UNIVERSITAT DE BARCELONA

Final Degree Project

Biomedical Engineering Degree

"Optimization of electrolytic anodization of Ti-6Al-7Nb surfaces"

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Abstract

Increased life expectancy leads to the increasing use of metallic prostheses. Titanium and its alloys are the most widely used materials for metallic prostheses thanks to their biocompatibility, but further work still necessary to improve bioactivity and reduce osseointegration problems.

Developing nanostructured titanium dioxide (TiO_2) coatings increases the biocompatibility of titanium prostheses. Using the electrolytic anodizing process, nanostructures can be achieved easily and economically.

This project aims to optimize the voltage and anodizing time conditions to obtain titanium dioxide nanotubes on the surface of Ti-6Al-7Nb alloy, as well as to propose ideas for industrial implementation of the project. To this purpose, a market study, a project implementation plan and a technical and economic feasibility analysis were carried out.

An electron microscope image processing method and a rigorous statistical analysis have been studied to obtain an average pore diameter quantify the effect of the studied variables.

Potentials of 15, 30 and 60 volts and anodizing times of 15 and 30 minutes were studied. The effect of the concentration of fluoride ions and the type of cathode used in anodizing has also been studied. The optimum conditions for the smallest pore size we have found are anodizing at 15V and 15 minutes, with a grid cathode. With these conditions, an average pore diameter of 0,48 ± 0,05 µm was obtained.

Table of contents

List of Figures

List of Tables

1. INTRODUCTION

During the last decade, life expectancy has increased because of the progress of technology and medicine. A higher life expectancy and other factors, such as the increasing number of traffic accidents especially among the young population, has risen the use of implants and prosthesis to repair or replace damaged tissues.

The biomaterial used to produce prostheses and implants must meet different requirements, optimal mechanical properties, good biocompatibility and low or no toxicity. Materials that meet these characteristics are stainless steel, cobalt-chromium alloys, titanium, titanium alloys and pyrolytic carbon, among others (1).

Titanium and its alloys are strictly considered bioinert materials, because they cannot stimulate bone formation on their surface, causing encapsulation of the implants by fibrous tissue, which can lead to dislocation and loosening of the implant. Therefore, it is necessary to create a layer that enhances osseointegration, i.e., the stimulation of early bone formation.

Bioceramics, which are biocompatible ceramic materials, are one of the materials proposed as an integration layer between the implant and the bone (2). The most popular bioceramic is hydroxyapatite (HA), which has excellent biocompatibility. Nonetheless, its mechanical properties have led to the search for other bioceramic materials that can replace it, such as titanium dioxide (3).

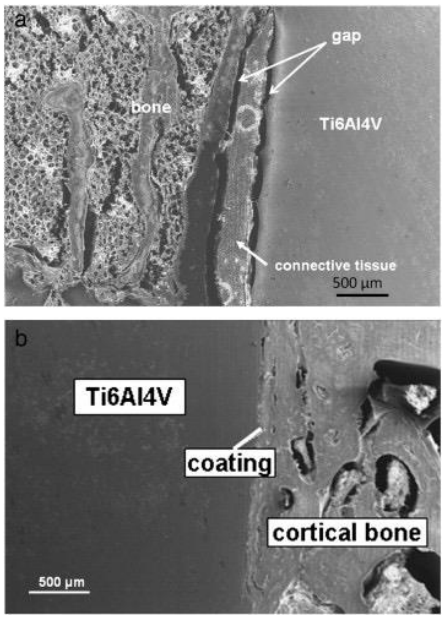

Figure 1 *Response of a) bioinert and b) bioactive titanium alloy* (5).

The convenience of using titanium is its ability to create a coherent layer[1] of titanium dioxide (TiO_2) on its surface. This bio-ceramic oxide layer improves bioactivity and stimulates early bone formation enhancing implant osseointegration. This among other characteristics makes titanium alloys suitable to be used to repair or substitute bone tissue (4).

The biocompatibility of metals can depend on being bioinert. Nonetheless, as can be seen in Fig. 1, for a bioinert implant there is a gap between the implant and the newly formed bone with a connective tissue encapsulating the implant due to lack of osseointegration. In contrast, in the image below, it can be seen that there is no encapsulation, thanks to the bioactive coating that has been fabricated on the surface of the implant (5).

Therefore, not only the biocompatibility of the implanted material must be taken into account, but also its bioactivity, for safer and longer lasting results.

[1] Coherent layer is an oxide layer formed on some metals that protects the bulk from becoming internally oxidized.

1.1. OBJECTIVES

The aim of this project is to improve the bioactivity and osseointegration of titanium implants using electrochemical methods to create a bio-ceramic layer of titanium dioxide on the surface of Ti-6Al-7Nb alloys. To fulfil this goal the followed objectives are proposed:

- Optimize the voltage applied to the samples during the anodization of the surface.
- Study of the effect of anodization time on the titanium dioxide layer.
- Characterize the morphology and composition of the surface.
- Identify the main limitations and challenges of the process.
- Propose improvements for its application on an industrial scale.

1.2. METHODS AND PROJECT STRUCTURE

This project has been carried out through several important steps. The first of these was intensive research focused on the improvement of bioactivity and biocompatibility of titanium implants by electrochemical methods. This research has been carried out by searching and obtaining information from the NCBI database.

The second step, the laboratory practice, was carried out in the Department of Materials Science and Chemical Physics of the Faculty of Chemistry of the University of Barcelona.

The structure of this work is presented in the table of contents. The first part of the work contains a brief introduction, the research objectives, and the state of the art. The second part includes the market analysis and the design engineering, explained more extensively in the detailed engineering section where the methods and results of the project are exposed. In the third part of this work the execution schedule, feasibility studies (technical and economic) and the legal aspects are described. Finally, the conclusions, which cover the entire project, with our retrospective view.

1.3. PROCESS DESCRIPTION

This project is based on the modification of the surface of titanium samples to produce a coherent bioceramic layer that improves bioactivity and osseointegration. For this purpose, the surface will first be prepared by several steps of grinding and polishing. The samples will then be treated according to a cleaning protocol. Afterwards, an electrolytic anodizing will be carried out using POWER SUPPLY 5M 400-AR-4 from Delta Elektronica controlling the voltage and the anodization time to create a titanium dioxide layer with a columnar nanometric morphology.

Then surface will be characterized using electronic microscopy, and the optimal variables will be selected based on the obtention of a homogeneous TiO_2 protective layer.

1.4. SCOPE AND REACH

This project covers the exhaustive study of the modification of the surface of prostheses by means of anodization for better osseointegration of the implant. It is situated in the field of biomedical engineering, specifically in the science of materials and biomaterials. The scope of this project is the study of the feasibility of anodization processes to obtain a tubular structure on the surface of prostheses.

One of the major limitations encountered in carrying out the project has been time, which has not allowed to expand the research and perfect the results. In addition, throughout the project, recalculation and re-planning has been necessary as different problems have arisen.

The project was intended to continue a previous work for the anodization of Ti-6Al-7Nb following the conditions obtained as optimal for the creation of nanotubes. The equipment used for the anodization in the previous research Quasar Q100 IP31 modular switch mode rectifier was substituted for more accurate equipment available in the electrochemical department of the chemistry faculty at the UB.

The attempt to anodize the same substrate using the conditions employed with Quasar Q100 IP31 equipment was unsuccessful and was necessary to modify the experimental plan for the optimization of the main variables (voltage applied and anodization time) using the new electrochemical devices.

Nonetheless, although we believe that this field of research can be developed further, we are proud of what we have achieved with a lot of patience and a willingness to learn from our mistakes.

2. BACKGROUND

A medical device is “any instrument, device, equipment, software, implant, reagent, material or other article, whether used alone or in combination, intended by its manufacturer for specific diagnostic and/or therapeutic purposes and which is involved in its proper functioning, intended by its manufacturer to be used for human beings” (6).

Implants have evolved throughout mankind, starting with the ancient Egyptians (2.500 years BC) with the first dental implants made of gold or artificial fingers made of wood (7). The technique has evolved over the course of history to the point where it is now necessary to improve its integration for a duration of more than fifteen years, or even for a lifetime.

2.1. IMPLANTABLE MATERIALS

As a result of advances in technology and medicine, people are increasing their quality of life, increasing their life expectancy. In addition to the increasing geriatric population, sport-related injuries and traffic accidents are also on the rise (8). Consequently, orthopedic implants are increasingly needed and are estimated to reach USD 6,2 billion by 2024 (9).

The lifespan of orthopedic implants is currently 15 to 20 years and depending on mechanical and biological factors there is a large percentage of implants which may need surgery for revision or even replacement (10).

Implants can be divided into three different generations. The first consists of bioinert materials, the second consists of bioactive and biodegradable materials, and the third are implants made of materials designed to stimulate molecular responses in the implanted body (11).

All implantable devices should be made of a biomaterial, i.e., ‘‘a substance that has been engineered to take a form which, alone or as part of a complex system, is used to direct, by control of interactions with components of living systems, the course of any therapeutic or diagnostic procedure, in human or veterinary medicine’’(12). These can be metals, ceramics, synthetic polymers, but also biopolymers, self-assembled assembled systems, nanoparticles, carbon nanotubes and quantum dots (12).

For orthopedics, different types of metals are commonly used due to their high mechanical strength. The most used materials are stainless steel, cobalt-chromium alloys and titanium and its alloys.

	Stainless steels	**Cobalt-chromium alloys**	**Ti and Ti alloys**
Young’s Modulus (GPa)	200	230	**106**
Tensile Strength (MPa)	540-1.000	900-1.540	900
Advantages	Cost; Availability; Good ductility; Processing	Wear resistance; Corrosion resistance; Fatigue strength	**Biocompatibility**; Corrosion resistance; Minimum modulus; Fatigue strength

Disadvantages	Long term behavior; High modulus	High modulus; Biocompatibility	Low wear resistance; Low shear strength
Applications	Temporary devices (fracture plates, screws, hip nails) for hip replacement	Dentistry castings; Protheses stems; Load-bearing components in joint replacement	Long-term permanent devices (nails, pacemakers); Intraosseous-dental implants

Table 1 *Comparison of some of the characteristics of metallic implant materials* (8)

Table 1 shows the different properties of these materials, showing that titanium has a crucial characteristic for implants: biocompatibility. That is "the ability of a material to perform with an appropriate host response in a specific application"(13). In addition, it is the material with the Young's modulus (106 GPa) closest to bone (≈ 80 GPa)(14).

2.2. UNDERSTANDING TITANIUM

Titanium and its alloys are the most used in medical implants mainly because of their excellent mechanical properties. Titanium can have two types of crystalline structures, the body-centered cubic (BCC), also called beta-phase, and the hexagonal close-packed (HCP) defined as alpha-phase (15). The structure can have an allotropic transformation from BCC to HPC from 882,5°C (allotropic temperature[2]) (16). The conformations of these two structures are shown in Fig. 2.

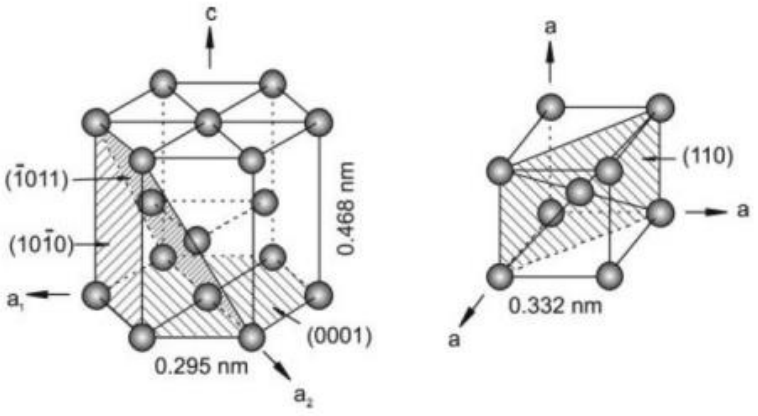

Figure 2 *a) Titanium HCP alpha-phase structure, b) Titanium BCC beta-phase structure* (15).

Depending on the alloying elements the allotropic temperature can increase or decrease. Alpha (α) elements as Al, O, N and C increase the allotropic temperature, while beta (β) elements as Nb, V and Mo decrease it. Titanium alloys are categorized into α, (α + β) and β, depending on the contribution of their elements, and each group has certain mechanical characteristics.

The alloy commonly used in implants is the (α + β) alloy Ti-6Al-4V due to its excellent mechanical properties and biocompatibility. Nonetheless, it has been found that the release of vanadium ions

[2] Allotropic temperature is the temperature at which the crystallinity of metals having different crystalline lattices changes.

can be toxic in the human body, increasing the expression of inflammatory factors and possibly reducing fertility.

To reduce the toxicity a new generation of (α + β) alloy has been developed using Niobium as a β-phase stabilizer. Ti-6Al-7Nb alloy presents excellent mechanical properties (ductile, fatigue resistant and has good fracture toughness), superior corrosion resistance and biocompatibility compared to Ti-6Al-4V. These properties reduce adverse tissue reactions and improve the growth of cells on the surface of this alloy (17).

2.3. SURFACE MODIFICATION

Titanium is a bioinert material, i.e., it does not interact with the tissue around it. This lack of interaction is the principal cause of implant failure (18). The importance of titanium alloys as metallic biomaterials is the ability to create a bioceramic layer of titanium dioxide that not only improves biocompatibility but also osseointegration.

A bioceramic layer improves the interaction of the implant with the surrounding tissues avoiding the encapsulation of the implant with fibrous tissue (19). To improve the bioactivity other bioceramics as hydroxyapatite (HA) can be used to coat titanium implants. HA coating consists of depositing this biocrystal on the surface of titanium substrates. This procedure is optimal when deposited on an already rough surface (20).

The improvement of bioactivity can also be achieved by increasing the roughness of the implants by sandblasting or acid etching. Sand or grit blasting consists of the projection of sand particles under pressure. Acid etching involves using a strong acid such as hydrofluoric (HF), nitric (HNO_3) and sulphuric (H_2SO_4) or a combination of the three to modify the surface roughness (21).

Lastly, the bioactivity of an implant can be improved by the development of a nanostructure that facilitates the adhesion of osteoblastic cells on the surface of the implant, as surface characteristics at the nanoscale are very important in tissue engineering. A nanostructure of TiO_2 can be prepared by sol-gel, electrophoretic deposition, and anodizing (19).

In this project, electrochemical anodization is used to develop a nanostructured TiO_2 due to its simplicity, low cost, and feasibility for a scale-up implementation.

Anodization is the process by which “the surface of a metallic component connected to the anode of an electrochemical cell is oxidized within a suitable electrolyte, while an inert material, i.e., graphite or platinum, is used as the cathode. An electrical potential is applied between the electrodes to induce oxidation on the surface of the anode” (22).

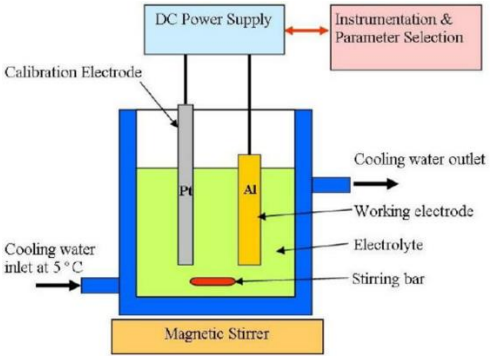

Figure 3 *Experimental scheme for anodizing an aluminum (Al) electrode with a platinum (Pt) cathode* (23).

By adjusting the electrochemical parameters, an oxide film with a nanostructure can be created in a controlled manner.

Anodization must be done with strict control of temperature (±2°C). To control the homogeneity of the electrolyte solution a magnetic stirrer should be used (23).

The resulting anodizing surface produces nano-sized structures which can take the form of pores or nanotubes (4).

In this work, the anodization of titanium was performed using a stainless-steel electrode as a cathode and a working electrode made of Ti-6Al-7Nb alloy is used as the anode.

2.4. TITANIUM NANOTUBES

Studies have shown that osteoblasts (the bone cells responsible for bone remodeling and development (24)) have a greater adhesion to the nanostructured surface of metals (particularly titanium and titanium alloys) than to conventional surface (25,26). Currently, titanium oxide nanostructures have diverse applications, such as fuel cells, energy storage, environmental sensors and systems, photocatalytic systems, biosensors, and biomaterials (27–30).

There are different methods currently available to manufacture titanium nanotubes. These methods are the assisted-template method, electrochemical anodic oxidation, hydrothermal treatment and sol-gel method.

The assisted-template method involves the use of a mold, usually an anodic aluminum oxide (AAO) membrane, that controls the size of the nanotubes. The anodizing process is explained above and allows high aspect ratio nanotubes to be obtained by controlling the voltage, electrolyte, pH and anodizing time. The hydrothermal treatment consists of a sonication pre-treatment, a hydrothermal treatment and a post-treatment, requiring a long time for the preparation of the nanotubes. The sol-gel method is often used in conjunction with the assisted-template method and involves the creation of a thin film by controlling its chemical characteristics (27,31).

In the future, titanium nanotubes will be increasingly used, as they are an easy and economically viable material to build. In addition, they can be used as fuel due to their low emission, as energy storage due to their high adsorption capacity and as a biocompatible material (27). Moreover, the future of titanium nanotubes will evolve to fill nanotubes with bioactive or more bone-compatible molecules, such as HA, leading to a third generation of implants (32).

3. MARKET ANALYSIS

In this section the market analysis has been carried out. First, the target public has been studied and research has been carried out on the history of the evolution of implants and titanium as a material. The possible competitors in the market have been determined and an analysis has been made of where the future of the project is heading.

In this way, it will be possible to determine the viability of the project to establish itself as a product in the world of implants.

3.1. TARGETED SECTORS

In 2021 the population in Spain was 47,35 million, according to data obtained from the INE (Spanish National Statistics Institute), of which 9,38 million people is over 64 years of age (≈19,8%) (33).

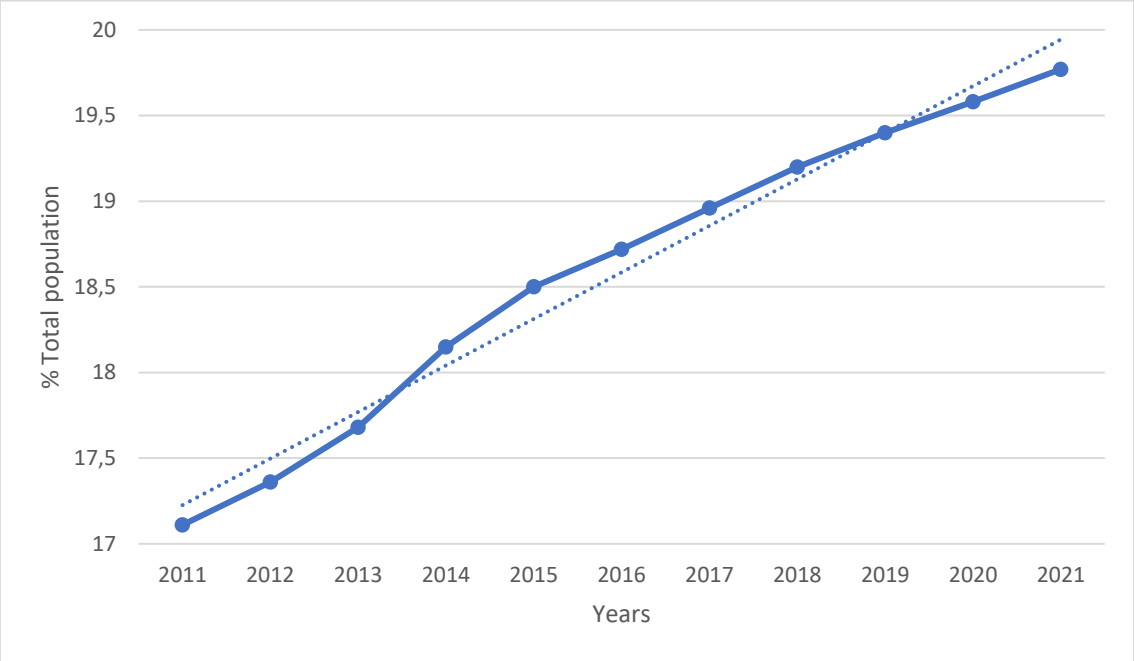

Figure 4 *Percentage of the population over 65 years of age in Spain in the last 10 years* (33)

As it can be seen in the following graph obtained from INE data, the percentage of the Spanish population over 65 years of age has been increasing since 2011. The trend line, marked with a dotted line in Fig. 4, indicates the steady increase in this age group. In addition, people between 65 and 69 years of age are the range with the highest incidence in Spain, an incidence that decreases as the age range increases (33).

This phenomenon is due to the constant increase in life expectancy, and together with the increment of traffic accidents – according to the DGT data – and the rise of sport-related accidents is the cause of an increasing need for orthopedic operations. These values will also increase worldwide, according to a US study, which predicts that total hip and knee revisions will grow by 137% and 601%, respectively, between 2005 and 2030 (34).

In addition to the increase in cases of orthopedic surgeries, dental implants performed in clinics, whose most used materials are titanium and zirconium, must also be considered. Implanted products using titanium are therefore increasing.

From the data obtained from the RNFC (Spanish acronym for National Hip Fracture Registry), it can be observed that in 2019 hip fracture cases and 30-day reinterventions increased compared to 2018 and 2017. Reintervention was due to dislocation of the prosthesis, revision of internal fixation and other reasons (35).

The need for reoperation is caused to a lack of osseointegration of the implant with the tissues, causing loosening of the implant because of an insufficient bone integration and/or fibrous tissue production or infection (20). To reduce re-interventions and implant failure, osseointegration must be improved, which is the goal of our project.

3.2. MARKET EVOLUTION OF IMPLANTS

As mentioned above, implants are divided into three chronological classes. The first generation of biomaterials “inert biomaterials” have been used extensively in the industry (11). The main problems with these implants were the generation of peri-implantitis (in dental implants) and fibrous tissue encapsulation, which can cause dislocation and loosening of the implant. Peri-implantitis is an inflammatory lesion and weakening of the surrounding bone (36), and fibrous tissue formation is a response by fibroblasts in reaction to a foreign body (37).

This is the reason second-generation implants appeared. Surface modification to improve osseointegration dates to 1980s, featuring surfaces with a roughness of 0,5 to 0,8 μm. Plasma spraying and HA spraying were later discovered, but the products had to be withdrawn from the market due to HA particle detachment. Other techniques were used to increase the roughness of implants, such as blasting, etching and anodizing techniques. These techniques achieved a roughness between 1 and 1,5 μm, with anodizing having the best osseointegration (38).

Inbio Biomaterials Solutions® has developed a wide range of biocompatible materials and composites with PEEK (Polyether ether ketone) for implantable medical devices (39). Nonetheless, the nature of these implants remains bioinert, requiring improvement for good osseointegration.

Most of today's implants belong to the second generation, as they are either bioactive and/or resorbable. Nonetheless, third-generation implants are starting to be developed, which consist in promoting the regeneration of living tissues around the implant. This can be achieved by means of a porous structure that acts as a scaffold for the cells (40).

Dr. Dalby et al. developed in 2012 a surface that could control stem cell differentiation, coated with 120-nanometer cavities (41). This surface enhancement was intended to ensure that mesenchymal cells differentiate into bone cells to improve osseointegration.

3.3. MARKET EVOLUTION OF TITANIUM

In the late 18th century, clergyman William Gregor discovered titanium as a mineral inclusion in Britain. Despite its great properties as a metal (as strong as steel but half as heavy), it was not until the early 20th century that it began to be used as a metal in the industry in the United States (42).

It is a material that appears bound to other elements, and therefore requires extraction, which is carried out using the Kroll method or the Hunter method. It is mostly found in Australia, South Africa and Canada, and is very abundant in the earth's crust.

In the 1950s and 1960s, the USSR began to use titanium for military and submarine applications. During the Cold War, it was considered a very important element, with the Russian company VSMPO-Avisma becoming the world's largest producer.

The titanium production process consists of four stages, the first is the reduction of the metal in the form of a porous sponge, the second is the melting of the sponge, the third is the manufacture of bars and sheets and the last is the manufacture of the final products (43).

Titanium's main applications today are in the aerospace and automotive industries, as well as implantable medical equipment, because of its compatibility with the human body. In the medical field, titanium and its alloys are used in arthroplasty and bone replacement, craniofacial, maxillofacial and dental implants, surgical instruments, medical devices and external and internal prostheses.

3.4. FUTURE MARKET SCOPE

There are now many companies using anodizing of their implants in order to achieve better osseointegration. Among them, are dental companies such as Nobel Biocare TM® with its TiUltra (44).

Nevertheless, the third generation of implants is now the key to the future of the orthopedic industry. Boosting a cellular response from implants may be the solution for more durable and effective implants. To this end, one proposed solution is to fill the pores of the nanotubes formed on the surface of the implants with bioactive molecules, both for cell development and for controlled drug delivery (4,45). An example of a bioactive molecule could be HA of animal origin, in particular bovine origin (46), for a greater cellular response than synthetic HA.

Another rapidly developing branch of engineering is 3D printing, which allows the creation of customized implants. The most widely used application of 3D printing in orthopedics, specifically spine orthopedics, especially polymer and metal printing. Other applications are dental and cranial implants (47).

The world of healthcare is evolving towards fully personalized medicine, for which 3D printing is a breakthrough. Nonetheless, the fourth generation of implants will have to make the leap from synthesized and processed materials to natural materials, biological implants and gene therapies.

Biological implants can be obtained from donors (allogeneic) and even from the patient (autologous). Science and medicine must advance to achieve bone transplantation for orthopedic devices, thus achieving total cellular response and full osseointegration.

4. CONCEPTION ENGINEERING

4.1. PROJECT CONCEPTION

The aim of this project is to modify the surface of prostheses and medical implants to improve their biocompatibility and enhance osseointegration. Therefore, it will be necessary to look for different options that facilitate the adhesion of cells to this type of surface. One of the requirements is to work with a process that can be carried out industrially.

Due to the great diversity of materials used in orthopedics, this section will focus on solutions that use the concepts explained in the background. Therefore, conception engineering will focus only on titanium metal implants, specifically those made of the Ti-6Al-7Nb alloy. In this way, attention will be directed to the most specific solutions, without considering those that fall outside our objectives.

4.2. STUDY OF THE SOLUTIONS

As explained above, there are multiple ways to modify the surface of metals to improve their osseointegration. Nevertheless, as our work focuses on titanium dioxide nanotubes, is considered only the study of the solutions to fabricate them.

Four methods are compared for the fabrication of TiO_2 nanotubes, the template assisted method, the sol-gel method, hydrothermal method, and electrochemical anodization method. Table 2 is a compilation of the advantages and disadvantages of each technique.

Fabrication method	**Advantages**	**Disadvantages**
Template assisted method	- Nanotube structure easily fabricated by using template prepared - Easy handling - Dimension of TNT controlled by the templates - **Uniform sizes**	- **Complicated process** - TNT could be damaged during the process - Large nanotubes are obtained - Time consuming due to prefabrication and post-removal of the templates - Contamination may occur during dissolution of template
Sol-gel method	- **Easy handling** - Flexible dimension - Safe and environmentally friendly	- Further process is needed to achieve a better structure - **TNT not achievable with only this method**
Hydrothermal method	- **Low-cost method** - Simple and easy process - Environmentally friendly - High surface area	- Highly concentrate NaOH needed - **Long duration process**

Electrochemical anodization method	- Controllable tube length - Longest tube length - High surface area - Low-cost method - **High aspect ratio**	- **TNT formation depend on electrolyte** - Nanotubes produced are in amorphous phase - Annealing is required

Table 2 *Advantages and disadvantages of titanium nanotubes fabrication methods* (4,27,48).

4.3. PROPOSED SOLUTION

In order to choose the best solution, it must be considered that the application of the solution will have to be carried out in the industry, therefore, it will be considered the economic factor, the time it takes to manufacture the nanotubes and above all the result.

Looking at the economic factor, the hydrothermal method is the most economical. Nonetheless, it takes a whole day to form the nanotubes and the conditions of temperature and pressure are hardly achieved in a large-scale process. Therefore, it is discarded as the best option.

Other methods that require prior preparation are the template-assisted and the sol-gel methods, as in the former the molds need to be created beforehand, and the sol-gel is a technique that complements the others; nanotubes cannot be obtained from this technique alone.

Therefore, the best way to obtain titanium dioxide (TiO_2) nanotubes is by means of the electrochemical anodization method, since the nanotube diameter can be controlled by controlling the voltage and time.

It must be considered that a previous study and a formalization of protocols will be necessary to find the optimum time and voltage with the right electrolyte. Once optimization has been carried out, anodizing surfaces with the desired nanostructures can be achieved.

5. DETAILED ENGINEERING

5.1. MATERIALS AND METHODS

In this section, an exhaustive analysis has been made of the reagents and equipment used throughout the project, as well as the process carried out to prepare the samples, from cleaning to anodizing. In this way, following the indications in this section, the same results can be obtained.

5.1.1. REAGENTS AND EQUIPMENT

The reagents that have been used throughout the project are:

- Sodium dodecylbenzenesulfonate ($CH_3(CH_2)_{11}C_6H_4SO_3Na$), CAS number 25155-30-0, Sigma-Aldrich.
- Sodium hydroxide (NaOH), CAS number 130-73-2, Sigma-Aldrich.
- Sodium carbonate (Na_2CO_3), CAS number 497-19-8, Sigma-Aldrich.
- Nitric acid 69 wt.% (HNO_3 69 wt.%), CAS number 7697-37-2, Sigma-Aldrich.
- Hydrofluoric acid (HF) concentrated, CAS number 7664-39-3, Sigma-Aldrich.
- Ethylene glycol ($C_2H_6O_2$), CAS number 107-21-1, Sigma-Aldrich.
- Ammonium fluoride 40 wt.% (NH4F), CAS number 12125-01-8, Carlo Erba).

The equipment used throughout the project is:

- Struers RotoPol – 21 for grinding, serial number 21599.
- Struers RotoPol – 21 for polishing, serial number 21599.
- Bibby Heated Magnetic Stirrer HB502, serial number L11694, L08537. (Fig. 5)
- VWR Ultrasonic Cleaner, serial number USC 1200.
- Delta Electronika POWER SUPPLY 5M 400 - AR – 4. (Fig. 6)

Figure 5 *Bibby Heated Magnetic Stirrer HB502*

Figure 6 *Delta Electronika POWER SUPPLY 5M 400 - AR - 4.*

5.1.2. SAMPLE CONDITIONING

A medical-grade Ti-6Al-7Nb plate was purchased from Yunch industry (China) who manufacture the plate by cold/hold rolling following the ASTM F1295 and UNA R58130. The plate had a thickness of 2mm and was cut in small pieces (1x0,5cm^2) using an industrial metal cutting machine (Fig. 7). A second type of larger samples (1,5x1,5 cm^2) were cut in order to study the anodizing on a larger surface (Fig.8).

Figure 7 *Small sample piece (1 cm x 0,5 cm).*

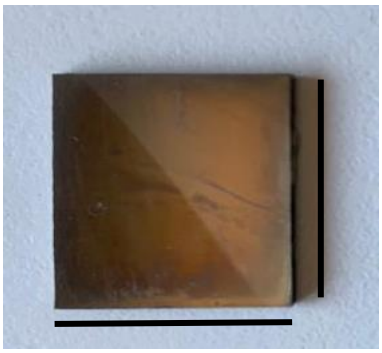

Figure 8 *Large sample piece (1,5 cm x 1,5 cm).*

The preparation of the sample consists of different procedures, the first one is the polishing of the sample until the obtention of a mirror like surface to reduce the influence of a rough surface on the shape of the nanotube. The second is composed by different steps of cleaning the surface and the last one is the chemical polishing of the surface to ensure the highest homogeneous surface.

As previously mentioned, the first preparation procedure is polishing. As the main problem of this stage is the measurement of the samples, it was necessary to embed all the samples of this project in a non-conductive resin to reduce the difficulty of the polishing steps. As the titanium samples are an easily scratchable material, the samples have been managed with extreme care.

To remove excess resin and in preparation for polishing, the samples have been grinded, where impurities are removed from the treated material by centrifugally rotating sanding discs in a grinding machine. The process requires an increase in the particles per inch of the disc, in this project a SiC paper #600, #1200 and #2400 have been used, reducing progressively the surface imperfections. During the entire grinding, the discs must be sprinkled with water so that the particles resulting from friction do not damage the sample.

When all the samples are grinded, i.e., the grinding lines go in the same direction, the polishing process follows. Its aim is to remove the scratches caused during the grinding process, achieving a mirror surface on the sample. For this purpose, it has been used 6 and 1 μm of colloidal-diamond particles, with their respective lubricant. With the samples polished, the samples can be further processed to achieve a homogeneous result.

5.1.3. CLEANING PROTOCOL

The second step is to clean the samples. The cleaning protocol has been carried out in the following steps:

1) First, a chemical degreasing is carried out, whereby the samples are cleaned of any traces of grease they may contain. The sample is placed in a glass bottle containing a solution of milli-Q water with a surfactant (Sodium dodecylbenzene sulphonate) and a magnetic stirrer, caring not to touch the samples, at constant speed for five minutes.
2) After the chemical degreasing, the sample undergoes an ultrasound cleaning process, where it is placed in a flask with milli-Q water for 5 minutes in an ultrasound cleaner, repeating the process with the water being renewed. The ultrasounds cause the phenomenon of cavitation that improve the removal of grease, surfactant molecules and other impurities on the surface.
3) Afterwards, a cathodic electrolytic cleaning is carried out for 2 minutes at 5 V with a degreasing agent composed of 35 wt.% NaOH and 65 wt.% Na_2CO_3.
4) The next step the sample etching by immersing it completely in a solution composed of 30 v/v% HNO_3, 3 v/v% HF and 67 v/v% H_2O for 10 minutes. The objective of this step is to eliminate the oxide layer formed spontaneously on titanium substrates.
5) Finally, each sample should be washed with milli-Q water and acetone or ethanol and dried.

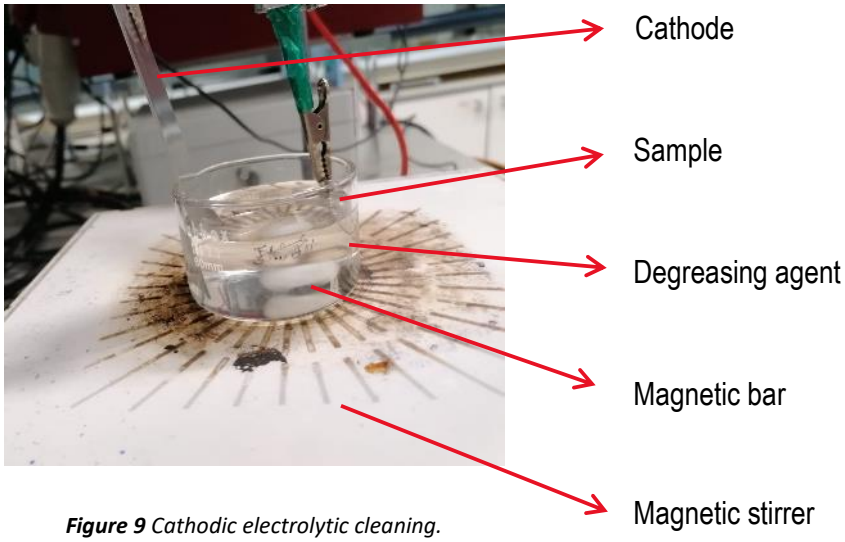

Figure 9 *Cathodic electrolytic cleaning.*

5.1.4. ANODIZATION

After the preparation and cleaning processes of the sample, the anodization was carried out resulting in the formation of Titanium nanotubes on the surface of our material. The steps have been followed with careful accuracy to ensure replicability and reproducibility.

The anodizing equipment, as can be seen in Fig. 10, consists of an anode (the sample), a cathode, a magnetic stirrer with a magnetic bar, an electric generator, a glass beaker, and an electrolyte.

The anode is connected to the sample and the cathode used is stainless steel. The electrolyte in which the reaction takes place is composed of 0,1 v/v % NH_4F, 2 v/v% H_2O and 97,9 v/v% ethylene glycol. Ammonium fluoride is a salt that allows fluoride ions to be present in the electrolyte, and fluoride ions are a crucial component to ensure the formation TiO_2 pore arrays uniformly aligned (48). Ethylene glycol is used as a viscous medium used to reduce the kinetics of the reaction to obtain a more controlled nanotube architecture.

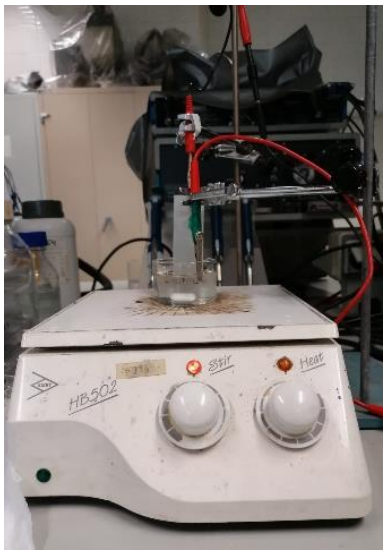

Figure 10 *Magnetic stirrer with anodizing equipment set-up.*

During a laboratory study with the same materials and reagents, a time and voltage for the anodizing of the samples were optimized to one hour at 60 V. Due to a change of the rectifier device in the laboratory, was necessary to reconsider the voltage required to anodize the sample homogeneously.

An optimization process has been carried out to obtain nanotubes. First, the samples were anodized at 60 volts and 60 minutes, obtaining a bluish color. The potential and time were then lowered to obtain an anodizing sample without color, up to 15 volts and 15 minutes.

Finally, a study was carried out to check the improvement of the results by changing the electrolyte and the anode. The results and their conclusions are explained later in the section of results of the paper.

5.1.5. SAMPLE NOMENCLATURE

In order to properly identify the samples, a standard nomenclature has been stablished. Each sample will vary according to date, electrolyte, voltage and anodizing time. As it can be seen in Fig 11 present an example of a sample with the nomenclature anodized on 17 March 2022, using electrolyte 2, at 15 volts for 15 minutes.

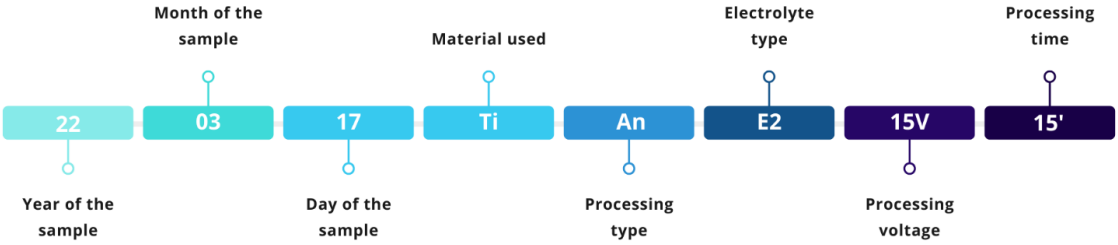

Figure 11 *Scheme of the sample nomenclature.*

The parts of the nomenclature that can be used are the date (year, month, and day), the type of electrolyte (which can be electrolyte 2 or 3), the applied voltage (which can vary between 60, 30 and 15 volts) and the anodizing time (which can range from one hour to 15 minutes). The material used has always been titanium alloy with aluminum and niobium (Ti-6Al-7Nb).

To facilitate the reading of the work, it will only be used the type of electrolyte, the voltage, and the processing time.

5.2. SAMPLE CHARACTERIZATION

This section describes the various tests carried out to analyze the anodizing samples. The results of the project are obtained from the visual and analytical analysis of the samples and a statistical study.

5.2.1. FESEM

A secondary electron microscope has been used to qualitatively analyze the surface morphology and the homogeneity of the composition. The SEM used an energy dispersive X-ray spectroscopy has been used in order to detect the chemical composition of the analyzed sample, using an elemental mapping of the samples to verify the homogeneity of the sample. It has been worded with a voltage of 10000KV and with a working distance of 20mm.

To obtain an approximate value for the diameter of nanotubes formed the SEM image was used. In the following set of images, the image processing has been carried out on each of the SEM images of the sample. To have a statistical representative result for each sample, at least 5 images of different parts of the sample have been taken.

In Fig. 12, an image obtained by SEM of the 60V15' sample can be seen. In Fig. 13 the threshold realized using the software ImageJ to identify the pores from the previous image can be seen. Fig. 14 shows the nanotubes profile obtained using the software. The software ImageJ can produce a list of the different nanotubes with their corresponding diameter. This process has been repeated

for each of the images of each sample, and the data obtained was used to compare the samples empirically by statistical methods.

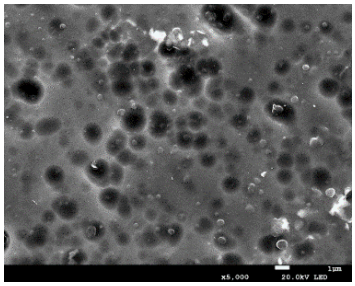

Figure 12 *SEM surface image of 60V15' at 5000x.*

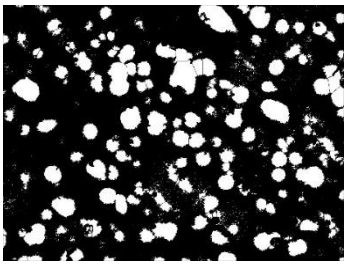

Figure 13 *ImageJ processed image of 60V15' at 5000x.*

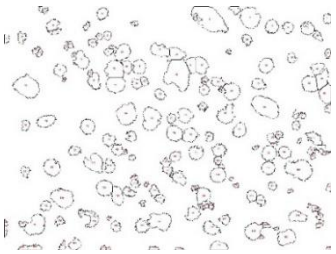

Figure 14 *ImageJ processed drawing of 60V15' at 5000x.*

After the obtention of the diameter of approximately 500 pores for each sample, a statistical treatment of the data was done using the Origin Software. To determine empirically if the data obtained for the nanotube diameter is a normally distributed sample population two normality tests were used, the Shapiro-Wilk and D'Agostino's K-Squared with a 90% of tolerance. The results obtained for all samples presented a non-normal distribution for the results of nanotube diameter.

Following the assumption of non-normal distribution, a non-parametric test was used to determine the statistical difference between the samples. To compare two independent samples a Mann-Whitney test and Kolmogorov-Smirnov test with a 90% tolerance were used. For the comparison of multiple independent samples, a Kruskal-Wallis ANOVA and Mood's Median with a 90% tolerance were applied.

5.2.2. DRX

The measured sample was a titanium alloy large piece, which has been placed in cylindrical standard sample holder of 3 centimeters of diameter and 1,5 centimeters of height. An X-Ray Diffraction test with PANanalytical X'Pert PRO MPD alpha1 powder diffractometer in Bragg-Brentano $\theta/2\theta$ geometry of 240 mm of radius and Cu $K_{\alpha 1}$ radiation (λ = 1,5406 Å) was performed. The $\theta/2\theta$ scan was from 4° to 120° (2θ) with step size of 0,026° and the measuring time was 150 seconds. In each measurement, three repeated consecutive scans were performed.

5.3. RESULTS

For the optimization of the anodization of Ti-6Al-7Nb substrates the variables studied were the potential (60V, 30V and 15V) and the anodization time (15 minutes and 30 minutes). The surface morphology of the obtained samples was characterized using SEM imaging and the chemical composition was characterized by EDS. Electron microscopy images were analyzed with ImageJ software to quantify the average pore diameter.

5.3.1. STUDY OF THE EFFECT OF ANODIZATION TIME

The aim of this experiment is to study if the anodizing time and voltage influences the diameter of the pores obtained when anodizing samples. Therefore, the optimum conditions will be found to obtain nanotubes with the equipment used in the work. The analytical and statistical results will define the differences between the samples studied to validate the conclusions.

Anodizing was carried out at 60 volts and the effect of anodizing time was determined by comparing 15 minutes and 30 minutes. The samples have been named 60V15' and 60V30', respectively, following the nomenclature explained previously.

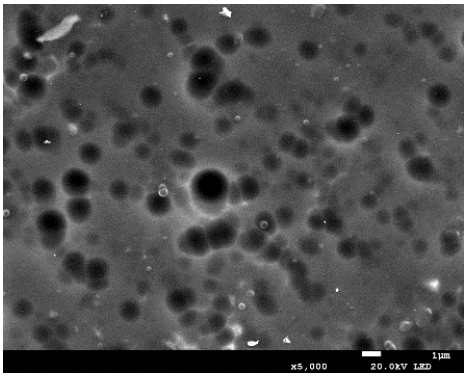

Figure 15 *SEM surface image of 60V15' at 5000x.*

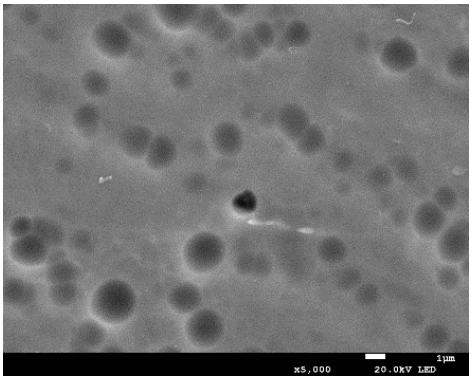

Figure 16 *SEM surface image of 60V30' at 5000x.*

Figures 15 and 16 show the difference in pore size and the number of pores for the samples anodized at 60V for 15 and 30 minutes. These images demonstrate the significant variations between the samples.

To quantitatively assess the diameter of the pores, several images obtained with FESEM were processed. After processing the data with ImageJ software, the average pore diameter in µm was determined discarding outliers, considering the standard deviation and statistically comparing the data obtained.

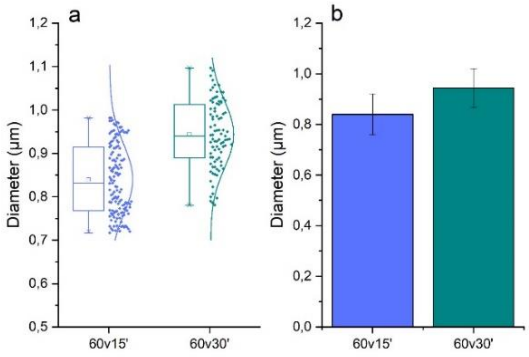

Figure 17 *Comparison of 60V15' and 60V30' with a) data distribution and b) mean diameter value and standard deviation.*

In Fig. 17.a can be seen that the data obtained for the diameter do not follow a normal distribution in the dispersion data. The mean value of the diameter is 0,84 ± 0,08 µm for 15 minutes and 0,94 ± 0,08 µm for 30 minutes.

With the statistical analysis, it has been found that there are significant differences between the two groups of samples. Therefore, it can be stated that statistically, there is an effect on the pore diameter depending on the anodizing time at 60V.

At an anodizing voltage of 60V there is an increase in the diameter of the nanotube obtained increasing the anodization time from 15 to 30 minutes.

The next step is to determine the effect of time using a smaller voltage. Titanium samples were anodized at 30 volts with a time of 15 and 30 minutes and the images were obtained in the FESEM. Figures 18 and 19 show a FESEM image of each of the samples.

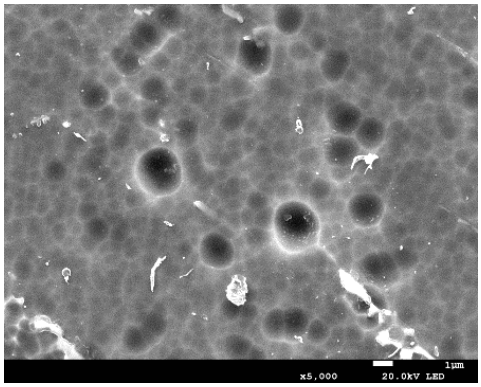

Figure 18 *SEM surface image of 30V15' at 5000x.*

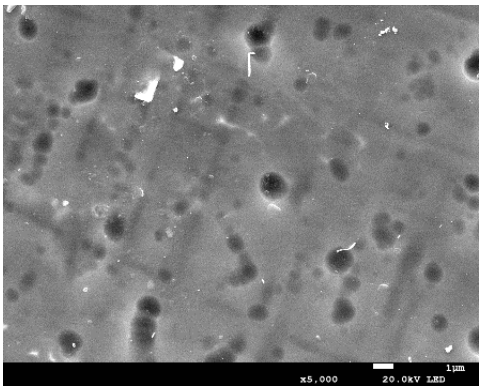

Figure 19 *SEM surface image of 30V30' at 5000x.*

Significant differences can also be observed in these two images, which will have to be demonstrated by statistical analysis. After analyzing the FESEM images, the pore diameter values have been obtained.

Fig. 20.a shows that the data distribution of the 30V15' and 30V30' samples are not normal. This is because the diameter values in the two samples have a large range of values and are proportionally distributed. That is why the average diameter values are expressed as the mean of the processed values with the standard deviation (Fig. 20.b).

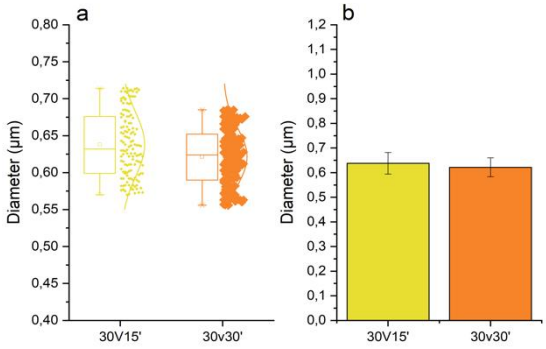

Figure 20 *Comparison of 30V15' and 30V30' with a) data distribution and b) mean diameter value and standard deviation.*

The mean diameter value obtained for the 30V15' sample is 0,64 ± 0,04 µm and for the 30V30' sample 0,62 ± 0,04 µm.

Although the statistical analysis of the data obtained indicates that there is a statistical significative difference between the two data distribution, the mean value for the diameter for the sample anodized at 30V for 15 minutes and 30 minutes can be considered as equal.

These results show that in anodization using 30V increasing the anodizing time from 15 to 30 minutes does not affect the nanotube diameter as in the previous experiment.

The last type of time-dependent experiment was anodizing samples at 15 volts for 15 minutes and 30 minutes. Figures 21 and 22 show the surface morphology of the samples 15V15' and 15V30', respectively. To corroborate the differences, the different images of each type of sample were analyzed with ImageJ software.

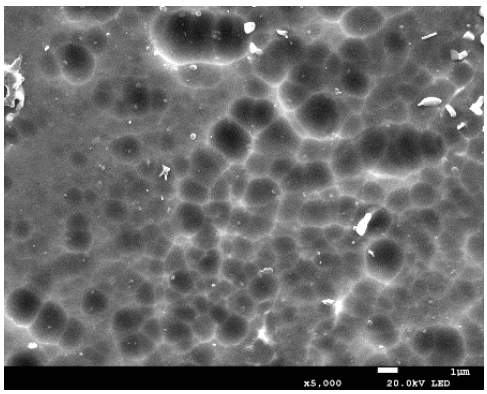

Figure 21 *SEM surface image of 15V15' at 5000x.*

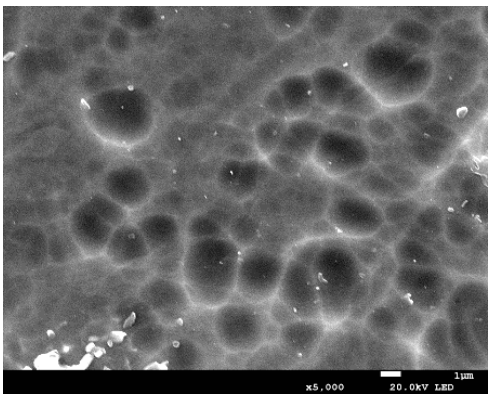

Figure 22 *SEM surface image of 15V30' at 5000x.*

After analyzing the data of nanotube diameter obtained with Origin software, it can be seen in Fig 23.a that the data do not follow a normal distribution. The statistical analysis of the two sets of data, with 90 % tolerance, indicates that there is a significant difference between the two data sets.

Fig 23.b presents the diameter mean results and the standard deviation. The diameters obtained are 0,57 ± 0,05 µm for the sample anodized at 15V for 15 minutes and 0,62 ± 0,06 µm for the samples anodized at 15V for 30 minutes.

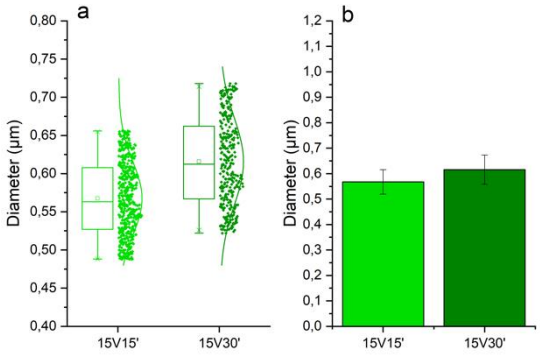

Figure 23 *Comparison of 15V15' and 15V30' with a) data distribution and b) mean diameter value and standard deviation*

After these experiments to study the effect of the anodizing time on the nanotube diameter using different potentials, it can be concluded that the anodizing time affects the pore diameter.

For both 60 V and 15 V samples, the increasing in the anodization time from 15 minutes to 30 minutes increases the average nanotube diameter. Is interesting to notice that for the samples anodized at 30 V the average nanotube diameter remains without a significative variation.

As conclusion can be highlighted that the lowest average for nanotube diameter is obtained with anodizations at 15V for 15 minutes. While the highest average value for nanotube diameters is obtained with anodizations at 60V for 30 minutes.

Further characterizations are needed to arrive at optimal results with the equipment used in the research project.

5.3.2. STUDY OF THE EFFECT OF ANODIZATION VOLTAGE

After analyzing the effect of time on the pore diameter of the anodizing samples, a study was carried out to analyze the effect of voltage. The aim of this experiment is to study if that the anodizing voltage influences the diameter of the pores obtained when different anodizing time are used.

The comparation of the average diameter obtained depending on the potential used is presented in Fig. 24 which compares the samples anodized for 15 minutes using 15 V, 30V and 60V.

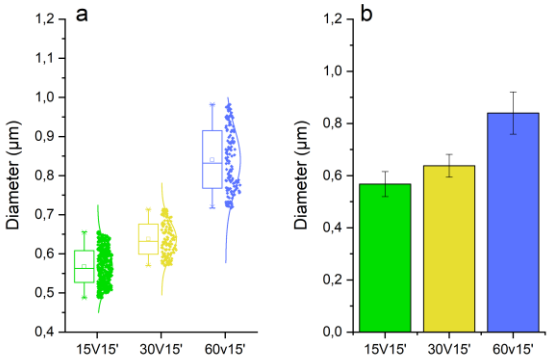

Figure 24 *Comparison of 15V15', 30V15' and 60V15' with a) data distribution and b) mean diameter value and standard deviation.*

Fig. 24 shows an increasing in the average diameter as the potential used for the anodization increases.

This result can be compared with the data presented in Fig. 25 where the average diameter obtained using 30 minutes anodization with a potential of 15 V, 30 V and 60 V.

The results presented in Fig. 25 shows an increasing on the average diameter for the sample anodized at 60 V for 30 minutes comparing with the sample anodized at 15 V for 30 minutes. The results obtained for the sample

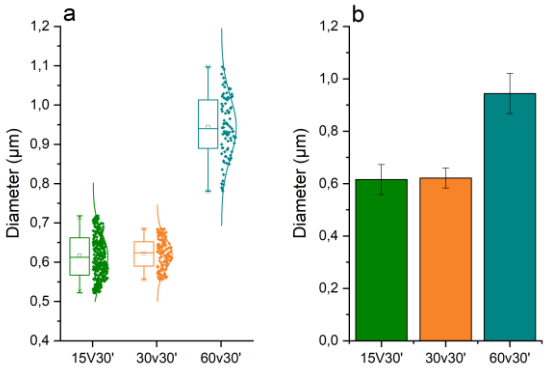

Figure 25 *Comparison of 15V30', 30V30' and 60V30' with a) data distribution and b) mean diameter value and standard deviation.*

anodized at 30 V for 30 minutes present a lower value than the expected. This unexpected data should be analyzed more careful and is advisable to prepare a couple of replicates to determine if this value can be considered as a trustworthy.

The plots in Fig. 25.a show a larger scatter in the data for the 15V and 60V samples, as opposed to the 30V data. The reason behind is the lower amount of data available for this sample compared to the ones obtained for the 15V30´and 60V30´.

After this study it can be concluded that further tests should be done to prove that the pore diameter is directly proportional to the voltage applied during anodizing.

5.3.3. STUDY OF THE EFFECT OF THE ELECTOLYTE

After having studied the effect of time and voltage during anodizing, the effect change in the composition of the electrolyte on the diameter of the titanium dioxide pores will be studied. This new electrolyte is composed of the same components as the previous one, increasing the fluoride concentration to 0,5 v/v %. This new electrolyte will be named E3, and the previous one E2, as explained above.

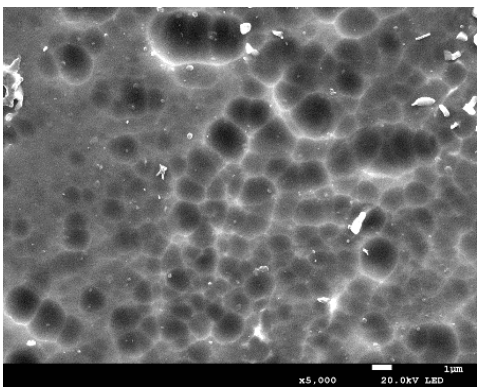

Figure 26 *SEM surface image of 15V15' anodized with E2 at 5000x.*

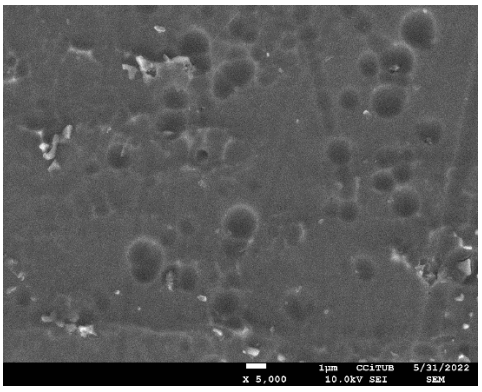

Figure 27 *SEM surface image of 15V15' anodized with E3 at 5000x.*

Figures 26 and 27 show differences between the two types of samples, but a numerical analysis is needed to reach a conclusion. After data analysis and processing, the results of the graphs in Fig. 28 were obtained.

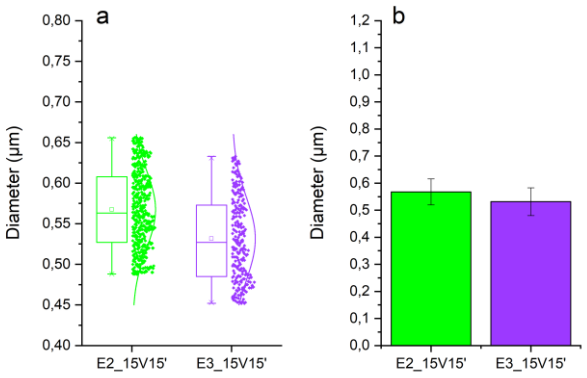

Figure 28 *Comparison of E2 and E3 at 15V15' with a) data distribution and b) mean diameter value and standard deviation.*

The distribution of the samples is not normal, and that the values of the diameters have a large variation.

The mean of the results for electrolyte 2 is 0,57 ± 0,05 µm and 0,53 ± 0,05 µm for the electrolyte 3.

Statistically speaking, it can be stated that there is a significant difference in the two sample groups, showing that there is an effect on the pore diameter depending on the concentration of fluorides in the electrolyte.

The results show a small reduction in the average diameter of pore as the increase content of fluoride ions in the electrolyte. The reduction of average diameter is not significative, and a further experiment should be done increasing much more the fluoride content in the electrolyte. Table 3 shows the comparison of electrolyte compositions and the results obtained with each electrolyte.

Electrolyte name	Reagent name	Concentration (v/v %)	Results
E2	NH_4F	**0,1**	**0,57 ± 0,05 µm**
	Ethylene glycol	97,9	
	Milli Q water	2	
E3	NH_4F	**0,5**	**0,53 ± 0,05 µm**
	Ethylene glycol	97,7	
	Milli Q water	2	

Table 3 *Comparative table of the composition of the electrolytes.*

Therefore, as a preliminary result it can be conclude that an increase in the concentration of fluoride ions in the electrolyte may decreases the value of the pore diameter. In this study, the pore size decreases, reaching a nanometric structure.

5.3.4. STUDY OF THE EFFECT OF THE CATHODE

A study of the effect of cathode type has been carried out since different anodizing conditions can interfere with the results. The cathode used for the rest of the experiment, which will be named C1, consists of a smooth and compact piece of stainless steel. The cathode used for this study, which will be named C2, consists of the same material as the previous one, but in the mesh shape.

It has been hypothesized that by decreasing the area of the electrode used, the electrons passing through the electrolyte would decrease, thus the control on the creation of nanotube structure will increase.

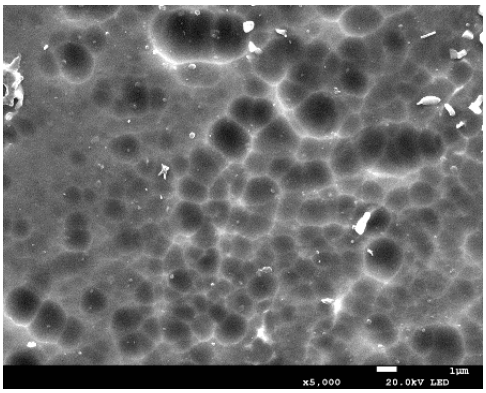

Figure 29 *SEM surface image of 15V15' anodized with C1 at 5000x.*

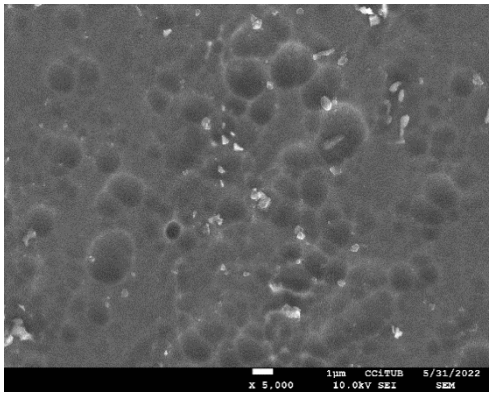

Figure 30 *SEM surface image of 15V15' anodized with C2 at 5000x.*

Figures 29 and 30 show the SEM images, which demonstrate the differences between the two types of samples. After analyzing the images and finding the average diameter of the surface pores, the results in Fig. 31 were obtained.

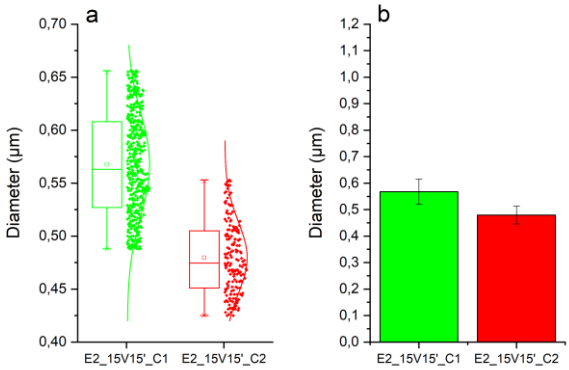

Figure 31 *Comparison of C1 and C2 at 15V15' with a) data distribution and b) mean diameter value and standard deviation.*

In Fig. 31.a the distribution of the data is presented. The data shown present a non-normal distribution. The data obtained for the average pore diameter for the sample produced using the solid cathode (C1) is significatively different to the data obtained for the samples produce using the mesh cathode (C2).

The Fig. 31.b shows the mean vale of the average diameter obtained for solid cathode is 0,57 ± 0,05 µm and for mesh cathode 0,48 ± 0,05 µm.

After the statistical study it can be stated that the type of cathode used in the anodizing process affects the result of the pore diameter.

The results presented in Fig. 31 demonstrate that the use of a mesh-shape cathode allows the reduction of the average pore size.

From this study it can be concluded that the result with the smallest diameter was 15V15' with cathode 2. Further tests should be done to ensure that stable and uniform nanotubes are achieved over the entire surface of the sample.

6. SCHEDULE OF EXECUTION

A research project requires a lot of time and dedication on the part of the author, the director, the tutor and the different supervisors who collaborate in the project. That is why it is necessary to plan the activities to be carried out, in order to try to keep to the previously established timetables and to recognize the exact point at which work is being done.

For this purpose, a WBS (Work Breakdown Structure) and its dictionary to qualify the tasks, a PERT (Program Evaluation and Review Technique) and its diagram to determine the times and a GANTT to evaluate the fulfilment of the schedules have been carried out.

6.1. WBS

The WBS is an organizational tool that consists of breaking down the different activities and objectives to be carried out during the project into sections. Thanks to this organization, the objectives to be achieved are hierarchized.

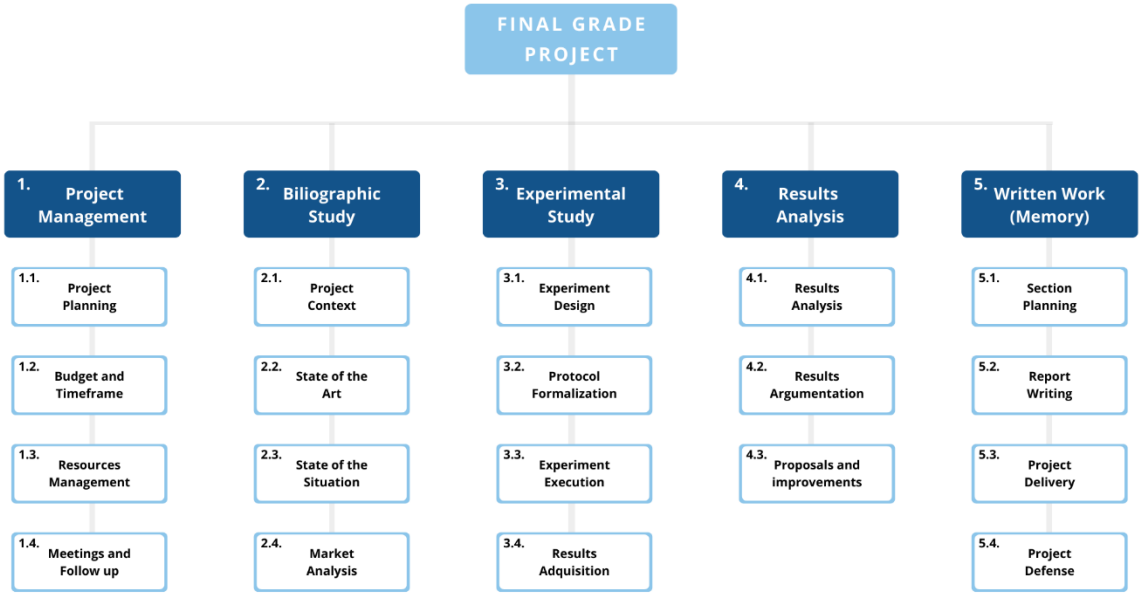

Figure 32 *WBS of the project*

In Fig. 32 it can be seen that the work is divided into five sections, the first is reduced to all the activities required for the organization of the project; the second is divided into the extensive study of the bibliography; the third is based on the experiments and the acquisition of results; the fourth section consists of the analysis of these results and finally, the fifth section includes everything that has to do with the written report and the oral presentation.

Along with this structure, a dictionary is required that specifies for each activity described in the WBS the description, the acceptance criteria, the deliverables expected at the end of the task, the assumptions, the resources allocated, the targets and the related cost. In each table described below it can be found each of these things mentioned above, for a better understanding of the WBS scheme.

ID# 1.1.	Control Account # 1	Latest update 06/06/2022
Description: Organization of project activities and tasks		
Acceptance criteria: Clearly define all the tasks to be performed throughout the project.		
Deliverables: PERT, GANTT		
Assumptions: It should be kept in mind that the time to devote to the work cannot be complete.		
Resources allocated: Author		
Duration: 3 days		
Goals: February 20th - PERT		
Cost: -		

ID# 1.2.	Control Account # 1	Latest update 06/06/2022
Description: Determination of budget and deadlines for delivery or completion of activities		
Acceptance criteria: A concrete budget must be created, along with a realistic schedule and activity table for each task.		
Deliverables: Budget and GANTT		
Assumptions: The budget will go primarily to pay for the human and material resources needed for the project.		
Resources allocated: Author		
Duration: 2 days		
Goals: February 21st - Budget February 22nd – GANTT		
Cost: -		

ID# 1.3.	Control Account # 1	Latest update 06/06/2022
Description: Determination of the resources allocated to each project activity.		
Acceptance criteria: The resources allocated to each activity must be clearly defined.		
Deliverables: -		
Assumptions: Deadlines are immovable. Each day corresponds to two hours of work.		
Resources allocated: Author		
Duration: 2 days		
Goals: February 24th - Resource Allocation		
Cost: -		

ID# 1.4.	Control Account # 1	Latest update 06/06/2022
Description: Description of follow-up meetings with the tutor and decision making throughout the project.		
Acceptance criteria: Minutes shall be taken for each meeting.		

Deliverables: Minutes of the meetings.
Assumptions: Meetings may be held online or in person, depending on the physical availability of the attendees.
Resources allocated: Director and author
Duration: 30-45 minutes each meeting, repeating throughout the project.
Goals: delivery of minutes after each meeting
Cost: -

ID# 2.1.	Control Account # 2	Latest update 06/06/2022
Description: Intensive study of the project context.		
Acceptance criteria: It should explain extensively the context on which the project is based.		
Deliverables: Project context		
Assumptions: A bibliographic study and a summary of it should be done, so you will be assigned enough hours to do it.		
Resources allocated: Author		
Duration: 20 days		
Goals: March 15th - Context of the project		
Cost: -		

ID# 2.2.	Control Account # 2	Latest update 06/06/2022
Description: Detailed description of the state of the art of the project.		
Acceptance criteria: Must define in detail the history of the technologies on which the project is based.		
Deliverables: State of the art		
Assumptions: State of art should be done, so you will be assigned enough hours to do it.		
Resources allocated: Author		
Duration: 25 days		
Goals: March 20th - Context of the project		
Cost: -		

ID# 2.3.	Control Account # 2	Latest update 06/06/2022
Description: Detailed description of the status of the situation.		
Acceptance criteria: It must define in detail the actuality of the technologies on which the project is based.		
Deliverables: State of the situation		
Assumptions: State of the situation should be done, so you will be assigned enough hours to do it.		
Resources allocated: Author		
Duration: 5 days		

Goals: March 1st - Context of the project
Cost: -

ID# 2.4.	Control Account # 2	Latest update 06/06/2022
Description: Conducting an analysis showing the different product proposals currently on the market to evaluate possible competition.		
Acceptance criteria: It must clearly illustrate the different options available.		
Deliverables: Market analysis		
Assumptions: State of the situation should be done, so you will be assigned enough hours to do it.		
Resources allocated: Author		
Duration: 2 days		
Goals: March 30th - Market Analysis		
Cost: -		

ID# 3.1.	Control Account # 3	Latest update 06/06/2022
Description: Detailed design of the experiment to be performed in the laboratory.		
Acceptance criteria: It must contain clear explanations of what is to be done.		
Deliverables: Experiment design		
Assumptions: The design will be guided by the project manager, due to lack of knowledge of the work author.		
Resources assigned: Director and author		
Duration: 5 days		
Goals: April 5th - Design of the experiment		
Cost: -		

ID# 3.2.	Control Account # 3	Latest update 06/06/2022
Description: Formalization of the protocols of action in the laboratory and creation of the necessary materials for the realization of the project.		
Acceptance criteria: It should clearly define the protocols to be followed in laboratory practices.		
Deliverables: Protocols		
Assumptions: The protocols will be guided by the project manager, for lack of knowledge of the author of the work.		
Resources assigned: Director and author		
Duration: 5 days		
Goals: April 10th - Protocols		
Cost: -		

ID#	Control Account #	Latest update

3.3.	3	06/06/2022
Description: Performance of the experiments defined in the experimental design.		
Acceptance criterion: Experiments that have followed the protocol should be counted as valid, whether they give a good or bad result.		
Deliverables: -		
Assumptions: The experiments conducted will follow the protocols determined above.		
Assigned resources: Author and supervision of a specialist		
Duration: 35 days		
Goals: May 15th - To have carried out the experiments.		
Cost: Material to carry out the experiments.		

ID# 3.3.	Control Account # 3	Latest update 06/06/2022
Description: Collection and arrangement of the results obtained.		
Acceptance criteria: It must contain detailed information on the results obtained in all the experiments performed.		
Deliverables: -		
Assumptions: When doing each experiment, the result will be noted.		
Assigned resources: Author		
Duration: 30 minutes after each experiment		
Goals: Record results after each experiment.		
Cost: -		

ID# 4.1.	Control Account # 4	Latest update 06/06/2022
Description: Analysis of the results obtained.		
Acceptance criteria: An exhaustive analysis of the results obtained must be made.		
Deliverables: Draft analysis		
Assumptions: Those obtained analyzed should be all those that comply with the protocols, whether they have gone well or not.		
Assigned resources: Author		
Duration: 6 days		
Goals: May 21st - Draft		
Cost: Characterization costs.		

ID# 4.2.	Control Account # 4	Latest update 06/06/2022
Description: Argumentation of the analyzed results.		
Acceptance criterion: The results analyzed should be discussed in such a way that the conclusion is clear.		
Deliverables: Draft of the argumentation		

Assumptions: The argumentation of the results should be supervised by the project director.
Assigned resources: Director and author
Duration: 10 days
Goals: May 31st - Draft
Cost: -

ID# 4.3.	Control Account # 4	Latest update 06/06/2022
Description: Proposed improvements to the design of the experiment, project objectives or implementation protocols.		
Acceptance criteria: It must present improvements and proposals for the future, so that they can be considered in the realization of a possible project of greater scope.		
Deliverables: Proposals and improvements		
Assumptions: An advance in technique made by professionals in the materials world will be considered.		
Assigned resources: Author		
Duration: 5 days		
Goals: June 2nd - Proposals and Improvements		
Cost: -		

ID# 5.1.	Control Account # 5	Latest update 06/06/2022
Description: Planning of the different sections of the report.		
Acceptance criterion: It must contain the order in which the report will be written on a basis.		
Deliverables: Work planning		
Assumptions: Guidelines will be provided by the project manager.		
Assigned resources: Author		
Duration: 2 days		
Goals: February 19th - Work planning		
Cost: -		

ID# 5.2.	Control Account # 5	Latest update 06/06/2022
Description: Complete drafting of the different sections of the project report.		
Acceptance criteria: It must contain all the sections mentioned in the planning of the sections of the report.		
Deliverables: Project report, report corrections		
Assumptions: The report shall be submitted with time in advance so that the various errors contained therein can be corrected.		
Resources assigned: Director and author		
Duration: 15 days		

Goals: June 1st - Memory June 7th - Correction of the report
Cost: -

ID# 5.3.	Control Account # 5	Latest update 06/06/2022
Description: Final delivery of the final degree project.		
Acceptance criteria: It must contain all the corrections to the report, together with the presentation and material necessary to complete the project.		
Deliverables: Final report, presentation		
Assumptions: The presentation will be the one to be used on the day of the memory defense. In case of needing other materials for the presentation (proofs, examples), they should also be submitted together.		
Resources assigned: Author		
Duration: 1 day		
Goals: June 8th - Final Report and Presentation		
Cost: -		

ID# 5.4.	Control Account # 5	Latest update 06/06/2022
Description: Defense of the Final Degree Project.		
Acceptance criteria: It must be done in front of the director and the tribunal assigned by the university and must be approved.		
Deliverables: Oral presentation		
Assumptions: The court will be merciful and will not only look at the results but will also assess the effort applied to the project.		
Assigned resources: Director, court and author		
Duration: 30 minutes		
Goals: June 15th - Oral presentation		
Cost: -		

6.2. PERT

Once the project tasks have been identified thanks to the WBS, the PERT can be carried out. This technique consists of giving a name to each task and assigning it a duration and the activities required to carry out the activity. If the activities prior to the new action have not been carried out, it will not be possible to start.

ACTIVITY	NAME	PREVIOUS ACTIVITY	DURATION
Planning	A	-	3 days

Budget and deadlines	B	A	2 days
Resource management	C	B	2 days
Meetings and follow-up*	D		0.02 days
Context of the project	E	C	20 days
State of the art	F	C	25 days
State of the situation	G	B	5 days
Market analysis	H	E	2 days
Experiment design	I	F, H	5 days
Formalization of protocols	J	I	5 days
Experiment performance	K	J	35 days
Results acquisition*	L		0,02 days
Results analysis	M	K	6 days
Argumentation of the results	N	M	10 days
Proposals and improvements	O	N	5 days
Section Planning	P	A	2 days
Report writing	Q	P, O	15 days
Project delivery	R	Q	1 days
Memory defense	S	R	0,02 days

Table 4 *Activity matrix of the PERT*

Thanks to the activity matrix, the PERT diagram can be created, which allows us to visually see the progress of the project. The critical path can be seen in Fig.33, marked in red, which contains the activities: A, B, C, F, I, J, K, K, M, N, O, Q, R and S.

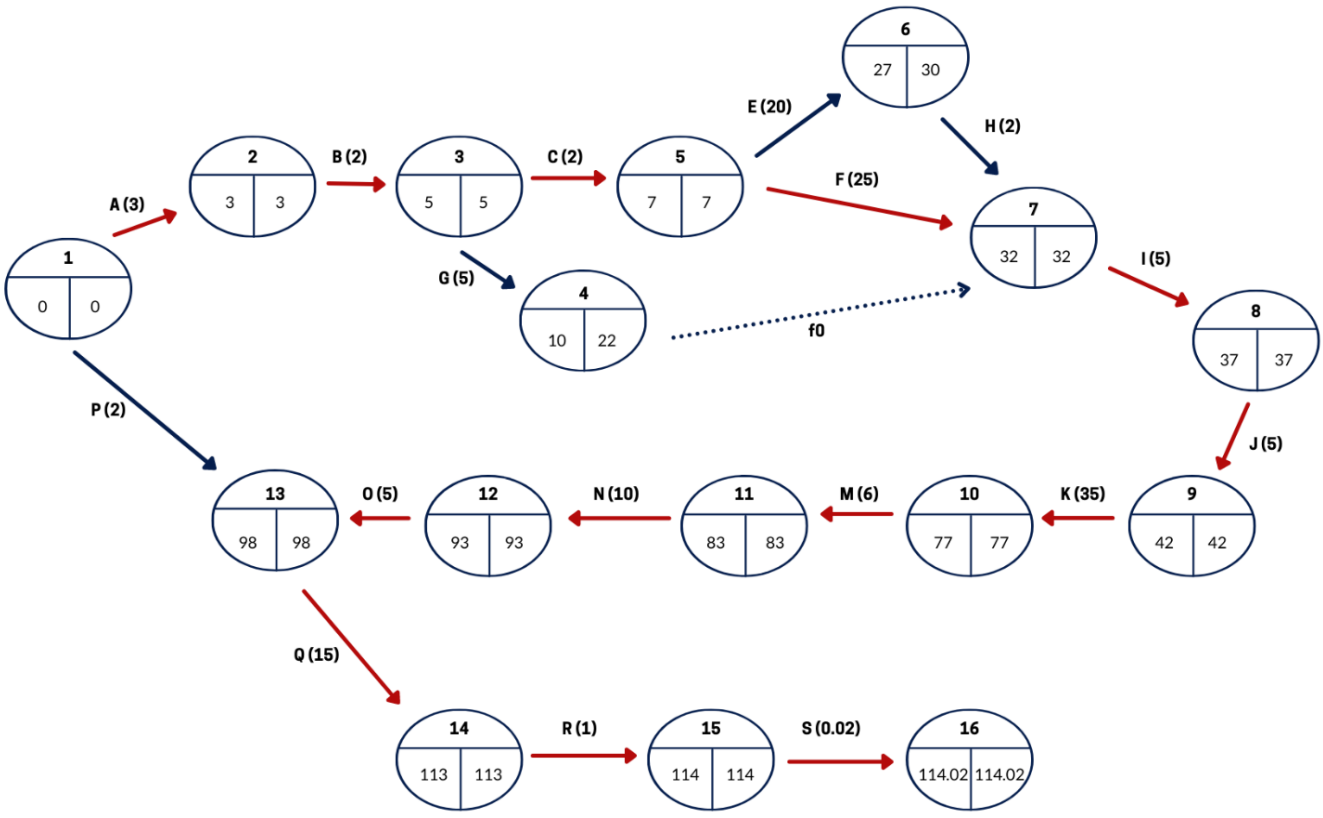

Figure 33 *PERT diagram with the activities of the project*

6.3. GANTT

The GANTT diagram is a graphical planner for a project with different activities. By setting the start and finish time of the theoretical objectives, it can be compared with the actual times, reflecting in a graph the fulfilment of the times of each activity.

In the following figure, it can be seen the GANTT chart. In the legend you can see the complete duration of the plan, the theoretical and actual start and the percentage completed. In this case, the first activities started later than expected and took longer than expected. The last activities, on the other hand, have started later and finished before the established time.

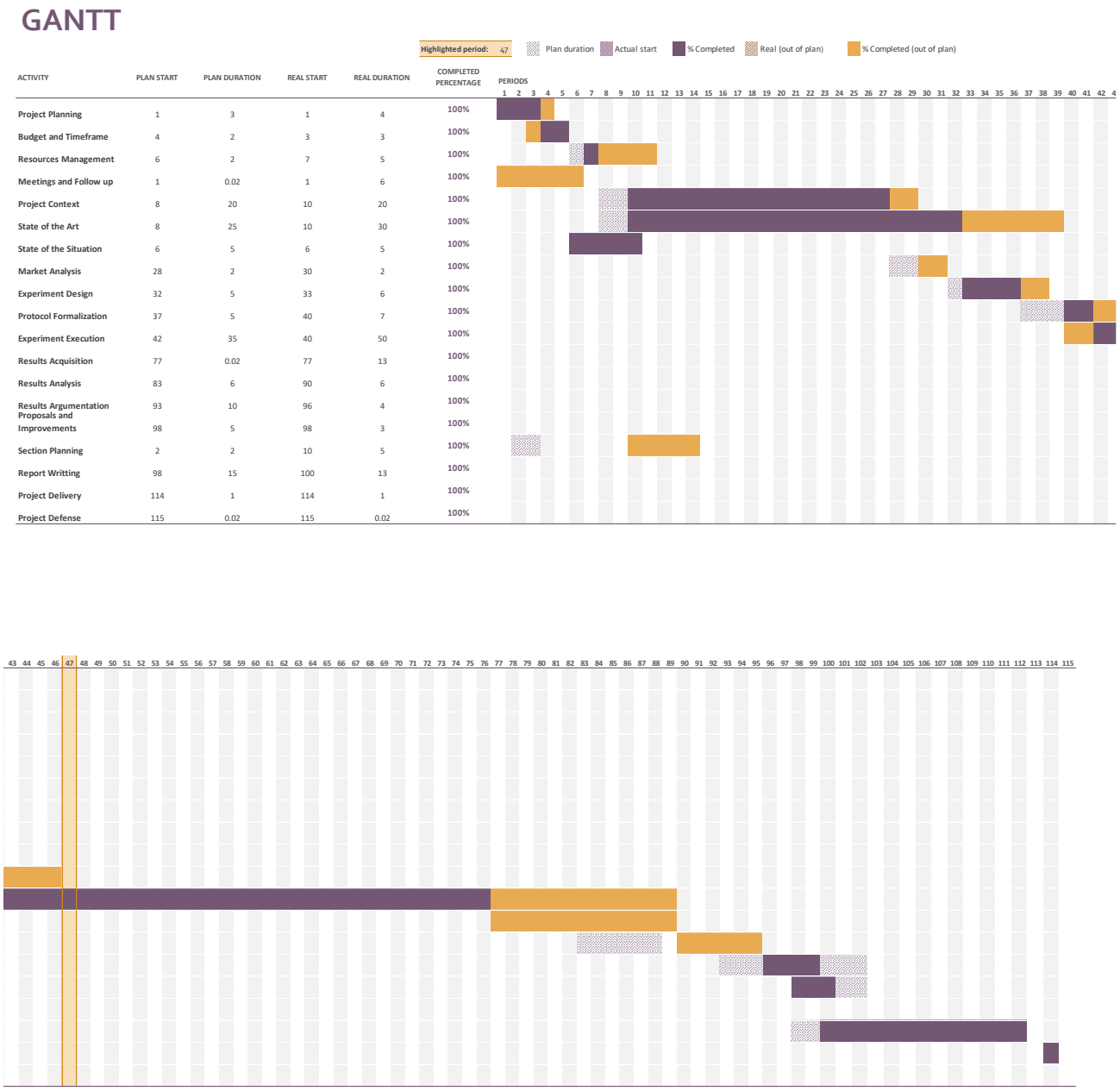

Figure 34 *GANTT diagram*

7. TECHNICAL FEASIBILITY STUDY

In this section, a technical study has been carried out on the feasibility of the project to be implemented in an industrial way. In this way, it will be known whether it is possible to turn this project into a marketable product.

In order to carry out a complete study, a SWOT analysis has been carried out, i.e., a study of the strengths, weaknesses, opportunities and threats that the project has in the current market niche.

7.1. INDUSTRIAL FEASIBILITY

To carry out a project in an industrial way requires processing of the samples, quality control of the samples and testing the viability of the processed samples. In addition, post-processing must be done to achieve a biological response from the patient's cells with the implant.

7.1.1. ANODIZING PROCESS

The process to be implemented industrially is the anodizing of the titanium surface to produce titanium dioxide nanotubes. This requires anodizing instruments, the electrolyte and control of the voltage and time used for anodizing.

Anodizing is a well-known technique in industrial surface treatment, with a very low price, as it is very commonly used for anodizing aluminum (49,50). This process is normally carried out using large electrolytic baths, which allow large surfaces to be anodized at the same time (49,50).

Prostheses and implants shall be anodized by electrolytic bathing, following pre-established protocols to optimize the results of their surfaces. Several companies such as Nobel BioCare TM, Aesculap Implant Systems or Medtronic have anodizing implant prostheses, thus this process can be brought to the industry.

The only difference with these companies will be the anodizing time and voltage applied, as well as the electrolyte used in the process.

7.1.2. QUALITY CONTROL

Once the implants and prostheses have been anodized, quality control must be carried out to ensure that the surface of the product obtained contains the nanotubes. To do this, the surface must be studied by image analysis and corrosion tests. The pores can be observed with electron microscopy (SEM) and the diameter distance can be analyzed using image analysis software. It will also be possible to study the roughness of the samples using confocal microscopy.

This control should be carried out at a previously established frequency, as well as every time the protocols or the established machinery changes. In this way, consistent results will be obtained, and customers will be satisfied with the safety of the implants.

7.1.3. BIOLOGICAL VIABILITY

In addition to controlling the quality of the pores, an added value for bringing the product to industry would be to test the biocompatibility of the implants based on cell culture studies. These studies could demonstrate the biocompatibility of processed implants compared to unprocessed implants.

For this purpose, human osteoblastic cells isolated from femoral trabecular bone from a knee joint after an arthroplasty would be cultured. After cell culture, which can last up to four weeks, a quantitative study would be carried out to assess the cytotoxicity and proliferation of the cells on the processed implant.

With these analyses, the biocompatibility of the anodizing implants and prostheses can be verified, assuring customers of the osseointegration capability of the products.

7.1.4. POST PROCESSING

A further step in the industrial implementation of our project would be to carry out post-processing to make the implants third generation. This, as it has been already explained in the market analysis, could be achieved through the application of components that promote tissue generation in the implants.

To do this, a component very similar to bone, such as hydroxyapatite, must be coated. Hydroxyapatite production could be carried out by sol-gel technique (40), and its deposition by electrochemical deposition (32).

If post-processing is implemented, the quality control and biological feasibility study should be repeated to ensure improved osseointegration capability of the product. In addition, several clinical trials will have to be carried out before the product can be marketed.

7.2. SWOT ANALYSIS

In order to bring a product to the market, it is not only necessary to look at whether the project is industrially feasible, but also to be aware of the internal and external factors of the project. For this purpose, a SWOT analysis has been carried out, which analyses the positive and negative aspects of the project from an internal and external point of view.

For this purpose, a SWOT diagram has been designed to show briefly all the factors involved in the project, which can be seen in Fig. 35.

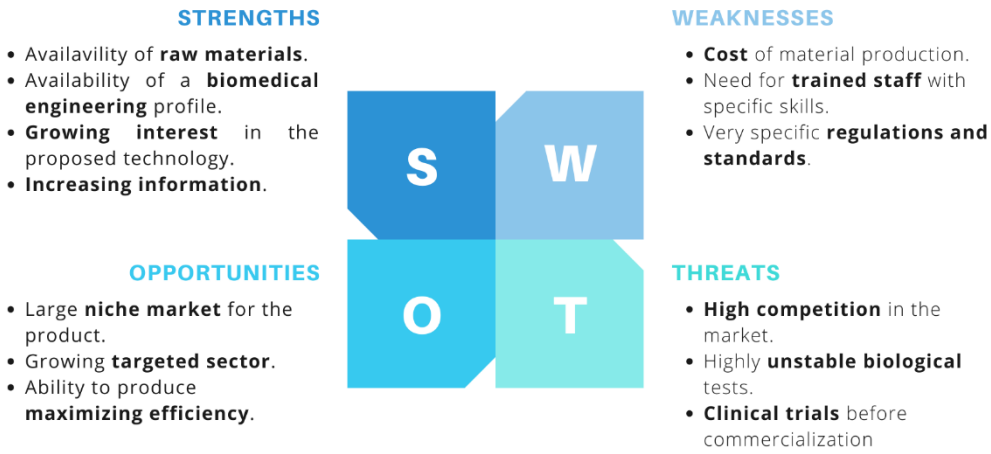

Figure 35 *SWOT analysis diagram.*

In the SWOT analysis it can be observed that the strengths are the possibility of finding raw material, as titanium is a very abundant material in the earth's crust. The creation of the figure of biomedical engineer makes the proposed project possible. In addition, there is a great interest in reaching out to solve medical problems with the world of technology. Finally, there are more and more articles and training available on biocompatible materials and the improvement of osseointegration.

The opportunities presented by the market are a large niche for the product, a targeted sector that is growing over time and the ability to produce a large amount of product while minimizing costs, thanks to the industrial application of the project.

On the other hand, the weaknesses of the project are the cost of obtaining materials, the need for a specific profile trained to obtain the product and the obligation to comply with the standards and regulations of medical devices, which are very strict.

To conclude the analysis, the threats outside the project must be considered. These consist of the high competitiveness in the market due to the rise of these technologies, a high instability in biological tests and the need for clinical analysis before marketing the product.

After this analysis it can be concluded that the project is commercially feasible, as, despite its weaknesses and threats, it is a pioneering product in the healthcare world. Its many strengths and opportunities far outweigh the negative points of the project.

8. ECONOMIC FEASIBILITY STUDY

In this section, the economic study of the project will be carried out, in order to know the budget required to carry out the production of the project. It should be considered that the real cost of the project has been lower, since previously purchased equipment and reagents have been used, as well as the laboratory infrastructures employed.

If one wanted to start the project from scratch, one would have to consider the need for a physical space to carry out the experimental work, as well as the training of the personnel. The costs of sample characterization have been counted separately, as it is preferable to hire a service and a technician rather than to purchase the necessary equipment and train to use it.

8.1. SAMPLE PROCESSING COSTS

In calculating the cost of processing the samples, the machines used, the laboratory equipment and the reagents needed were taken into account. If a laboratory with its own equipment is required, only the reagents must be purchased.

Equipment name	Use	Time used/sample	Cost/sample	Equipment cost
Grinding machine	Pre-processing sample	2 hours	0,33 €	1.750 €
Polishing machine	Pre-processing sample	1 hour	0,16 €	1.750 €
Magnetic stirrer	Cleaning protocol	7.5 minutes	0,02 €	68,43 €
	Anodizing	60 – 15 minutes	0,15 €	
Ultrasounds	Cleaning protocol	10 minutes	0,03 €	1.330 €
Power supply	Cleaning protocol	2.5 minutes	0,01 €	800 €
	Anodizing	60 – 15 minutes	0,16 €	
TOTAL EQUIPMENT COST			**0,86 €**	**5.698,43 €**

Table 5 *Equipment economic analysis.*

The price of processing is minimal, as the current electricity price of 0.27451 €/kWh has been considered, and the price of anodizing has been calculated using the power used per hour. If the entire equipment were to be purchased, a total of **5.699,29 €** would have to be paid for the processing of the sample.

Starting the project from scratch requires our own laboratory equipment, which we have calculated the cost of. In the case of this project, this laboratory equipment was already in possession, so this amount did not have to be paid for. Nonetheless, they have been considered indispensable for the correct implementation of the project.

Material name	Units	Cost/unit	Total cost
Titanium plate	15	0,67 €	10 €
SiC paper	15	3,25 €	48,75 €
Polishing disc	2	11,40 €	22,80 €
Diamond suspension	2	121,21 €	242,42 €
Glass beaker	6	4,54 €	27,24 €
Plastic tweezers	1	1,85 €	1,85 €
Spoon	1	4,33 €	4,33 €
Pipette	4	12,95 €	51,80 €
Magnetic bar	3	1,98 €	5,94 €
Cathode	2	2 €	4 €
Acetone (2.5 L)	1	28,91 €	28,91 €
Ethanol (1 L)	1	32,80 €	32,80 €
TOTAL MATERIAL COST			**480,84 €**

Table 6 *Material economic analysis.*

After having studied the laboratory materials needed to carry out the project, the quantity of reagents and their cost for the total number of samples processed (a total of 15 samples) was studied. The quantity of reagent used for each sample was calculated, the price of the reagent and by means of a rule of three the total price of the reagent for the 15 samples was calculated. The calculations can be seen in Table 7.

Reagent name	Use	Quantity used/sample	Price	Total price (15 samples)
Sodium dodecylbenzene sulfonate	Surfactant	8 gr	1640 €/kg	196,80 €
Sodium hydroxide	Electrolyte cleaning	35 ml	38 €/L	19,95 €
Sodium carbonate	Electrolyte cleaning	65 gr	85,60 €/kg	83,46 €
Nitric acid	Chemical pickling	30 ml	56,60 €/L	25,47 €
Hydrofluoric acid	Chemical pickling	3 ml	261 €/L	11,75 €
Ethylene glycol	Electrolyte	97,9 ml	121 €/L	177,69 €
Ammonium fluoride	Electrolyte	0,1 ml	79 €/L	0,12 €
TOTAL REAGENT COST				**515,24 €**

Table 7 *Reagent economic analysis.*

Therefore, as far as processing is concerned, if the project is started from scratch, the three prices acquired in this section should be added together, giving a total of **6.695,37 €**. The prices of equipment and material are approximate, as there is some discontinued equipment and some material that can be obtained through sales offers with other types of material.

8.2. CHARACTERIZATION COSTS

After having analyzed the cost of sample processing, a cost study of sample characterization will be carried out. The hours spent analyzing the samples in the FESEM as well as the SEM will be considered.

Characterization technique	Hours	Price/hour	Total price
FESEM	9,5	52,58 €	499,51 €
SEM	3	35,47 €	106,41 €
TOTAL CHARACTERIZATION			**605,92 €**

Table 8 *Characterization economic analysis.*

The scientific-technical services of the UB have been used, the JSM 7100 (FESEM) of the scanning microscopy department of the Diagonal Campus. Due to a breakdown in the JSM 7100, the electron microscopy services of the Casanova Campus (at the Faculty of Medicine of the Hospital Clinic of Barcelona) had to be used.

In both services used, a special price has been offered for belonging to a UB research group. If you belong to another company, public or private, the cost of the service would increase. The price has been calculated for the characterization of the updated tariffs for 2022 (51).

In addition to electron microscopy tests, two different characterization tests have been carried out. X-ray diffraction (XRD) allows the crystalline structure of the materials studied to be studied. X-ray photoelectron spectroscopy (XPS) allows the measurement of the spectra of photoelectrons induced by X-ray photons.

8.3. HUMAN RESOURCES COSTS

In order to carry out the project, a specific biomedical engineer profile is required. A biomedical engineer in Spain earns between 26k and 66k € (52). Considering that the biomedical engineer is a recent graduate, the engineer's salary will be 30k €. Taking into account the hours in a working year, it is estimated that the engineer will be paid 20 € per hour.

The supervisor who has been assisting the biomedical engineer throughout the project should also be paid a salary of 40 € per hour. With these salaries, and knowing the hours worked, the total cost of human resources has been calculated in Table 9.

Role	Hours (h)	Price/hour	Total price
Biomedical engineer	700	30 €	21.000 €
Supervisor	40	40 €	1.600 €
TOTAL HUMAN RESOURCES			**22.600 €**

Table 9 *Human resources economic analysis.*

8.4. TOTAL COSTS

In order to be able to calculate the total budget required to carry out the project, several necessary aspects to be covered have been considered. Firstly, the equipment necessary to process all the samples, calculating the energy expenditure for the time used for each piece of equipment. Secondly, the material needed to prepare the samples, clean them and process them by anodizing. Thirdly, the number of reagents needed and their price.

Then, the budget for the characterization of the samples by FESEM and SEM has been calculated. Finally, the salaries for two people, a biomedical engineer and a supervisor, have been estimated, thus calculating the budget for human resources. Table 10 shows the summary of all expenses.

Investment	Total price
Sample processing	6.695,37 €
Characterization	605,92 €
Human resources	22.600 €
TOTAL	**29.901,29 €**

Table 10 *Total economic analysis.*

As can be seen in the table, the cost of the project is around 30.000 €, considering that we are starting from scratch and that we do not have any of the elements necessary to process the titanium samples.

9. REGULATION AND LEGAL ASPECTS

In this section it will be discussed the standards and regulations that our project will have to comply with or entail. It is important to bear in mind that there are different rules and regulations in each country, so they may vary depending on where the product is marketed.

9.1. APPLICABLE LEGISLATION: RULES AND REGULATIONS

In order to know the legislation applicable to our project, it is necessary to know the class of medical device to which it belongs. There are three classes of medical devices, depending on the risk to the patient, the time needed and their use. This project aims to improve the surface of implants, and therefore the focus will be on medical devices belonging to orthopedics and dental implants.

In the FDA (Food and Drug Administration) classification it has been found that these long-lasting implantable medical devices belong to class III (53, 54). These products require pre-market approval procedures, known as PMA (Pre-Market Approval) procedures.

In order to bring the product to the market it should comply with several existing national and European standards and legislation. The national legislations are as follows:

- Royal Decree 1591/2009 of 16 October 2009, which regulates medical devices.
- Royal Decree 437/2002 of 10 May 2002 establishing the criteria for the granting of operating licenses to manufacturers of custom-made medical devices.
- Order SCO/3603/2003 of 18 December 2003 creating the national implant registers.

The latter order is specific to implanted medical devices and consists of organizing a national implant registry to make it easier to locate patients with a given implant. (55)

European legislation is determined by Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 (6). Our product is an implantable product, defined as "any product intended to be partially introduced into the human body by medical intervention and to remain in place after such intervention for a period of at least thirty days". The general safety and performance requirements that impact our project are as follows.

- It shall be designed and manufactured so that its use does not compromise the clinical condition or safety of patients, users or others. (Point 1)
- The product must meet high quality and safety standards, as described in the Treaty on the Functioning of the European Union (TFEU). (Point 2)
- Manufacturers shall establish, implement, document and maintain a risk management system. (Point 3)
- Its manufacture must be done in such a way that the result does not change over time, thus changing its functionality. (Point 7)
- It shall be designed in such a way as to minimize the risk of infection. (Point 11)
- The product must be accompanied by the information necessary for its use and full safety, with identification on the label and instructions for use. The label must include the name of

the manufacturer, product identification, serial code and specific conditions of the product. (Point 23)

- Patients who are implanted with a device should be provided with clear and accessible information about the implanted device. (Point 39)
- Manufacturers shall summarize the main safety aspects and the outcome of the clinical evaluation in a public document. (Point 48)

In addition, our product must bear the EC declaration of conformity, guaranteeing the quality of the product. For this purpose, a quality assessment must first be requested, and an audit must be carried out. Afterwards, an EC design examination certification and EC verification must be requested. Afterwards, a quality control by the manufacturer must be carried out to guarantee the safety and quality of the product.

CE-marked medical devices do not require compliance, but it is highly recommended. In our case they should be observed:

- ISO-10993, which is in line with the biological evaluation of medical devices (56).
- ISO-13485, referring to the quality management system applicable to medical devices (57).
- ISO-14971, which includes the risk management of health care products (58).

9.2. OTHER LEGAL ASPECTS

According to the informative note on the monitoring of labelling indications and instructions for use of health products of the Ministry of Health and Consumer Affairs, these are compulsory, therefore, our product will be labelled and with the instructions for use.

10. CONCLUSIONS

To conclude this project, conclusions will be presented, which will be an analysis of the work carried out and a proposal for the future continuation of this project.

- With the methodology described in this project the optimum voltage to anodize the samples is 15 volts for the obtention of the nanopores with the smallest diameter.
- An increase in the anodizing time increases the average diameter of the pores.
- The determination of the average pore diameter of the samples by scanning electron microscopy and image processing is a suitable methodology for a fast and easy qualitative characterization of the surface.
- The main limitations of the process have been the sample preparation time and the problems encountered in the characterization of the samples, which are common among researchers.
- For industrial application, this project could be extended to post-processing of the samples to obtain third-generation implants and prostheses.

In addition to having achieved the objectives, we would like to conclude this project by proposing work ideas for the future of the project.

- Firstly, to continue optimizing the anodizing conditions in terms of time, voltage and fluoride concentration of the electrolyte, thus achieving a nanometric structure and optimal results.
- Secondly, to coat the nanotubes created with bioactive elements, such as synthesized or bovine hydroxyapatite.
- Thirdly, study the bioactivity, mechanical and cytotoxic properties of the samples by means of tests and standards.

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