Antibiotic-loaded Porous Poly(methyl methacrylate) for Space Maintenance and Local Drug Delivery

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Statement of Purpose: Reconstruction of traumatic craniofacial bone defects is facilitated by a two-stage approach: 1) optimization of the wound bed and 2) definitive repair. Porous space maintainers have been developed to encourage the surrounding soft tissue to heal while preventing soft tissue collapse into the defect before definitive repair. This stage of healing is often complicated by infection, a significant clinical challenge that can result in wound dehiscence and failure of bone regrowth. In addition, the emergence of antibiotic-resistant bacterial strains is an important concern. Clinicians are concerned about adequate delivery of antibiotics to the infected site as well as minimizing the systemic toxicity. Local delivery of antibiotics by antibiotic-loaded porous space maintainers may be able to address these concerns by providing sustained release of a desired drug directly to the site. A porous poly(methyl methacrylate) (PMMA) space maintainer loaded with antibiotic-containing poly(lactic-*co*-glycolic acid) (PLGA) microspheres has been developed for the controlled release of four different classes of antibiotics: clindamycin hydrochloride, doxycyline hyclate, ciprofloxacin, and tobramycin sulfate. We hypothesize that these constructs will release antibiotics over at least 21 days at concentrations above the minimum inhibitory concentration (MIC) for relevant clinical species of bacteria.

Methods: Antibiotic-loaded and blank PLGA microspheres were fabricated using a water-in- oil-in-water (W/O/W) double-emulsion solvent evaporation technique. The microspheres were loaded with 20 wt% clindamycin HCl, doxycycline hyclate, or tobramycin sulfate or 10 wt% ciprofloxacin. Porous PMMA constructs were fabricated using commercially available bone cement, 9 wt% carboxymethylcellulose (CMC) in water as a porogen, and antibiotic-loaded PLGA microspheres. The final constructs contained 10 wt% PLGA microspheres and 30 wt% CMC. Release of antibiotics from microspheres and porous PMMA constructs in PBS was determined over 28 days by HPLC. Susceptibility testing of the released antibiotics against the *S. aureus* (ATCC 29213) and *P. aeruginosa* (ATCC 25922) was performed according to ISO 20776.

Results: Antibiotic released from PLGA microspheres is effective against relevant strains of either *S. aureus* or *P. aeruginosa* at both early (<7 days) and late (>17 days) timepoints (Table 1).

Table 1. Susceptibility testing using eluted antibiotics.

	S. aureus		*P. aeruginosa*	
	Early	Late	Early	Late
Clindamycin	S (0.1875)	S (0.1875)	N/A	N/A
Doxycycline	S (0.125)	S (0.125)	N/A	N/A
Ciprofloxacin	N/A	N/A	S (0.125)	S (0.125)
Tobramycin	S (1)	S (1)	S (1)	S (1)

S = Bacterial strain is susceptible to antibiotics.
MIC as determined by ISO 20776 is reported in parentheses [ug/ml]

Antibiotic release from PLGA microspheres is shown in Fig. 1. At 28 days, cumulative release for clindamycin is 50.7 ± 18.1%, for doxycycline is 60.1 ± 1.0%, for ciprofloxacin is 92.3 ± 5.1%, and for tobramycin is 63.7 ± 11.6%.

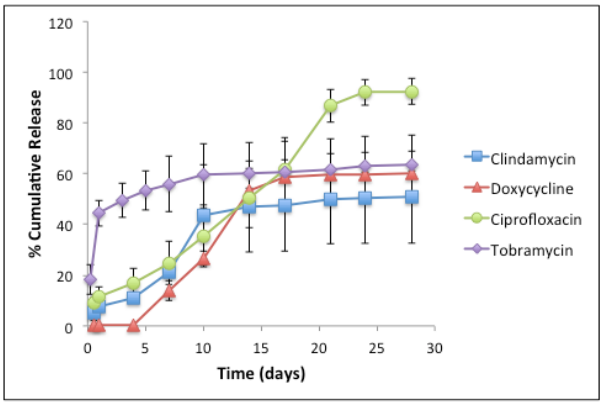

Figure 1. Antibiotic release from PLGA microspheres.

Antibiotic release from PMMA/CMC/PLGA constructs is shown in Fig. 2. At 28 days, cumulative release for clindamycin is 93.9 ± 0.9%, for doxycycline is 50.0 ± 3.0%, for ciprofloxacin is 96.9 ± 4.1%, and for tobramycin is 116.0 ± 9.8%.

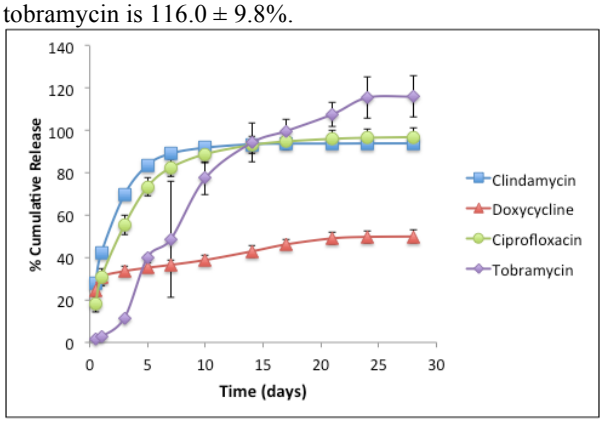

Figure 2. Release of antibiotics from PMMA constructs.

Conclusions: Porous PMMA constructs are suitable for the local delivery of antibiotics. While their main purpose is to maintain the volume of the defect for later definitive repair, prevention and treatment of infection is critical to achieving definitive repair, as infection is a known inhibitor of wound healing. Porous PMMA/CMC/PLGA constructs are capable of delivering antibiotics to combat infection for at least 28 days, making them an attractive solution to the problem of space maintenance with concomitant infection. Future studies will involve testing antibiotics eluted from the PMMA constructs against relevant bacterial strains and *in vivo* testing of these constructs in an infected defect.

References: (Shi, M. *J Control Rel.* 2011; 152: 196-205)