Biodegradable Polymer-Sol Gel Composite Controlled Release Wound Dressings For Chronic Pain Treatment

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Statement of Purpose: Severe combat wounds, particularly those resulting from high energy explosive devices, involve substantial tissue damage that produces sustained and often intense levels of pain throughout and beyond the early tissue healing process. The current understanding of pain mechanisms is that nerve injury following major trauma or amputations leads to plastic imprinting changes in the central nervous system associated with chronic pain symptoms[1-3]. Continuous peripheral nerve block by local delivery of anesthetics immediately following trauma or surgical procedures has been suggested as having the potential to prevent chronic pain. The functional plastic changes with sensitization of second order neurons may be prevented by local anesthetic blockade before but not after injury[3], and preemptive multimodal techniques may reduce the prevalence of chronic pain following orthopedic surgery[2]. We focus here on delivering local anesthetics in a time-controlled fashion to severe combat wound sites with a novel composite wound dressing. Both the sol gel ceramics (also called xerogels) and tyrosine-PEG-derived poly(ether carbonate) copolymers that comprise our composite wound dressing are highly biocompatible and their resorption produces degradation products that are safely excreted. In this study we describe the *in vitro* release kinetics of bupivacaine from the sol gel granules, the tyrosine based copolymers, and the composites made from these components.

Methods: Approximately 30mg of samples used for the *in vitro* drug delivery studies (xerogels, copolymers and composite films) were incubated in 6 mL PBS at 37°C and 100 rpm using a Julabo SW2 water bath shaker. Periodically, the incubation medium was completely withdrawn and replaced with 6 mL fresh buffer. The withdrawn samples were diluted 1:1 (v/v) with acetonitrile and analyzed by HPLC. All experiments were performed in triplicates. The bupivacaine concentrations were assayed by high performance liquid chromatography (HPLC) using a Waters 2695 HPLC system equipped with a Waters 2489 UV/Vis detector that was set at 210 nm for BP detection. Chromatographic separations were achieved using a Perkin-Elmer Pecoshere HS-3 C18 reversed-phase column, 3µm particle size, 33x4.6 mm, at 25°C. Standard calibration curves were prepared at concentration ranging from 0.97µg/mL to 0.25 mg/ml and exhibit linear behavior over this range of concentration. The detection limit was 0.23µg and it was determined based on the standard deviation of the response and the slope of the calibration curve.

Results: Figure 1 shows the release profiles from R_s15-200 xerogel (16.7% bupivacaine), poly(DTO-20%PEG carbonate) loaded with 8 wt % bupivacaine and the composite of poly(DTO-20%PEG carbonate) with 50 wt% bupivacaine containing R_s15-200 xerogel.

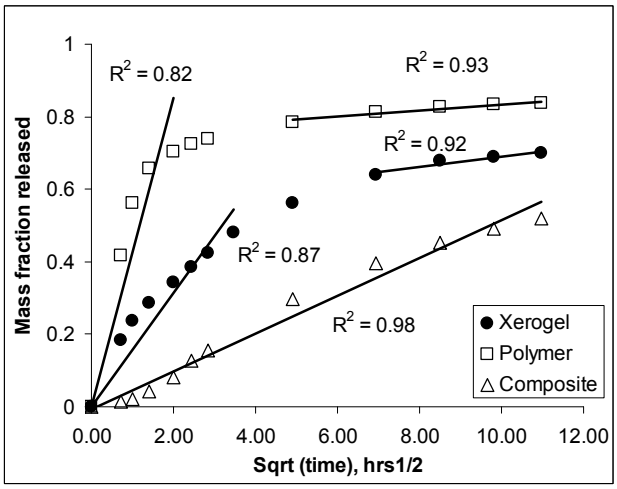

Figure 1 The bupivacaine release kinetics from xerogels, polymer-drug complexes and composites

Generally, for both the drug-loaded xerogels and polymer-drug complexes the bupivacaine release consists of two stages, an initial faster release, followed by a slower stage. However, when the drug-loaded xerogels are embedded in a well-chosen polymer matrix to form a composite, the release profile changes significantly, shifting from two-stage release towards a single stage, pseudo first-order release kinetics, as apparent from Figure 1. The release kinetics of the composite can be tuned by individually adjusting the two components in terms of water:tetraethoxylsilane ratio, pH, drug loading and catalyst used during synthesis (in the case of xerogels), the PEG content and the length of the pendent ester group (in the case of copolymer).

Conclusions: Composite wound dressings have been prepared from drug-loaded xerogels and tyrosine-derived polycarbonates and they have been shown a pseudo first-order drug release kinetics over seven days. The release profiles can be tailored by adjusting various parameters for both the xerogels and polymers.

Acknowledements

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References:

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