Emulsified Sol-Gel Microspheres for Controlled Drug Delivery: *In Vitro* Release and Stability

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Introduction: Room temperature processed silica-based sol-gels are porous, resorbable and biocompatible controlled release materials (1-4). Antibiotics, proteins and growth factors can be controllably released in a biologically active form (1, 4). Sol-gel granules are usually obtained by an acid-catalyzed hydrolysis followed by casting, aging, drying, grinding and sieving. In this study, we synthesize controlled release microspheres by a novel, two-step process: sol formation followed by emulsification (5). Antibiotic (Vancomycin) and an analgesic (Bupivacaine) were used for incorporation in the microspheres. Herein, we report on the long-term release and stability of emulsified sol-gel microspheres *in vitro*.

Methods: Sol-gel derived silica microspheres were synthesized using an acid-base catalyzed hydrolysis of tetraethoxysilane (TEOS, Strem Chemicals, Newburyport, MA) followed by emulsification (5). 30 mg/g of vancomycin (Abbott Labs, Chicago, IL) and 50 mg/g of bupivacaine (Spectrum, New Brunswick, NJ) (drug/SiO_2, w/w) were added to acid-catalyzed sols with water/TEOS ratios (R) of 6 or 8. After addition of the base, 0.08 M NH_4OH, the sol was applied to a vegetable oil stirred at speeds varying from 220 to 880 rpm. The precipitated microspheres were separated from the oil and then rinsed with DI water. The acid-base catalyzed sols were also used to produce ground granules (210-500 μm).

The morphology and size of spheres varied with the speed of stirring. Smooth spherical particles were obtained at speeds equal or above 330rpm. At speeds 660-880 rpm, most of the spheres were in the range 20-100 μm.

In vitro release and degradation properties of emulsified microspheres and ground granules were studied in phosphate buffered saline (PBS, Gibco, pH=7.4) at 37^0C. The release of vancomycin and bupivacaine was measured spectrophotometrically at 280 and 265 nm, respectively. The degradation rate was monitored by measuring the Si concentration by Atomic Absorption Spectroscopy (AAS).

Results/Discussion: The release and dissolution properties of vancomycin-containing microspheres (MS) and ground granules (G) are shown in Figures 1 and 2, respectively. In comparison to granules, microspheres with vancomycin showed a major change of the kinetics of release (Fig.1). The results for bupivacaine release were similar (not shown). The granules showed a fast, short-term release, whereas the release from microspheres was slower and longer. Whereas 90% of vancomycin was released from granules by 7 days, the microspheres released only 36% by 14 days. Analysis of the release profiles plotted against the square root of time revealed two stages of first-order release from granules: an initial, fast release followed by a slower release. In contrast, the microspheres showed three stages of first-order release: an initial, slow release followed by a faster release and a subsequent, slower release. First-order release typically reveals a diffusion-controlled mechanism of release (6).

The difference in the patterns of release from granules and microspheres is related to difference in dissolution rates (Fig. 2). As measured at the linear stage of the dissolution profiles, there was a 4-fold decrease in the Si-release rate from microspheres in comparison to that from granules.

Release of drugs from resorbable materials such as porous silica sol-gels involve both diffusion and dissolution, which is also a diffusion-controlled process of first-order. These data demonstrate that emulsification affected both the kinetics of release and the kinetics of dissolution.

Conclusions: Controlled release, emulsified sol-gel microspheres were produced by a two-step process. The data demonstrate the effect of emulsification on the release and degradation properties of sol-gel particles. Enhanced stability and long-term release were achieved.

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Figure 1

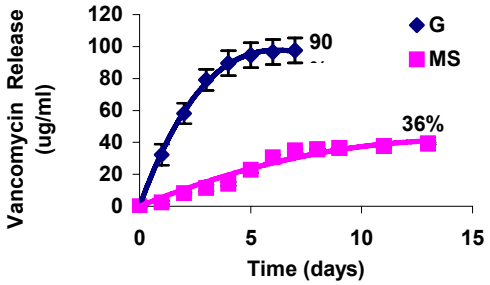
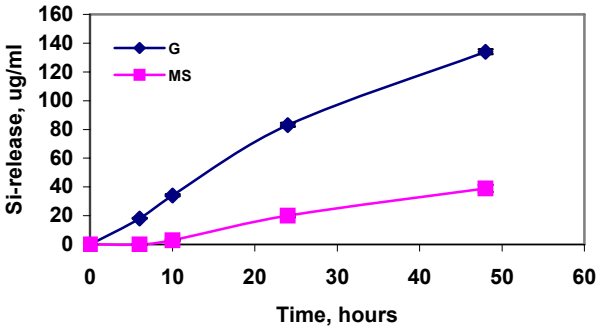


Figure 2



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