A Hydrogel-Based Foam Dressing Controls Wound Infection and Provides Self-tuning Moisture Balance

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Statement of Purpose: Chronic wounds afflict over 50 million patients worldwide, with a surging prevalence due to increased diabetes incidence and aging population. Chronic wounds cause a financial burden to patients as well as extreme pain, serious health threats, and significantly declined life quality. Two significant challenges in chronic wound healing are wound moisture maintenance and infection control. Wound moisture balance is needed for the transportation of healing agents in the wound bed and the establishment of a favorable environment for cell behavior. Bacterial infection induces local persistent inflammatory responses that drastically impede wound healing and can progress to systemic sepsis, organ dysfunction, and limb infection that requires upper- or lower-extremity amputation. Therefore, there is an urgent need to develop a cost-effective wound dressing that provides moisture balance and controls bacterial infection. Our approach is to develop a highly porous hydrogel dressing with excellent absorbency and moisture maintenance that delivers antimicrobial agents to non-healing wounds. The absorbent hydrogel foam dressing removes excessive exudates or moisturizes dry wounds via a hydrophilic hydrogel network, allowing for moisture balance in chronic wounds. A new antimicrobial agent, gallium maltolate (GaM), has been shown to inhibit bacterial growth with no demonstrated bacterial resistance and actively promote pro-healing cell behaviors. Herein, we develop a hydrogel foam dressing loaded with GaM-loaded microspheres to achieve both self-tuning moisture balance and inhibit wound infection simultaneously.

Methods: *GaM-loaded PLGA microspheres:* GaM (6 w/v%) and PLGA (10 w/v%) were first dissolved in dichloromethane. GaM-loaded PLGA microspheres were fabricated by electrospraying the solution at a 0.4 mL/hr flow rate, 20 kV charge, 18G needle, and 20 cm distance to the collection plate. *Blank and GaM-loaded hydrogel foam dressing:* Poly (ethylene glycol) diacrylate (PEGDA) was dissolved in deionized water with a trifunctional crosslinker, photo-initiator, and surfactant. The solution underwent a foaming process and was cured via UV-initiated polymerization. To fabricate the GaM-loaded hydrogel foam, GaM-loaded PLGA microspheres were added to the solution before foaming and curing. *Hydrogel foam characterization:* Hydrogel foams, bulk hydrogels, and clinical dressings were weighed during swelling and dehydration. The hydrogel foam dressing's water vapor transmission rates (WVTRs) were then measured at 0%, 50%, and 100% hydration levels. *Antimicrobial effect of GaM:* The planktonic suspension of a wound-specific methicillin-resistant *Staphylococcus Aureus.* (MRSA) strain was cultured at $5x10^5$ CFU/mL and treated with GaM from 19.5 to 5000 µM, as well as a clinically used antibiotic, gentamicin. Both antimicrobial agents' minimal inhibitory concentrations (MIC) and minimal bactericidal concentrations (MBC) were identified. *GaM release:* The daily GaM release from the GaM-loaded hydrogel foam was monitored with UV-vis spectroscopy at a wavelength of 306 nm for five days.

Results: As shown in **Figure 1A**, the hydrogel foam reached equilibrium swelling in 10 minutes, the same as the PolyMem (clinical control) and much faster than the bulk hydrogel (2 hours). The water uptake ratio of the hydrogel foam was measured as 21.3 ± 0.3, which was approximately **twice** that of the PolyMem (9.7 ± 0.4) and **four times** that of the bulk hydrogel (5.7 ± 0.1). The hydrogel foam also retained moisture longer than the other two dressings. These results indicate that the hydrogel foam can provide rapid wound exudate removal while maintaining the wound moisture for a longer period. In addition, at 0%, 50%, and 100% hydration, hydrogel foam WVTRs were measured as 1842.0 ± 25.8, 747 ± 26.7, and 487.4 ± 15.1 (g H_2O/m^2•24 hr), respectively, indicating an adjustable and self-tuning moisture balance of the hydrogel foam. The hydrogel foam displayed minimal dimensional change after swelling; whereas, the bulk hydrogel diameter increased by a factor of two, **Figure 1B**. In regards to infection control, GaM displayed a lower MIC than gentamicin against MRSA (625 µM vs. 2500 µM) with the same MBC of 5000 µM. Furthermore, GaM-loaded microspheres were successfully fabricated with target sizes (3.3 ±0.8 µm) and incorporated into hydrogel foam during fabrication (**Figure 1C**). The GaM-loaded hydrogel foam provided daily release amounts (205 ± 36 µg/cm2 at Day 1, over 20 µg/cm2 from Days 2 to 5) above concentrations that previously demonstrated infection eradication and improved wound healing in vivo.

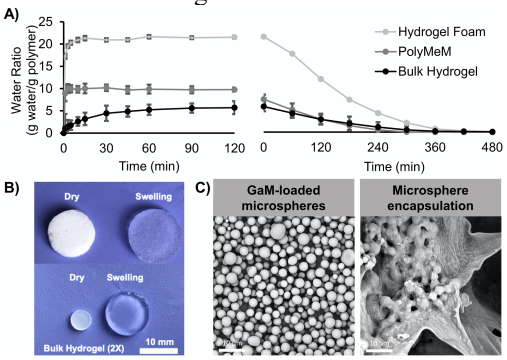

Figure 1: A) Swelling and dehydration kinetics of the hydrogel foam, PolyMem (clinical control), and bulk hydrogel B) Dimensional changes of the hydrogel foam and bulk hydrogel after swelling C) SEM images of GaM loaded microspheres and microspheres incorporated into the hydrogel foam walls.

Conclusion: In this work, we have developed a new hydrogel foam dressing with high absorbency, rapid swelling, and minimal dimensional change. It also featured self-tuning moisture balance at different hydration levels. Furthermore, the GaM-loaded hydrogel foam demonstrated potential for effective infection control with sustained GaM release over five days. Future work will evaluate the efficacy of this hydrogel foam dressing in an infected equine lower extremity wound model.