# Formulation of a Controlled Release Antibacterial Wound Protectant for Austere Environments

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**Statement of Purpose:** The rate of battlefield wound infection and amputation is unacceptably high. The US military's Tactical Combat Casualty Care guidelines recommend that an injured soldier receive a tourniquet to control bleeding and later receive either oral moxifloxacin or IV/IO/IM ertapenem sodium.[1] We aim to create an antibacterial wound protectant that

- can be applied by "buddy-care" in austere environments all over the world
- adheres to blood-contaminated tissue
- generates high local concentrations of antibiotic for at least 3 days.

A semisolid lipid depot approach was utilized for controlled release of moxifloxacin HCl from a thin layer.

**Materials and Methods:** Candidate formulations for semisolid gels were formed by blending crystalline lipid solids into biocompatible oils. Solids consisted of cholesterol (Chol), hydrogenated castor oil (HCO), and glyceryl mono- and di-stearates (GMSII). Oils consisted of soybean oil (Soy), glyceryl monocaprylocaprate (GMCC), oleic acid (OA), and ethyl oleate (EO). Semisolid lipid depots were produced by dissolving or melting components at 110-160 °C, cooling, and mixing as a semisolid. Melting temperatures were evaluated by DSC at 10 °C/min. Syringe expression force from a 5 mL syringe was tested at 1 mm/sec at room temperature and at 4.0 °C. Adherence to blood-contaminated tissue was evaluated on beef muscle tissue dipped in defibrinated sheep blood and then rinsed in saline. The material was applied followed by irrigation with 250 mL saline. *In vitro* release of moxifloxacin HCl with 10% loading was evaluated according to USP <1724> Immersion cell B, 50 RPM, 32 °C PBS, and a 0.5 mm thick sample holder.

**Results and Discussion:** Our formulation target was a semisolid lipid depot with a broad thermal range, in which the lipid crystals would not melt in a desert environment, and the oil would not freeze in cold temperatures. For GMCC-based formulations, expression from a syringe at 4 °C required >30 lbf; however, blending with 6% EO reduced peak syringe expression to 4.2 lbf. Lipid crystals composed of Chol and HCO were advantageous in obtaining high semisolid melting points. Formulating with GMCC and OA depressed formulation melting point versus soybean oil.

Table 1: Melt point data by DSC

| Formulation Ratios (Mass:Mass) | Tm, Peak (°C) | Tm, End Set (°C) |
|---|---|---|
| 20:10:52:18 Chol:HCO:GMCC:Soy | 62.9 | 65.9 |
| 25:15:31:29 Chol:GMS II:Soy:OA | 48.2 | 54.3 |
| 22:12:66 Chol:HCO:Soy | 76.8 | 80.4 |
| 22:12:66 Chol:HCO:GMCC | 61.3 | 65.6 |
| 22:12:66 Chol:GMS II:Soy | 56.1 | 61.0 |
| 22:12:33:33 Chol:GMS II:Soy:GMCC | 41.4 | 47.1 |

Soybean oil-based formulations were challenging to apply to blood-contaminated tissue and were not resistant to irrigation. The incorporation of GMCC or OA to soy-containing formulations provided acceptable tissue adhesion and irrigation resistance.

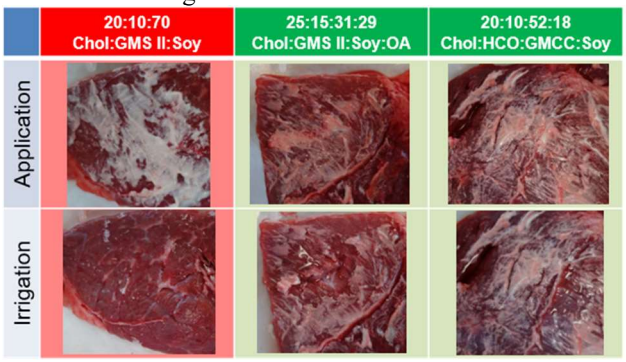


Figure 1: Adherence to blood-contaminated tissue

*In vitro* elution of moxifloxacin could be enhanced by modifying a Chol-HCO-Soy formulation by substituting GMCC for Soy or substituting GMSII for HCO.

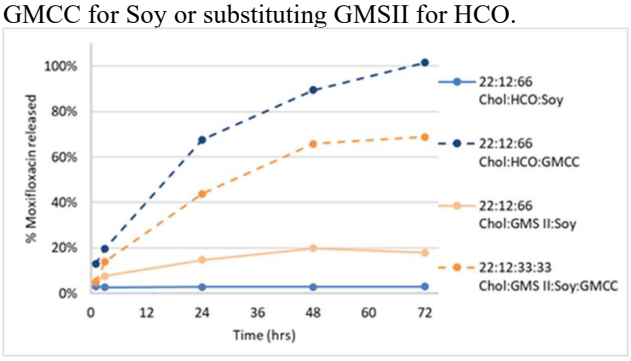


Figure 2: Increase in elution with GMCC or GMSII

Optimized release antibiotic profiles were achieved by adjusting the GMCC:Soy ratio in Chol-HCO formulations or the OA:Soy ratio in Chol-GMSII formulations.

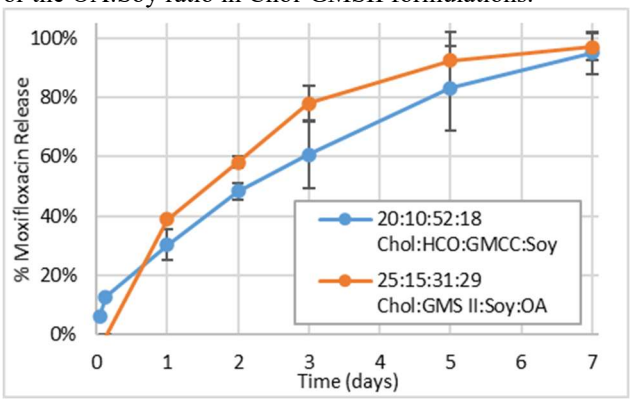


Figure 3: Optimized elution curves for two formulations

**Conclusion:** We have developed an antibacterial wound protectant with optimized handling properties and *in vitro* antibiotic release characteristics for use in austere environments. Selected formulations are being tested in a sheep model of biofilm-contaminated traumatic wounds.

**References**: [1] Tactical Combat Casualty Care Guidelines 05-Nov-2020

**Acknowledgements:** This work was funded in part by CDMRP PRORP award W81XWH-20-1-0378