Hydrothermal Synthesis and Characterization of Hafnium Oxide Nanoparticles for Biomedical Applications

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Statement of Purpose: Hafnium oxide (HfO_2) nanoparticles (NPs) possess unique functional properties for use as an X-ray contrast agent [1,2], mid-infrared biosensor [1,3], and radiosensitizer [4,5]. In particular, HfO_2 exhibits greater X-ray attenuation compared with other compositions at clinical X-ray tube potentials [1,2]. However, methods for synthesizing HfO_2 NPs have been limited by low yield, high temperatures, and agglomeration. Hydrothermal reactions are amenable to the direct synthesis of oxide NPs at low temperature and high yield [6]. Therefore, the objective of this study was to investigate methods for hydrothermal synthesis of HfO_2 NPs exhibiting tunable size and colloidal stability in aqueous media for biomedical applications.

Methods: A solution of 0.2 M potassium hydroxide (KOH) was added dropwise to 0.05 M hafnium chloride to form a hafnium hydroxide precursor which was collected, washed, and redispersed in either 0.3 M oleic acid or 0.5 M KOH and 0.1 M citric acid. The precursor solution was heated in a pressure reactor to 300°C in 1 h, held at 300°C for 30 min under 550 rpm stirring, and then quenched in a room temperature water bath. Other parameters that were investigated included the reaction pressure, temperature, solution pH, capping agent, capping agent concentration, and stirring rate. The crystalline phase and crystallite size were characterized using X-ray diffraction (XRD). NP size and morphology were characterized using transmission electron microscopy (TEM). The colloidal stability of NPs was characterized by the hydrodynamic diameter and zeta potential over several days using dynamic light scattering (DLS). NP cytocompatibility was assessed using human monocyte (THP-1, ATCC) and epithelial (HeLa, ATCC) cell lines, incubated with 0.098, 0.45, and 0.833 mg/mL HfO_2 NPs. Mitochondrial activity and cell viability were measured at 4 and 24 h for each concentration of HfO_2 NPs using MTT (n = 6/group) and Live/Dead (n = 3/group) assays, respectively, and normalized to controls which contained no NPs.

Results: The size, shape, and agglomeration of as-synthesized HfO_2 NPs was affected by the reaction pressure, precursor pH, capping agent, and capping agent concentration. The NP size was able to be controlled over an approximately ten-fold range (Fig. 1). Interestingly, single crystal HfO_2 NPs, ~10 nm in diameter, were able to be prepared using oleic acid as the capping agent (Fig. 1a,c). However, increasing the reaction pH with 0.5 M KOH and using citric acid as the capping agent led to aggregative growth of smaller crystallites to form HfO_2 NPs ~100 nm in diameter (Fig. 1b,d). As-prepared HfO_2 NPs exhibited a highly negative surface charge (Fig. 2) which aided colloidal stability in aqueous media. The hydrodynamic diameter (Fig. 2) remained stable in various culture media over 10 days. HfO_2 NPs exhibited no cytotoxicity at concentrations up to 0.833 mg/mL in both HeLa and THP-1 cells.

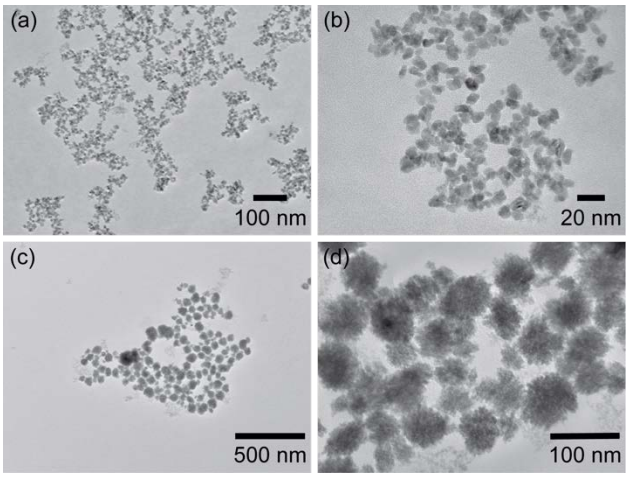

Figure 1. Representative TEM micrographs showing hydrothermally-derived HfO_2 NPs: (a,b) ~10 nm NPs were synthesized using 0.3 M oleic acid as a capping agent, (c,d) ~100 nm NPs were synthesized using 0.5 M KOH and 0.1 M citric acid.

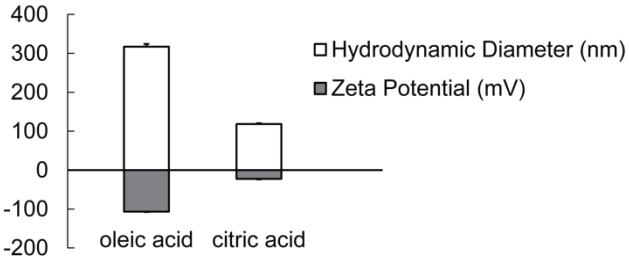

Figure 2. Hydrodynamic diameter and zeta potential of as-synthesized HfO_2 NPs (Fig. 1) measured by DLS. Error bars show one standard deviation of the mean.

Conclusions: HfO_2 NPs exhibiting tunable size, colloidal stability in aqueous media, and cytocompatibility were prepared at high yield and low temperature using hydrothermal synthesis methods.

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