**Evaluation of Drug Release Profiles for Combinations of Antibiotics and Calcium Sulfate Bone Cements**

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**Introduction:** Local delivery of antibiotics for osteomyelitis may be advantageous over standard treatments[1] which include intravenous therapy and implantation of polymethylmethacrylate (PMMA) beads with antibiotics. Minocycline (M) and rifampin (R) are a patented antibiotic combination shown to be clinically effective against common orthopedic infections[2]. Given an appropriate release profile within a relevant period of time, M and R may be useful for mixing with biodegradable implants, such as calcium sulfate ($CaSO_4$). This may aid in osseous repair by delivering high doses of antibiotics locally and can mitigate risk of second surgery morbidity. This study evaluates the release profile of a combination of M and R in conjunction with the normal degradation process of a calcium sulfate mixture.

**Methods:** Mixed powders of 60% BonePlast™ $CaSO_4$ hemihydrate (Biomet Irvine, Inc., Irvine, CA), and 40% Calcigen S™ $CaSO_4$ dihydrate (Biomet Orthopedics Inc., Warsaw, IN) were combined with dry M and/or R and an acidic setting solution and allowed to set to form composite beads (6-mm diameter). Group 1: Control (no drugs) Group 2: $CaSO_4$ + M/R (62.5mg M, 62.5mg R), Group 3: $CaSO_4$ + M/R (12.5mg M, 12.5mg R), Group 4: $CaSO_4$ + M (12.5mg M) and Group 5: $CaSO_4$ + R (12.5mg R). Samples (n=10) were submerged in 10ml of water or phosphate buffered saline (PBS) at 25 ºC with mild agitation. Fluids were changed daily for the first two weeks and then twice per week for the remainder of the experiment. Antibiotic-laden eluent was measured with a UV spectrophotometer (Genesys Thermo Electron; Pittsford, NY) at 350 nm and 470 nm to detect M and R. Excitation wavelengths for these antibiotics were confirmed with a UV scan beforehand. Standard curves were created for both antibiotics to derive the cumulative % of release for each group and the results were plotted. A separate batch of pellets was also created to measure mass loss over time. These pellets were lyophilized and weighed every 5 days.

**Results:** Release profiles for M and R in $H_20$ and PBS from Groups 1 thru 5 are presented in Figures 1 and 2, respectively. Overall, antibiotics in PBS released slightly faster than in $H_20$. By day 1, approximately 80% of antibiotics released in PBS, while it took 4 days for 80% release in $H_20$. The shape of the release profile in PBS was independent of the amount of M or R contained in all Groups and antibiotics released slowly after an initial burst, with complete release by Day 9. Conversely, antibiotic release in $H_20$ took 17 days with a slow release rate seen in Group 3. Roughly 50% mass loss was seen in all samples in water and PBS at 10 days. After 10 days, the resorption rate of the pellets decreased significantly. Normal resorption of $CaSO_4$ was not halted by the addition of antibiotics.

**Discussion:** The release profile of M and R in PBS closely matches the critical period of intervention for postoperative infections. Moreover, the combination of M and R has been shown to be exceptionally effective against gram-positive staphylococci, and gram-negative bacteria. Broad-spectrum activity makes this a useful device in the fight against osteomylelitis.

In this study, M and R did not affect the resorption profile of the carrier, and the carrier did not significantly affect the release rate of M and R. The in vitro release rate from this experiment may be limited in its direct applicability to clinical results because there are many other parameters that need further study, such as agitation rate, antibiotic concentration, and container orientation effects on liquid convection. However, the general time frame of release is still clinically relevant even if altering the experimental conditions changes it by plus or minus 50%.

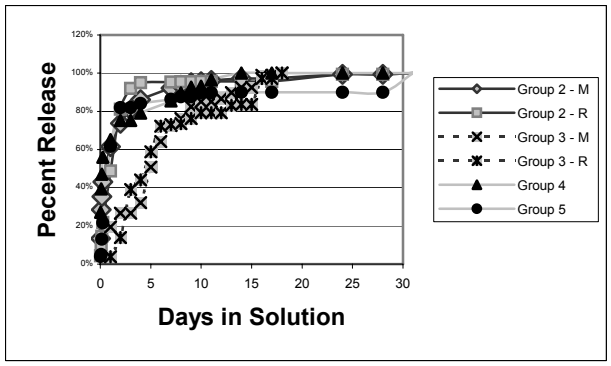


Figure 1: Release Profile of M and R in $H_20$

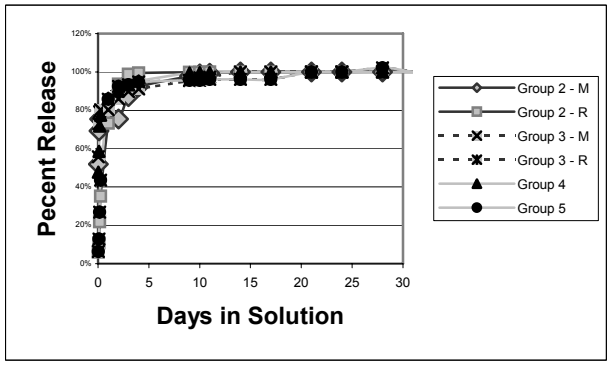


Figure 2: Release Profile of M and R in PBS

**Conclusions:** M and R release from CaSO4 has clinical potential because it closely matches the clinical need for prophylactic antibiotic treatment in the first post-operative week. Though this study only evaluated two drugs, mixing and optimizing ratios of $CaSO_4$ Hemi to Di combinations may be useful for delivery of other antibiotics for prophylactic care of osteomyelitis.

**References:**

1. Gitelis S, Brebach G; J Orthop Res 10(1):53-60, 2002
2. Thornsberry C, Hill B, Swenson J, McDougal L; Rev Inf Diseases 5(S3):412-417, 1983.