Alginate dialdehyde-gelatin bioinks exploiting internal gelation mechanism for cardiac tissue engineering

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Cardiovascular diseases are the leading cause of death worldwide. New resolutive therapies are highly demanded due to heart tissue limited regenerative capabilities. 3D bioprinted cell-laden constructs are a promising approach as *in vitro* models for new drug preclinical discovery and validation, in agreement with the 3R's principles.

Alginate (Alg)-based bioinks have been widely studied thanks to Alg cost-effectiveness and tunable features. Alg internal ionic gelation mechanism allows to obtain homogeneous self-standing 3D printed filaments without the use of support baths or post-printing crosslinking treatments. However, Alg presents no cell adhesion and poor *in vivo* degradability. The aim of this work was to combine Oxidized Alginate (ADA), Alg and Gelatin (Gel) to produce bioinks suitable for cardiac tissue engineering.

Firstly, Alg/ADA bioink composition was tailored varying polymer weight ratio and calcium ion to achieve cardiac tissue-like viscoelastic properties. Alg-ADA hydrogels showed a time-dependent shear thinning behavior suitable for 3D bioprinting, due to the gradual pH-triggered release of calcium ions over time. Moreover, Alg-ADA samples showed higher degradation rate (40% weight loss) compared to Alg samples (25% weight loss) after 21 days in PBS.

Gel incorporation into Alg-ADA was optimized to support Adult Human Cardiac Fibroblasts (AHCF) adhesion, producing shear thinning inks with tunable viscoelastic properties (G' 650-1300 Pa) and degradation profile (40-80% weight loss after 21 days in PBS) by varying Gel concentration. Alg-ADA-Gel showed good cytocompatibility *in vitro* according to ISO-10993-5. Finally, 3D AHCF-laden Alg-ADA-Gel bionks could be successfully printed and the samples with the highest gelatin content (25% w/v) allowed AHCFs adhesion after 24 hours of incubation, showing potential application for cardiac tissue modeling.

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