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Nanoengineered silica: Properties, applications and toxicity

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ABSTRACT

Silica nanoparticles are widely used for biomedical purposes, but also in cosmetic products, food, the car industry, paints, etc. Considering their mega production, one should not ignore their potential hazardous effects on humans, flora and fauna. Human exposure to nanosilica can occur unintentionally in daily life and in industrial settings. Here, we review the common methods of silica nanoparticle production and its applications in biomedical investigations and nanotoxicology. The use of silica nanoparticles in biomedicine is discussed in terms of drug delivery, their responsiveness to different stimuli, theranostic applications and their uses in the food and cosmetic industries. Advantages and limitations of silica nanoparticles are presented and the effects of these nanoparticles are discussed in relation to their route of entry and impact on biochemical and epigenetic processes in human and animal cells.

1. Introduction

A considerable number of consumer products and biomedical tools contain nanoparticles (NPs) (Foglia et al., 2011). “The Nanodatabase” is an inventory of commercially available products that contain engineered nanoparticles on the European consumer market. Most products fall into the category of health and fitness (close to 2000), and about one sixth of all products fall into the category of home and garden. More than 700 are personal care products and about 400 are used in clothing. The most abundant nanomaterial employed for these purposes is silver, mainly due to its well-known antibacterial activity, followed by titanium and silicon (http://nanodb.dk/en/). Silicon is one of the most abundant elements on Earth and crystalline silica in the form of quartz is the most abundant mineral in the Earth's crust. Silicon is recognized as an essential nutrient, but detrimental health effects manly associated with dust inhalation have also been reported (Heinemann et al., 2013).

The properties and cytotoxic effects of silica nanoparticles (SiNPs) have not been fully defined (Mebert et al., 2013), but those with high specific surface areas are generally more cytotoxic (Oberdörster et al., 2005; Yu et al., 2009). The cytotoxic effects of SiNPs also depend on their size, charge and concentration (Gonzalez et al., 2014; Santo-Orihuela et al., 2016). The rapid growth of nanotechnological applications and the associated concern about human and environmental exposure are the main driving forces for nanotoxicological investigations (Oberdörster et al., 2007).

SiNPs with favourable properties, such as biocompatibility and biodegradability, have been exploited in the pharmaceutical industry (Alvarez Echazu et al., 2016), mainly to disperse poorly water-soluble therapeutic agents in aqueous media (Castillo et al., 2017). Size, shape and surface functionalization (Mamaeva et al., 2013), as well as modifications needed for active targeting or stimulus-responsive drug release, were described in more detail elsewhere (Martínez-Carmona et al., 2015; Baeza et al., 2015).

SiNPs have been also employed as fillers because they can promote cell adhesion and proliferation. Their biodegradability, high mechanical strength and ability to stimulate tissue repair have been exploited (Lima and Mano, 2015; Pina et al., 2015; Song et al., 2015). In addition, colloidal silica has long been considered a safe additive to food and pharmaceutical formulations.

This review provides an overview of SiNP synthesis methods, and their applications in cosmetics, the food industry and biomedical research. Potential exposure risks associated to SiNPs via different routes (e.g. dermal, oral, intranasal) are also discussed. Finally, the epigenetic changes caused by SiNPs are highlighted.

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2. Silica nanoparticles

2.1. Synthesis of silica nanoparticles

A well-known method to produces non-porous SiNPs is the so-called “Aerosil” method. Particles are produced at high temperatures (around 1000 and 2500 °C) by flame hydrolysis from $SiCl_4$ (siliciumtetrachloride)(Sepeur, 2008). Other industrial methods to produce amorphous silica are precipitation and gelification. Details of industrial synthetic methods are provided in “Reference Document on Best Available Techniques for the Manufacture of Large Volume Inorganic Chemicals—Solids and Others industry” (EUROPEAN COMMISSION, 2007).

Colloidal SiNPs can be synthesized by sol-gel processes based on the Stöber method. In 1968, Stöber et al., reported a system of chemical reactions whereby hydrolysis of alkyl silicates and subsequent condensation of silicic acid in alcohol solutions, using ammonia as a catalyst, resulted in the controlled growth of spherical SiNPs of uniform size (50–2000 nm diameter)(Stöber et al., 1968). During the process, Si-OR and Si-OH containing species condensate into siloxane compounds by forming siloxane bonds (Si-O-Si). Condensation takes place by either alcohol or, more often, water elimination (Fig. 1)(Levy and Zayat, 2015). Some of the advantages of sol-gel methods are that the synthesis is straightforward, scalable and controllable. Particle size, distribution and morphology can be controlled by changing the reaction parameters (Singh et al., 2014a).

The microemulsion method is widely used for nanoparticle preparation (Tan et al., 2011). Porous SiNPs (Fig. 2) can be prepared in water-in-oil (W/O) microemulsions. The alkyl silicate molecules solubilized in the oil phase of microemulsions diffuse to the surfactant layer and penetrate into the water pool, where the hydrolysis reaction takes place (Yamauchi et al., 1989). The advantage of this method – compared to the one-phase reaction – is that the reaction is more easily controlled (Sepeur, 2008). The use of organic solvents and surfactants in the microemulsion methods is a disadvantage because of high costs, need for purification and nanoparticle recovery for large-scale synthesis (Wang et al., 2011). Mesoporous SiNPs (MSNs) with variable pore sizes are generally synthesized in the presence of a supramolecular assembled surfactant that acts as a structure-directing template. Spherical SiNPs with regular pores, consisting of unidimensional, hexagonally shaped cavities, can be obtained by adding a cationic surfactant to the reaction mixture. These nanoparticles have large surface areas and adjustable pore sizes (Wang et al., 2015b), which makes them promising drug nanocarriers. The effect of pH in the reaction mixture, the characteristics of surfactants or copolymers as well as the concentration and source of silica have been reviewed by Wu et al. (2013). In their study, the synthesis of hollow SiNPs (HSNs) with a large cavity using hard (i.e. polymer beads, inorganic nanoparticles) and soft (i.e. micelles, vesicles) templates was also proposed. Zhao et al. synthesized NPs using amphiphilic triblock copolymers to direct the organization of polymerizing silica species (Zhao et al., 1998). SiNPs with different morphologies prepared by the procedures described in this section are summarized in Fig. 2 (A-E). Among the complex particles are core-shell nanoparticles with a silica core or silica shell (Fig. 2F)(Ghosh Chaudhuri and Paria, 2012), york/shell (Fig. 2G) hybrid structures consisting of a movable core inside a hollow shell of the same or different material (Purbia and Paria, 2015) and Janus (Fig. 2H) nanoparticles with heterogeneous surfaces (Schick et al., 2014).

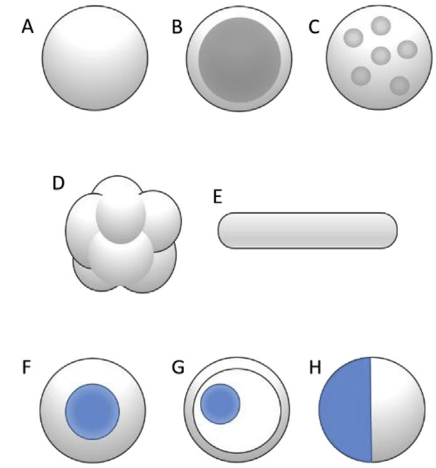

Fig. 2. Schematic representation of (A) non-porous, (B) hollow, (C) mesoporous, (D) amorphous, (C) rod, (E) core-shell, (F) yolk/shell and (G) Janus SiNPs.

3. Applications of nanosilica in the food industry

SiNPs have been used in processed food production and food storage. Amorphous silica has been employed as anticaking agent, antifoaming agent or flow aid in powdered food. Silicon dioxide is listed as food additive in the European Union under code E551. The United States Food and Drug Administration classifies silicon dioxide and amorphous silica as anticaking agents. Silica is used as clarifying/fining agent in the juice, oil and brewery sectors, or as flavor/aroma carrier (Barahona et al., 2016). The daily intake of silica from food is estimated to be 9.4 mg/kg, of which 1.8 mg/kg is within the nano-size range. In food products containing synthetic amorphous silica, up to 43% of the total content was shown to be nano-sized (van der Zande et al., 2014). Powdered products like

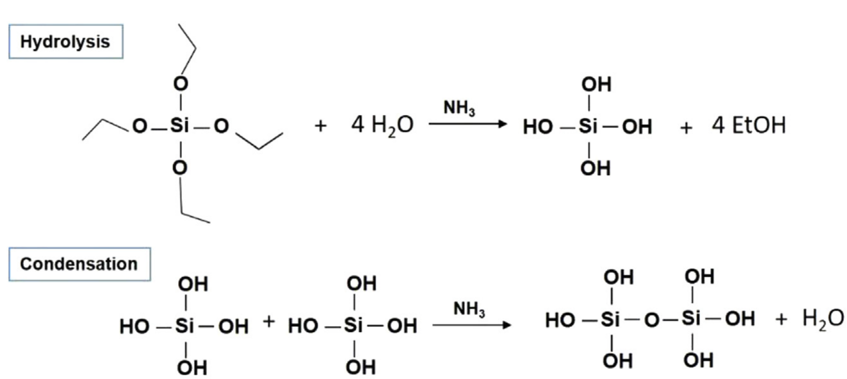

Fig. 1. Schematic representation of possible hydrolysis and condensation steps of the Stöber method reactions.