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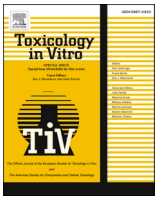

Dissolution of titanium dioxide nanoparticles in synthetic biological and environmental media to predict their biodurability and persistence

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ABSTRACT

Investigating the biodurability and persistence of titanium dioxide nanoparticles (TiO_2 NPs) is of paramount importance because these parameters influence the particles' impact on human health and the environment. Contrary to most research conducted so far, the present study elucidates the dissolution kinetics, namely the dissolution rates, rate constants, order of reaction and half-times of TiO_2 NPs in five different simulated biological fluids and two synthetic environmental media to predict their behaviour in real life situations. Results have shown that the dissolution of TiO_2 NPs in all simulated fluids was limited. Of all the simulated biological media tested, acidic media such as phagolysosomal and gastric fluid produced the highest dissolution of TiO_2 NPs compared to alkaline media such as blood plasma, Gamble's fluid, and intestinal fluid. Furthermore, when the particles were exposed to simulated environmental conditions, the dissolution was higher in high ionic strength seawater compared to freshwater. The dissolution kinetics of titanium dioxide nanoparticles followed first order reaction kinetics and were generally characterized by low dissolution rates and long half-times. These findings indicate that TiO_2 NPs are very insoluble and will remain unchanged in the body and environment over long periods of time. Therefore, these particles are most likely to cause both short and long-term health effects and will remain persistent following release into the environment.

1. Introduction

Titanium dioxide nanoparticles (TiO_2 NPs) have a wide range of innovative application due to their physicochemical properties. They have the ability to filter UV radiation, have antimicrobial properties, and are excellent inhibitors of corrosion (Musial et al., 2020; Nia et al., 2015; Shi et al., 2013; Syngouna et al., 2022). As a result, they are incorporated in a wide variety of commercial products including preservatives, colourants, paint coatings, sunscreen, solar-cells and photo-catalysts (Freyre-Fonseca et al., 2016; Hulla et al., 2015; Kao and Cheng, 2020; Yu et al., 2017). Additionally, TiO_2 NPs can be used as an adsorbent for the removal of organic compounds from wastewater (Stefanarou and Chrysikopoulos, 2021; Syngouna and Chrysikopoulos, 2017, 2019). As the use of TiO_2 NPs increases exponentially so does their potential to be released into the environment and cause adverse health effects to humans and the environment.

Biopersistence is defined as the extent to which nanomaterials are able to resist chemical, physical, and other physiological clearance mechanisms in the body and therefore is considered to be one of the main contributors to their toxicity and hence pathogenicity. Biodurability, defined as the ability of nanomaterials to resist chemical/biochemical alteration, is a significant contributor to biopersistence. Dissolution, defined as release of molecules and/or ions of nanomaterials, is used as a measure of their biodurability and therefore the determination of dissolution rates has provided an insight on how nanomaterials may interact with different biological and environmental surroundings. Subsequently, if nanomaterials release ions at a fast rate, their short-term toxic effect could be identical to those of the dissolved ions. On the other hand, if they release ions at a slow rate, there is a greater likelihood that they will be the cause of the observed adverse effects (Utembe et al., 2015). The application of nanoparticles is most likely to involve the particle being in contact with biological and environmental media and therefore, it is of utmost importance to elucidate the dissolution of TiO_2 NPs in these different media to investigate their

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dissolution kinetics to predict their behaviour in real-life conditions.

Generally, TiO_2 NPs are considered chemically stable and undergo negligible dissolution under usual biological and environmental media (Nam et al., 2012; Shinohara et al., 2017). Even though these particles are thought of as stable, there is sizable research that has been conducted which elucidates titanium dioxide nanoparticle dissolution in media (Schmidt and Vogelsberger, 2006, 2009; Shkol'nikov, 2016; Wang et al., 2014). Several factors have been identified which affect TiO_2 NP dissolution. These factors include the pH, chemical composition and ionic strength of simulated fluids, particle size and crystal form of the nanoparticles (Nia et al., 2015). For example, Avramescu et al. (2017) investigated how the effects of the pH of physiological fluids, particle size and crystal form of titanium dioxide nanoparticles affects their solubility. It was observed that when the particles were exposed to media characterized by low pH conditions the higher the chances of particle solubility. Furthermore, the crystalline form in which TiO_2 NPs existed in was also found to influence solubility where nano-anatase was observed to be more soluble than nano-rutile (Shkol'nikov, 2016). Similar to crystalline form, it was also shown by other investigators that particle size influences the solubility of TiO_2 NPs, and it has been concluded that those smaller in magnitude have a significantly higher solubility than larger particles (Murugadoss et al., 2020). As the formation of aggregates increase the size of TiO_2 NPs it is expected that it will decrease the exposed surface area thereby inhibiting dissolution (Zhong et al., 2017). The chemical composition of simulated fluids has the potential to influence nanoparticle dissolution and thereby the salts containing charged ions interact with the nanoparticle surface thereby promoting or inhibiting dissolution (Larue et al., 2011; Tsai et al., 2016).

Due to the incorporation of these nanoparticles in consumer products their production may lead to their release in the environment. As a result, a study was conducted to assess their accumulation and impact on plants. It was found that TiO_2 NPs do not significantly alter plant germination and root elongation (Larue et al., 2011). Studies have also shown the importance of particle agglomeration in aquatic toxicity testing. For example. It was observed that TiO_2 NPs exposed to aquatic media reach a point of zero charge under neutral pH conditions and become stable thereby increasing the chances of posing toxicity threats to aquatic organisms (Cupi et al., 2016). Yang et al. (2013) investigated the environmental fate and bioavailability of TiO_2 NPs in aquatic invertebrates and the influence of dissolved organic matter. It was concluded that the stability of TiO_2 NPs can be altered by adsorption of dissolved organic matter (Zhong et al., 2017).

Although there has been extensive research on the dissolution of titanium dioxide nanoparticles in simulated media, most studies ignored the importance of determining their dissolution rates, dissolution rate constants, determine their half-times or elucidate the order of reaction. Knowledge of these parameters will assist in assessing their biodurability in different biological and environmental media which in turn will contribute in their biopersistence in these media. In this work we elucidate the dissolution kinetics of titanium dioxide nanoparticles in a wide pH range of simulated physiological fluids and synthetic environment to predict their biodurability in real life situations.

2. Materials and method

2.1. Characterization of TiO_2 NP powder

A unit of standard reference material (SRM) 1898 was purchased from the National Institute of Standards and Technology (NIST). The initial stock suspensions nanoparticles of were prepared from this dry agglomerated powder SRM under sterile conditions. Morphological alterations of the nanoparticles were monitored using the Transmission Electron microscope (TEM) (JOEL Ltd. JEM-2100) (Lireweg, The Netherlands. Nanoparticle suspensions were deposited onto TEM grid (200 mesh size Cu-grid) coated with a lacey carbon film. The images of the nanoparticles were verified using a digital charge coupled device (CCD) camera connected to the TEM. The PANayltical X'Pert Pro powder diffractometer instrument was used to determine the crystalline structure of TiO_2 NPs and to confirm whether they existed in the anatase or rutile crystal phase. This instrument was fitted with 1D X'Celerator detector, 10 mm programmable divergence slit and sample spinner (Spinner PW3064) with a rotation time of 1 s. The X-ray radiation source was Cu Kα ($\lambda = 0.15405$ nm) tube, operating at 40 kV and 40 mA conditions. The measurement was carried out under Gonio scan axis with continuous scan type, step size, scan step time and 2θ range of 0.0170^0, 2θ, 87 s and (5 to 90^0), respectively. The P-XRD sample was transferred onto the low background silicon sample holder. After the X-ray measurements, raw data was interpreted by using High Score (Plus) software with ICDD PDF-4^+ 2019 database. The particles were further characterized by the Varian Ultraviolet-Visible 50 Conc. spectrophotometer (UV–vis) (Agilent Technologies, California, United States). The concentration of dissolved Ti ions was obtained using inductively coupled mass spectrometer (ICP-MS) (Agilent Technologies, 7700 series ICP-MS, Santa Clara, California, United States).

2.2. Experimental procedure

Composition of body fluids and environmental media.

Nanoparticles can enter the human body via various routes, but the focus of this present research study was inhalation, ingestion, intravenous and environmental exposure through waste disposal. Therefore, simulated phagolysosomal fluid (PSF) and Gamble's fluid (GF) were chosen to represent lung fluids found in cellular lysosomes and deep within the lungs at pH 4.5 & pH 7.4, respectively. Whereas gastric fluid (GIF) and intestinal fluid (IF) were representative of stomach fluids at pH 2.0 and pH 7.5 respectively. Lastly, blood plasma (BP) at pH 7.2 which is a fluid that carries blood components throughout the body. The synthetic environmental media of choice were freshwater (FW) and seawater (SW). The preparation of all the simulated fluids was adopted from the procedure presented by Marques et al. (2011) using the reagents listed in Table 1. Synthetic environmental media were prepared following the procedure recommended by the United States (U·S) Environmental Protection Agency (EPA). These reagents were dissolved in 700 mL of d-H_2O in the order given in Table 1, and the pH was adjusted with either 1 M hydrochloric acid or 1 M Sodium hydroxide. The final volume was then adjusted to 1 L with d-H_2O. A 51 μL alkylbenzyldimethylammonium chloride (ABDC) the anti-fungal agent was added to each beaker to preserve the simulated biological fluids and synthetic environmental media.

2.3. Dissolution tests

In vitro acellular tests were used to assess the dissolution of TiO_2 NPs in simulated biological fluids and environmental media. The simulated fluids were prepared in a simplified way such that the influence of certain biological compounds like organic chelators, enzymes, proteins and organic matter was eliminated. A 1 mg TiO_2 NP powder was weighed and transferred into centrifuge tubes each containing 5 ml of simulated biological fluids and environmental media to make nanoparticle suspensions. The murky white nanoparticle suspensions were sonicated at room temperature for 15 min to re-disperse the particles. The stock suspensions were then transferred into decontaminated dialysis membranes (SnakeSkin Dialysis tubing, 3.5 K MWCO, 22 mm-dry diameter) sealed and submerged in beakers filled with 500 mL simulated biological fluids and synthetic environmental media. A dialysis membrane with a significantly smaller pore size was chosen such that titanium in the particle form typically will be fully retained in the dialysis membrane, and species such as charged ions from the nanoparticle surface will dialyze out of the tubing. The beakers were kept in water baths maintained at physiological temperature (37 °C) while synthetic environmental media were kept at 25 °C. Furthermore, the experiments were kept under a closed system in an airtight vessel to eliminate

Table 1
Components and extrinsic properties of simulated biological fluids and synthetic environmental media.

Simulated fluid	Ionic strength (mol L^{-1})	pH	Chemical composition (g L^{-1})
Blood plasma	0.15	7.2	Sodium chloride (NaCl) (8.035), Sodium hydrogen carbonate ($NaHCO_3$) (0.355), Potassium chloride (KCl) (0.225), Potassium phosphate dibasic trihydrate ($K_2HPO_4.3H_2O$) (0.231), Magnesium chloride hexahydrate ($MgCl_2 \cdot 6H_2O$) (0.331), 1 M HCl (39 ml), Calcium chloride ($CaCl_2$) (0.292), Sodium sulphate (Na_2SO_4) (0.072), Tris(hydroxymethyl) aminomethane ($NH_2C(CH_2OH)_3$) (6.118)
Gamble's fluid	0.17	7.4	Magnsium chloride ($MgCl_2$) (0.203), Sodium chloride (NaCl) (6.019), Potassium chloride (KCl) (0.298), Sodium hydrogen phosphate (Na_2HPO_4) (0.142), Sodium sulphate anhydrous (Na_2SO_4) (0.017), Calcium chloride dihydrate ($CaCl_2.2H_2O$) (0.368), Sodium acetate (CH_3COONa) (0.953), Sodium hydrogen carbonate ($NaHCO_3$) (2.604), Trisodium citrate dihydrate ($C_6H_9Na_3O_9$) (0.097)
Gastric fluid	0.16	2.0	Sodium chloride (NaCl) (2.922), Potassium chloride (KCl) (7.007), Potassium hydrogen phthalate ($C_8H_5O_4K$) (0.243), Pepsin (1 ml mL^{-1}), Mucin (3 mg mL^{-1})
Intestinal fluid	0.16	6.8	Potassium chloride (KCl) (0.298), Calcium chloride ($CaCl_2$) (0.499), Magnesium chloride ($MgCl_2$) (0.190), Urea (0.300), Bile salts (9 ml mL^{-1}), Pancreatin (9 mg mL^{-1})
Phagolysosomal fluid	0.34	4.5	Sodium hydrogen phosphate (Na_2HPO_4) (0.142), Sodium chloride (NaCl) (6.650), Sodium sulphate (Na_2SO_4) (0.072), Calcium chloride dihydrate ($CaCl_2.2H_2O$) (0.029), Glycine (0.450), Potassium hydrogen phthalate ($C_8H_5O_4K$) (4.086)
Freshwater	0.05	6.8	Sodium hydrogen carbonate ($NaHCO_3$) (0.012), Calcium sulphate anhydrous ($CaSO_4$) (0.075), Magnesium sulphate anhydrous ($MgSO_4$) (0.0075), Potassium chloride (KCl) (0.0005)
Seawater	3.5	8.0	Sodium chloride (NaCl) (21.03), Sodium sulphate (Na_2SO_4) (3.52), Potassium chloride (KCl) (0.61), Potassium bromide (KBr) (0.088), Borax (0.034), Magnesium chloride ($MgCl_2$) (9.50), Calcium chloride anhydrous ($CaCl_2$) (1.320), Strontium chloride ($SrCl_2$) (0.02), Sodium hydrogen carbonate ($NaHCO_3$) (0.17)

background interreferences. The simulated fluids were stirred using magnetic stirrers and experiments were conducted in the dark over a period of 10 days. Samples were collected from the bulk fluid outside the dialysis membrane in 30 min intervals for the first 4 h and twice a day for the next 10 days. Throughout the duration of the dissolution experiments, the pH of simulated fluids was monitored and maintained using a Jenway 3510 pH meter. Samples were collected in triplicates and analysed on ICP-MS with a limit of detection of 0.1 ppb to determine the concentration of dissolved Ti ions. Reported in the results section is an average of the three measurements.

2.4. Kinetic model for dissolution process

Nanoparticle biodurability and persistence can be predicted by calculating the nanoparticle dissolution rate including half-time. In general, the dissolution of most nanoparticles follows the first order reaction kinetics as predicted by the Noyes-Whitney equation. In this present research study, the Noyes-Whitney equation was modified into eq. 1 to determine the dissolution rate and half-time of TiO_2 NPs exposed to simulated body fluids and synthetic environmental media in order to predict their biodurability and persistence (Wang et al., 2016).

$$\frac{d[Ti0_2NPs]}{dt} = -D\frac{A}{d}\left([Ti]_T - [Ti]_{dis}\right) \quad (1)$$

where $[TiO_2\ NPs]$, $[Ti]_T$ and $[Ti]_{dis}$ represent the initial concentration of the titanium dioxide nanoparticle suspension, the concentration of titanium ions during the dissolution process and lastly the amount of dissolved titanium ions at the end of the dissolution experiments, respectively.

A denotes the surface area of TiO_2NPs powder, D is the diffusion coefficient of titanium ions, and d is the diffusion layer thickness.

The total mass balance of titanium ions in the system is represented by eq. 2.

$$[Ti]_T = [TiO_2\ NPs] + [Ti]_{dis} \quad (2)$$

The $[TiO_2NPs]$ then substituted by eq. 3 in the formula:

$$[TiO_2NPs] = [Ti]_T - [Ti]_{dis} \quad (3)$$

However, $[Ti]_T - [Ti]_{dis}$ can be re-written in the following form represented by eq. 4:

$$[Ti]_T - [Ti]_{dis} = [Ti]_T\left(1 - \frac{[Ti]_{dis}}{[Ti]_T}\right) \quad (4)$$

$$\text{So that } [TiO_2NPs] = [Ti]_T\left(1 - \frac{[Ti]_{dis}}{[Ti]_T}\right) \quad (5)$$

If we substitute eqs. 5 into eq. 1 we obtain the following eq. 6:

$$[Ti]_T\frac{d\left(1 - \frac{[Ti]_{dis}}{[Ti]_T}\right)}{dt} = -D\frac{A}{d}[Ti]_T\left(1 - \frac{[Ti]_{dis}}{[Ti]_T}\right) \quad (6)$$

Upon dividing by $[Ti]_T$on both sides of the equation, eq. 6 is transformed into eq. 7:

$$\frac{d\left(1 - \frac{[Ti]_{dis}}{[Ti]_T}\right)}{dt} = -D\frac{A}{d}\left(1 - \frac{[Ti]_{dis}}{[Ti]_T}\right) \quad (7)$$

If we let $\left(1 - \frac{[Ti]_{dis}}{[Ti]_T}\right) = x$.

Then eq. 7 becomes:

$$\frac{dx}{dt} = -D\frac{A}{d}x \quad (8)$$

To re-arrange the variables and bring x and dt to the left hand-side & right hand-side of the equation respectively, the above equation is divided by x and multiplied by dt on both sides of the equation:

$$\frac{dx}{x} = -D\frac{A}{d}dt \tag{9}$$

Upon integration, the above equation becomes:

$$lnx = c - D\frac{A}{d}t \tag{10}$$

where $k = -D\frac{A}{d}$ and c is a constant and therefore, k is the slope representative of the dissolution rate constant.

Ultimately the integration of Eq. 7 yields Eq. 11

$$ln\left(1 - \frac{[Ag]_{dis}}{[Ag]_T}\right) = c - kt \tag{11}$$

By plotting $\ln\left(1 - \frac{[Ti]_{dis}}{[Ti]_T}\right)$ vs time we are able to calculate the dissolution kinetics of titanium dioxide nanoparticles and predict how long they would remain unchanged in the body and the environment.

Consequently, dissolution predicted by this kinetic model follows first order reaction kinetics and half-time of a first order reaction can be obtained by the following equation:

$$t_{½} = \frac{ln2}{k} \tag{12}$$

2.5. Statistical analysis

The dissolution data are expressed as mean ± standard deviation of at least three independent measurements. A multiple variable ANOVA analysis using RStudio version 1.2 software was performed to determine significant differences between the dissolution behaviour of TiO_2 NPs in various simulated body fluids and synthetic environmental media. Statistical significance was accepted at $P < 0.05$.

3. Results

3.1. Characterization

3.1.1. TEM

The TiO_2 NPs were characterized by using TEM, UV–vis and XRD to monitor their dissolution behaviour in simulated body and environmental fluids and link their changes to physicochemical properties. Fig. 1 shows size distribution curves and TEM images of TiO_2 NPs immediately after having been suspended in simulated biological fluids and synthetic environmental media (marked as before) and after the end of the 10-day dissolution experiments.

The particles size diameter was analysed using image J software (National Institute of Health, version no Java1.8.0_172) by measuring individual particles. Despite the differences in pH and chemical

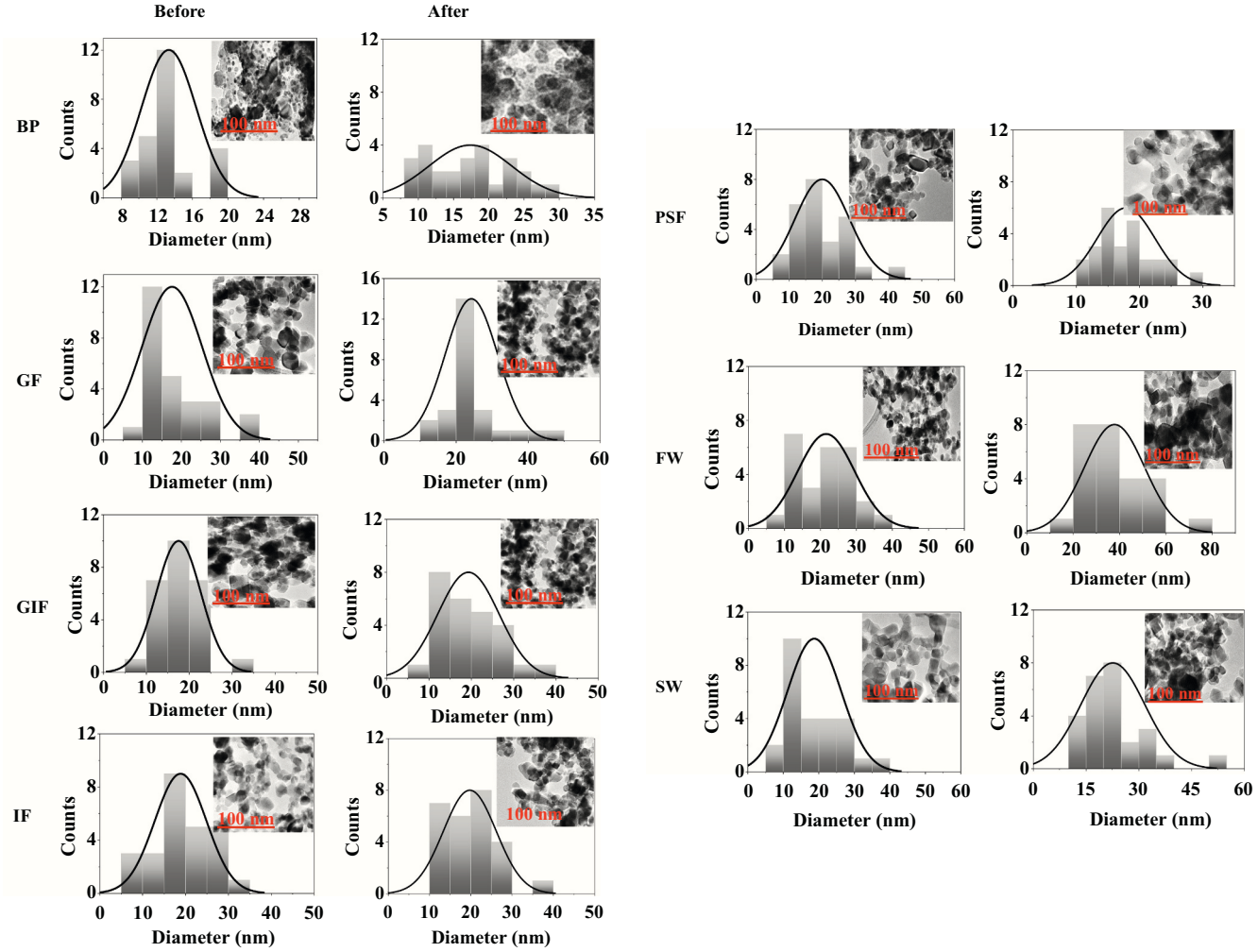

Fig. 1. Size distribution curves and TEM images of TiO_2 NPs in simulated body fluids and environmental media before and after dissolution experiments. Simulated biological fluids are BP- Blood plasma, GF- Gamble's fluid, GIF-Gastric fluid, IF- Intestinal fluid & PSF- Phagolysosomal fluid. Synthetic environmental media are FW- Freshwater and SW- Seawater.

composition of all the simulated biological and environmental media, there was an observable particle aggregation in all fluids with the surface area changing to larger particles after the dissolution experiments as indicated by the size distribution curves and TEM images presented in Fig. 1. During aggregation, particles form a union of nanoparticles through weak van der Waals forces thereby reducing the surface area. All particles showed marked increase in surface area which was more pronounced after the end of the 10-day experiments. It appears that the media composition promotes interactions on the nanoparticle surface thereby encouraging formation of aggregates (Taurozzi et al., 2013). These data indicate that particles will change surface area regardless of the chemical composition and pH of the surrounding media. Particles were partly irregular and semi spherical in shape. There were no observable changes in morphology before and after dissolution experiments. These results were comparable to those observed by other studies Anandgaonker et al. (2019); Korábková et al. (2021); Zhong et al. (2017).

3.1.2. UV–vis

The UV–vis absorption spectra of TiO_2 NPs suspended in simulated biological fluids and synthetic environmental media before and after dissolution experiments are shown in Fig. 2. The surface plasmon resonance of titanium dioxide nanoparticles is usually centred around 300 nm as can be seen in Fig. 2. However, there was a shift to higher wavelengths (320 nm) after exposure to simulated fluids indicative of particle aggregation as the time of exposure to simulated fluids increased. During aggregation smaller particles come together to form a union of nanoparticles with weak van der Waals forces. The number of plasmons as a result of contact decreases, because the specific surface of nanoparticles in the aggregate decreases. This explains the drop in absorption intensity after the particles were in contact with simulated physiological fluids and synthetic environmental media. These results were in agreement with those observed by researchers such as Zhong et al. (2017) whereby metal oxides nanoparticles showed high degrees of aggregation as soon as they were in contact with simulated physiological media. This increase in absorbance intensity at longer wavelengths also has been reported by other studies and has been attributed to the formation of larger NPs through either particle aggregation (De Matteis et al., 2016; H. Wang et al., 2014). Studies have shown that larger particles scatter ultra-violet light at longer wavelengths compared to smaller particles (De Matteis et al., 2016). These results are in strong agreement with the TEM images in Fig. 1 which show nanoparticle aggregation. The NP suspension did not change colour after dissolution experiments, it remained murky white before and after exposure to simulated fluids. There were no observable changes in absorption intensity for all fluids.

3.1.3. XRD

The powder was characterized to determine the crystal phase in which TiO_2 NPs existed in, whether it was rutile or anatase or a mixture of both. The XRD pattern of the TiO_2 nanoparticles is shown in Fig. 3 together with the peak positions at 2θ and their corresponding Miller indices. Research has shown anatase to be more toxic than rutile therefore, in this present research study it was crucial to determine the crystal phase of TiO_2 nanoparticle powder (Endo et al., 1986).

The TiO_2 XRD data demonstrated very sharp peaks. The strong diffraction peaks exhibited by the XRD pattern at angles 25°, 37°, 47°, 55°, 62°, 68°, 70°, 75° and 82° correspond to Miller indices of (101), (004), (200), (211), (204), (116), (220), (215) and (224) plane respectively. The major component of the TiO_2 NPs sample was confirmed to be anatase. However, there was a minor presence of rutile which is represented by the peaks corresponding to (110) and (211) planes. These results are in strong agreement with the standards reported by Endo et al. (1986). Other research have also used SRM NIST 1898 NP reference material and found the composition to be made up of both anatase and rutile (Salou et al., 2020).

3.2. Dissolution in simulated fluids

The dissolution curves of the dissolved titanium ions in various simulated biological fluids and synthetic environmental media are presented in Fig. 4. The dissolution curves are expressed in the amount of dissolved titanium ions (ug L^{-1}) and as a percentage of dissolved ions to the total mass added to the reaction vessel vs time. This method was adopted from these researchers De Matteis et al. (2016); Keller et al.

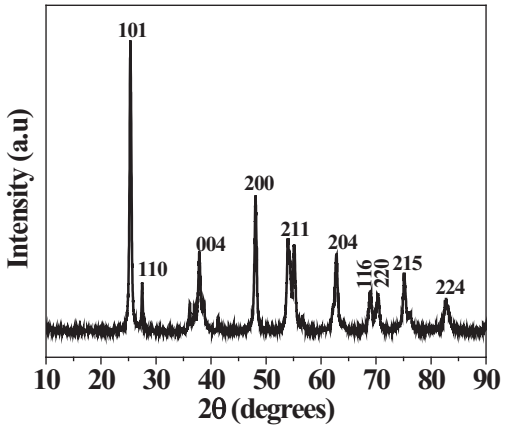

Fig. 3. X-ray diffraction pattern of TiO_2 NPs powder.

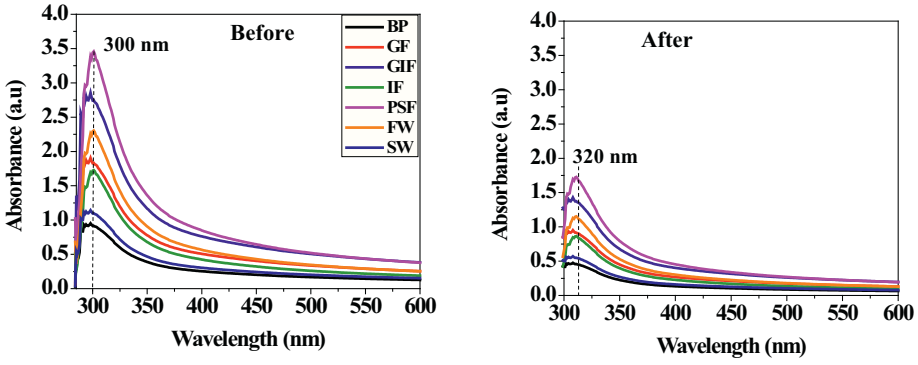

Fig. 2. UV–vis spectra of TiO_2 NPs in simulated body fluids and environmental media before and after dissolution experiments. Simulated biological fluids are BP- Blood plasma, GF- Gamble's fluid, GIF-Gastric fluid, IF- Intestinal fluid & PSF- Phagolysosomal fluid. Synthetic environmental media are FW- Freshwater and SW- Seawater.

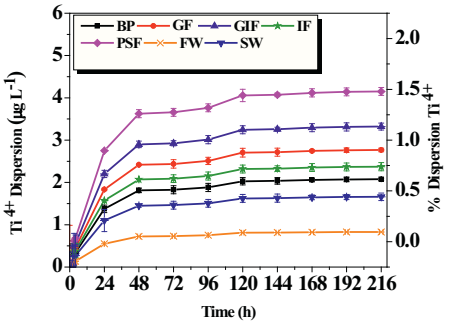

Fig. 4. Concentration of Ti ions dissolved in simulated body fluids and environmental media over a period of 10 days. Simulated biological fluids are BP- Blood plasma, GF- Gamble's fluid, GIF-Gastric fluid, IF- Intestinal fluid & PSF- Phagolysosomal fluid. Synthetic environmental media are FW- Freshwater and SW- Seawater.

(2020); Mbanga et al. (2021).

Very low amount of Ti ions was detected in all simulated fluids meaning TiO_2 NPs did no readily release titanium ions in all the simulated fluids. These low dissolution levels are corroborated by Endo et al. (1986); Murugadoss et al. (2020); Schmidt and Vogelsberger (2006); Taurozzi et al. (2013). A steady increase in the concentration of Ti ions between 0 h to 120 h was observed and reached a plateau after 120 h. These results indicate long-term dissolution is required to get to equilibrium. Under simulated biological conditions, TiO_2 NPs showed significantly higher dissolution in acidic media namely PSF and GIF compared to alkaline media such as BP, GF, IF. In simulated alkaline biological fluids, TiO_2 NPs had higher dissolution in Gamble's fluid but was not statistically significant compared to dissolution in blood plasma and intestinal fluid. Furthermore, when the particles were exposed to simulated environmental conditions, the dissolution was higher in high ionic strength sweater compared to freshwater. Freshwater reaches a point of zero charge whereas the presence of divalent ions in seawater promoted the formation of charged complexes of Ti NPs thereby weakening the metal oxygen bond thus releasing titanium ions (Raza et al., 2016).

3.3. Dissolution kinetics

The kinetic model for dissolution shown in the materials and method section was used to calculate the dissolution kinetics including the dissolution rates and half-times of TiO_2 NPs. Table 2 summarizes the dissolution parameters of TiO_2 NPs in simulated biological fluids and synthetic environmental media.

Titanium dioxide nanoparticles displayed significantly higher dissolution rates in simulated biological media characterized by low pH than at neutral pH. As a result, these nanoparticles released titanium ions significantly faster in phagolysosomal and gastric fluids compared to all other fluids and would take 259 days and 307 days respectively for this process to occur. However, this process would occur at a much slower rate for Gamble's fluid, intestinal fluid and blood plasma taking about 400 days, 400 days, and 409 days respectively before any form of dissolution can occur. Freshwater had the least capacity to dissolve these particles as a result they would take about 881 days for titanium ions to be released from the nanoparticle surface. The half-times of TiO_2 NPs followed the order PSF > GIF > GF=IF> BP > SW > FW.

Table 2
Dissolution kinetics of TiO_2 NPs in simulated biological fluids and synthetic environmental media.

Nanoparticles	Simulated fluids	DF	k (h^{-1})	$t_{1/2}$ (days)	*p-value*
		8			
TiO_2	BP	1	1.69E-03	409	0.0578
TiO_2	GF	1	1.73E-03	400	0.0598
TiO_2	GIF	1	2.25E-03	307	0.0055
TiO_2	IF	1	1.73E-03	400	0.0594
TiO_2	PSF	1	2.26E-03	259	0.0142
TiO_2	FW	1	7.86E-04	881	0.0029
TiO_2	SW	1	8.12E-04	853	0.0042

4. Discussion

These results were comparable to those obtained by other researchers such as Vogelsberger et al. (2008) who investigated the solubility of various oxides in aqueous solution as a function of time. Initially they observed a dissolution maximum which reaches a point of saturation towards the end of the experiments. This phenomenon is known as the kinetic size effect and is inversely related to particle size, meaning that the kinetic size effect decreases with increasing particle size (Vogelsberger et al., 2008). The steady increase in the concentration of Ti ions at the beginning of the dissolution studies, is because for the first few hours the degree of aggregation is not pronounced therefore there still exists enough surface area for the nanoparticle surface to interact with the components of the biological media. Research has indicated that monodispersed particles are more prone to dissolution than particles which combine to form a union via van der Waals forces because monodispersed particles have a larger surface-area-to-volume ratio compared to aggregates. Therefore, this difference in surface area causes monodispersed particles to have a greater ability for dissolution due to the availability of the surface area (León-Silva et al., 2016; Schmidt and Vogelsberger, 2009; Yang et al., 2013).

However, as the period of exposure to simulated fluids and synthetic environmental increased, TiO_2 NPs formed aggregates. The degree of aggregation was more pronounced for all simulated fluids especially towards the end of the dissolution experiments. High concentration of electrolytes in simulated fluids encourage the formation of particle aggregates by reducing the electrostatic forces between the individual particles. Therefore, this causes a reduction in the surface area of the particles thereby inhibiting dissolution. Consequently, this leads to slow dissolution rates of titanium dioxide nanoparticles. This explains the longer half-times of TiO_2 NPs in simulated blood plasma, Gamble's fluid, intestinal fluid, freshwater and more especially seawater. Other researchers have observed that the greater the degree of nanoparticle aggregation, the slower the dissolution rates (Murugadoss et al., 2020).

Similar to particle aggregation, the pH of simulated fluids is a factor that influences the dissolution kinetics of nanoparticles. In this present research study, it was observed that titanium dioxide nanoparticles suspended in simulated acidic media namely phagolysosomal and gastric had significantly higher dissolution rates and shorter half-times. This is because under acidic conditions titanium exists in these charged complexes $[Ti(OH)_2]^+$ and $[Ti(OH)_3]^+$ which facilitate the breakage of the metal – oxygen bond thereby liberating the titanium ions leading to dissolution. However, the higher the pH of simulated fluids the less charged the nanoparticle surface becomes. Schmidt and Vogelsberger (2009) state that the dissolution of oxide nanoparticles is greatly influenced by the surface charge of the respective nanoparticle. Therefore, under alkaline conditions titanium complexes reach a point of zero charge and generally low amounts of Ti ions get released under these circumstances (Xu et al., 2018). This would explain the low dissolution of TiO_2 NPs when exposed to simulated Gamble's fluid, intestinal fluid, blood plasma and freshwater.

Cupi et al. (2016) states that the presence of divalent cations and high ionic strength encourages formation of soluble complexes. When the components of simulated fluids are able to form soluble complexes with the released ions from the nanoparticle's dissolution is enhanced. This could explain high dissolution rate observed for synthetic seawater compared to freshwater. From these results it could be deduced that the dissolution of TiO_2 NPs is strongly influenced by pH and ionic strength of the simulated fluids whereby higher pH resulted in low dissolution whereas high ionic strength encouraged the dissolution of TiO_2 NPs.

There is a lack of research investigating the dissolution of titanium dioxide nanoparticles because they are assumed to be insoluble. This research demonstrate that they are most likely to remain persistence in the environment and under biological conditions and further confirms that are most likely to cause long terms health effects. A study conducted by Zhu et al. (2010) confirm these conclusions.

5. Conclusion

Dissolution is a significant factor that determines the biodurability and persistence of nanoparticles. It can be used to investigate the behaviour of nanoparticles and predict their potential effects on human health and the environment. Significant differences in dissolution behaviour were observed among the studied simulated fluids, which could be connected to pH effects, the ionic strength, and the chemical composition of the simulated media. In all the simulated body fluids and environmental media, the dissolved Ti ions were present in very low concentrations. Furthermore, most of the titanium dioxide nanoparticles remained in particulate form after having been exposed to simulated fluids for a period of 10 days. This is indicative of insoluble particles. The dissolution kinetics of titanium dioxide nanoparticles follow first order reaction kinetics and are generally characterized by low dissolution rates and long half-times. Therefore, these nanoparticles are resistant to dissolution and will most like accumulate in the body, remain persistent in the environment, and cause both short- & long-term health effects and show high environmental persistency.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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