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Formulation and characterization of poloxamine-based hydrogels as tissue sealants

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ABSTRACT

In situ cross linkable polyethylene glycol (PEG)-based polymers play an increasing role in surgical practice as sealants that provide a barrier to fluid/gas leakage and adhesion formation. This study investigated the gelation behavior and physical properties of hydrogels formed from homogeneous and blended solutions of two acrylated poloxamines (Tetronics® T1107 and T904) of various molecular weights and hydrophilic/lipophilic balances relative to a PEG control. Hydrogels were formed by reverse thermal gelation at physiological temperature (T1107-containing formulations) and covalent crosslinking by Michael-type addition with dithiothreitol. All poloxamine-based hydrogels exhibited thermosensitive behavior and achieved significantly reduced swelling, increased tensile properties and increased tissue bond strength relative to the PEG hydrogel at physiological temperature. Swelling and tensile properties of all poloxamine-based hydrogels were significantly greater at 37 °C relative to 4 °C, suggesting that their improved physical properties derive from cooperative crosslinking by both noncovalent and covalent mechanisms. Poloxamine-based hydrogels were cytocompatible and underwent hydrolytic degradation over 2–5 weeks, depending on their T1107/T904 composition. In conclusion, select poloxamine-based hydrogels possess a number of properties potentially beneficial to tissue sealant applications, including a substantial increase in viscosity between room/physiological temperatures, resistance to cell adhesion and maintenance of a stable volume during equilibration.

1. Introduction

Sutures and surgical staples are the most widely used methods of wound closure, despite limitations, including the requirement for anesthesia; risk of infection; time and skill required; and difficulty in application/retention in soft tissues such as internal organs [1,2]. This has generated considerable interest in the development of in situ curable polymeric materials that may be used as tissue adhesives/sealants either alone or as an adjunct to sutures. One major group of these materials are tissue glues based on naturally derived materials such as fibrin glue, gelatin–resorcinol–formaldehyde glue and, more recently, BioGlue® (CryoLife) composed of bovine serum albumin crosslinked by glutaraldehyde. Fibrin and BioGlue® are FDA approved and have been used successfully in many clinical applications [3–5]. Although advantageous because of their intrinsic biodegradability, naturally derived materials involve risks of possible viral transmission, hypersensitive reactions to bovine proteins and relatively low mechanical properties. In addition, cytoxicity has been reported with the use of low molecular weight aldehyde-based crosslinkers [6]. To overcome these limitations, recent studies have focused on the development of fully synthetic alternatives.

Alkyl-2-cyanoacrylates were the first materials investigated as synthetic tissue adhesives. These low molecular weight monomers undergo rapid polymerization upon exposure to weak bases present in tissue. Cyanoacrylates with short side chains (methyl/ethyl) were first studied, but deemed unsuitable due to high stiffness and evidence of cytotoxicity and tissue necrosis [7,8]. Butyl (Indermil®, Covidien and Histoacryl®, Tissueseal) and octyl (Dermabond®, Closure Medical) derivatives have been approved for topical wound closure and as bacterial barriers [9–11]. However, internal use of cyanoacrylates remains limited due to their relatively slow degradation and concerns about toxicity of the degradation products. Recent developments in materials for internal applications have focused on various polyethylene glycol (PEG)-based hydrogels such as FocalSeal® (Genzyme BioSurgery), CoSeal® (Baxter) and DuraSeal™ (Confluent Surgical). FocalSeal® consists of PEG diols modified with hydrolytically degradable ester linkages and terminal acrylates for photoinitiated polymerization [12]. It has been successfully used for sealing lung air leaks, but its widespread adoption has been hindered by relatively slow curing and the additional surgical equipment required [13,14]. CoSeal® and DuraSeal™ are both crosslinked by step-growth polymerizations of 4-arm PEG-based macromonomers with degradable linkages and terminal reactive groups. CoSeal® and Duraseal™ are FDA

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