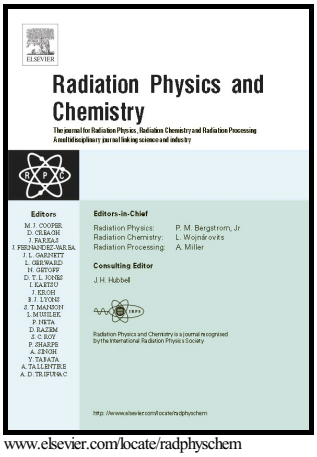
Author's Accepted Manuscript



www.elsevier.com/locate/radphyschem

Hemostatic granules and dressing prepared from formulations of carboxymethyl cellulose, kappa-carrageenan and polyethylene oxide crosslinked by gamma radiation

Bin Jeremiah D. Barba, Charito T. Aranilla, Lorna S. Relleve, Veriza Rita C. Cruz, Jeanina Richelle Vista, Lucille V. Abad

PII: S0969-806X(17)30651-5
DOI: http://dx.doi.org/10.1016/j.radphyschem.2017.08.009
Reference: RPC7614

To appear in: *Radiation Physics and Chemistry*

Received date: 28 June 2017
Revised date: 8 August 2017
Accepted date: 11 August 2017

Cite this article as: Bin Jeremiah D. Barba, Charito T. Aranilla, Lorna S. Relleve, Veriza Rita C. Cruz, Jeanina Richelle Vista and Lucille V. Abad, Hemostatic granules and dressing prepared from formulations of carboxymethyl cellulose, kappa-carrageenan and polyethylene oxide crosslinked by gamma radiation, *Radiation Physics and Chemistry,* http://dx.doi.org/10.1016/j.radphyschem.2017.08.009

Hemostatic granules and dressing prepared from formulations of carboxymethyl cellulose, kappa-carrageenan and polyethylene oxide crosslinked by gamma radiation

Bin Jeremiah D. Barba, Charito T. Aranilla, Lorna S. Relleve, Veriza Rita C. Cruz, Jeanina Richelle Vista, Lucille V. Abad

Philippine Nuclear Research Institute, Department of Science and Technology, Commonwealth Avenue, Diliman, Quezon City, Philippines 1101

KEYWORDS: hemostatic agents, hemorrhage control, carboxymethyl cellulose, kappa carrageenan, polyethylene oxide, radiation crosslinking

ABSTRACT: Uncontrolled hemorrhage remains a persistent problem especially in anatomical areas where compression and tourniquet cannot be applied. Hemostatic agents are materials which can achieve control of bleeding in acute, life-threatening traumatic coagulopathy. In this study, we prepared biocompatible hydrogel-based hemostat crosslinked by ionizing radiation. Granules made from carboxymethyl cellulose and dressing from kappa carrageenan and polyethylene oxide were characterized by FT-IR, SEM, and gel analysis. Gamma radiation with a dose of 25 kGy was used for sterilization process. Stability studies indicate that the products remain effective with a shelf life of up to 18 months based on accelerated aging. Both hemostatic agents were demonstrated to be effective in *in vitro* blood clotting assays showing a low blood clotting index, high platelet adhesion capacity and accelerated clotting time. Hemostat granules and dressing were also used in a femoral artery rat bleeding model where hemorrhage control was achieved in 90 s without compression and resulted in 100% survival rate after a 7 and 14-day observation.

1. INTRODUCTION

Profuse bleeding following traumatic injury is responsible for over 35% of pre-hospital deaths and can begin a cascade of life-threatening medical problems such as impaired resuscitation, shock, inflammation, organ failure and coagulopathy with severity depending on overall blood loss (Kauvar, et al., 2006; Heckbert, et al., 1998). Control of intra-operative hemorrhage is obtained with several traditional techniques: direct pressure, electro-cautery or suture ligature. Although the latter two work in the controlled setting of a hospital, combat and civilian emergency injuries mostly rely on compression, which is usually only amenable on superficial wounds. Non-compressible bleeding occurs on areas of the chest, abdomen, pelvis and back where pressure cannot be easily applied, and they remain the leading cause of potentially survivable deaths (Kisat, et al., 2013; Granville-Chapman, et al., 2011). Hemostatic agents (or hemostat) are employed as an alternative to traditional modalities of hemorrhage control. There have been several hemostats investigated with focus interest in biomaterials such as chitosan, cellulose, gelatin, collagen, etc. owing to their biocompatibility . CELOX™ (chitosan, MedTrade Biopolymers Inc., Crewe, England), TraumaDEX® (starch, Medafor, Inc., Minneapolis, USA), HemCon Bandage® (chitosan, HemCon, Inc., Portland, USA) and Surgicel® (oxidized cellulose, Ethicon, Inc., New Jersey, USA) are some of the polymer-based products available in the market. Although the intrinsic biological properties of natural polymers make them advantageous, mechanical properties of these materials are usually poor (Doppalapudi, et al., 2015). This can be easily remedied by radiation crosslinking which forms a three-dimensional structure that will allow the product to hold water and blood, concentrate coagulation factors while acting as a physical sealant. It is an effective alternative to thermal and chemical processing that may impair biocompatibility.

Here, we introduce a simple method of making hemostatic granules and dressing from polymers crosslinked by gamma irradiation, specifically carboxymethyl cellulose (CMC) and kappa carrageenan (KC)-polyethylene oxide (PEO)-polyethylene glycol (PEG) composite. The polymers used were identified as promising raw materials in previous screening experiments (Barba, et al., 2016). CMC, a cellulose derivative, has been investigated and found to aid in blood coagulation using physical (mechanical plug), chemical (adhesion surface) and physiological (negatively charged catalyst) mechanisms (Wang, et al., 2007). KC has been used in wound dressing hydrogels because of its efficiency in absorbing pseudo-extracellular fluid solution . However, as a primarily radiation degrading product , a synthetic polymer such as PVP, PVP and PEO is usually blended with KC to form mechanically stable interpenetrating networks (Aranilla, et al., 1999; Wu, et al., 2001; Abad, et al., 2003). PEO is a biocompatible hydrophilic polyether compound clinically used in the agglutination of blood (called potentiator) by osmotic drawing of water . PEO blends have been demonstrated for effective bone hemostasis and spinal cord hemorrhagic contusions . Addition of PEG in the dressings was meant to aid in the wound sealing and/or adhesion function (Lewis, et al., 2014). Despite several references on their potential hemostatic function, there have been no studies on hemostats made from these materials or their combinations crosslinked by ionizing radiation making these novel prototypes.