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Hemolytic properties of synthetic nano- and porous silica particles: The effect of surface properties and the protection by the plasma corona

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ABSTRACT

Novel silica materials incorporating nanotechnology are promising materials for biomedical applications, but their novel properties may also bring unforeseen behavior in biological systems. Micro-size silica is well documented to induce hemolysis, but little is known about the hemolytic activities of nanostructured silica materials. In this study, the hemolytic properties of synthetic amorphous silica nanoparticles with primary sizes of 7–14 nm (hydrophilic vs. hydrophobic), 5–15 nm, 20 nm and 50 nm, and model meso/macroporous silica particles with pore diameters of 40 nm and 170 nm are investigated. A crystalline silica sample (0.5–10 μm) is included for benchmarking purposes. Special emphasis is given to investigations of how the temperature and solution complexity (solvent, plasma), as well as the physicochemical properties (such as size, surface charge, hydrophobicity and other surface properties), link to the hemolytic activities of these particles. Results suggests the potential importance of small size and large external surface area, as well as surface charge/structure, in the hemolysis of silica particles. Furthermore, a significant correlation is observed between the hemolytic profile of red blood cells and the cytotoxicity profile of human promyelocytic leukemia cells (HL-60) induced by nano- and porous silica particles, suggesting a potential universal mechanism of action. Importantly, the results generated suggest that the protective effect of plasma towards silica nanoparticle-induced hemolysis as well as cytotoxicity is primarily due to the protein/lipid layer shielding the silica particle surface. These results will assist the rational design of hemocompatible silica particles for biomedical applications.

1. Introduction

The unique physicochemical properties of nanostructured materials (arbitrarily defined as materials with structures between 1 and 100 nm, at least in one dimension) offer a promising future for myriad applications in the biomedical field, such as drug delivery, gene delivery and diagnostics [1]. Size in the nanometer range endows them with the ability to minimize recognition and clearance by the reticuloendothelial system and therefore to enhance blood circulation time. Optimal pharmacokinetics have generally been identified for nanoparticles with a mean diameter of ~100 nm and a neutral and hydrophilic polymer-extended surface (such as polyethylene glycol (PEG)), with a plasma elimination half-life of a few hours [2]. Interestingly, a toxicology study showed that 22-nm Fe_2O_3 particles were able to persist in the circulation with a plasma elimination half-life as long as 22.8 days following intratracheal instillation in rats [3]. The nano-size of materials is also particularly useful for tumor tissue targeting by exploiting their characteristic large vasculature and defective lymphatic drainage which possess enhanced permeation and retention effects for substances <200 nm in size [4]. Moreover, a class of porous materials with pore diameters between 2 and 50 nm, termed mesoporous materials, offer attractive advantages for loading and releasing large quantities of biomedical agents such as drugs, genes and proteins [5–7]. In recent years, the scientific community has witnessed growing interest in nanostructured silica materials for biomedical purposes, either per se [7] or as surface coatings over other functional materials [8], owing to their high biocompatibility and versatile surface engineering properties [9].

These materials are intended to be directly administered into the circulation following intravenous injection, or they may end up in the circulation following other routes of administration such as oral administration. They are also intended to prolong blood circulation half-time. Any material in contact with the blood encounters red blood cells (RBC). Moreover, the hemolysis assay is recommended as a reliable test for material biocompatibility [10]. Micro-size silica, in both crystalline and amorphous form, is well known to induce hemolysis of RBC [11–13]. It was further suggested that surface silanol groups (ionized or unionized) of silica

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