Ice-templated Hierarchically Porous 3D Silica Nanoparticle Assemblies for Controlled Drug Delivery

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Background: Controlled and sustained delivery of drugs at a therapeutic level from local drug-eluting depots has been a major challenge for various clinical applications. Drug delivery scaffolds with hierarchical porosity offers higher drug loading and much sustained drug release. In recent years, ice-templating or directional freezing has been explored as an efficient approach to produce 3D porous materials for various biomedical applications as it is a simple, versatile, and 'green' technique compared to other methods, without the need for organic solvents. The unidirectional freezing of aqueous colloidal solutions to produce 3D assemblies of nano and micro particles has been previously studied. However, the unique porosity of these 3D assemblies has not been exploited for drug delivery applications. In this study, we investigate for the first time, the directional freezing of 3D porous silica nanoparticle (PSiNPs) assemblies with hierarchical porosity for controlled drug release applications. We hypothesized that smaller pores of the PSiNPs and the larger pores between the nanoparticles in PSiNP 3D assemblies together could provide a higher drug loading. Additionally, a faster initial drug release from the larger interparticle pores, followed by a slower sustained drug release from the smaller nanoparticle pores might provide an immediate and sustained therapeutic effect. Hence, we studied the interparticle porosity of the 3D assemblies developed from PSiNPs with various sizes for optimal drug loading and controlled release applications.

Methods: Monodisperse polymer grafted PSiNPs with diameters ranging from 28 nm to 97 nm (27.8 ± 4.7 nm, 46 ± 4.8 nm, and 96.8 ± 7 nm) were synthesized by using polyacrylic acid/L-arginine polyelectrolyte complexes as a template. Directional freezing of colloidal suspension at –20 °C was employed to form the porous 3D assemblies of PSiNPs. FE-SEM and N_2 gas adsorption and desorption studies were utilized for the characterization of 3D assemblies.

Results: Upon unidirectional freezing of homogeneously dispersed PSiNPs in aqueous media, the growing ice crystals expelled the PSiNPs from the forming ice phase and compact them within the channels between ice crystals to yield 3D assemblies of PSiNPs. FE-SEM images revealed that the 3D nanoassemblies possessed a fibrous morphology with diameters ranging from 3-6 µm based on the size of the PSiNPs (average diameters of 3.55 ± 0.85 µm, 3.45 ± 0.65 µm and 5.6 ± 0.68 µm were observed for fibres assembled from 27 nm, 46 nm and 96 nm PSiNPs respectively). In addition, fibers assembled from larger NPs were found to have greater interparticle pore diameters than the fibres formed from smaller NPs. This result clearly demonstrates that the size of the PSiNPs directly influences the interparticle pore size of the resulting fibres. Doxorubicin (dox) was successfully loaded into interparticle pores of the fibres by simply mixing dox with PSiNPs before directional freezing. Dox loading in fibres assembled from 27 nm, 46 nm and 96 nm PSiNPs was found to be 52.15 ± 2.7 µg/mg, 47.8 ± 5.6 µg/mg and 47.5 ± 6 µg/mg respectively. Furthermore, a biphasic controlled release of the dox from the fibres with an initial burst release followed by slow release was observed in pH = 7.4 phosphate buffered saline over a period of 9 days. Moreover, a higher dox release from fibres possessing larger pores compared to fibres with smaller pores indicated that the drug release rate is controlled by the tuneable interparticle pore sizes of the fibres.

Conclusions: The results of this study demonstrated that the 3D assemblies formed from the directional freezing of colloidal PSiNPs of diverse sizes have the potential to control the drug release by attaining tuneable interparticle pore sizes. These results demonstrate a simple and green strategy for the fabrication of controlled drug releasing systems for various clinical applications.