**Addition of Minocycline and Rifampin to Calcium Sulfate Cement Slows Bulk Ceramic Resorption**

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**Introduction:** Current treatment standards for osteomyelitis involve prophylactic administration of intravenous antibiotics, which may be inadequate for fighting infection if the surgery site is poorly vascularized or necrotic. The mixing of bone void fillers, such as calcium sulfate, with antibiotics for local drug delivery can minimize this disadvantage. Minocycline and rifampin are a patented antibiotic combination shown to be clinically effective against common orthopedic infections, such as S. Aureus[1,2], and calcium sulfate is one of the oldest biomaterials, which has been in continuous medical use since the 19th century. This study evaluates the release profile of a combination of minocycline and rifampin in conjunction with the normal degradation process of calcium sulfate. Interactions between drug release and carrier degradation are explored.

**Methods:** BonePlast™ $CaSO_4$ cement (EBI, L.P., Parsippany, NJ) was manually combined with minocycline (M) and/or rifampin (R) and allowed to set to form composite beads (6-mm diameter). Group 1: $CaSO_4$ control, Group 2: $CaSO_4$ + M/R (0.625% w/w M, 0.625% w/w R), Group 3: $CaSO_4$ + M/R (0.125% M, 0.125% R), Group 4: $CaSO_4$ + M (0.125% M) and Group 5: $CaSO_4$ + R (0.125% R). Samples from each group (n=10) were submersed in 10 cc of phosphate buffered saline (PBS) at 25 ºC with mild agitation. PBS fluid was changed daily for the first four days and then twice per week for the remainder of the experiment. At 4 days, half of the beads (n=5) were separated out, lyophilized for 48 hrs, and weighed. After weighing, beads were resubmerged and lyophilized/weighed again at 16 and 25 days. Extracted solutions from the rest of the beads were measured with a UV spectrophotometer (Genesys Thermo Electron; Pittsford, NY) at 350 nm and 470 nm. Standard curves were created for both M and R to derive the cumulative % of release for each group and the results were plotted (error bars are standard error of the mean).

**Results:** Total minocycline release over the course of the experiment was negligible (less than 5% cumulative). For Group 3, rifampin exhibited a burst effect to 40% cumulative release was seen during the first 24 hours, followed by a slow release that peaked at 10 days and approximately 75% cumulative release. As seen in Figure 1, control beads (Group 1) exhibited 27% mass loss at 25 days. However, no mass loss was seen among the other groups over the course of the experiment, and beads in Group 5 actually gained mass (approximately 17% increase). Normal resorption of $CaSO_4$ was apparently halted by the addition of antibiotics, and in one case even slightly reversed.

**Discussion:** M and R are known to be extremely effective against the major bacterial species that cause osteomyelitis. The minimum inhibitory concentrations for R against S. Aureus and P. Aeruginosa, for example, as determined by agar diffusion assays, were 0.015 µg/mL and 64 µg/mL respectively[2]. M is effective against E. Coli and K. Enterobacter at 25 µg/mL and many other gram-positive and gram-negative organisms as well[3]. Both M and R are broad spectrum and are not antagonistic in combination, though they can be occasionally synergistic[4]. They are also not known to exhibit immunogenicity or allergic reactions in patients. This made M and R good candidates for evaluation with $CaSO_4$ cement.

The unexpected result of this study was that M and R greatly affected the resorption profile of the carrier. Though further study is needed for proof, the lack of mass loss seen in Groups 2, 3, and 4 may revolve around reprecipitation of calcium phosphate at the surface of the beads using the phosphate ions available in PBS coupled with M and R acting as facilitators or nucleation sites for the precipitated crystals. The mass loss normally expected from elution of the drugs may have been counteracted by a corresponding increase in mass due to reprecipitation. Further evidence of this possibility is seen in Group 5, which experienced a gain in mass.

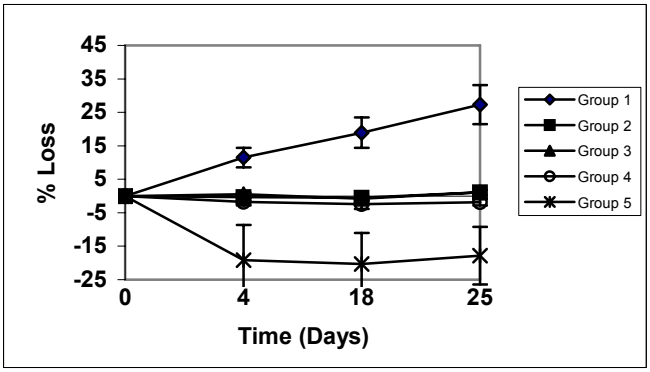


Figure 1. Mass loss profile for $CaSO_4$ cement beads

**Conclusions:** Minocycline did not have a clinically useful release profile from $CaSO_4$ cement, although Rifampin showed a typical burst release which plateaued at 75%. Interestingly, these drugs affected resorption and mass loss characteristics of $CaSO_4$ cement greatly. Though this study only evaluated two drugs, $CaSO_4$ cement may be a useful carrier for delivery of other antibiotics for prophylactic care of osteomyelitis.

**References:**

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