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Control and prediction of degradation of biopolymer based hydrogels with poly(ε-caprolactone) subunits

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ABSTRACT

Complex hydrogels consisting of natural and synthetic polymers, stabilized by combining different physical and chemical cross-linking methods, were assessed by *in vitro* degradation tests performed at 37 °C in phosphate buffer solution. Four biopolymer-based hydrogel series were comparatively evaluated as sponge or dense films as regards mass loss, morphology changes and thermal behavior over the fixed incubation period, considering as main factors of influence the composition, the adopted stabilization mode and the microstructure of the 3D construct. To facilitate the selection of the appropriate material for envisaged applications, matching the specific needs, the obtained data were used to generate an artificial neural network (ANN) model, able to establish correlations of the examined formulations and preparation parameters with mass loss. The comparison of experimental and calculated data showed that the developed ANN shows reasonable predictive performance ($r^2_{\text{training/validation}} = 0.99$).

1. Introduction

Recent biomedicine development focuses on multifunctional materials based on natural polymers, due to the unique advantages of abundance, and specific bio-characteristics of this class of macromolecules, *e.g.* structural similarities with the extracellular matrix (ECM), good biological performance, high chemical versatility, and enzymatically controlled degradability [1]. One of the most attractive options is collagen [2,3]. However, the use of native collagen as a biomaterial has a few drawbacks, mainly related to its origin, the difficulties to form it into complex shapes, lack of mechanical stability and fast degradability. Combination with other polymers and cross-linking are among the most used alternatives to adjust the properties of collagen-based biomaterials, matched to the targeted clinical application. In the case of collagen-based hydrogels the specific properties are prescribed by the intrinsic properties of the included polymers, the cross-linking characteristics (*i.e.* amount, type, and size of cross-linker), the microstructure, as well as the environmental conditions. These factors are also controlling the degradation behavior of the 3D material, which is essential for its use in functional tissue regeneration, for designing systems for the release of bioactive molecules or for parts of wound dressings. An often used solution to yield materials of tailored physical, biologic and mechanical properties, as well as a predictable degradation consists in the inclusion of poly(ε-caprolactone) (PCL) in the composition, taking advantage of the low *in vivo* degradation kinetics of this synthetic semicrystalline polyester, which allows to adjust material biodegradability to reach the desirable biologic response [4,5].

In an effort to design a 3D construct with improved integrity addressing these issues, we developed earlier some hybrid ECM-mimetic hydrogels based on biopolymers (atellocolagen – AteCol – combined or not with a hyaluronic acid – HA – derivative) cross-linked with a bifunctional derivative of PCL (long-range cross-linking) [6,7]. An improved control of biodegradability may be also obtained through a multiple cross-linking strategy [8]. Thus, to further stabilize the materials resulted as porous sponges or dense films, these were subjected to UV irradiation (short-range cross-linking). The inclusion of dimethylsilandiol hyaluronate (DMSHA) in some formulations was intended to improve the material bioactivity and its durability due to silanol action as a cross-linker and to HA ability to yield biocomposites with proteins through hydrogen bonding [9–11].

The objective of the present work was to study comparatively the degradation of the mentioned complex materials, considering the different levels of stabilization. The main factors governing

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