Sintesi

Every year millions of people around the world face serious medical complications due to tissues/organs damages/failure, still leading to death in a large number of cases. In fact, just in the European Union 21 patients die every day while waiting for an organ transplant. However, a chronic lack of donors is a global phenomenon with kilometric organs waiting lists; 150’000 patients were waiting for organ donation in 2018 just in the EU. The arrival of tissue engineering at the beginning of this century intended to give a solution to the problem, merging the principles of engineering and life science into an interdisciplinary field toward the development of biological substitutes able to replace, restore or maintain the tissue features. Hydrogels play a unique role within this field, thanks to their unique structure similarity with the mammalian extracellular matrix. Principally natural polymers-derived hydrogels formed by photopolymerization emerged in the last decades as a “greener” and sustainable option to create scaffolds. Indeed, while the natural sources origin and properties of natural polymers (often extracted from industrial wastes) are hardly reproducible in laboratory, the process of photopolymerization (especially performed with visible light) presents the physiological conditions of temperature, pH and solvent (aqueous, buffer or cell culture medium) necessary in biological applications. In this dissertation, a wide range of photocurable natural polymer-derived hydrogels are develop with applications in the tissue engineering field, exploiting both synthesis procedures and hydrogel characterization while pursuing, when possible, the creation of 3D-printed detailed geometries able to mimic the complex and intrinsic architectures characteristic of the human body. After a brief overview on the hydrogels state of arts and historical progress (Chapter 1), the photo-crosslinking process and technologies are exploited on Chapter 2. The first experimental investigation (Chapter 3) exploits a green and sustainable manner to synthetize a photocurable methacrylated chitosan through microwave-assisted organic chemistry (MAOS). The low reagent amount used, coupled with a relatively high degree of substitution achieved makes the process a sustainable alternative compared to traditional thermal synthesis, giving rise to stiff and biodegradable hydrogels employable on in-vitro investigations for lung tumoral cells models.

However, just simple extruded grids were 3D-printed in the aforementioned experimental chapter on methacrylated chitosan, due to a poor reactivity of the compound in water environments. Within Chapter 4, the additional contribution of a natural derived quinizarin dyes on the pristine formulation tune up the

methacrylated polysaccharide reactivity, enabling the creation of complex and detailed geometries with a DLP 3D-printer, both in terms of final structure resolution and CAD fidelity. Moreover, a biological characterization proved the maintenance of the hydrogels biocompatibility, favoring the implementation of the system toward the creation of scaffolds to be employed as substitutes for soft tissues applications.

Chapter 5 focus on the development of alginate hydrogels obtained through thiol-yne reactions. The reason of the study on "click chemistry" reactions reside on their shorter propagation rate of radicals, able to facilitate unintended cells necrosis behaviors. After incorporation of alkyne moieties on the alginate backbone with good results in terms of substitution, two different water-soluble dithiol crosslinkers were employed to create hydrogels through visible light photopolymerization. The subsequent biological characterization certifies the good biocompatibility of the system, validating the proposed direction for the development of surgical fillers/medical patches for tissue engineering applications.

A possible improvement to create photocurable hydrogel is presented on Chapter 6, where a fully modified alginate suitable for thiol-ene reactions was investigated. Apart for radicals, also a necrotic critical response to overwhelming chemical conditions done by small molecules can lead to an unprogrammed form of cells death, as in the case of the previous reported usage of dithiol crosslinkers. Within this chapter, various chemical approaches were investigated to synthesize two batches of ene/thiol-substituted alginate, resulting in the creation of the first thiol-ene hydrogel formed without the addition of external crosslinkers. The improved stiffness, as much as is good biocompatibility, asses the hydrogel employment in the creation of scaffolds for stiffer soft tissues, such as intestines or tendons.

Lastly, the incorporation of unmodified gelatin into a well-known biocompatible polymer (poly-ethylene glycol diacrylate) is the main focus of Chapter 7. In fact, natural polymers never possess intrinsic chromophore moieties suitable to create photopolymerizable crosslinked networks, so antecedent steps of synthesis are always required to make them processable with this technique. In this framework, an easy and low-cost way to chemically incorporate gelatin within the polymer network, without previous modification, demonstrate an interesting method to create substrates or models able to promote cell attachment and proliferation for in-vitro studies.