A Combination of Computational Modelling, Simulation and Experimental Work: Titanium dioxide nanoparticle toxicity with different shapes and sizes evaluated based on solution pH

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1. Introduction

Nanomaterials (NMs) are at the forefront of modern materials science [1]. The analysis of NMs involves considering the physicochemical properties of the NMs because their biological impact relies on these properties. Size and shape are two of these properties that should be considered [2]. The theory of nanoscience can be translated to practical applications by manipulating these materials on the nanoscale [3]. Titanium dioxide (TiO_2) is regarded as one of the most significant nanoparticles (NPs) due to its abundance in nature and numerous applications such as sunscreens, in drug delivery systems and in food enhancement [4]. The toxicity of TiO_2 as it pertains to its various properties across its various applications has thus become of great interest. In this work, we first investigate the toxicity of TiO_2 NPs qualitatively and *in-silico*. This is done by considering the effect that different simulated shapes and sizes have on the production and/or release of free radicals when they are placed in an acidic, basic and neutral substances. Reactive Oxygen Species (ROS) are highly reactive molecules containing oxygen that can cause damage to cells and tissues in the body. Furthermore, we investigate this, for ultrasmall NPs, since it has been established that these show a high level of toxicity in vivo, however very little is known about their biosafety [5]. We then proceed to verify our qualitative simulation results with experimentally obtained data.

2. Procedure

Nanorods (NRs), nanocubes (NCs) and nanospheres (NSs) were constructed *in silico* and three different sizes between 1.0 nm – 6.9 nm were chosen. Water molecules were constructed. Varying numbers of water molecules were adsorbed onto the different sized and shaped NPs to determine the number of free ions. The number of free ions observed served as an indication of the toxicity of these NPs in water. This was repeated for water molecules with an excess of hydrogen ions (H^+) which simulated the substance with an acidic pH level. This was repeated again for water molecules with additional hydroxide ions (OH^-) to simulate a substance with a basic pH level. These models were then verified by obtaining experimental data where these NPs were synthesised, and their pH correlated to the free-ion concentration in the solution.

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3. Results

A representative example of the simulated spherical TiO_2 NP is shown in figure 1 with the water molecules adsorbed. It can be seen that for the 1.1 nm particle (Fig. 1 (left)) most of the H_2O interact with the NP. The same is true for the 2.0 nm NP where most of the OH-ions interact with the NP (Fig. 1(middle)), but by changing the NP size just slightly (from 2.0 to 2.6 nm) the interaction of OH-ions seizes (Fig. 1(right)).

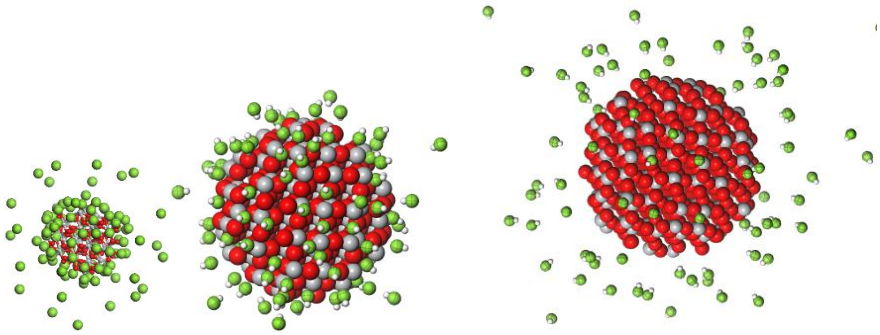

Figure 1: Simulated ultrasmall, spherical anatase TiO_2 NPs with (left) 100 H_20 molecules adsorbed on 1.1 nm NP, (middle) 100 OH-ions adsorbed on 2.0 nm NP and (right) 100 OH-ions adsorbed on 2.6 nm NP.

The corresponding binding energies for the particles with their ligands from figure 1 are shown in table 1. From this we can see that the 2.0 nm particles have the highest binding energy. This implies that this system would be much more stable compared to the slightly larger 2.6 nm system where no bonds between the OH-ions and TiO_2 NP are observed. The consequence of this on the release of Ti-ions will be further explained in this work. Many studies have led to a general agreement about TiO_2 NPs toxicity, in particular for anatase form, but no mechanistic details have been provided yet. In this study, among other things, we evaluate (qualitatively) the role of titanium (Ti) ions released by TiO_2 NPs in different pH conditions.

Table 1: The simulated particle sizes with their corresponding ligand and binding energies.

Size of NP (nm)	Ligand	Total System Energy (eV)	Nanoparticle Energy (eV)	Ligand Energy (eV)	Binding Energy (eV)
1,1	H_2O	-144,88	-59,97	7,25	-92,16
2,0	OH^-	-2442,93	713,14	1240,62	-4396,69
2,6	OH^-	-1194,24	-1194,24	0,00	0,00

Figure 2 shows the number of Ti-ions released, that were found over a 96-hr time period adapted from Matteis *et. al*, [5].

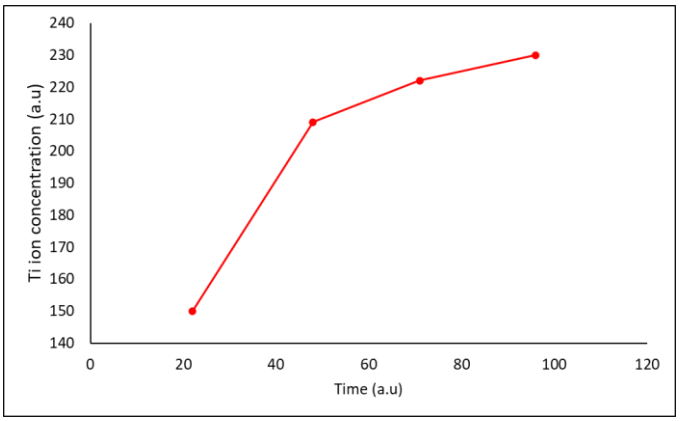

Figure 2: Effects of time and pH on titanium ions released by TiO_2 anatase NPs at a pH of 4.5 [5].

Figure 2 confirms that the TiO_2 anatase NPs are more reactive in an acidic environment and undergoes degradation which indicates a greater toxicity. Furthermore, a greater ion release is observed which results in greater ROS production which is also a descriptor of toxicity.

We observed (from our computational work) that no free Ti-ions were observed for the NP in water. Experimental work confirmed that no free Ti-ions were observed. Furthermore, experimental work by Matteis *et. al*, [5] confirmed this observation for water and reported that they could not detect any Ti-ions that were released into the solution which suggested that the NP degradation did not occur. More free radicals caused by the Ti-ions released were quantitatively observed (both *in silico* and experimentally) for a solution with low pH values. Thus, qualitatively, oxidative stress is higher for low pH values and the NPs may therefore be more toxic.

4. Conclusion

In conclusion, this work aimed to combine computational modelling and simulations with physical experimentation. Firstly, the results obtained from the simulation modelling suggested water (as a neutral substance) played no role in destabilizing specific sizes (i.e. 1.1 nm) of TiO_2 (anatase) NP and therefore no oxidative free radicals were observed. The simulations were experimentally verified.

Furthermore, more free radicals were observed *in-silico* for solutions with low pH values. It was established that the more acidic environment leads to major ionization and consequent free radical release. The effect that the NP size and shape has on this ionization was qualitatively determined *via* computational modelling and simulation and then confirmed experimentally by observing the change in pH and other physio-chemical characteristics of the synthesized NPs.

5. References

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