Novel Sol-Gel Synthesis of Microspheres for the Control Delivery of Drugs

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Introduction: Room temperature processed silica-based sol-gels are novel, resorbable and biocompatible controlled release materials (1-5). Controlled release of various molecules such as antibiotics, proteins and growth factors has been shown (1). Sol-gels can be shaped as discs, granules, and coatings. Previously, controlled release sol-gel granules were produced through the process of casting, aging, drying, grinding, and sieving. Since these particles are angular, microspheres have the potential of a more favorable tissue response. Sol-gel controlled release microspheres have never been synthesized before. Here, we report on the synthesis parameters of microspheres that affect optimal controlled release and apply these principles to the release of an antibiotic (Vancomycin) and an analgesic (Bupivacaine).

Methods: Sol-gel derived silica microspheres were synthesized using an acid-base catalyzed hydrolysis of tetraethoxysilane (TEOS, Strem Chemicals, Newburyport, MA) followed by emulsification. TEOS, de-ionized (DI) water and 0.1 M HCl were mixed to form an acid-catalyzed sol with DI/TEOS ratios (R) of 5, 6 or 8. Sols with 20 mg/g Vancomycin (Abbott Labs, Chicago, IL) and 50 mg/g Bupivacaine (Spectrum, New Brunswick, NJ) (drug/SiO_2, w/w) were prepared by adding corresponding amounts of the drugs. At R smaller than 5, immediate precipitation of the drugs was observed. This suggested that, in contrast to previously used water-free sol-gel synthesis of microspheres (5), incorporation of drugs requires the presence of water at R equal to or greater than 5. The base, 0.08 M NH_4OH, was added dropwise to the sol, and then, prior to gelation the sol was applied to stirring vegetable oil. Microspheres formed only when the time to gelation of acid-base catalyzed sol was 20-40 minutes. Precipitated microspheres were separated from the oil and then rinsed with DI water and alcohol. The acid-base catalyzed sols were also used to produce ground granules (210-500 µm).

Morphology and the size distribution of the microspheres were determined microscopically using an image analysis system (Image-Pro Plus 4.0).

In vitro release was studied in phosphate buffered saline (PBS, Gibco, pH=7.4) at 37^0C with daily solution exchange. The release of vancomycin and bupivacaine was measured spectrophotometrically at 280 and 265 nm, respectively.

Results / Discussion: By using the sol-gel/emulsification procedure, drug-containing spheres with ideally smooth, defect-free surfaces were synthesized. The size of spheres varied with the speed of stirring during emulsification. In the speed range of 330-440 rpm, 60% of the spheres were in the range of 210-350 µm.

Cumulative release of vancomycin and bupivacaine from microspheres (MS) is shown in Figures 1 and 2, respectively. In both figures the release from spheres is compared to the release from ground granules. In addition, Figure 1 shows the effect of DI/TMOS ratio (R8 vs. R5) on the release of vancomycin. The data demonstrate a striking difference between the kinetics of release from microspheres and from ground granules. In contrast to a fast release of both drugs from ground granules, microspheres show a slower release. Whereas over 60% of the drug load was released from the granules within 3 days, the release of both drugs from spheres was extended over much longer period of time. The data also suggest that the release kinetics from the spheres are affected by the DI/TEOS molar ratio.

The distinct release patterns between granules and microspheres could be associated with the differences in geometry and surface morphology. Possible differences in ultrastructure could also affect the release kinetics. The effect of ultrastructure is the subject of ongoing study.

Conclusions: We have demonstrated that it is possible to synthesize sol-gel derived microspheres with long-term controlled release properties. The data suggest that the release kinetics of these microspheres primarily depend on the synthesis parameters.

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Figure 1

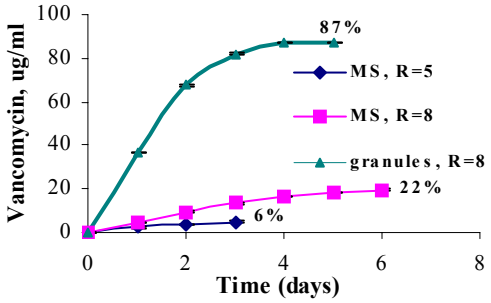
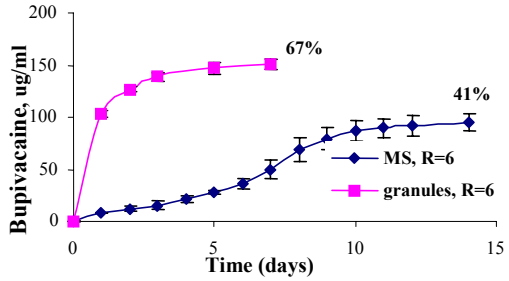


Figure 2



References: (1) Radin S et al. 2004 Kluwer 59-74; (2) Ahola M et al. 2000 Int J Parm 195:219-27; (3) Radin S et al. 2001 Biomed Mater. Res. 57:321-26; 4) Radin S. et al. 2005 Biomaterials 26: 1043-52; (5) Pope E et al. 1998 Soc for Experimental Biology and Medicine 218:365-369.