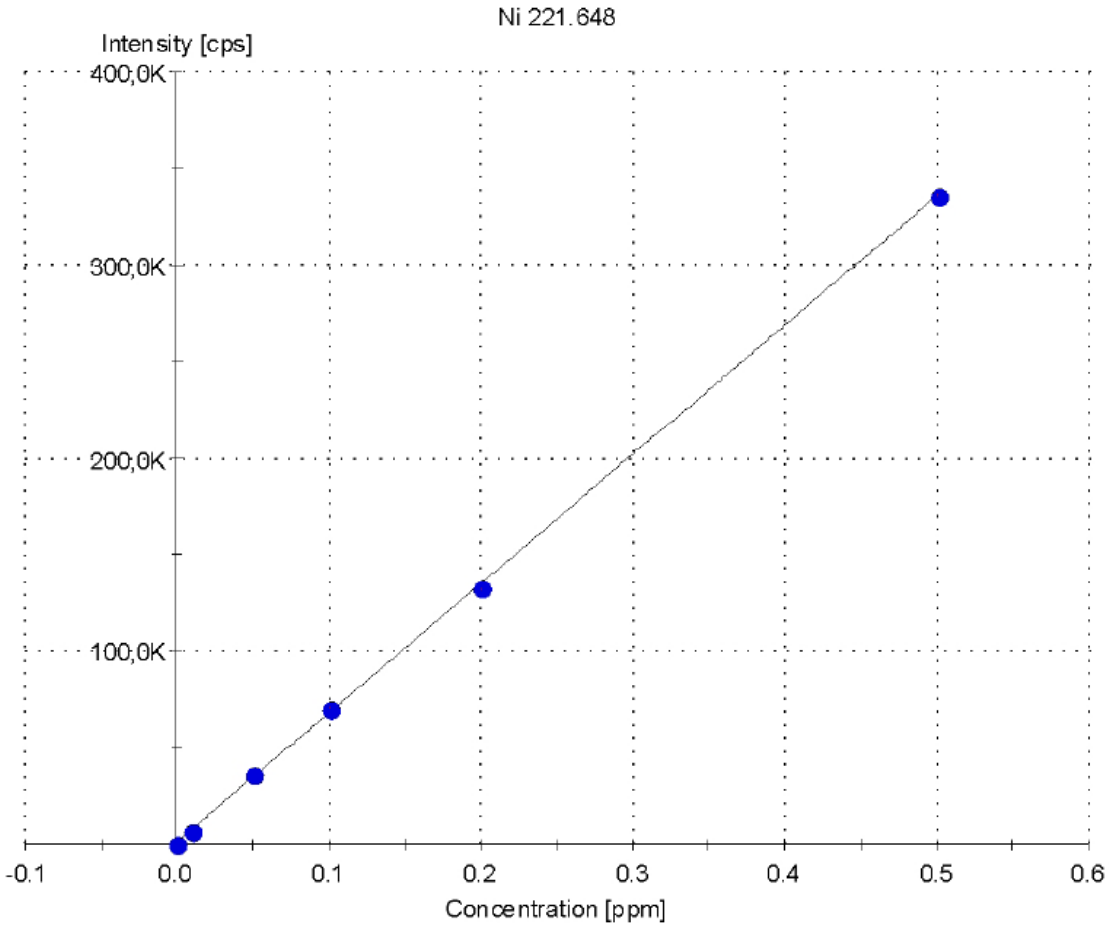

Figure 1. Calibration curve of ICP-OES for nickel element

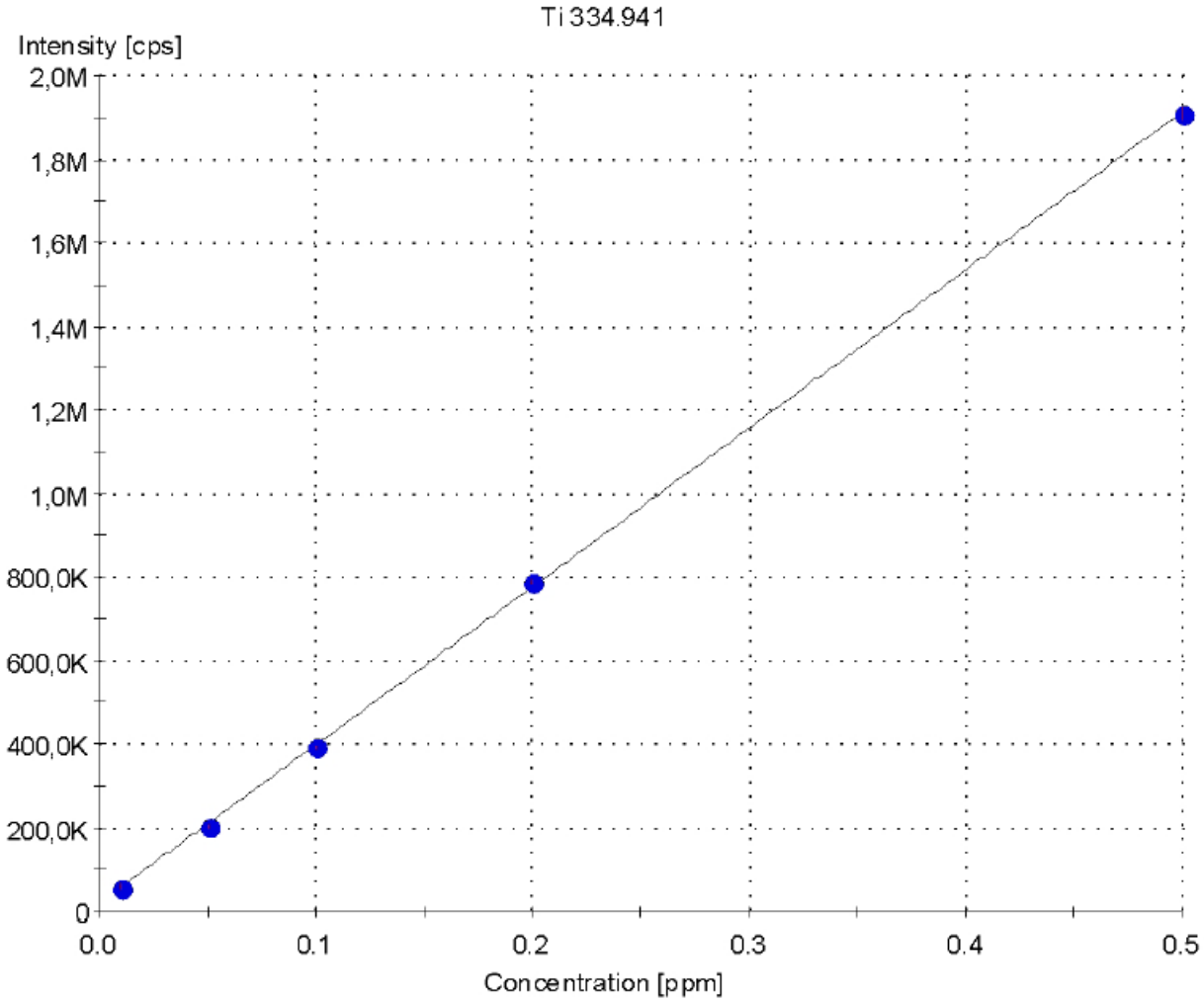

Figure 2. Calibration curve of ICP-OES for titanium element

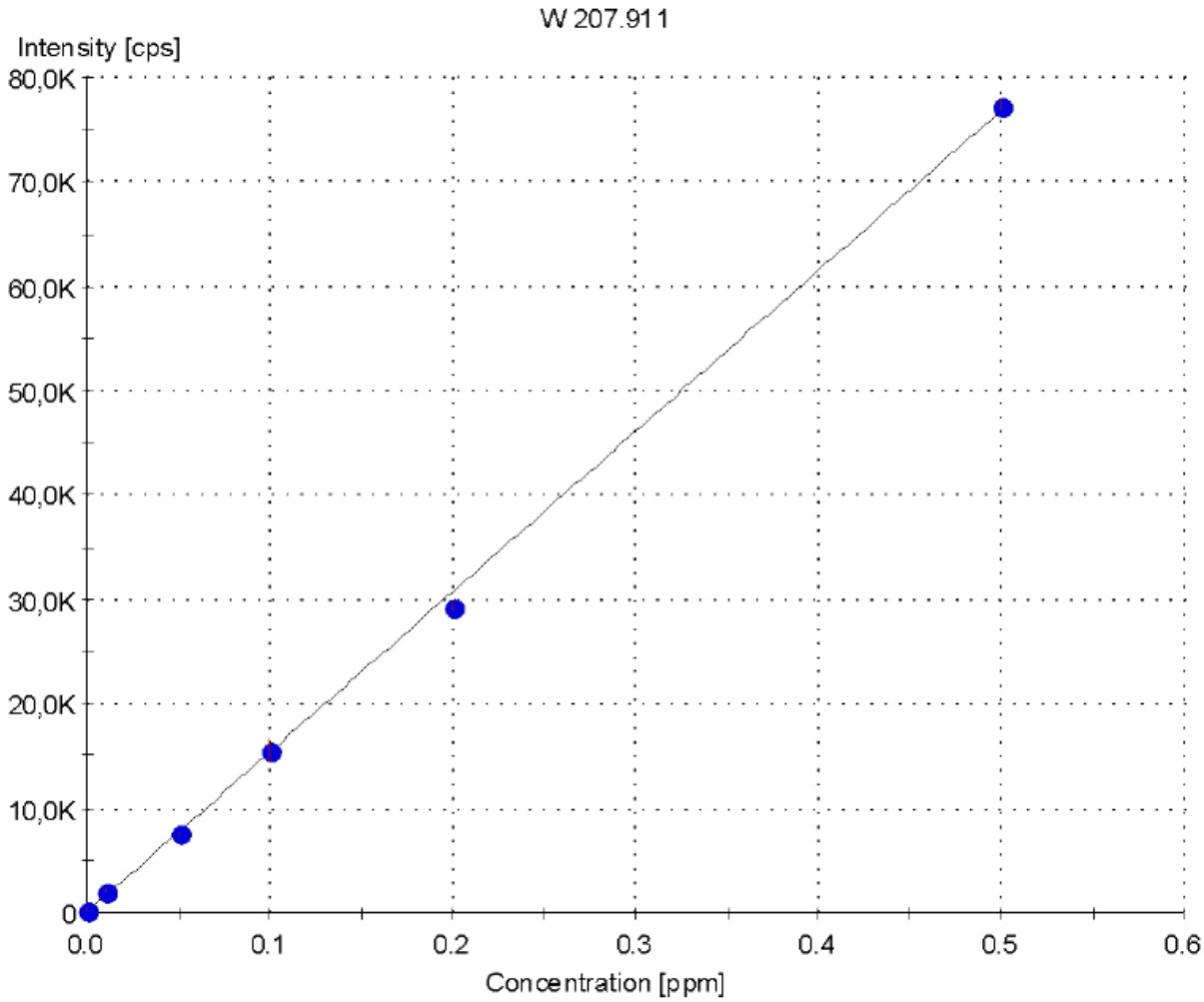

Figure 3. Calibration curve of ICP-OES for tungsten element

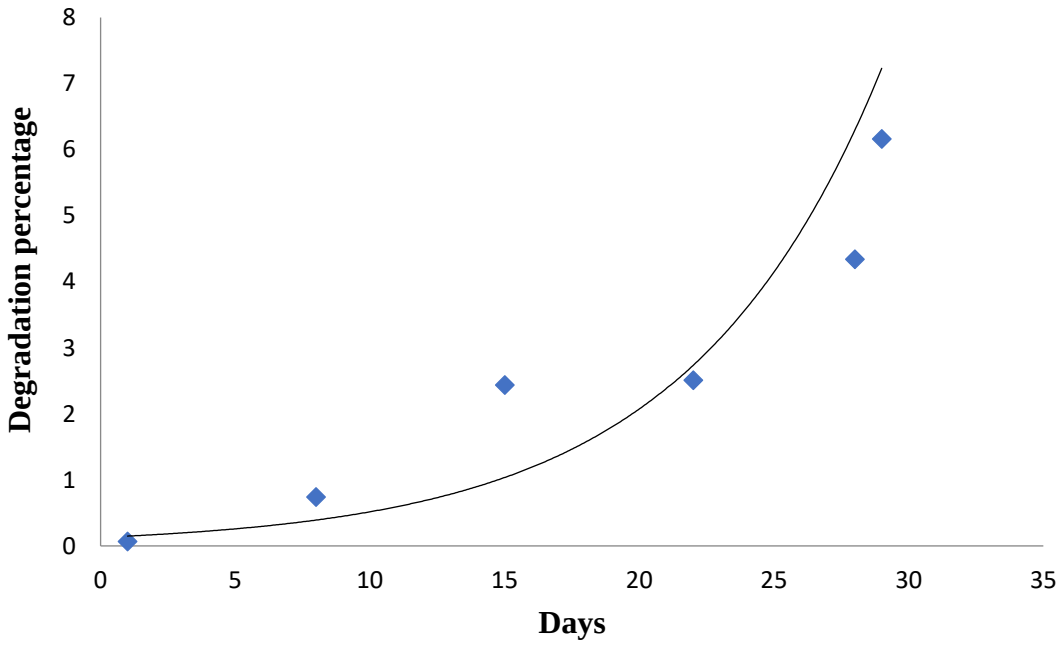

Figure 4. Graph showing the degradation percentage of nitinol stent through 28 days

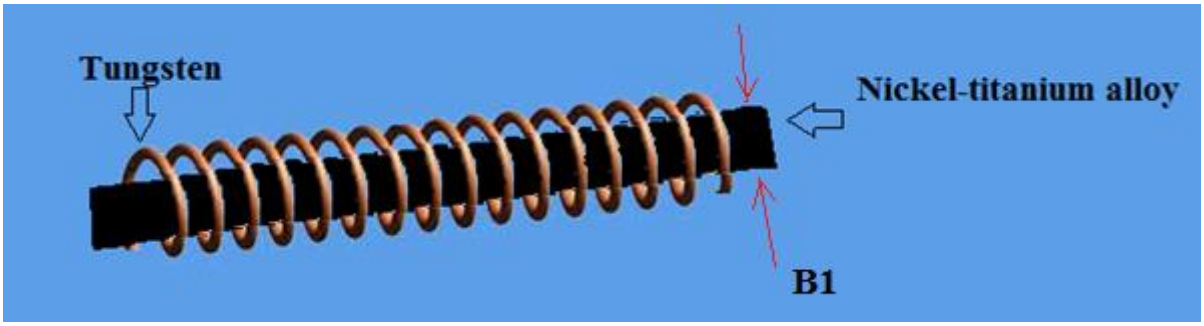

Figure 5. Schematic picture of nitinol stent ; tungsten wire coiled over the nitinol wire

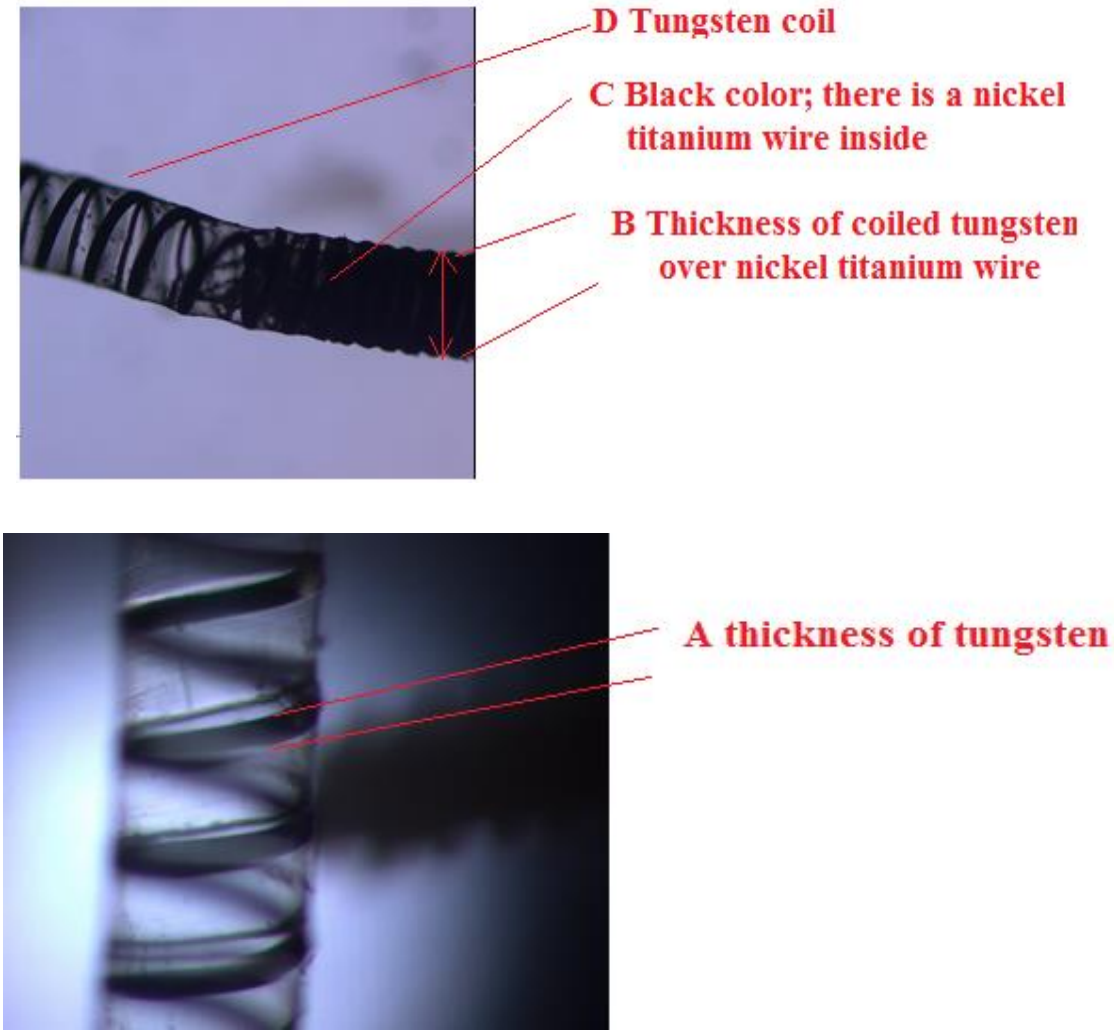

Figure 6. Light microscope pictures of nitinol stent

Table 1. ICP-OES operating conditions

Parameters	Value
Plasma power	1435 W
Pump speed	30 rpm
Coolant flow	13 L/min
Auxilory flow	0.80 L/min
Nebulizer flow	0.70 L/min
Number of replicates	3
Integration time (s)	3 s
Sample uptake rate (µL/min)(speed)	0.3

Table 2. Released metal ion values of blank PBS and degradation liquid(values were measured with ICP-OES device), LOD and LOQ values of the device were given for tungsten, titanium, and nickel elements

Experiment name	**Tungsten**	**Titanium**	**Nickel**	**pH value**
Measurement of **blank PBS**	50ppb	<8ppb	<0	7,4
Degredation liquid (PBS -28 days)	191ppm	<8ppb	252ppb	6,99
ICP-OES LOD dedection limit (Low dedection limit)	1ppb	8ppb	0,5ppb	-
ICP-OES LOQ dedection limit (Low quantification limit)	3ppb	24ppb	1,5ppb	-

Table 3. Thickness changes of nitinol stent parts before and after degredation experiment

Diameter measurements explanation	**Figure explanation**	**Thickness**
Tungsten coil wire diameter **before degradation**	Figure6 _ A named	58 µm
Tungsten coil wire diameter **after degradation**	Figure6 _ A named	51 µm
Whole nitinol wire diameter **before degradation**	Figure6 _ B named	486 µm
Whole nitinol wire diameter **after degradation**	Figure6 _ B named	440 µm
Nickel-titanium core wire **before degradation**	Figure 5 _B1 named	297 µm
Nickel-titanium core wire **after degradation**	Figure 5 _B1 named	295 µm

Table 4. Spectro X-Lab measurement program X-REF measurement results before and after the degradation of stent sample

Element name	**Element concentration before degradation**	**Element concentration after degradation**
Titanium	% <0.00020	%5.944
Nickel	% 1.239	%4.64
Tungsten	%92.22	%84.78
Iron	%2.46	%2.298
Gold	%2.49	%1.017

Table 5. Accelerated degradation values of stent samples from 1 to 28 days at 70 degree celcius.

Days	Corresponding time month	Sample Weight	Weight After Degradation	Degradation Percentage
1	0,3	48,15	48,12	0,03
8	2,6	44,79	44,46	0,73
15	5	48,07	46,9	2,43
22	7,3	53,48	52,14	2,50
28	9,3	50,5	48,31	4,34
29	9,7	52,45	49,22	6,16

5. Conclusion

The present study examined the in vitro degradation of an endobronchial nitinol coil according to 10993-13 (Biological evaluation of medical devices — Part 13: Identification and quantification of degradation products from polymeric medical devices). The possible usage of this coil and the toxicological distribution of the elements released were evaluated. After one month of degradation the level of tungsten released, 191 ppm, was lethal and toxic, while the levels of nickel and titanium were acceptable within the scope of toxicological studies.

Furthermore, degradation of the tungsten coil showed that after 1 year most of the tungsten wire would be dissolved when the 7 μm/month decrease in the diameter of the tungsten wire is considered. The decrease in diameter for nitinol was 2 μm/month. With the possible aging time calculated, after approximately 12 years the whole nitinol core wire would be dissolved and released into the body.

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