Extended Dual Antibiotic Delivery from Modified Calcium Sulfate Delivery Systems

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Statement of Purpose: Calcium sulfate can be used as a bone graft substitute and as a drug delivery matrix for local application of therapeutic substances to orthopedic defects. Among its advantages are its complete biodegradability and osteoconductivity, which contrast with standard PMMA antibiotic beads requiring removal.[1] However, one of the disadvantages of currently available calcium sulfate systems it the characteristic high burst release of drug during the first day followed by sub-optimal release afterward. Coating calcium sulfate with polymeric materials, such as chitosan, has been shown to provide a physical and chemical barrier to the release of antibiotics, resulting in decreased burst release and extended elution time.

Because of the polymicrobial nature of contaminating organisms, it is also desirable to have local delivery of antibiotics with activity against a broad spectrum of bacteria. Release of both tobramycin and vancomycin during the healing process will provide a preventative therapy for infections from multiple problematic bacterial strains such as *Pseudomonas aeruginosa* and *Staphylococcus aureus*. In this study pellets of vancomycin were embedded within a matrix of calcium sulfate containing tobramycin. To control the elution and burst release of antibiotics, different components within the system were coated with chitosan. In this study we investigate the elution characteristics of different systems of coated and uncoated calcium sulfate, comparing embedded systems with controls of separate components. The goal was to identify a system with extended elution of two different antibiotics over a period of 28 days.

Methods: *Pellet casting.* Cylindrical pellets 1.9mm in diameter were cast in a stainless steel mold by mixing 1 g $CaSO_4$ hemihydrate with 52 mg vancomycin (MP Biomedicals) and mixing with 0.23 ml of distilled water. Pellets 4mm in diameter were cast in a silicone mold by mixing 5 g of $CaSO_4$ hemihydrate with 256 mg of tobramycin (MP Biomedicals) and 1.15 ml of distilled water.

Coating pellets. A mixture of 3 wt% chitosan (Primex, 80% degree of deacetylation) in 1v/v% acetic acid was thoroughly mixed. To coat pellets, each was dipped into chitosan solution and placed on a mesh screen to dry for 1 hour. This process was repeated for a total of 5 coatings.

Embedded pellets. Embedded pellets were created by carefully placing two of the smaller vancomycin pellets into the larger pellet mold immediately after casting. The following groups were analyzed for this study:

1.) coated vancomycin pellets embedded within a coated tobramycin pellet, 2.) uncoated vancomycin pellets embedded within a larger uncoated tobramycin pellet, 3.) separate coated vancomycin small pellets and coated tobramycin large pellet, and 4.) separate uncoated vancomycin small pellets and coated tobramycin large pellet.

Results: Tobramycin was released from the outer calcium sulfate layer in a burst release from all pellets, although coating with chitosan significantly reduced the amount released in the initial burst (Fig.1a). Vancomycin within the embedded pellets demonstrated a delayed burst beginning on day 3.(Fig. 1b). In addition, release of vancomycin was extended up to day 14 for embedded systems.

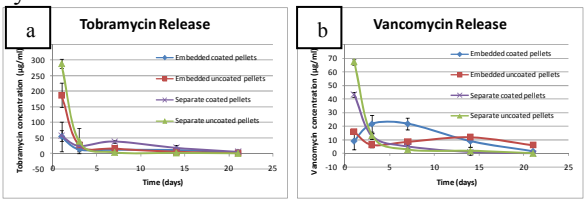

Figure 1. Elution profile of a.) tobramycin, and b.) vancomycin from different calcium sulfate systems.

In coated embedded systems, the initial burst of vancomycin was delayed, resulting in a more even elution profile compared to that of tobramycin in the outer layer (Fig.2).

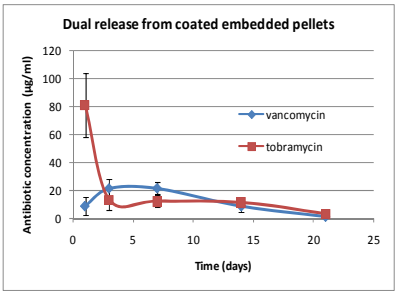

Figure 2. Elution profile of both vancomycin and tobramycin from the coated embedded system.

Conclusions: Modifications to calcium sulfate drug delivery systems have been developed that effectively limit the burst release of antibiotics. These advanced systems allow for delivery of multiple antibiotics, with different elution profiles. This extended dual delivery provides protection against multiple infecting organisms during the healing process, while providing an osteoconductive substrate for bone ingrowth. Future work includes investigations of different chitosan coating techniques to achieve further control over the elution profile. Activity of eluted antibiotics against bacteria will also be determined through microbiological assays and confirmed in *in vivo* models.

Acknowledgements: Funding for this study was provided by the NIH (AI069087). The authors would like to thank Mark Smeltzer, PhD, and also the members of the Biomaterials Association of Memphis (BAM) for assistance.

References:

1. McLaren AC. Alternative materials to acrylic bone cement for delivery of depot antibiotics in orthopaedic infections. Clin Orthop Relat Res 2004(427):101-6.