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ScienceDirect

Procedia CIRP 110 (2022) 249–254

www.elsevier.com/locate/procedia

V CIRP Conference on Biomanufacturing

A new generation of highly customized Mg alloy-based implants

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Abstract

In the last years, the precision and personalized medicine is pushing the biomedical research efforts towards the direction of implant surgery requiring only 1-step approach: this goal has been achieved after the introduction of resorbable implants. The resorbable prosthetic support is indicated for temporary prosthetic applications, such as bone fractures fixation, or all those conditions usually treated with metal implants then removed with a second surgery, just after the healing of the bone defect. Biodegradable, bioactive and customizable implants for the treatment of bone fractures, both efficient in bearing the functional loads, and showing good biocompatibility and degradation properties matching the bone tissue healing, are still lacking. These premises have led to consider Magnesium (Mg) and its alloys as very promising candidates for the development of temporary, resorbable implants. However, the very high corrosion rate of Mg is the main problem, not yet solved. The material needs to be properly treated/coated, as well as manufactured, in order to design the most suitable duration of the temporary prosthesis permanence in situ. An innovative and interdisciplinary approach has been developed within the M.Era-Net ISIDE project and it is here briefly detailed with a special focus on the highlighted application fields.

Keywords: Reabsorbable implants; Mg alloys; customade prostesis.

1. Introduction

In the last years, the demand of implants has grown significantly, due to an increasing outbreak of bone pathologies. In the specific context of cranial and maxillofacial prosthesis, the market is expected to reach US$6.54 billion by the end of 2025 and it is supposed to increase considerably if implant removals and second surgeries are considered as well [1].

10.1016/j.procir.2022.06.045

Traditionally, materials such as stainless steel or titanium have been employed in the production of implants for reconstructive surgery due to their biocompatibility, mechanical strength and fracture toughness. Recently, due to some negative aspects arisen after implantation [2,3], including the release of metal particles during the corrosion process [4,5], the attention was focused on Magnesium (Mg) alloys for the development of temporary implants [2,6], mostly when the bone repairing or regeneration has to be guaranteed. In fact, within the regenerative medicine, the use of bioresorbable implants has become a growing priority; at the same time, the attention has to be focused on the corrosion resistance of the material itself, because the corrosion rate may depend on several overlapped co-factors, such as the biological environment the implant is in contact with. Mg alloys are characterized by a very high corrosion rate [7,8]; therefore, it is important to develop a substrate able to slow down it, in order to have a control on the biodegradation process, and to contemporaneously improve the surface functionalization with bioactive coatings able to ensure the local releasing of therapeutic molecules with an effective and controlled kinetics.

Concerning the techniques used to control the biodegradation of Mg implants, the introduction of alloying elements can contribute to improve the mechanical properties by solid solution strengthening, precipitation hardening and grain-refinement strengthening, through heat and mechanical treatments [9]. The corrosion rate is also affected by the composition of bulk alloy and, in general, the Mg surfaces need to be treated before any biomedical application, in order to limiting their resorption rate. Other methods used for increasing the corrosion resistance consist in covering the material surface with Ni-plating, and in preparing active or passive coatings [10]. Different treatments have been developed during the last years for improving the surface properties of implanted biomaterials, and therefore their ability to promote the osseointegration. The most used is the application of stoichiometric hydroxyapatite (HA); however, the so-treated material is then characterized by a long deterioration time [11]. Recent studies have shown that the bioactivity of HA may be enhanced by the incorporation of Si in the HA lattice [12,13], but just in case of soft tissue. Other coatings can include the main macromolecules belonging to the local extracellular matrix (ECM), such as proteins, specific peptide sequences or glycosaminoglycans (GAGs) [14], which can prevent the occurrence of inflammatory reactions, local infections or unbalanced coagulation processes [15].

The aim of this study is to design and manufacture a customized prosthesis perfectly fitting the bone defects developed in several anatomic districts, by means of innovative processes. Briefly, this study aims to propose a workflow able to: (i) reduce the risk of the implant's failure (mostly due to infections or osteointegration issues) thus, consequently, ensuring a successful healing of the bone defects; (ii) avoid a second surgery that certainly represents an issue for the patients and a cost for the healthcare managers. The latter issue represents a big challenge; in fact, the implant removal following the tissues/bone healing, represents a redundant surgical procedure that has the effect to increase both the patient's morbidity, and the duration of hospitalization, with a severe impact on biological and healthcare costs [6,16].

To reach this ambitious aim, a resorbable material, the Magnesium, has been here investigated. More in detail, suitable metal sheet forming processes have been adopted in order to shape the temporary implant, so that it can correctly fit the patient's anatomy. The implant surface can be functionalized to get the optimal characteristics in terms of corrosion, degradation rate after implantation and biological behaviour.

2. Case study definition

Nowadays, the bioabsorbable implant is a biomedical tool commonly used in orthopedics and maxillofacial surgery as safe and suitable alternative to the conventional fixed devices. Although the latter type of implants provides more stability, they are characterized by the strong limitation for the need of a surgical removal. Since the introduction of polylactide plates for mandibular fractures, bioabsorbable materials have been used to treat bone fractures in adults and children [17,18]. In recent years, the market for bioabsorbable materials has increased, as well as their field of application, due to the not negligible positive aspects for patients and surgeons.

During the last 10 years, the only studies on Mg alloys for biomedical implants focused on screws for forefoot applications [19]. In the ISIDE project, carefully described in this work, a new clinical application has been investigated: the zygomatic region, a highly aesthetic zone. Several studies investigated the anatomic and functional success of bone fixation in orbital-zygomatic-maxillary (OZM) fractures. Typically, the use of three-point fixation with titanium (mini)plates has been reported in the literature; nevertheless, the use of bioresorbable devices has gained growing interest in such aesthetic regions, to limit the potential postoperative complications and to reduce the surgeons looks into the surgical site [PMID: 15785282]. In this landscape, the ISIDE project has been consequently focused also on the zygomatic area.

More in detail, an artificial damage in the cheekbone area has been simulated on a human skull simulacrum by producing a small size defect, which was obtained via drilling, as depicted in Fig. 1.

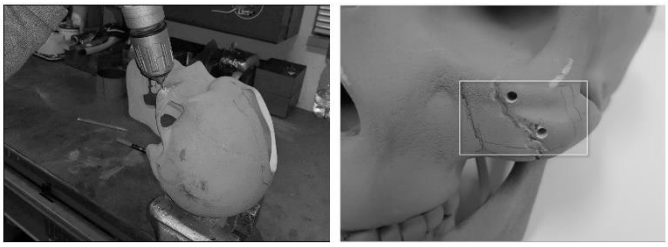

Fig. 1. Artificial reproduction of a damage on a human skull simulacrum.

A micro-CT of the simulacrum was also performed for obtaining the virtual geometry of the skull. On the virtual CAD of the skull (Fig. 2a), the damage area (Fig. 2b) was highlighted for the necessary design of the customized prosthesis.

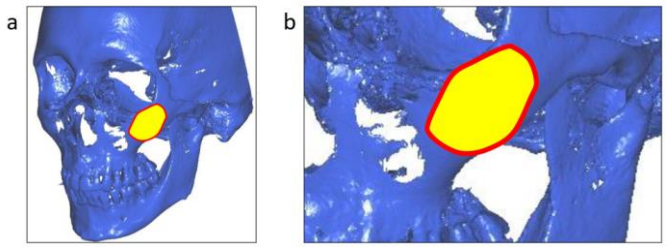

Fig. 2. (a) 3D CAD model of the skull; (b) highlight of the damaged surface.

3. Methodology

3.1. Mg alloy and bio-functionalization

The material considered in this project is the AZ31B Mg-alloy, containing 3% of Al and 1% of Zn as the main alloying elements (its chemical composition is reported in Table 1); the letter B indicates that AZ31B is the second standard alloy according to the American Society for Testing and Materials (ASTM).

Table 1. Nominal composition (wt.%) of AZ31B according to [20].

Al	Zn	Mn	Ca	Cu	Fe	Ni	Si	Mg
2.5-3.5	0.6-1.4	0.2-1.0	<0.04	<0.05	<0.005	<0.005	<0.1	BAL

The mechanical properties of the investigated Mg alloy measured from specimens fabricated by rolling are reported in Table 2:

Table 2. Mechanical properties of AZ31B [21].

Density	Young's modulus	Young's modulus	Yield strength [0.2%]	Tensile strength
1738 kg/m3	44.8 GPa	44.8 GPa	145 MPa	255 MPa

The investigated alloy has a proper corrosion behavior that results fast if measured with respect to the specific application field. The surface morphology alteration of AZ31 sample immersed in orthophophoric acid (OPA) and NaCl solution for 21 days is reported in Fig. 3.

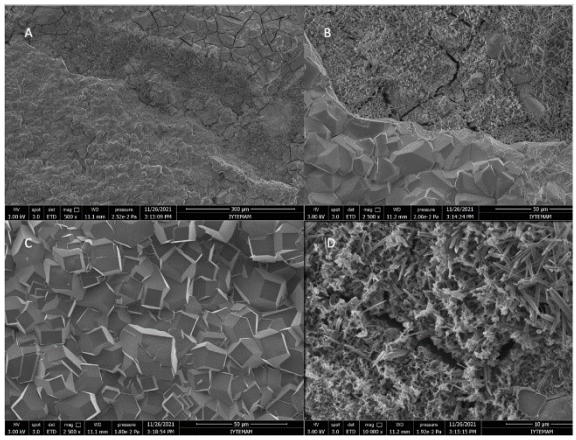

Fig. 3. Surface morphology of AZ31B sample immersed in orthophosphoric acid (OPA) and NaCl solution for 21 days (A) 500X, (B) 2500X, (C) 2500X, (D) 10000X.

The poor performance in terms of corrosion behavior of this Mg alloy will be exceeded by employing specific coatings on the external surfaces. Moreover, the tailored corrosion behavior and the bio-functionalization of implant surfaces will be targeted by multi-layered coatings obtained by means of innovative procedures, like for example the development of surface-binding peptides, able to be further decorated with drugs, molecules, or biological agents (e.g. stem cells homing). These coatings will also be able to improve the antibacterial effects, the osteoinductive/osteoconductive processes, and the proper osseointegration (e.g. osteogenesis promotion); the control of corrosion phenomena due to novel biomaterials used in ISIDE are currently under investigation. Based on the specific target of implants, the innovative coatings will be then chosen, prepared and optimized following different routes, such as the biological one (i.e. peptide binding and antibiotic coating), the physical one (i.e. sputtered bioactive coating) and the chemical one (i.e. in situ conversion via acid-base reaction for achieving high coating stability/adhesion with the base metal substrate).

In detail, the development of novel antibacterial coatings able to prevent bacterial infections (molecules acting on bacterial wall and adhesion) and/or to treat initially developed infections (molecules against anaerobic bacteria) in order to drastically reduce the implant failure is one of our main outcomes. Then, the development of peptide layers for tethering the antibacterial properties, by immobilization and controlled release or the development of an in situ forming Mg phosphate cement coating for self-passivation of the alloy could be chosen. Finally, another option under investigation is the preparation of bioactive coatings by magnetron sputtering technique, which will greatly improve the performance of the implant in terms of osseoinduction, and decrease Mg alloy dissolution rates, due to the inorganic additives (Mg or MgSi) in the structure of HA coatings, in both crystalline and amorphous phases. These innovative products will be applied to bone implants and to all the prosthetic components that are typically used in cranio-maxillofacial applications, like the cheekbone prosthesis chosen as case study.

3.2. Resorbable prostheses design

The design of custom resorbable prostheses is a complex, time-consuming task, even critical for the success of the final implant surgery. In this work, an efficient and optimized procedure has been developed and proposed. The schematic flow of the whole procedure is reported in Fig. 4. The starting point of the prosthesis design is the computed tomography (CT) scan of the region of interest (ROI), which includes the bone defect and the surrounding zone.

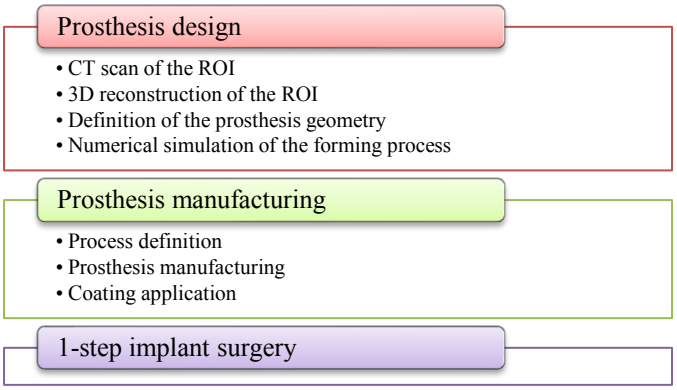

Fig. 4. Schematic overview of the whole process for design and manufacturing of resorbable prostheses.

The first output is the Digital Imaging and COmmunications in Medicine (DICOM), which is being manipulated to obtain the 3D model of the bone, including its defect. The resulting Standard Triangulation Language (STL) file format of the ROI is then imported in a CAD software for the definition of the prosthesis geometry. The virtual 3D model in the CAD environment of the ROI allows, firstly, to reconstruct the bone defect and, subsequently, to define the prosthesis geometry as shown in Fig. 5 for the identified case study, i.e. a cheekbone prosthesis.

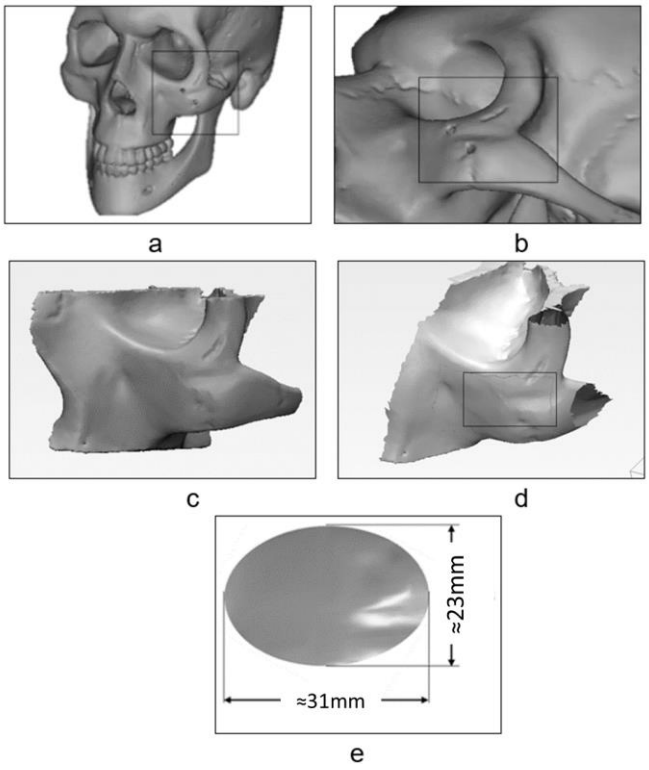

Fig. 5. Prostheses geometry determination:(a) CAD model from DICOM, (b) CAD model repaired, (c) final shape, (d) extracted ROI, and (e) final prosthesis geometry.

The prosthesis geometry was finally used for designing the two sheets metal forming processes investigated in ISIDE: namely, Single Point Incremental Forming (SPIF) and Superplastic Forming (SPF).

Due to the large number of parameters involved in both the processes, the prosthesis manufacturing was designed by means of a Finite Element (FE) based approach.

In particular, in the case of the SPIF process, the appropriate tool trajectory was validated starting from the tool path coming from the CAD/CAM with the aid of FE simulations performed by the FE commercial code Abaqus/CAE. In detail, the blank was modelled as a deformable body with S4R elements and 5 integration points along the thickness, whereas the tool was modeled as a rigid body (R3D4 and R3D3 shell rigid elements). The periphery of the blank was pinned. The contact was modeled using the Surface-to-Surface algorithm, setting a Coulomb friction coefficient equal to 0.1 between the tool and the blank. Finally, the numerical problem was solved with the implicit integration scheme. Fig. 6.a shows the modeled assembly for the SPIF simulation.

Similarly, the SPF process was simulated using the FE commercial code Abaqus/CAE. Starting from the geometry shown in Fig. 5, the SPF die was created and modelled as a rigid body whereas the blank as a deformable shell body (for the sake of clarity, only half of the modelled system is reported in Fig. 6.b). The material behavior was modelled according to the constitutive equation proposed by Backofen, whose constants were analytically calculated [22] from the alloy characterization based on free inflation tests [23]. The outer region of the blank was pinned to properly simulate the action of the blankholder during the forming. An Abaqus internal subroutine was used to calculate the gas pressure profile in order to keep the applied strain rate close to the optimal value.

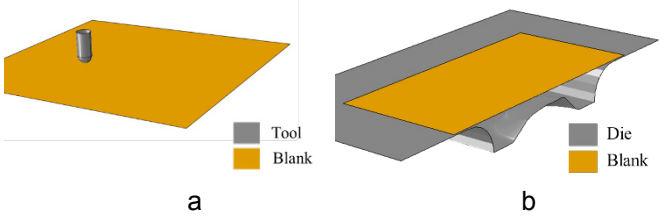

Fig. 6. FE-based process design: (a) SPIF and (b) SPF.

4. Prototyping

This section deals with an overview of two different routes for prototyping the same cheekbone prosthesis via sheet metal forming, i.e. SPIF and SPF, whit a focus on the manufacturing operations. In both cases, after the forming process, the most suitable implant coating is applied.

4.1. SPIF

The above-described cheekbone prosthesis was produced by SPIF using a hemispherical head punch tool with a diameter of 6 mm and a step depth of 0.05 mm. The SPIF process was carried out on a Mazak Nexus 410 milling machine equipped with a heating chamber able to heat the sheet up to 250°C during the forming process, being kept constant for the required process time. A feed rate of 0.5 m/min and a spindle speed of 4000 RPM were used. A D321R Molykote spray was employed as lubricant. The final geometry of the prostheses was cut with the same milling machine by using a milling cutter with a

diameter of 4 mm. Fig. 7 shows the equipment for the SPIF manufacturing process.

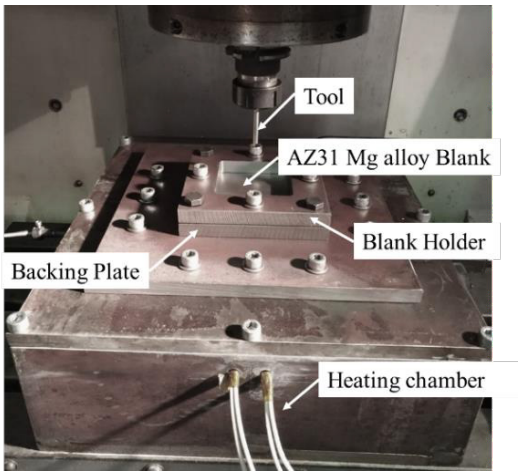

Fig. 7. Equipment for the SPIF manufacturing process.

Finally, the prosthesis was cleaned with cotton wool soaked with acetone before additional cleaning in deionized water for 10 min in an ultrasonic bath at room temperature.

4.2. SPF

Experimental SPF tests were carried out on a 250 tons electro-hydraulic press machine, equipped with heated tools (maximum temperature equal to 1000°C, see Fig. 8.a) whose temperature was regulated by a PLC. The die was composed of a massive metallic frame and an expendable ceramic insert in order to reduce the manufacturing costs (Fig. 8.b) [23]. Once the test temperature (850°C) was reached, the tools were slightly opened and square blanks (150 mm edge) – previously sprayed with graphite to avoid sticking with the tools' surfaces – were positioned between them and clamped setting a Closing Force equal to 490 kN to prevent any material drawing during the forming process. Mg blanks were deformed under the action of Argon gas which was inflated according to the pressure profile calculated by means of the FE simulations in order to keep the strain rate experienced by the material in the range able to emphasize the superplastic behavior of the investigated Mg alloy.

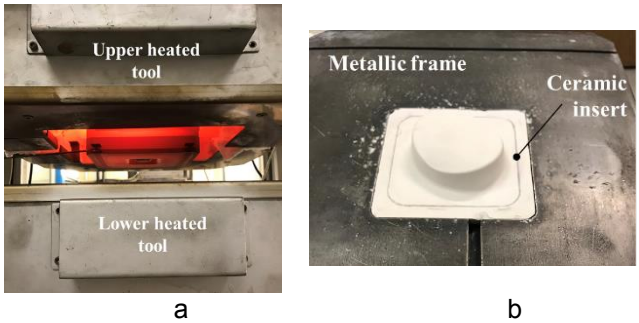

Fig. 8. (a) SPF press machine: details of the ceramic insert and (b) the heated tools.

5. Experimental outcomes

Both the processes investigated in the present work have confirmed to be suitable for producing custom made resorbable prostheses, made by AZ31B Mg alloy. The samples obtained at the end of the SPIF and SPF processes are reported in Fig. 9.

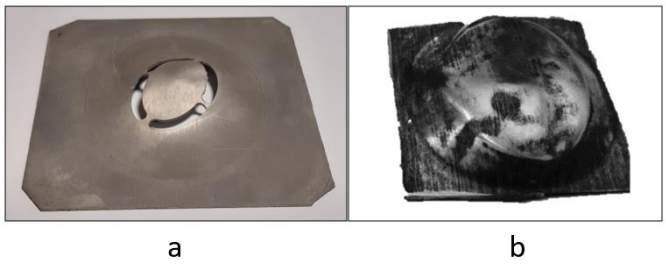

Fig. 9. (a) Prostheses produced by SPIF and (b) SPF.

The post-forming characteristics of the two prostheses obtained by SPIF and SPF were evaluated in terms of Shape Accuracy (SA), average thickness, and Surface Roughness (Ra).

The evaluation of SA, which quantifies the process capability to reproduce in the best way the target shape, was performed using a 3D laser scanning system and quantified by means of the measurement of Root Mean Squared Deviation (RMSD). Furthermore, the roughness measure (Ra) was performed by the Mitutoyo Surftest SV1000 (resolution: 0.001mm; accuracy equal to ±2 µm +2L/100, being L the traversing length), as well the average thickness (t_{ave}) was so measured. The obtained values for both the prostheses are reported in Table 3.

Table 3. Outcome measures.

	RMSD	Ra [µm]	t_{ave} [mm]
SPIF	0.1002	4.84	0.94
SPF	0.0809	2.57	0.57

The overall accuracy reached by the experimental investigation is reported for both the prostheses in the subsequent Fig. 10 where the geometrical error is graphically reported.

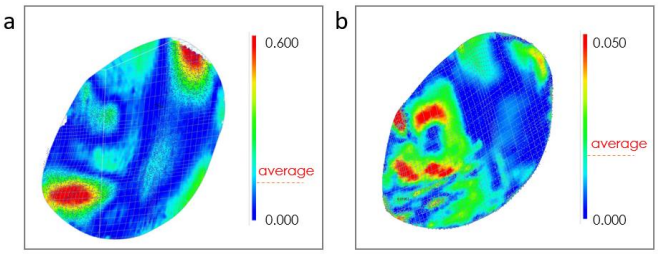

Fig. 10. Geometrical precision measured overlapping the skull and the manufactured (a) SPIFed and (b) SPFed prosthesis.

6. Conclusion

Beyond the above-mentioned results, some highlights need to be pointed out:

- the proper initial prostheses design allows the prototyping of an accurate device, both for SPIF and SPF. More specifically, the application of the customised procedure allows to reduce the conventional SPIF inaccuracy, thus obtaining a good precision for both the investigated processes, as highlighted in previous Fig. 10;
- for both for SPF and SPIF techniques, the manufactured surfaces present high values of roughness, which could represent a problem for the fast corrosion of the sample; the presence of irregularities on the surface are points where the corrosion mechanism could start quickly, thus reducing the service life of the prostheses;
- while the prosthesis produced by SPF device is more homogeneous, the one produced by SPIF present a dissimilar roughness between the inner and the outer surface (the outer is smoother than the inner); for the biomedical application, such a result represents a further point that needs deeper investigations;
- SPF process returns a thinner implant that, in terms of corrosion behaviour, penalizes the whole service life of the device; this aspect should be properly considered during the prosthesis design, including an initial thickness over-compensation;
- for both implants, the subsequent prostheses functionalization is mandatory to compensate the highlighted drawbacks.

Acknowledgements

The activities in the present work are based on the activity of ISIDE project which is funded by the European framework M-Era.Net by specific regional office of the involved Country.

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