Photopolymerization of cell-encapsulating hydrogels: Crosslinking efficiency versus cytotoxicity

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Abstract

Cell-encapsulating hydrogels used in regenerative medicine are designed to undergo a rapid liquid-to-solid phase transition in the presence of cells and tissues so as to maximize crosslinking and minimize cell toxicity. Light-activated free-radical crosslinking (photopolymerization) is of particular interest in this regard because it can provide rapid reaction rates that result in uniform hydrogel properties with excellent temporal and spatial control features. Among the many initiator systems available for photopolymerization, only a few have been identified as suitable for cell-based hydrogel formation owing to their water solubility, crosslinking properties and non-toxic reaction conditions. In this study, three long-wave ultraviolet (UV) light-activated photoinitiators (PIs) were comparatively tested in terms of cytotoxicity, crosslinking efficiency and crosslinking kinetics of cell-encapsulating hydrogels. The hydrogels were photopolymerized from poly(ethylene glycol) (PEG) diacrylate or PEG–fibrinogen precursors using Irgacure® PIs I2959, I184 and I651, as well as with a chemical initiator/accelerator (APS/TEMED). The study specifically evaluated the PI type, PI concentration and UV light intensity, and how these affected the mechanical properties of the hydrogel (i.e. maximum storage modulus), the crosslinking reaction times and the reaction’s cytotoxicity to encapsulated cells. Only two initiators (I2959 and I184) were identified as being suitable for achieving both high cell viability and efficient crosslinking of the cell-encapsulating hydrogels during the photopolymerization reaction. Optimization of PI concentration or irradiation intensity was particularly important for achieving maximum mechanical properties; a sub-optimal choice of PI concentration or irradiation intensity resulted in a substantial reduction in hydrogel modulus.

Cytocompatibility may be compromised by unnecessarily prolonging exposure to cytotoxic free radicals or inadvertently enhancing the instantaneous dose of radicals in solution, both of which are dependent on the PI type/concentration and irradiation intensity. In the absence of a radical initiator, the short exposures to long-wave UV light irradiation (up to 5 min, 20 mW cm−2, 365 nm) did not prove to be cytotoxic to cells. Therefore, it is important to understand the relationship between PIs, light irradiation conditions and crosslinking when attempting to identify a suitable hydrogel formation process for cell encapsulating hydrogels.

1. Introduction

Hydrogels are hydrophilic polymeric networks that are widely used in a variety of applications [1]. Their high water content mimics the permeability of the extracellular matrix (ECM) for optimal transport of oxygen, nutrients and waste products, making them ideal for medical applications. Depending on their composition, hydrogels can be designed with cellular biocompatibility and thus can be utilized as cell carriers in cell therapy [2], cell scaffolds for tissue engineering [3], delivery vehicles for drug molecules [4] and conduits for guided in vivo tissue regeneration [5]. The three-dimensional (3-D) hydrogels in cell therapy, for example, provide structural support for cells, enable proper diffusion of metabolites and can offer immunoisolation or local protection from host inflammation [6].

Hydrogels are usually classified into categories depending on their macromolecular precursors, and the crosslinking reaction that forms the network. Hydrogels can be formed from biological, synthetic and semi-synthetic hybrid macromolecules that are physically or chemically crosslinked in the presence of water [7]. Biological hydrogels are inherently bioactive, but have limitations in controlling physical properties, which is essential for many biomedical applications. Synthetic polymer hydrogels, which do offer control over physical properties, are devoid of biological signaling for cells and tissues in the body, rendering them biologically inert. The integration of biological and synthetic polymers to form a biosynthetic hydrogel network permits both controlled physical