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Polymer-coated mesoporous silica nanoparticles for the controlled release of macromolecules

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ABSTRACT

With the goal of achieving constant release of large biological molecules over an extended period of time we focused on hybrid inorganic/organic nanoparticles. We synthesized poly(ethylene glycol) (PEG)-coated mesoporous silica nanoparticles (MSNs) with incorporated trypsin inhibitor (TI), a model protein molecule for growth factors. Due to the goal of incorporating large protein molecules the pore size of the as-synthesized MSNs was expanded by a hydrothermal treatment prior to TI incorporation. In vitro release from the MSNs without the thin polymer film shows an initial burst followed by continuous release. In the case of polymer-coated MSNs the initial burst release was completely suppressed and approximate zero order release was achieved for 4 weeks.

1. Introduction

Controlled release of therapeutics is often preferred over traditional therapeutic administration in which the drug is delivered as a bolus, as this may result in drug concentrations exceeding the maximum tolerated dose upon initial administration, and may have a limited time frame of efficacy as the concentration in the body is depleted. A delivery method that provides a nearly constant drug concentration within the therapeutic window would allow more effective disease treatment and would minimize potential toxicity risks. Additionally, controlled release may reduce the dosage frequency and offer site-specific delivery of the therapeutics.

The development of biocompatible, controlled release systems for macromolecules has evolved to the point that biologically active factors can be delivered to a targeted site [1]. It remains a critical issue with most controlled release systems, though, to slowly release drugs of large molecular weight such as proteins, including growth factors [2]. In fact, many controlled release formulations release an initial large bolus of drug immediately upon placement in an in vitro medium or an in vivo site, before the release achieves a stable profile. This phenomenon is typically referred to as "burst release", which leads to high initial drug delivery and also reduces the effective lifetime of the therapeutic [1–6].

Among controlled release materials polymers, bioactive ceramics and glasses have been widely investigated as materials for use as both artificial bone graft substitutes and controlled release materials [7–15]. However, when bioactive calcium phosphates were used as carriers for biologically active molecules they met with mixed success [7,16–19]. Most of these systems also suffered from the phenomenon of burst release [20].

A class of oxide-based controlled release systems has shown much greater promise. They are low temperature processed silica sol–gel materials. These materials, originally developed for engineering applications, have also been studied for both the entrapment and sustained release of biologically active compounds [21–29]. Some of the important benefits associated with the sol–gel processing of these silica-based glasses are the excellent biocompatibility, as demonstrated in vivo [25], and the ability to control the release kinetics [26].

Yet another group of oxide materials are the mesoporous silica materials characterized by a large specific surface area (>800 $m^2 g^{-1}$), a large pore volume and a pore size in the range 2–40 nm [30–32]. In addition, they also display a narrow pore size distribution. By virtue of these properties applications in the fields of catalysis, lasers, sensors and solar cells have been pursued successfully [30–32].

Recent breakthroughs in the synthesis of mesoporous silica materials with high specific surface areas (>800 $m^2 g^{-1}$) and tunable pore sizes (2–10 nm) have led to the development of a series of new delivery systems, with various guest molecules, such as pharmaceutical drugs, fluorescent imaging agents, and others. Many molecules have been incorporated into the mesopores and were then released in a controlled fashion [33–35].

Recently reports have appeared describing functional mesoporous silica materials in which the pore surface was decorated with

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