Polymer coated mesoporous silica controlled release nanoparticles for macromolecules

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Statement of Purpose: Finding solutions to deliver drugs in a controlled fashion is not a contemporary issue; however, it remains an important biomaterials and pharmacological goal. It remains a critical issue with most controlled release systems to slowly release drugs of large molecular weight such as proteins, e.g., growth factors. Mesoporous silica nanoparticles (MSNs) show great potential for use as controlled release drug carriers due to unique features. These include a network of ordered uniformly sized pores, a high pore volume and an easily modifiable silanol-containing surface [1]. The issue of these MSNs is, however, that the pores within these nanoparticles are open at both ends. As a result of this, active molecules start being "leached" just after the dispersion. When considering release from polymeric controlled release nanoparticles, the release of encapsulated compounds from many current polymeric drug delivery systems is also typically initiated immediately upon dispersion of the particle in the aqueous milieu [2].

The objective of this work is to synthesize composite hybrid large molecule delivery systems which combine robust inorganic cores with functionally grafted polymeric surfaces. Here we developed MSNs coated with a thin layer of PEG on the surface, with the goal to develop a prolonged release form. We used trypsin inhibitor as a model molecule and we studied its *in vitro* release kinetics.

Methods: The carboxylated MSNs were prepared as follows: first, 1.00 g of surfactant Cetyl trimethylammonium bromide (CTAB) was dissolved in 480 ml nanopure H_2O and the temperature was raised to 75^{o}C. The solution was made basic by the addition of 3.5 ml of 2.00M NaOH; 5 ml Tetraethyl orthosilicate (TEOS) and 1 ml 3(trimethoxysilyl) propyl succinic anhydride was added dropwise. The reaction temperature was maintained at 75^{o}C for 2h while white precipitates formed. The mixture was filtered in a centrifuge, then washed with deionized water and ethanol until the supernatant shows neutral pH (~7). The samples were left to dry in an oven for 2 days. In order to accommodate large molecules pores of the carboxylated MSNs were expanded by hydrothermal treatment at 110 ^{o}C in the presence of dimethylhexadecylamine (DMH) for 3 days. The surfactants were removed by refluxing the MSNs in acidic alcoholic solution for 18 hrs. Trypsin inhibitor (TI) was loaded by stirring the pore-expanded MSNs with the solution of trypsin inhibitor in 1% acetic acid for one day. A thin layer of PEG-bis-amine was covalently attached to the TI loaded carboxylated MSNs in the presence of crosslinking molecule EDAC. MSN morphology was characterized by TEM and XRD. FTIR was used to confirm the carboxyl groups and PEG-bis-amine on the surface of MSNs. The porosity of MSNs before and after the pore expansion was determined using BET. The release study was performed by placing 30 mg of TI loaded sample in three different test tubes and adding 5 ml Phosphate Buffered Saline (PBS). The tubes were placed on a shaker in a 37^{oC} oven for the following times: 30 min, 1h, 2h, 4h, 6h, 8h, 10h, 24h, 33h, 48h and subsequent measurement was performed every 24h up to 27 days. The trypsin inhibitor concentration in the supernatant was measured by gold nanoparticle assay using a UV-vis spectrophotometer.

Results: BET results (Fig.1a) confirmed the successful pore expansion from a pore diameter of 2.6 nm of as synthesized MSN to 3.6 nm after the hydrothermal treatment. Fig. 1(b) shows the *in vitro* release kinetics of TI from as synthesized MSNs, pore expanded MSNS and PEG coated pore expanded MSNs. From the release kinetics it is clearly evident that the PEG coating completely reduce the initial burst release of TI in case of non-coated samples and provide sustained almost zero ordered controlled release of TI for 27 days. This release trend can be explained on the basis of the slow dissolution of the polymer coating. This slow dissolution allows for a more controlled and sustained release.

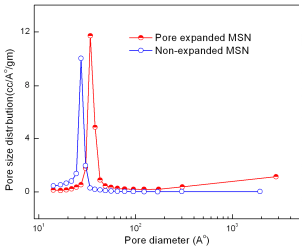

Fig. 1. (a)

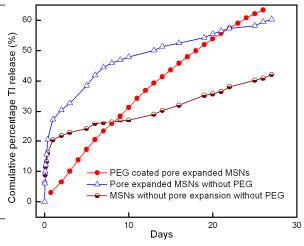

Fig. 1(b)

Conclusions: We have shown that PEG coated mesoporous silica nanoparticles can provide quasi zero order release of macromolecules like trypsin inhibitor for a long duration of 4 weeks.

References:

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2. Hatefi A, Amsden B. Biodegradable injectable *in situ* formingdrug delivery systems. J Control Release; **80**, 9-28 2002.