Dendritic Hydrogels as Portable Systems for Hemostasis of Abdominal and Extremity Wounds

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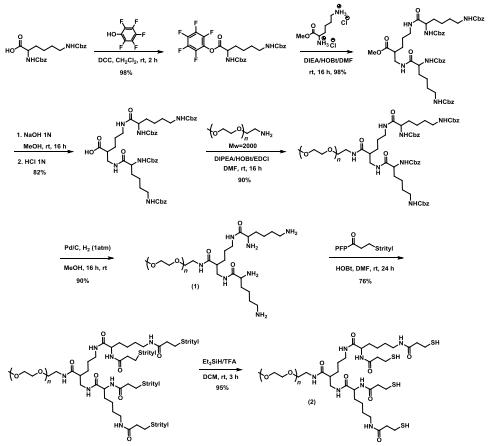
Statement of Purpose: Severe high energy and penetrating traumas can result in acute shock and death. Emergent care at the scene is essential for optimal outcome prior to surgical care, as uncontrolled bleeding can result in death. An ideal hemostatic agent for field use that is effective, easy to use, safe, practical and provide consistent hemostasis for several hours is needed.[1] We report, herein, the synthesis of peptide dendrons, the formation of cross-linked hydrogels, the analysis of hydrogel physical properties and the use of these biomaterials as hemostats for wound closure. Hydrogels possess several advantages over conventional wound dressings including independency of coagulation factors, stability in serum, ease of use, non-toxicity and biocompatibility.[2]

Methods: To prepare the hydrogels, dendron **1** or **2** was dissolved in borate buffer, pH 9 and reacted with a solution of poly(ethylene glycol di-SVA) of 3400 *Mw* (SVA-PEG-SVA) in PBS buffer, pH 6.5. The ratio of amine or thiols to SVA was 1:1, and the total concentration of polymer in solution was either 10 or 30% w/w. Cylindrical hydrogel samples of 8-mm diameter and 2-mm thickness were prepared and analyzed after setting at 25 °C for 2 h. The mechanical properties were measured at a frequency of 1 Hz.

Results: To afford a hydrogel under mild aqueous conditions while maintaining chemoselective cross-linking and a high tolerance to a range of chemical functionalities, we selected the formation of an amide or a thioester linkage between the macromers to render a cross-linked hydrogel. The difference in hydrogel structures (amide or thioester linkages) was chosen for comparison purposes. These linkages between an amine or a thiol and a SVA group occur quickly at room temperature and are stable over a pH range from ≈ 5 to 9. The synthetic route to peptide dendrons **1** and **2** is detailed in Scheme 1.

A hydrophilic gel formed spontaneously within seconds upon mixing the two aqueous solutions of dendron **1** or **2** with SVA-PEG-SVA (see Methods) at either concentration. The gels exhibited viscoelastic properties and were transparent. The storage modulus (G') for the 30% w/w hydrogels prepared from **1** or **2** was 14×10^3 or 44×10^3 Pa, respectively (Figure 1). The increase in modulus is consistent with the increase in the % w/w of the polymer (44×10^3 Pa (30%) *vs.* 5000 Pa (10%) of hydrogel **2**). Next, we tested the adherence of the gels on human skin tissue. A solution of 30% of hydrogel **1** or **2**, dyed with nile red dye (hydrogel **1**) or green food coloring (hydrogel **2**), was applied on a human skin tissue (2cm*1cm) and gelled after few seconds (Figure 2). The hydrogels strongly adhered on the skin and were flexible under different stress conditions (Data not shown).



Scheme 1. Synthetic route to peptide dendrons **1** and **2**.

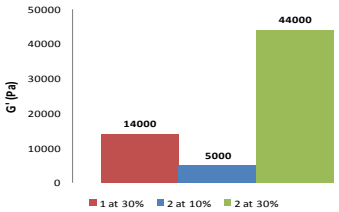


Figure 1. Mechanical properties of hydrogels **1** (30% w/w) and **2** (10 and 30% w/w), at 1 Hz and 10 Pa oscillatory stress.

Figure 2. Photographs of dyed hydrogels **1** and **2** adhered on human skin tissue.

Conclusions: In summary, new polymerizing hydrogels are reported that gel within seconds from the multiple amide or thioester linkages formed between the amine or thiol residues of dendrons **1** or **2** and the poly(ethylene glycol) macromers, SVA-PEG-SVA. The use of a hydrogel sealant for wounds as opposed to commercially available dressings may provide a facile method to safely and effectively seal the wound while reducing potential complications. These results further support the synthesis and evaluation of dendritic macromolecules for medical applications, where a high level of molecular control can be used to vary and optimize chemical, physical, and mechanical properties.

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References: 1. Alam HB *et al.* Military Medicine 2005:170:63-69; 2. Wasiak J. *et al.* Cochrane Database of Systematic Reviews 2008, Issue 4. Art. No.: CD002106. DOI:10.1002/14651858.CD002106.pub3.