Acta Biomaterialia 47 (2017) 91–99

Contents lists available at ScienceDirect

Acta Biomaterialia

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

Full length article

A shape memory foam composite with enhanced fluid uptake and bactericidal properties as a hemostatic agent

T.L. Landsman [a], T. Touchet [a], S.M. Hasan [a], C. Smith [a], B. Russell [b], J. Rivera [b], D.J. Maitland [a], E. Cosgriff-Hernandez [a,b,*]

[a] Department of Biomedical Engineering, Texas A&M University, College Station, TX 77843-3120, USA
[b] Institute of Biosciences and Technology, Texas A&M University System Health Science Center, Houston, TX 77030-3303, USA

ARTICLE INFO

Article history:
Received 1 May 2016
Received in revised form 15 September 2016
Accepted 5 October 2016
Available online 6 October 2016

Keywords:
Wound dressing
Hemostasis
Composite
Shape memory polymer
Hydrogel

ABSTRACT

Uncontrolled hemorrhage accounts for more than 30% of trauma deaths worldwide. Current hemostatic devices focus primarily on time to hemostasis, but prevention of bacterial infection is also critical for improving survival rates. In this study, we sought to improve on current devices used for hemorrhage control by combining the large volume-filling capabilities and rapid clotting of shape memory polymer (SMP) foams with the swelling capacity of hydrogels. In addition, a hydrogel composition was selected that readily complexes with elemental iodine to impart bactericidal properties to the device. The focus of this work was to verify that the advantages of each respective material (SMP foam and hydrogel) are retained when combined in a composite device. The iodine-doped hydrogel demonstrated an 80% reduction in bacteria viability when cultured with a high bioburden of *Staphylococcus aureus*. Hydrogel coating of the SMP foam increased fluid uptake by 19× over the uncoated SMP foam. The composite device retained the shape memory behavior of the foam with more than 15× volume expansion after being submerged in 37 °C water for 15 min. Finally, the expansion force of the composite was tested to assess potential tissue damage within the wound during device expansion. Expansion forces did not exceed 0.6 N, making tissue damage during device expansion unlikely, even when the expanded device diameter is substantially larger than the target wound site. Overall, the enhanced fluid uptake and bactericidal properties of the shape memory foam composite indicate its strong potential as a hemostatic agent to treat non-compressible wounds.

Statement of Significance

No hemostatic device currently used in civilian and combat trauma situations satisfies all the desired criteria for an optimal hemostatic wound dressing. The research presented here sought to improve on current devices by combining the large volume-filling capabilities and rapid clotting of shape memory polymer (SMP) foams with the swelling capacity of hydrogels. In addition, a hydrogel composition was selected that readily complexes with elemental iodine to impart bactericidal properties to the device. The focus of this work was to verify that the advantages of each respective material are retained when combined into a composite device. This research opens the door to generating novel composites with a focus on both hemostasis, as well as wound healing and microbial prevention.

1. Introduction

Hemorrhage control remains a significant concern of military and civilian trauma centers across the world. Uncontrolled hemorrhage accounts for over 30% of trauma deaths world-wide and over half of these occur before emergency care can be reached [1]. Current hemostatic treatments often rely on compression wraps or gauze as the standard of care. These treatment options are effective in ceasing the hemorrhage but are often ineffective for deep wounds that are irregularly shaped and not amenable to tourniquet application. Newer treatment options include alginates, polymer sponges, chitosan, and gauze impregnated with procoagulants, such as zeolite and kaolin [2,3]. However, these newer technologies focus primarily on acute cessation of blood flow, rather than

* Corresponding author at: Department of Biomedical Engineering, Texas A&M University, 5033 Emerging Technologies Building, 3120 TAMU, College Station, TX 77843-3120, USA.
E-mail address: cosgriff.hernandez@tamu.edu (E. Cosgriff-Hernandez).

http://dx.doi.org/10.1016/j.actbio.2016.10.008
1742-7061/

long-term healing and infection prevention. The three primary wound dressing technologies employed in Iraq during Operation Iraqi Freedom were HemCon® (HemCon Medical Technologies, Inc., Portland, OR), QuikClot® (Z-Medica Corporation, Wallingford, CT), and CELOX™ (SAM Medical, Tualatin, OR) [4].

HemCon® is a chitosan-based wafer which adheres to tissues upon contact with blood to effectively seal the wound boundary. This dressing has proven to be successful in establishing hemostasis in specific wounds, but the stiffness of the bandage makes packing small, narrow wounds very difficult [5,6]. CELOX™ is another chitosan-based hemostat in which granules are poured or injected into the wound which gel together upon contact with blood to provide a physical seal that promotes hemostasis. Although CELOX™ is often deployed in civilian and military trauma situations, re-bleeding and mortality rates of 25% and 13%, respectively, have been reported [7]. QuikClot® Combat Gauze is a device consisting of gauze impregnated with kaolin, an inorganic material that has demonstrated the ability to enhance blood coagulation without causing thermal injury to wound tissue [8]. However, re-bleeding rates as high as 37% have been reported for deep, narrow wounds treated with QuikClot® Combat Gauze [9]. Although each device has proven highly effective in preventing exsanguination in the battlefield, they have proven less useful for smaller, deep wounds incurred by small-caliber firearms and improvised explosive devices [4]. Current dressings are also only indicated for a number of hours, and as such, require frequent changes to prevent bacterial and fungal infection. To address the risk of infection, the standard of care has become the use of a broad spectrum antibiotic regimen; however, bacterial and fungal resistance has forced a series of alternative antibiotics [10].

New hemostatic technologies, such as XStat™ (RevMedx, Inc., Wilsonville, OR) have demonstrated significantly improved time to hemostasis, ease of application, and survival rates compared to conventional hemostats [11]. The XStat™ device is an applicator filled with numerous compressed cellulose sponges that rapidly expand to fill and apply pressure to deep, non-compressible wounds. Despite the numerous advantages of the XStat™ technology, the nature of inserting approximately 92 miniature sponges into an open wound can lead to a 22-fold increase in device removal time compared to conventional gauze due to the need to remove each individual sponge from the wound bed [12]. This may cause patient discomfort during prolonged device removal, as well as increased procedural time and costs.

Shape memory polymer (SMP) foams have previously demonstrated exceptional biocompatibility and hemostatic properties in porcine aneurysms [13,14]. In acute porcine studies, SMP foams have demonstrated hemostasis within an artery in less than 90 s after device deployment, as determined by cessation of contrast flow past the device under X-ray [15]. The rapid hemostasis provided by the large surface area and porous morphology of the foams make them strong candidates for controlling hemorrhage. Furthermore, the ability of SMP foams to recover over greater than400% plastic strain during expansion would enable insertion of a small, crimped device into the wound that would rapidly expand upon contact with blood until the device is completely apposed to an irregular-shaped wound boundary, Fig. 1 [16]. However, SMP foams have an inherently limited capacity for absorbing fluid [17]. In the realm of hemostatic wound dressings, the ability to absorb blood and wound fluid is critical for rapid hemostasis, wound healing, and preventing bacterial infection [18].

In this study, an antimicrobial hydrogel coating was applied to the SMP foam to create a foam-hydrogel composite with enhanced fluid uptake. Specifically, the SMP foam was coated with an n-vinylpyrrolidone (NVP) and polyethylene glycol diacrylate (PEGDA) hydrogel. In addition to increasing the fluid uptake of the composite, the hydrogel is able to directly complex with iodine to form a povidone-iodine (PVP-I_2) complex, which is one of the most widely used iodine antiseptics in surgical care. PVP-I_2 is a stable complex of polyvinylpyrrolidone (PVP) and elemental iodine that is used to kill a variety of viruses, bacteria, fungi, protozoa, and yeast, and there have been no documented cases of microbial resistance to PVP-I_2 [19]. The composite presented here combines the volume filling and rapid hemostasis of SMP foams with the fluid uptake and bactericidal action of iodine-doped hydrogels to create a highly advantageous hemostatic wound dressing prototype. The primary goal of this study was to ensure that the advantageous characteristics of the hydrogel and SMP foams were successfully combined in the composite wound dressing. To accomplish this, the first goal was to optimize the formulation of each device component. Four different hydrogel formulations were investigated for maximum fluid uptake and expansion studies were conducted on three different SMP foam formulations to determine the most rapid shape recovery. The hydrogel formulation with the greatest swelling capacity was then combined with the fastest expanding foam formulation for full characterization as a shape-memory hemostatic agent.

2. Materials and methods

2.1. Materials

All chemicals were used as received and purchased from Sigma Aldrich (Milwaukee, WI) unless otherwise noted. Foams were fabricated using N,N,N′,N′-Tetrakis(2-hydroxypropyl)ethylenediamine (HPED), 2,2′,2″-nitrilotriethanol (TEA, 98%; Alfa Aesar Inc., Ward Hill, MA), 1,6-diisocyanatohexane (HDI; TCI America Inc., Portland, OR), surfactants DC 198 and DC 5943 (Air Products and Chemicals, Inc., Allentown, PA), and deionized (DI) water (greater than17 MΩ cm purity; Millipore water purifier system; Millipore Inc., Billerica, MA). The CellTiter 96® AQ_{ueous} One Solution Proliferation Assay (Promega Corp., Madison, WI) was used for antibacterial studies to obtain a quantitative value for the absorbance of bacterial units after being cultured with iodine-containing hydrogel films.

2.2. Hydrogel preparation

Polyethylene glycol diacrylate (PEGDA) was synthesized according to a method adapted from Hahn, et al. Briefly, 4 M equivalents of acryloyl chloride were added dropwise to a solution of PEG (6 kDa and 10 kDa; 1 M equivalent) and triethylamine (2 M equivalents) in anhydrous dichloromethane (DCM) under nitrogen. After the addition was complete, the reaction was stirred for 24 h. The resulting solution was washed with 2 M potassium bicarbonate (8 M equivalents). The product was precipitated in cold diethyl ether, filtered, and dried under vacuum. FTIR spectroscopy and proton nuclear magnetic resonance (1H-NMR) spectroscopy were used to confirm functionalization of PEGDA. Control and functionalized polymers were solution cast directly onto KBr pellets to acquire transmission FTIR spectra using a Bruker ALPHA spectrometer. Successful acrylation was indicated by an ester peak at 1730 cm^{-1} and loss of the hydroxyl peak at 3300 cm^{-1} in the spectra. Proton NMR spectra of control and functionalized polymers were recorded on Mercury 300 MHz spectrometer using a TMS/solvent signal as an internal reference. All syntheses resulted in percent conversions of hydroxyl to acrylate endgroups of greater than 90%. 1H NMR (CDCl3): 3.6 ppm (m, –OCH2CH2–), 4.3 ppm (t, –CH2OCO–) 5.8 ppm (dd, CH = CH2), 6.1 and 6.4 ppm (dd, -CH = CH2).

PEGDA-polyvinylpyrrolidone (PEG-PVP) hydrogels were prepared by dissolving PEGDA (6 kDa or 10 kDa) and N-vinylpyrrolidone (NVP) (1:96 M ratio) to a 5 or 10 wt% solution