Size-dependent study of water adsorbed iron oxide nanoparticles: a computational and experimental study

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1. Introduction

The significant growth in nanotechnology has resulted in the formation of various nanoparticle (NPs) types. These NPs have diverse applications, making them attractive for use in drug delivery, cosmetics, medicine, electronics, and as contrast agents for magnetic resonance imaging (MRI), among other fields. Iron oxide magnetic NPs may be used as MRI contrast agents and as vehicles for targeted drug delivery, angiogenic therapy, and chemotherapy [1]. Their small size allows them to actively travel intravascularly or intracavity for drug delivery [2].

Despite their advantages, the toxicity of iron oxide NPs (IONs) remains largely unexplored, especially for ultra-small IONs. Several studies have indicated that the potential toxicity, including cytotoxicity and genotoxicity, caused by IONs are due to the generation of reactive oxygen species (ROS) [3]. Therefore, it is essential to investigate their toxicity, especially considering that different types of NPs exhibit size-dependent toxicity. In recent studies, it has been observed that ultra small NPs (i.e. <5 nm in size) specifically Fe_3O_4, is able to stimulate cells to produce ROS. However, larger NPs (>5 nm) do not exhibit a significant induction of ROS. Therefore, the generation of ROS appears to be influenced by the size of the NPs. The toxicity of ultrasmall Fe_3O_4 NPs is thought to be related to ferroptosis, a form of programmed cell death characterized by the excessive accumulation of iron and the buildup of lipid peroxides [4].

Furthermore, under certain specific conditions, these IONs can release iron ions (Fe^{2+} or Fe^{3+}) into the environment with which it interacts. These ions can react with water to form hydroxide ions (OH^-) and protons (H^+), affecting the pH. Thus, we hypothesise that there might be a correlation between the pH of a solution containing IONs, and the resulting toxicity. It is necessary to investigate and provide a detailed explanation of IONs toxicity and potential risks to human health [5]. The toxicity of NPs is attributed to their specific physico-chemical properties, including their high surface-to-volume ratio, chemical composition, size, dosage, retention in the body, shape, organ-specific toxicity, breakdown, and elimination from the body [6].

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In this study iron oxide (Fe_3O_4) NPs of different sizes and shapes were modelled and simulated (different ultrasmall sizes (1.2 nm, 2.6 nm and 5.6 nm)) where 100 H_2O molecules were absorbed. We qualitatively determined the change in pH of the solution and how this affected the release of Fe-ions (which could lead to the generation of ROS). The corresponding binding energies were then calculated and used as a descriptor of these NPs stability.

2. Atomistic computational modelling and simulation and experimental setup.

Spherical, cuboidal, and rod-like shapes of IONs (Fe_3O_4) ranging from 1.0 nm to 6.5 nm in diameter were simulated *in-silico*. These shapes represent the most common geometries found for these kinds of NPs in experimental literature. The NPs were simulated in an aqueous environment, where different concentrations of water molecules were allowed to interact with the IONs in a simulated absorbance scheme.

This setup allowed for the investigation of how the different shapes and sizes of IONs interact with water molecules and may influence the generation of free radicals – particularly Fe^{3+} and Fe^{2+} ions. The generation of free radicals is a crucial aspect to consider, as it can lead to oxidative stress and potentially harmful effects in biological systems. Additionally, the interaction of IONs with water molecules can lead to changes in pH. By comparing the effects of various shapes and sizes of IONs on the generation of free radicals and pH changes in an *in-silico* environment, we attempted to qualitatively described the toxicity of these NPs.

3. Experimental setup

Co-precipitation was used to synthesize these NPs and the resulting pH was measured for different sizes. The qualitative results were compared with the simulation results. Further characterization of the physicochemical properties was performed, in particular PXRD and FTIR.

4. Results

Figure 1 illustrates a spherical model of Fe_3O_4 with different sizes which shows the water molecules attached to the NP.

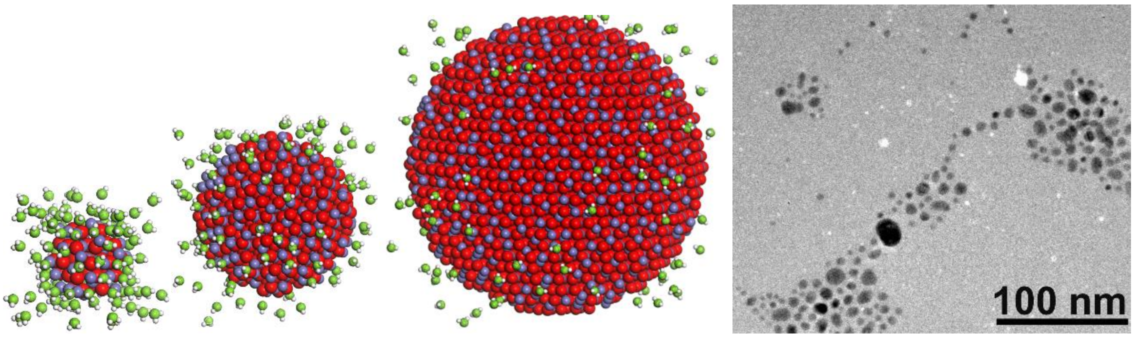

Figure 1: Simulated ultrasmall, spherical and bare magnetite (Fe_3O_4) NP with the adsorbed H_2O molecules. From left to right the sizes are 1.2, 2.6 and 5.2 nm respectively. The image on the right shows a representative TEM image of the experimentally prepared NPs.

NP Size (nm)	Total System Energy (eV)	Nanoparticle Energy (eV)	Ligand Energy (eV)	Binding Energy (eV)
1.2	267,89	700,74	58,66	-491,52
2.6	-2918,90	-2812,85	11,09	-117,15
5.2	-32392,80	-32390,26	0,08	-2,62

Table 1: The different simulated particle sizes 1.2nm, 2.6nm, 5.2nm with the corresponding total system energies, NP energy and ligand energy with the calculated binding energy.

Figure 1 shows the simulated magnetite NPs and the adsorbed H2O molecules. By using the insights gained from the simulation study, the same NPs could be synthesized experimentally (Figure 1, right).

In Table 1 it is observed that as the NP size increases the binding energy decreases. Thus, more H_2O molecules interact with smaller sized NPs than the larger sized ones. This interaction may lead to the desorption of Fe-ions which in turn could result in the generation of ROS. Furthermore, this could lead to the generation of hydroxyls. Wu *et al.* [6] observed that, after intravenous injection, a significantly elevated OH level in the heart, serum, and multiple organs was detected. Among these organs, the heart showed the highest OH level due to the high distribution of ultrasmall Fe_3O_4 NPs, leading to the acute cardiac failure and death. Therefore, in our study, the correlation between the generation of OH groups, H-ions and pH was qualitatively studied to aid in our mechanistic study of the NP toxicity.

5. Conclusions

Through computational modelling we could observe that ultrasmall Fe_3O_4 NPs showed high toxicity. This was done by qualitatively determining the correlation between pH and the release of Fe-ions, OH-ions and H-ions. Now since we know that the toxicity was related to both the iron element and size [6] these findings may provide a novel insight into the toxicology of ultrasmall Fe_3O_4 NPs, and highlight the need of comprehensive evaluation which could be done with Molecular Dynamics, i.e. computational modelling and simulations.

6. References

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