Novel mesoporous silicon particles as an efficient sustained delivery system for antibiotics

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ABSTRACT

One of major challenges in orthopedics is chronic osteomyelitis infection. Systemic antibiotic therapy is required along with soft tissue and bone debridement in the therapy. The aim of this study was the preparation of biodegradable mesoporous silicon microparticles containing different antibiotics for chronic osteomyelitis produced by bacteria. To optimize the total yield, particle size, surface characteristics, pore size, loading capacity and in vitro release characteristics of the microparticles were demonstrated as well as stability assessment of drug under biological condition. Surface modification provides an efficient and reliable system for controlled release. Microbiological assay was performed using different bacterial strains. Different antibiotics loaded into silicon microparticles were characterized by energy-dispersive X-ray spectroscopy (SEM-EDS), and high performance liquid chromatography (HPLC). Antibiotic-loaded surface modified microparticles resulted to prolonging the release up to one month, depending on surface chemistry and pore sizes. The results of the microbiological assay show that the loading of antibiotics into microparticles is able to enhance the anti-bacterial activity of the drug significantly. These results persuade us to pursue attempts to simplify the management of bone infection without obvious intolerance to the patient.

Keywords: Antibiotic; drug delivery; mesoporous; silicon; microparticles, drug release

1 INTRODUCTION

Despite particular treatment, open fractures (broken bones in communication with the environment) present high rates of complications because of the risk of bacterial infections and chronic osteomyelitis that can threaten the viability of the limb and even the life of the patient. Standard care for open fractures requires irrigation, debridement, stabilization, and antibiotic therapy and often results in multiple procedures according to the severity of the wound and the onset of infections. [1] Delivery systems able to release antibiotics over an extended period of time can solve all these issues and provide efficacious alternative solutions to the current approaches. The ultimate objective of this study is to prove that mesoporous silicon (MPS) can be effectively used in combination with orthopedic implants and with scaffolds for bone tissue engineering to reduce the onset of infections and to enhance the ability of bone to heal in a timely fashion. MPS offers significant advantageous properties for drug delivery applications as it favorably extend drug pharmacokinetics, stability as well as bio-absorbability.

We recently developed a multistage delivery system [2] based on biodegradable MPS with well-controlled shapes, sizes and pores. The size of the pores confines the space for the entrapment of the antibiotic of choice while MPS surface chemistry affects the stability and duration of its interaction with the antibiotic. The size of the pores and the surface chemistry can be easily altered and controlled to tune release kinetics (Fig.1.a-b). [3] The ability to load drugs within the porous matrix of the particle at room temperature enabled the use of MPS also with sensitive compounds susceptible to temperature dependent degradation or inactivation. Moreover, we successfully integrated MPS in polymeric matrices to form composite materials for orthopedic applications. [4,5]

We successfully demonstrated the loading of several antibacterial and antifungal drugs into MPS with different pore geometries and sizes (Fig.1.c-d). We characterized the release rates over time and correlated it with the physico-chemical properties of the MPS particle. Finally, we developed several coating and capping strategies to avoid the burst release of the antibiotic from the pores and to achieve its sustained release over the course of a week (Fig.1.e-f).
Absence, the growth of MPS microparticles treated cells counts for non-treated cells was higher than microparticles with(out) antibiotics. As it was expected, the affect of MPS antibiotic loaded with saline controls, incubation time and growth media were discrete selection variables.

The significance of antibiotic delivery of MPS interaction we have shown requires further investigation to determine dosage dependency, microparticle size, shape, and surface chemistry. Table 1 demonstrates what is the affect of MPS microparticles with(out) antibiotics. As it was expected the count for non treated cells was higher than antibiotic loaded MPS microparticles treated cells. However, when drug was absent, the growth efficiency was not significantly changed.

In addition, in vitro assays of Staphylococcus aureus was used to evaluate the influence of mesoporous silicon microparticles with(out) antibiotics on S. aureus growth. S. aureus treated by MPS was dilution-plated. In in vitro assays, each time point sample was collected accordingly and plated to estimate the S. aureus growth counts. Drugs or saline controls, incubation time and growth media were discrete selection variables.

Figure 1. A) Scanning Electron Microscopy of MPS. B) High magnification of the surface of MPS shows the relative size of the pores in SP (small pores), MP (medium pores), LP (large pores), XSP (extra-small pores). C) Loading efficiency of different types of MPS particles D) Release rates of Vancomycin from unmodified MPS particles with different pore sizes E) Loading efficiency of Cefazolin sodium into MP2 MPS particles F) Release rate of Cefazolin from MP2 MPS particles modified with various capping and coating strategies.

Table 1. Agar plates S. Aureus. (WT) Wild type strain (WT+XSP) Wild type strain treated with saline loaded XSP MPS (WT+CFZ XSP) Wild type strain treated with Cefazolin loaded XSP MPS

Future work will focus on the antimicrobial activity of the delivery system on different strains of clinically relevant bacteria (anti-lincosamide and Gram positive bacteria i.e. *Staphylococcus aureus*), and the prevention of biofilm formation on orthopedic implants and bone scaffolds.

**REFERENCES**


