Development of Biomimetic Systems for the Treatment of Traumatic Brain Injuries

Student: Alessia D'Andrea

Department of Engineering, PhD level, INSTM RU,
Niccolò Cusano University, Via Don Carlo Gnocchi 3, 00166, Roma, Italy
alessia.dandrea@unicusano.it

Mentor: Ilaria Cacciotti

Department of Engineering, INSTM RU,
Niccolò Cusano University, Via Don Carlo Gnocchi 3, 00166, Roma, Italy
ilaria.cacciotti@unicusano.it

Abstract. *Traumatic Brain Injuries are very common and have been treated with a variety of approaches over time. In this context, skull repair has been attempted with several materials, which need to show appropriate mechanical and biomimetic properties. Among the most interesting materials for cranial implants, polymers represent a valid alternative, because of their low cost, the many manufacturing options and their easy functionalisation.*
In this work, we focused on poly-lactic acid implants produces by Additive Manufacturing, namely through the Fused Deposition Modelling technique, and functionalised through a bio-ceramic coating to promote bone regeneration. We also developed a Drug Delivery System in order to prevent inflammation phenomena: in particular, we engineered poly-ε-caprolactone microparticles encapsulating a glucocorticoid (dexamethasone) for a regulated drug release. This Drug Delivery System has been implemented into the implants to confer optimal characteristics to the 3D-printed prosthetics.

Keywords. Biopolymers, glucocorticoids, microparticles, 3D-printing, drug delivery system, traumatic brain injuries

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1 Introduction

A Traumatic Brain Injury (TBI) is caused by a bump, blow, or jolt to the head, or a penetrating head injury that disrupts the normal function of the brain [1].

After the evaluation and resolution of medical issues such as swelling, haemorrhage and brain damage among others, cranial reconstruction is of the utmost relevance for reinstating a physical barrier and preventing or controlling alteration in the cerebrospinal fluid, the blood flow and the metabolic demands of the brain [2].

Cranial reconstruction has been performed by using several materials over time, among which bones from the same patient (autograft), bones from cadavers (allograft), bones from animals (xenograft) and inorganic materials such as metals (cranioplasty).

At the moment, the most used materials for cranioplasty are titanium and poly-methyl methacrylate (PMMA) [3]. Both of them present several advantages, among which the tailorable features, the good mechanical properties and the absence of significant negative reaction by the immune system after implantation.

Nonetheless, both of the materials listed above also present drawbacks (as do all the possible substrates for cranial reconstruction). Among those downsides are the cost and conductivity of titanium, together with its tendency to produce artefacts during imaging, and the high risk of fragmentation and degradation of PMMA [4]–[6].

For these reasons, efforts are continuously made in the biomedical field in order to improve the characteristics of cranial implants.

In particular, following the biomimetic approach (aimed at mimicking the composition and microstructure of the bone tissue to regenerate), it is important to formulate composite materials, based on organic and inorganic materials, and to appropriately engineer structures characterised by hierarchic porosity. As a matter of fact, the extracellular matrix of the bone tissue is composed of hydroxyapatite nanoparticles and collagen fibres, and presents a hierarchic organisation [7]. The combination of a selected biopolymer and calcium phosphate oxides or other ceramic materials would therefore allow to obtain comparable properties to those of the bone, as would the engineering and production of 3D structures through Additive Manufacturing (AM) techniques followed by proper functionalisation of the prototypes. This work aims at overcoming the limits of the traditional approaches, tackling the issue by functionalising 3D-printed biopolymeric structures with appropriate bioactive substances.

The chosen biopolymer for the AM of the structures in this work was poly-lactic acid (PLA), characterised by biocompatibility, biodegradability, ease of manipulation and printability by Fused Deposition Modelling (FDM) [8]. Despite that, it is not capable of mimicking the properties and functionalities of the bone, and can be characterised by the induction of inflammation and/or infections. Therefore, one of the aims of the project was to devise an effective strategy for the deposition of a bioactive ceramic coating (titania or hydroxyapatite) on PLA 3D-printed structures, in order to improve their performances and the potential applications in the bone regeneration field (Figure 1). Another objective was to provide anti-inflammatory properties to the produced structures, loading them with glucocorticoid drugs, due to their well known ability to avoid/reduce the inflammation occurrence.

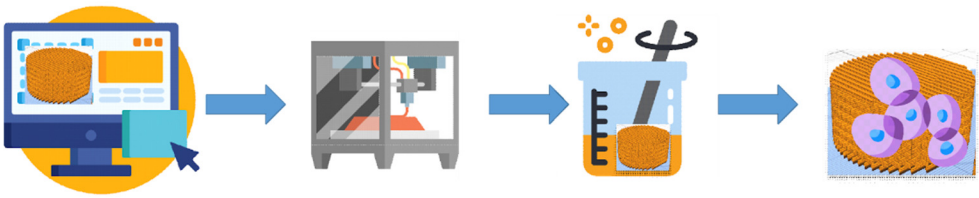

Figure 1. Functionalisation of 3D printed scaffolds: from the design to the biological characterisation.

2 Materials and methods

In order to optimise the 3D-printing of PLA structures, different FDM conditions in terms of extrusion and bed temperatures, and printing speeds, were tested, as well as different patterns and porosities. Moreover, an effective procedure for coating the 3D printed structures with hydroxyapatite (HAp) or titania was set up. To provide anti-inflammatory properties, selected glucocorticoids, e.g. dexamethasone, were immobilised on the scaffolds surface, both free and encapsulated within bio -polymeric microparticles, produced by emulsion.

The obtained structures were characterised by observation at the scanning electron microscopy (SEM);, as well as by uniaxial tensile tests and differential scanning calorimetry (DSC) measurements.

3 Results

The printing parameters of the PLA structures were optimised by trial and error. In particular, the chosen nozzle diameter was 0.2 mm in order to ensure good precision, and two different hierarchic patterns with fixed measures were selected, one with triangular and one with square pores. Other parameters, such as the nozzle and bed temperature, were assessed on the basis of the overall quality of the finished prototypes. The measures of the pores in the structure were chosen to best host cells.

The 3D-printed structures were also characterised from a thermal point of view by Differential Scanning Calorimetry (DSC) and compared to the properties of the PLA filament before printing. The collected data showed slight but sensible variations (1-3 °C) for the glass transition temperature, the cold crystallisation temperature and enthalpy and the melting point and enthalpy. These pieces of information are coherent with the usual thermal changes implied by 3D-printing of the used polymer.

As for the mechanical properties, we were able to identify the stress and strain at break and the Young's modulus, which were all coherent with the literature values known for the PLA [9].

The coating on the PLA structures was attempted with titanium oxide and HAp by following different synthetic processes and coating techniques. The final results consisted in a mass increase of around 10% for the HAp and a much lower one for the titania, combined with a better overall homogeneity of the HAp coating. The samples were morphologically tested through SEM (data not shown).

In order to provide anti-inflammatory properties, specific glucocorticoid drugs were immobilised on the 3D printed structure surface, both free and encapsulated within bio-polymeric microparticles. A partial degradation of the printed structure was observed after its dipping within the corticosteroid solution, due to the PLA solubility in the used solvent. Following the second approach, it was possible to demonstrate the embedding of some particles within the printed PLA porosities, but further adjustments and tests are to be conducted on the implemented system.

4 Conclusions

This work is promisingly addressing the issue of cranioplasty through affordable, versatile means while also overcoming some criticalities of the field. The functionalisation of a low cost polymer, tailored for the cranial implants of the patients through simple approaches, is showing interesting results both on the matter of the anti-inflammatory properties and of the osteo-integration and bone regeneration properties. In the future, the work plan includes biological tests such as MTT assays, drug release tests and cellular differentiation tests, and further improvements of the whole system to better tune it for the intended purposes.

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