Visible light crosslinkable chitosan hydrogels for tissue engineering

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Abstract

In situ gelling constructs, which form a hydrogel at the site of injection, offer the advantage of delivering cells and growth factors to the complex structure of the defect area for tissue engineering. In the present study, visible light crosslinkable hydrogel systems were presented using methacrylated glycol chitosan (MeGC) and three blue light initiators: camphorquinone (CQ), fluorescein (FR) and riboflavin (RF). A minimal irradiation time of 120 s was required to produce MeGC gels able to encapsulate cells with CQ or FR. Although prolonged irradiation up to 600 s improved the mechanical strength of CQ- or FR-initiated gels (compressive modulus 2.8 or 4.4 kPa, respectively), these conditions drastically reduced encapsulated chondrocyte viability to 5% and 25% for CQ and FR, respectively. Stable gels with 80–90% cell viability could be constructed using radiofrequency (RF) with only 40 s irradiation time. Increasing irradiation time up to 300 s significantly improved the compressive modulus of the RF-initiated MeGC gels up to 8.5 kPa without reducing cell viability. The swelling ratio and degradation rate were smaller at higher irradiation time. RF-photoinitiated hydrogels supported proliferation of encapsulated chondrocytes and extracellular matrix deposition. The feasibility of this photoinitiating system as in situ gelling hydrogels was further demonstrated in osteochondral and chondral defect models for potential cartilage tissue engineering. The MeGC hydrogels using RF offer a promising photoinitiating system in tissue engineering applications.

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1. Introduction

Injectable hydrogels that can form polymer networks in situ offer many advantages in tissue engineering applications [1,2]. In situ gelling hydrogels allow for the delivery of cells and bioactive molecules to tissue defects in a minimally invasive manner, circumventing the need for any surgical incisions. In addition, injectable gelling systems facilitate attachment of bioactive ingredients to the complex structure of the defect area.

Polymerization techniques using light became available for dental restoration in the early 1970s. Since then, photopolymerization has been widely used in biomedical applications due to the relatively mild processing conditions involved [3,4]. The rapid polymerization process with minimal heat production enables cells and proteins to be readily encapsulated within degradable polymers for tissue engineering [5–9]. Photoinitiated polymerization mechanisms allow spatial and temporal control over the polymerization process. In situ photopolymerization, with arthroscopic options or transdermal illumination, can further enhance the therapeutic potential in the treatment of tissue defects.

Chitosan is a naturally occurring polysaccharide and is widely used in biomedical applications, such as in controlled drug delivery systems and tissue engineering scaffolds [10–13]. In addition to having biocompatible and biodegradable characteristics, the abundant amino groups along its chemical chains allow for modification with photocrosslinkable groups [14–16]. Photopolymerizable chitosan has been developed previously through styrenation and polymerized in the presence of camphorquinone (CQ) photoinitiator upon visible light irradiation [15]. Glycol chitosan (GC), a water-soluble chitosan derivative, has been prepared to increase the solubility of chitosan in physiological solvents, which is favorable for direct cell encapsulation in the gels, and converted to a photopolymerizable polymer through methacrylation [14]. Methacrylated glycol chitosan (MeGC) can be crosslinked using ultraviolet (UV) light and Irgacure 2959 photoinitiator, and its cytocompatibility has been demonstrated using a chondrocyte cell line.

Photopolymerization is initiated by free radicals produced by photoinitiators upon UV or visible light irradiation. The produced radical species attack the double bond of monomers and propagate to form crosslinked polymer networks; however, the radical species produced are highly reactive and can react with not only the polymerizable monomers but also can damage cellular macromolecules, such as cell membranes, proteins and nucleic acids [17–20]. Although the cytotoxicity of photopolymerizable chitosan was assessed by seeding cells on the prefabricated gel surface,