Acta Biomaterialia 8 (2012) 3261–3269

Contents lists available at SciVerse ScienceDirect

Acta Biomaterialia

journal homepage: www.elsevier.com/locate/actabiomat

Rapidly curable chitosan–PEG hydrogels as tissue adhesives for hemostasis and wound healing

Eugene Lih, Jung Seok Lee, Kyung Min Park, Ki Dong Park *

Department of Molecular Science & Technology, Ajou University, 5 Woncheon, Yeongtong, Suwon 443-749, Republic of Korea

ARTICLE INFO

Article history:
Received 10 January 2012
Received in revised form 23 April 2012
Accepted 1 May 2012
Available online 19 May 2012

Keywords:
Chitosan
Poly(ethylene glycol)
Hydrogel
Tissue adhesive
Hemostasis

ABSTRACT

Chitosan–poly(ethylene glycol)–tyramine (CPT) hydrogels were rapidly formed in situ using horseradish peroxidase and hydrogen peroxide to explore their performance as efficient tissue adhesives. A poly(ethylene glycol) modified with tyramine was grafted onto a chitosan backbone to enhance the solubility of the chitosan and to crosslink into three-dimensional networks. The elastic modulus of the hydrogels could be controlled by changing the crosslinking conditions, and the mechanical strength influenced the tissue adhesiveness of the hydrogels. The hydrogels showed the adhesiveness ranging from 3- to 20-fold that of fibrin glue (Greenplast®). The hemostatic ability of the hydrogels was evaluated on the basis that bleeding from liver defects was significantly arrested by the combined effect of the adhesiveness of the hydrogels and the hemostatic property of the chitosan materials. The enzymatic crosslinking method enabled the water-soluble chitosan to rapidly form hydrogels within 5 s of an incision into the skin of rats. Histological results demonstrated that the CPT hydrogels showed superior healing effects in the skin incision when compared to suture, fibrin glue and cyanoacrylate. By 2 weeks post-implantation, the wound was completely recovered, with a newly formed dermis, due to the presence of the CPT hydrogels in the incision. These results suggest that the in situ curable chitosan hydrogels are very interesting and promising tissue adhesive devices for biomedical applications.

1. Introduction

Tissue adhesives have attracted rapidly growing interest as sealants, hemostatic agents and non-invasive wound-closure devices [1]. The adhesives are required to perform a variety of functions, including sealing leaks, stopping bleeding, binding tissues and preferably facilitating a healing process [2]. Adhesion to biological tissues is a highly challenging task because the adhesive materials should exhibit suitable physical properties (elasticity, tensile and adhesive strength), biocompatibility and biodegradability in contact with physiological fluids. Fibrin glues are widely used as biological tissue adhesives in surgical practices, but sometimes their mechanical property is not sufficient and they are required to be applied on dry substrates [3,4]. Cyanoacrylates are a class of synthetic glues that rapidly solidify upon contact with weak bases (water or blood) and guarantee a high degree of adhesiveness [5]. However, the acrylic derivatives exhibit toxicity, due to aldehydes, which are the degradation products of the glues [6–8]. There have been considerable efforts to develop various synthetic-material-based tissue adhesives (acrylates and poly(ethylene glycol) (PEG) hydrogels), biological adhesives (fibrin glues, polysaccharides and proteins) and hybrid systems [9–13].

One of the prime candidates, chitosan has been used as a wound dressing material due to its superior tissue- or mucoadhesive property, hemostatic activity, low toxicity, relevant biodegradability and anti-infection activity [14–16]. Chitosan is a cationic polysaccharide and its adhesive properties are mainly based on ionic interactions with tissues or mucus layers [17,18]. Low-molecular-weight chitosan is particularly known to facilitate closer interaction with the surface of the epithelial cells [14,19]. Despite the advantages, the rigid crystalline structure of chitosan makes it hard to dissolve in water, and this has partially retarded its potential for such application [20]. Modification of the chitosan with PEG can enhance the water solubility of chitosan and permit the formation of chitosan-based hydrogels by crosslinking of the PEG.

Although in situ forming hydrogels have been suggested as ideal injectable biomaterials, certain properties, like weak mechanical strength, rapid dissolution and cytotoxicity of the hydrogels, need to be considered. Recently, enzyme-mediated in situ crosslinkable hydrogels have received a great deal of attention in tissue engineering because of their tunable mechanical property, rapid gelation time and low toxicity, and the mild crosslinking conditions [21–25]. Park and colleagues reported in situ formation of hydrogels based on tyramine-conjugated Tetronic® or gelatin–PEG via

* Corresponding author. Tel.: +82 31 219 1846; fax: +82 31 219 1592.
E-mail address: kdp@ajou.ac.kr (K.D. Park).

1742-7061/$ - see front matter © 2012 Acta Materialia Inc. Published by Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.actbio.2012.05.001