New Materials and Processes Developed for Cranioplasty

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Abstract. Traumatic brain injury is the leader in the ranking of mortality and invalidity. The surgical repair of a defect of the skull by cranioplasty has been practiced since ancient times, when materials of non-biological origin were used for this purpose. New materials and processes are sought to improve osseointegration of implants. Like any surgical procedure, cranioplasty involves complications that may be related to the surgical technique and/or to the patient's tolerance to the material used. This work described a biocompatible medical device that include two supported meshes for providing mechanical strength and osseointegration properties of the implant, and a multiplayer porous material in between them that is loaded with the required bioactive antibacterial compound to promote a controlled and sustained release of the pharmaceutical agents at the site of surgical intervention. To increase osseointegration, meshes are designed with an open structure and coated with biocompatible materials such as hydroxyapatite. The composition gradient in the multilayer porous material is attained by loading successive layers of porous material with different amounts of bioactive materials and then stacking them to create a gradient of composition across the porous material.

1. Introduction
Traumatic brain injury is the leader in the ranking of mortality and invalidity. Of the total number of patients with severe head and intracranial injuries, more than 70% will remain with certain physical and mental disabilities. Also, it is recognized that every 11 minutes a child suffers from a head and brain trauma that causes significant disorders in their motor, linguistic and cognitive functioning throughout their life. In the literature, the disturbance of mnesic function is most often associated with intracranial trauma, which affects not only memory, but also other cognitive functions, such as learning.

Intracranial traumas are the most common cause of death of people between the ages of 0 and 44 years old. Currently, about 11.5 million of Europe's population that survived from brain trauma suffers from certain forms of physical disabilities or mental impairment. There are approximately 500,000 - 600,000 cases of head injury in the US annually, of which more than 10% are fatal. While intracranial traumas have various mechanisms of occurrence, the most common causes are car accidents, aggression, trauma in sports and trauma by firearms. The trauma of the skull and brain is the most common type, more serious and in continuous ascension, of injury at childhood. There has been an increased incidence of severe head and brain trauma in children requiring surgical treatment.
2. Cranioplasty and Methods to Fix Implant

The surgical repair of a defect of the skull by cranioplasty has been practiced since ancient times, when materials of non-biological origin were used for this purpose. In the literature, there are data that attest that bone defects closed with silver plate or coconut bark were found in the collection of skulls of the Incas. In the etiological structure of acute brain lesions, brain trauma is in the first place, followed by vascular accidents (ischemic, haemorrhagic strokes), brain tumours, and diffuse post-resuscitation and post-strangulation cerebral hypoxia.

The pathophysiological process secondary to a craniocerebral trauma is the occurrence and the propagation of cerebral edema, which results in increased intracranial pressure, decreased cerebral oxygenation and irreversible ischemic lesions that lead to permanent deficits and, in many cases, to death. Since the early 1970s, decompressive craniectomy is a neurosurgical method of combating refractory cerebral edema in drug therapy, due to the significant reduction of intracranial pressure and flow into the cerebral blood vessels. Although this aggressive way of lowering intracranial pressure has proven to be effective in saving the patient's life, severe deficiencies that may occur later have sparked controversy among neurosurgeons.

Like any surgical procedure, cranioplasty involves complications that may be related to the surgical technique and/or to the patient's tolerance to the plastic material used. It is known that a large variety of surgical techniques, materials and medical devices are used in performing cranioplasty procedures. With the evolution of the manufacturing systems, novel medical devices used in the reconstruction of the defects of the bone system have emerged in terms of the types of materials used and of the constructive forms, so that they are as close as possible to the anatomy of the patient.

Well-fitting prosthetic implants are required in large cranial defects to protect the patient's brain from trauma or infection, while it performs an aesthetic mission to restore the shape to the patient's head. Malleable and biocompatible materials are used to make an implant when not enough cranial bone is available for grafting. Dean et al. [1] presents a computer aided design method for producing an implant for a patient prior to operation using a non-invasive 3D (3-dimensional) scan of the patient's defect site that digitally represents the area that will receive the implant; designing and validating an implant on a computer based on digital data generated from a volume image of the patient; and fabricating the implant based solely on the implant design data generated on computer. Due to the advantages, the manufacture of personalized prostheses is currently considered the one that brings the most benefits in terms of compliance with the patient's needs. Also, a personalized prosthesis significantly reduces the duration of surgery and, implicitly, postoperative complications. However, an intracranial prosthesis that is custom made implies higher production costs compared to the standardized devices available on the market. However, drilling holes in skull is the main method used in cranioplasty to secure the cranial implant in place.

3. Surface Modification of Implants

Besides searching for methods to secure in place the cranial implant, researchers have sought different ways to improve surface properties of implants to promote adherence, osseointegration and reduce inflammation. Pacifico et al. [2] presents a composition as bone haemostat, bone adhesive, bone void filler, or bone cement. The surface of the plate has to be modified to ensure adherence. To obtain nanostructured surfaces, the prosthesis is modified by mechanical methods using abrasive materials, chemical methods using acid etching and electrochemical processes, physical methods or a combination of these methods. There are also other methods that involve different coatings on the surface of the implants. These coatings include hydroxyapatite, calcium phosphate biomimetic layers, biomolecule layers, but also coatings that have a combined synergistic effect. The main purpose of all these surface modification treatments is to improve the bioactivity, biocompatibility, wear resistance and corrosion of titanium and titanium alloys for their particular applications in medicine.

Surface modification of medical devices, such as cranial implants made of titanium mesh, can be applied to help induce the process of osseointegration. There are many clinical cases where the osseointegration process of Ti and its alloys is not enough but an osseo-inductive behaviour of the
implant surface is required, especially when rapid healing or bone quality and/or bone quantity is mandatory. One of the main objectives of the current research on biomaterials is the complex system of biological inducements and surface responses, including interface processes [3]. Antibacterial surfaces capable of avoiding biofilm formation are extremely important for implants that are in direct contact with bone tissues. It was found that fewer macrophages and inflammatory reactions are reported on Ti and its alloy surfaces compared to stainless steel or polyether ketone surfaces. Titanium is well tolerated by the body, as long as the prosthesis is in perfect condition, mechanically stable and uninfected. If these conditions are not met, the prostheses may be associated with an acute or chronic inflammatory reaction, osteolysis, weakening and failure of the prosthesis. Therefore, the implant should have both osseointegration and antibacterial properties.

Human osteoclasts can corrode stainless steel, cobalt and Ti alloys, leading to the production of metal ions, which are toxic for the body and responsible for inflammatory reactions. The healing reaction in the case of a prosthesis made of Ti can occur by osseointegration, by fibrous encapsulation or by chronic inflammation. The last two reactions indicate the failure of the procedure. The events related to the inflammatory response of the body to the prosthesis is complex and include exudation, adsorption of the protein surface, development of a provisional blood-based matrix, recruitment of cells of the innate immune system (leukocytes, platelets), neutrophil migration, monocyte substitution and macrophage differentiation, foreign body reaction, production of reactive oxygen species, fusion of mono-cytes/macrophages to form giant cells or apoptosis.

Different strategies to obtain bioactive and antibacterial titanium surfaces have been also investigated. The inorganic antibacterial agents that have been considered are mainly metal ions and nanoparticles, as well as their oxides (e.g. Ag, Cu, Zn and Ce). Among organic agents, mainly antibiotics have been considered. The strategy to reduce the resistance to infections involves the modification of the biomaterial, that is, the modification of the design of the polymeric material following two main directions: 1) modification of the surface to minimize the adhesion of the bacteria; 2) incorporation of antimicrobial species with the role of destroying bacteria that contaminate the vicinity of the prosthesis (e.g. incorporation of antibiotics, silver, silver compounds etc).

The advantages of inorganic antibacterial agents are the broad spectrum of activities that allow the treatment of polymicrobial infections, the prevention of contamination with unknown bacteria and the development of resistance. Therefore, the problem of resistant bacterial strains is currently one of the most important problems regarding the use of antibiotics. However, the main disadvantages are their applications, which involve difficulties that come both from the field of bureaucracy, but especially with regard to finding the optimal therapeutic window, which will allow an effective antibacterial behaviour, without cytotoxic effects.

The placement, fixation and fastening the implants to the bone structure are generally done by suturing or screwing the implant to the skull via holes. Drilling holes is the main method used in cranioplasty to repair a defect or deformity of the skull. Implant migration and micro-movements may hinder osseointegration and even result in rejection of the implant. Bone screws, tacks and the like are destructive intrusions into the bone structure and, once applied, exert (lateral) compressive forces on the bone structure. Compressive forces in turn may cause resorption of bone and loosening of the fixing means. Micro-movements due to play between different parts of the implant or the fixing means or between the fixing means and the bone structure and/or implant may increase damage and loosening and should be prevented. Further, the implant and its fixation means form an invasive volume inside the patient's body. Such volume should be minimal, in particular for a cranial implant to prevent damage to the brain.

4. Novel Biocompatible Implant
We present a novel biocompatible implant that include two supported meshes for providing mechanical strength and osseointegration properties of the implant, and a multiplayer porous material in between that is loaded with the required bioactive antibacterial compound to promote a controlled and sustained release of the pharmaceutical agents at the site of surgical intervention.
4.1. Porous Material with Gradient porosity

The porous multilayer is presented in Figure 1 and consists of successive layers of various porosities. The layers are arranged either in ascending or descending order of porosity. The biocompatible implant integrates the multilayer porous material in between two structural meshes (Figure 2). The thickness of the multi-layered assembly is equal or less the thickness of the skull.

![Figure 1](image_url)

**Figure 1.** Illustration of the porous multilayer with simple gradient composition made of nanofibers.

The porous material includes a multitude of porous membranes that are formulated with the highest amount of bioactive material in the most porosity layer. Successive layers of polymeric nanofibers can be obtained by electrospinning. By varying the electrospinning variables conditions, various nanofibers sizes and porosities of the resulted membrane can be obtained. Nanofibers layer are obtained with progressive increased porosity.

The drug diffusion is the mechanism by which the drug is released in the body. In practice, blends consisting of a drug and polymer or blends of polymers are used. The morphology of the material and the molecular size of the drug are only a few factors that influence the diffusion of the drug into the body. The rate of releasing of a drug shows that a large amount of drug is discharged first, which indicates that the transport is nonlinear with a plateau. For the same drug, the rate of releasing is slowed down due to the resistance of polymer film [4]. The stack of ultrathin membranes of various porosities can be arranged in a simple gradient of porosity or in a double gradient of porosity as shown in Figures 1 and 2, respectively. In Figure 2, an illustration of the biocompatible implant having, in between 2 meshes, a porous biomaterial comprising of successive layers of various porosities and stacked up from high to low porosity from the inside toward outside of the material.

Each membrane of a specific porosity is loaded with bioactive agents, the amount of the drug being related to the amount of the drug retained by the membrane. Stacking up the membranes in a pre-set order controls the release the drug in a desired and precise fashion. The controlled release refers to the release of the pharmacuetic agents from the inside of a medical device to surface at a predetermined rate. The bioactive compound does not come off in an unpredictable fashion in a controlled release system, i.e. it does not discharge erratically in contact with a biological environment unless specifically intended to do so. Reducing the thickness of the layers, a continuous change in porosity can be obtained.

In certain applications, an initial burst of drug may be desirable followed by a more gradual release thereafter. The release rate may be steady state (commonly referred to as “timed release” or zero-order kinetics), that is the drug is released in even amounts over a predetermined time (with or without an initial burst phase) or may be a gradient release. A gradient release implies that the concentration of drug released from the device surface changes over time. The difference in porosity between adjacent layers can be used to control the release. In early stages of diffusion, the quantity of the bioactive compound delivered can be controlled by its distribution across the layers. Increasing the number of the layers with contrasting properties, the release profile can be engineered to better control the drug
release. The effects of the relative thickness of the layers and the relative resistance to diffusion offered by each layer’s composition on the drug release profile are critical. The dissimilarity in porosities of two adjacent layers can be used to control the release, while the quantity of drug delivered can be modified by varying the distribution of drug across the layers. Therefore, both microstructural and loading variances between multi-layers with porosity gradient can be used to tune the properties of the coating materials to obtain the desired drug release profile for a given application.

Figure 2. Illustration of the biocompatible implant showing a porous biomaterial of successive layers of various porosities and dual gradient composition in between 2 meshes.

Nanofibers used in the porous multilayer stack can be obtained by electrospinning, which is the method of choice to produce fibers. Electrospinning uses electric force to draw charged threads of polymer solutions or polymer melts up to fiber diameters in the order of nanometers. The process does not require coagulation or high temperatures to produce solid threads from solution. This makes the process particularly suited to the production of fibers using large and complex molecules. Electrospinning ensures that no solvent can be carried over into the final product. Depending on the size of the collector, large areas of membranes can be obtained. Electrospinning have been used for medical purposes. The electrospun scaffolds made for tissue engineering applications can be penetrated with cells to treat or replace biological targets. Nanofibrous wound dressings have excellent capability to isolate the wound from microbial infections. Other medical textile materials such as
sutures are also attainable via electrospinning. Through the addition of a drug substance into the electrospinning solution or melt diverse fibrous drug delivery systems and transdermal patches can be prepared.

4.2. Mesh Structure and Function

To increase osseointegration, meshes are designed with an open structure and coated with biocompatible materials such as hydroxyapatite, titanium materials and compounds, synthetic resins, bone cements etc. Surface modification of medical devices, such as cranial implants made of titanium mesh, can be applied to help induce the process of osseointegration. There are many clinical cases where the osseointegration process of Ti and its alloys is not enough but an osseo-inductive behaviour of the implant surface is required, especially when rapid healing or bone quality and/or bone quantity is mandatory. Several strategies have been investigated; some of them are based on the bioactivity approach (i.e. hydroxyapatite precipitation induced “in vivo”) and other are based on osteoblast stimulation through surface roughness. For Ti and its alloys, the bioactive behaviour can be obtained by applying a layer of foreign material such as apatite or a bioactive glass using electrochemical processes such as anodic oxidation, or surface chemical treatments in acids or oxidative media. A classification of bioactive surfaces can be done according to the mechanism of bioactivity, which can be related to ion exchange process with the body fluids and/or with the effects of the topography of the surface of the prosthesis at micro and nano scale. Currently, the clinical demand has been oriented towards multifunctional surfaces, which are capable of simultaneously providing a specific response due to both colonization by different bone cells such as osteoblasts, fibroblasts, macrophages, and colonization with infectious agents such as bacteria and viruses.

Polymethyl methacrylate (PMMA) can be reinforced with titanium mesh to increase its mechanical strength but also to increase the osteo-conductive properties of the titanium mesh. PMMA is a synthetic resin produced from the polymerization of methyl methacrylate, was first used in medicine in the 1960s and is a polymerized organic combination of acrylic acid, transparent and easy to shape and. During the polymerization, the material solidifies in a short period of time, making it suitable for use in surgical procedures. The viscosity of the mixture increases rapidly, therefore the surgeon must model the cranial prosthesis in a very short time, which is why PMMA is suitable only for modeling small-sized cranial prostheses. In medical applications, however, we must take into account the chemical toxicity of the methyl methacrylate monomer but also the exothermic polymerization reaction to obtain PMMA. After polymerization, the low elasticity, but also the low resistance to mechanical stresses, makes PMMA susceptible to fracture under high mechanical pressure, which results in the production of particles by rubbing PMMA with a hard material surface. Thus, PMMA particles can provoke a cellular inflammatory response that can lead to osteolysis. This phenomenon is known as “cement disease”. In order to improve the X-ray or CT examinations, zirconium dioxide can be added to PMMA. The most important advantages of PMMA are: transparency, ease of modeling, mechanical properties and low price. PMMA is well tolerated by the body so that immediately after implantation, fibrous tissue will develop at the interface between the material and surrounding tissue, and the osseointegration process will begin with a host reaction. The body's immune response is expressed both locally and systemically by activating macrophages.

In neurosurgery, PMMA is used in stabilizations and replacements of the vertebrae, but also in cranioplasty, either in the form of cement or in the form of solid pre-molded prosthesis. Thus, for small defects in the vertebrae or in the skull, the cement is prepared and molded intraoperatively, then fixed by the surgeon. For large skull defects, the preformed solid prosthesis should be very well sized and designed based on the patient's imaging results.

In addition, the use of PMMA cement is limited by the increase in temperature during polymerization, the toxicity of the liquid monomer and the reduction of vascularization at the interface between the material and surrounding tissue after implantation. In spine surgery, these factors can promote bone resorption, followed by failure of the procedure, while in cranial neurosurgery, increased temperature can affect surrounding tissues, causing even thermal necrosis of the healthy
bone, thus affecting the nervous system. When PMMA is used in cranioplasty, the cranial prosthesis can be obtained by different methods such as modeled by hand during surgery, prefabricated or obtained intraoperatively using modern design methods. In the first case, the modeling of the cranial prosthesis by hand by the surgeon, intraoperatively, is a method used only in the case of very small size defects with relatively regular margins. In this case, no special tools are needed for cranial reconstruction. The surgeon models the prosthesis, then, after it is hardened, fixes it inside the cranial defect. The second situation is specific for larger head defects. In this situation, the prosthesis is performed before surgery, based on imaging investigations. Intraoperatively, the prefabricated prosthesis can be adjusted by the surgeon and then fixed by the patient's skull. The third situation involves the use of modern computer-aided design techniques, but also the use of a 3D printer. The prosthesis thus obtained is used as a mold for the prosthesis that the surgeon will model intraoperatively. After the material hardens and the prosthesis is to be implanted, holes are made at its periphery. The prosthesis is then placed inside the intracranial defect, and then fixed by the skull through suture threads. This technique is used especially for large skull defects with irregular edges. The prosthesis made in this way, by using the modern means of design and printing, will perfectly cover the cranial defect, the aesthetic result being clearly superior to the other two mentioned methods. The mesh made of titanium has been used as a support for PMMA placement, thus reducing the fracture potential of PMMA, especially in large-scale reconstructions of the skull cap. In addition, the base network may allow the intracranial prosthesis to be embellished when using PMMA.

Hydroxyapatite (HA) can also be used to impregnate the titanium mesh, in order to increase the osteoconductive properties of the titanium mesh. Hydroxyapatite is a calcium phosphate stable in aqueous media, with the chemical formula Ca10(PO4)6(OH)2. HA contains approximately 40% calcium and 18.5% phosphorus (as a percentage by mass). The Ca/P ratio of hydroxyapatite is 1.667, which is an important indicator used to evaluate different processes for obtaining this material. It is known that about 70% of human bone is made from a non-stoichiometric form of hydroxyapatite, so that this material can be considered as an ideal bone replacement. Bone apatite contains the following elements: magnesium 0.7% wt, sodium 0.9% w; potassium 0.03% wt, chlorine 0.13% wt, fluorine 0.03% wt, trace elements: Sr²⁺, Pb²⁺, Zn²⁺, Cu²⁺, Fe²⁺.

Hydroxyapatite has no cytotoxic or carcinogenic effect on the human body. It is characterized by high calcium content and high biocompatibility with regard to soft and hard tissues. For this reason, intracranial prostheses made of this type of ceramic material, can be used in direct contact with the bone. Also, the structure of synthetic hydroxyapatite may be similar to that of natural bones. By different manufacturing methods the size and number of pores can be controlled in the case of porous HA. The porous surface of the intracranial prosthesis can be covered by the new bone tissue that forms at the interface, which allows for a strong and lasting connection between the bone and the prosthesis. Currently, various forms of porous hydroxyapatite are available that are used either to repair bone defects or to support bone tissue regeneration in the human body. The solubility of HA is also a very important parameter, as these materials are designed to fill cavities or to be embedded in the surrounding bone tissue. This solubility depends on several factors such as i) the pH and solvent type (hydroxyapatite is insoluble in bases, but soluble in acids), ii) in potassium, sodium, magnesium and strontium salt solutions it dissolves better than in distilled water according to the following order Sr>Ba>Mg>Na>K, iii) the presence of amino acids, proteins, enzymes and other organic compounds. The solubility of HA under "in vivo" conditions is highly dependent on the degree of crystallinity, the size of the crystal, the amount of crystalline defects, stress level and porosity. Intracranial prostheses made from porous hydroxyapatite dissolve faster than densely structured prostheses due to the larger contact surface. Hydroxyapatite is manufactured and used in medicine both in dense and porous forms, as well as in granules and powders. The production process consists of several stages including obtaining powders, making prostheses, compaction and sintering, final treatment (sharpening the sharp edges), sterilization and packaging. In the process of manufacturing intracranial prostheses, antibiotics, growth factors and hormones or other cell types (drug delivery, cell cultures) may be introduced.
However, the HA geometry, the porosity and the substitution network remain the most important features involved in the healing process of bone defects. These properties have been tested on animals. In order to evaluate the biological properties of the non-stoichiometric form of hydroxyapatite, cell cultures were evaluated in terms of their chemical composition. Following the evaluation it was observed that hydroxyapatite with high carbonate content increased the activity of the osteoclasts, which suggests that bone resorption (the phenomenon underlined by the activity of the osteoclasts) is directly influenced by the functional groups incorporated in the crystalline hydroxyapatite network. Another conclusion relates to the substitutions of fluoride ions, which stimulate cell proliferation. However, there are some major disadvantages of hydroxyapatite, represented by its fragility that is specific ceramics, by the reduced resistance to stretching and by the high risk of infection after surgery. Larger bone defects can be difficult to repair with hydroxyapatite, due to the reduced osseointegration process and structural changes that occur in contact with the cerebrospinal fluid.

Titanium mesh can also be impregnated with calcium phosphate. Calcium phosphate is the main component of human bone and has been used since the 1890s to stimulate bone regeneration. However, positive results were obtained only in 1920, when Albee discovered that tricalcium phosphate stimulates bone formation. In the 70’s, it was discovered that the bioglass, i.e. glass containing calcium phosphate and hydroxyapatite ceramics, are osteoconductive. From that moment, calcium phosphate was widely used in medicine, in the research of novel medical prostheses and coatings.

The most used calcium phosphate ceramics include hydroxyapatite, tricalcium phosphate (TCP) and mixtures thereof (BCP - dicalcium phosphate). The dissolution behavior is the only important thing that differentiates them and implicitly the bioresorption rates. HA ceramics obtained from coral or synthetic apatite powder dissolve extremely slowly, compared to TCP ceramics which dissolve much faster. Although the TCP resorption rate is influenced to the same extent by both macrostructure and microstructure, TCP ceramics is considered a bioresorbable ceramic. These ceramics are characterized by a low mechanical strength, which is why their use in making prostheses is limited. However, they can be used to obtain cranial prostheses, but of small size. They are widely used as coatings for prostheses used in orthopedics but also for titanium nets used in cranioplasty. The metal matrix has the role of conferring the mechanical resistance necessary for the prosthesis, and the calcium phosphate comes with the osteoconductive properties that favor the process of osseointegration. HA, calcium phosphate cranioplasty prostheses are considered to have important regeneration and reintegration properties. For instance, Engstrand et al. [5] has shown that an intracranial prosthesis made of calcium phosphate was manufactured by a casting technique, sterilized and then surgically implanted. After approximately 50 months after surgery, a revision of this prosthesis showed that the prosthesis was integrated and a vascularization network was developed. Also, the histological examination revealed a compact bone that was in direct contact with the remains of inert ceramic materials.

In another embodiment, natural polymeric film encapsulating propolis nano-formulation for cutaneous wound healing can be used. Cavalu et al. [6, 7] produced collagen films containing propolis encapsulated in chitosan nanoparticles, for biomedical applications such as cutaneous wound healing. The vibrational marker bands of propolis were well preserved in the final polymeric mixture, indicating the stability of bioactive compounds upon the encapsulation procedure. The antibacterial effect depends on the nanoparticles concentration in collagen film, the effect being more evident with respect to E. coli than S. aureus, while the antioxidant capacity indicated a synergic effect of chitosan nanoparticles matrix and propolis extract, incorporated in collagen films.

4.3. Clamping System
Part of the biocompatible implant is the clamping device that helps place, fix and fasten the implant to the bone structure. More particularly, the clamping system provides a fast attachment of the biocompatible implant to the bone structure and a rapid placement of the three layers of porous material with different properties: i.e. the two meshes that promote osseo-integration of the implant
and one multilayer porous material loaded with bioactive compounds having a gradient composition to control the release of the drugs incorporated in the porous material.

The clamping system that allows fixing the biocompatible implant to the defect is presented in Figure 3. The clamps further allows fixation such that the implant is placed and remains in position when the holding force between the fastener and the implant is reduced. The implant may not be custom made pre-operatively; instead the meshes and the multilayered porous material may be cut on the spot to fit the anatomic shape of the defect. The clamp-like mounting piece is pre-assembled at the extended position in a fast and secure way to the bone, while the actual assemble of the successive layers is hold in place by the fastening mechanism. The main function of this system is to fix the medical device to the bone structure, and to support and connect the meshes used in the implant for remodelling and restoring bone tissue such as cranial implants. Mashes may have a flat or a convex/concave surface to fit the original shape of the skull. As illustrated in Figure 3, the clamping system consists of three pieces: the lower piece, the upper piece and the middle piece, as follows:

- **Lower piece** has a cylindrical part that sits on a support. The cylindrical part has a notch that corresponds to the exterior groove cut into the cylindrical part of the middle piece. The support of the middle piece has a knock on which the first mesh is placed.

- **Middle piece** helps adjust the height of the clamp to fit the thickness of the skull and supports the upper mesh. The middle piece has an external groove on the cylinder that helps adjust the height of the clamp. The bar that has the role to fasten the clamp to the bone structure.

- **Upper piece** fastens together the clamp to the bone structure and to the biocompatible medical device. The upper part has a lever and a knob that fix in place the clamp system. The upper lever comes over the upper mesh when the level is rotated to a closed position.

![Figure 3](image)

Figure 3. Illustration of the clamping system that can be used in cranioplasty containing 3 pieces that allow for placing and immobilizing the biocompatible implant.
4.4. Assembling the device
The attachment of the implant to the skull includes attaching the clamping system to the edge of the cranial orifice at different points, creating a base for attaching the lower mesh. First, the lower and the middle pieces are pre-assembled at the maximum extension length, and then mounted at the edge of the skull and then tightened up until it is secured at the edge of the skull. This is possible because both parts have a gear rack-like system that allows the two parts to be tightened up but do not allow them to move so that the assembly remains fixedly attached to the edge of the skull orifice. Then the first mesh is placed and hooked to the knock. The lower piece has a hook on the side of the support that is oriented away from the skull, which has dual roles, i.e. to fasten the clamp to the skull and to attach the first mesh. After the lower mesh is placed, the multilayered porous material can be placed on the first mesh. This layer has anti-microbial properties with slow release of the drug. Then the top mesh is placed and the upper piece is inserted and rotated to the ideal position for gripping and immobilizing the mesh.

![Figure 4. Illustration of the clamping system that fixes an implant in a defect in the skull containing 3 pieces that allow for placing, immobilizing, and rearrangement of the implant.](image)

In Figure 3, the attachment of the implant is irreversible, i.e. the implant is fixed in place Figure 4 present a similar configuration for the clamping system presented in Figure 3, but the implant is reversible such that the implant may be removed if complications, such as bleeding, occur. The additional key permits to lock and unlock the clamping system.

5. Conclusions
We presented a novel biocompatible medical device that includes both an implant and a clamping system. The device presents the following advantages: i) it decreases the surgical craniotomy time by simply pressing the clips and insert the plates; ii) the two meshes doesn’t have to be costumed made;
iii) the surgical procedure is more efficient due to the easiness of mounting operations including attaching the clips, laying the bottom mesh, laying the intermediate material, laying the upper mesh and fixing the upper mesh; the clamping system has a minimum height profile that helps to reduce the protrusions; iv) the clamping system does not involve any invasive procedure for clamping the implant, such as drilling and screw clamps; v) easy placement of the gradient loaded multi-layered porous material in between the meshes; vi) a good contact interface of the upper mesh at the surface of the skull.

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