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The role of natural processes and surface energy of inhaled engineered nanoparticles on aggregation and corona formation

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Abstract

The surface chemistry of engineered nanoparticles (ENPs) becomes more important as their size decreases and enters the nanometer-range. This review explains the fundamental properties of the surface chemistry of nanoparticles, and argues that their agglomeration and the formation of corona around them are natural processes that reduce surface energy. ENP agglomeration and surface corona formation are further discussed in the context of inhaled ENPs, as the lung is a major port of ENP entry to the body. The pulmonary surfactant layer, which the inhaled ENPs first encounter as they land on the lung surface, represents a unique environment with a variety of well-defined biomolecules. Many factors, such as hydrophobicity, surface charge of ENPs, protein/phospholipid concentrations of the alveolar lining fluid, etc. influence the complex processes of ENP agglomeration and corona formation in the alveolar lining fluid, and these events occur even before the ENPs reach the cells. We suggest that molecular dynamic simulations can represent a promising future direction for research of the behavior of inhaled ENPs, complementing the experimental approaches. Moreover, we want to remind biologists working on ENPs of the importance relationship between ENP surface energy and size.

Keywords

nanoparticle; surface energy; agglomeration; corona formation; pulmonary surfactant; molecular dynamics

Introduction

When the size of particles is much larger than the size of their components (atoms, molecules), their behavior can be described using a concept of continuum. However, as the size of particles decreases and enters the nanometer-range, the particle components start to be seen more like individual entities, thus a concept of continuum may be no longer applicable. The size-dependent properties of engineered nanoparticles¹ (ENPs) (e.g.,

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Grassian et al., 2015) may be classified into two categories; i) properties which change gradually with decrease in particle size, which depend on the ratio of atoms at the surface relative to atoms in the bulk, expressed as a *surface-to-volume ratio*, A/V . As these properties change gradually with the changes in particle size, they may be described by both discrete and continuum concepts. ii) Quantum effects which are discontinuous behavior of the ENPs, and these are associated with the dislocation of electrons.

This review paper mainly focuses on the first category of characteristics, readers interested in the quantum effects can find excellent articles elsewhere (Harrison 2005; Roduner 2006). The goal of this article is to explain that aggregation and corona formation with bio-molecules are two ways to reduce surface energy of inhaled ENPs.

In the following, we will first explain why surface atoms have higher energy (i.e., energy needed to break bonds between atoms to create a surface) than the atoms at the interior and why this difference increases as the size of particles gets smaller. We will also describe the difference in energy levels between the surface and the interior of the ENPs in thermodynamic terms. Then, we will discuss how ENPs reduce their excess surface energy by an increase in their size (using ENPs in water as an example) or by modifying their surface by adsorbing surrounding bio-molecules. We focus on the events that occur after ENPs deposit on the surface of the lung. We will conclude this review by discussing molecular dynamic approaches in the study of ENP behavior in biological environments. We will suggest future directions, the most efficient and systematic ways we envision to study this important subject.

Section 1 Surface vs. core of the particles: Thermodynamical considerations

The environment of the atoms at the surface of ENPs is different from that of the atoms in the interior (or bulk) (Fig. 1). While each atom in the interior of ENPs is surrounded by similar ones in all directions (Fig. 1a), the atoms at the surface have asymmetrical environment, namely, they have neighbor atoms only on one side of the interface (Fig. 1b). As a result, while there is no net force exerted on the bulk atoms, the atoms at the surface experiences asymmetrical force field.

This difference in force field is manifested in higher energy levels for surface atoms than that of the bulk atoms. This excess energy at the surface called surface energy (e.g., Roduner 2006; Somorjai & Li, 2010; Cao & Wang, 2011). It is important to note that higher² surface energy means an energetically unfavorable/unstable condition (otherwise, the bulk would tend to break into many pieces and to create more surfaces in order to achieve more energetically favorable state).

¹According to Merriam-Webster dictionary, the definition of nanoparticle is that a microscopic particle whose size is measured in nanometers. Definitions of nanoparticles and nanomaterials by various organizations are listed in Table 1. 1 of Horikoshi and Serpone (2013)

²The high surface energy of nanoparticles can be used for catalytic activity (Somorjai & Li, 2010).

As mentioned in the Introduction, one of the size-dependent variables of ENPs is expressed as *surface-to-volume ratio*, A/V (e.g., Oberdorster et al., 2005). For spherical particles of diameter d , A/V is given as

$$\frac{A}{V} = \frac{4\pi(\frac{d}{2})^2}{4\pi(\frac{d}{2})^3} = \frac{6}{d} \quad \text{eq. (1)}$$

As the ratio³, A/V , is a continuous function of d , thus the size-dependent effects of ENPs expressed by A/V occur continuously and proportionally with changes of particle size (Fig. 2). In other words, to describe this size-dependent effect of ENPs, the demarcation between the applicability of the “discrete” and “continuum” concepts is not as obvious as in the case of the quantum effects.

Following Somorjai and Li’s excellent argument (Somorjai and Li, 2010), surface phenomena can be summarized in terms of thermodynamics as follows. Suppose that the ENP contains a total of N atoms. Now, let E and S denote the energy and entropy⁴ of the ENP per atom, respectively. E^S and S^S denote specific values (per unit area) of surface energy and surface entropy, respectively, where the superscript “ S ” indicates surface. With these symbols, the total energy (E_{total}) and total entropy (S_{total}) of the ENP can be expressed as

$$E_{total} = NE + AE^S \quad \text{eq. (2)}$$

$$S_{total} = NS + AS^S \quad \text{eq. (3)}$$

where A is surface area. Similarly, Gibbs total free energy⁵ (G_{total}) of the ENP may be expressed as

$$G_{total} = NG + AG^S \quad \text{eq. (4)}$$

If the change in Gibbs total free energy dG_{total} is due only to the change in surface free energy (we assume that the pressure P and temperature T in the bulk are constant),

³The ratio A/V can also be expressed in terms of a ratio between the number of atoms on the surface and atoms in the interior, which is called the dispersion F (Rudner 2006). Suppose that the ENP contains a total of N atoms. The diameter d be scaled with the inverse third power of the number of atoms, therefore the dispersion F is given as a function of $N^{1/3}$.

⁴Entropy of a system is a state value which measures the number of ways the energy can be stored in that system. It can be interpreted as the degree of disorder in the system.

⁵Gibbs total free energy is the energy that can be converted into work at constant temperature and pressure.

$$(dG_{total})_{T,P} = d(G^S A) = \left(\frac{\partial(G^S A)}{\partial A} \right)_{T,P} dA = \left[G^S + A \left(\frac{\partial G^S}{\partial A} \right)_{T,P} \right] dA \quad \text{eq. (5)}$$

If the new surface is created by adding atoms from the bulk (rather than fixing the number of atoms at the surface, e.g., stretching the already existing surface, so that Gibbs surface free energy G^S does not change with A),

$$\left(\frac{\partial G^S}{\partial A} \right)_{T,P} = 0 \quad \text{eq. (6)}$$

Thus, with eq. (6), eq. (5), the change in Gibbs total energy dG_{total} becomes,

$$(dG_{total})_{T,P} = G^S dA \quad \text{eq. (7)}$$

At the same time, dG_{total} can also be written in terms of P and T with the inclusion of the surface work (γdA , where γ denotes surface tension) (Somorjai and Li, 2010) as,

$$dG_{total} = -SdT + VdP + \gamma dA \quad \text{eq. (8)}$$

In the case of constant P and T as the above eqs. (5) – (7) are written, the eq. (8) can be reduced to

$$(dG_{total})_{T,P} = \gamma dA \quad \text{eq. (9)}$$

Comparing eq. (7) and eq. (9) the specific surface free energy G^S is equal to the surface tension γ .

$$G^S = \gamma \quad \text{eq. (10)}$$

As γ is always positive (Somorjai and Li, 2010), G^S must be always positive. Since in the thermodynamic equilibrium, the minimum energy is the favorable state, positive surface energy is not an energetically favorable situation. Therefore, the surface energy of ENPs is reduced by the naturally occurring processes of (i) agglomeration (i.e., reducing the surface-to-volume ratio) and/or (ii) adsorption of molecules from the surrounding to lower surface energy (e.g., Wohlleben et al., 2016). In what follows, we demonstrate these processes by

describing the ENPs' aggregation in water and the formation of corona on the surface in hypophase as examples, respectively

Section 2 ENPs' aggregation in water

When ENPs are in close proximity, they tend to agglomerate to increase the particle size, thus to reduce surface energy. This process occurs by taking advantage of the attractive van der Waals interaction forces which act between the ENPs. When the particles are within a "double layer"⁶ distance, however, electrostatic repulsive forces develop between them and these counter-balance the attractive van der Waals interaction forces. The DLVO theory (first developed by Boris Derjaguin [1939], then extended jointly with Lev Landau [1941], and later by Evert Verwey and Jan Overbeek [1948])⁷ describes that the behavior of ENPs in a solution is the result of the combination of these two forces as a function of the distance between the ENPs (Fig. 3).

In the DLVO theory, there are two energy minimums (the primary and the secondary) separated by an energy barrier. If the size of the energy barrier (repulsion vs. attraction) is small, the kinetic energy of the ENPs in the secondary minimum would overcome the energy barrier and could move to the primary minimum which is a more preferable state than the secondary minimum (due to lower energy state). This causes agglomeration of the ENPs. Since the van der Waals attraction force is strong in short distance, re-dispersion of the ENPs is difficult to achieve once the ENPs are in the primary minimum.

We explained above the ENPs' natural agglomeration process based on the DLVO theory, however, the theory is usually introduced to describe electrostatic stabilization (i.e., avoiding ENPs agglomeration). As both the van der Waals attractive forces and electrostatic repulsive forces are determined by many factors (e.g., ionic strength of solution), the combination of these two forces (i.e., the shape of the red line in Fig. 3) can be manipulated in many ways to control the size of the energy barrier of ENPs in solution. If we can make the energy barrier large enough (which usually requires additional energy), the ENPs remain in the secondary minimum and do not agglomerate. Although the stabilization techniques aimed to prevent agglomeration are outside of the scope of this review, it is worth mentioning that a variety of methods have been developed to achieve this goal (e.g. steric (polymeric) stabilization (Rivera-Gil et al, 2013). Readers interested in these techniques can find excellent articles elsewhere (e.g., Norde 2003; Cao & Wang, 2011).

⁶When an ENP is suspended in solution, it often exhibits charge on its surface due to asymmetrical bonds of surface atoms, or simply adsorb ions on the surface. To balance the surface charge, ions with the opposite charge move towards the surface and form a layer, called Stern layer (Fig. 4). For instance, let us consider the situation that a negatively charged ENP is suspended in water and positively charged hydrogen parts of water molecules bound to the surface. The outside of the Stern layer will be a layer, called "diffusion layer" which is rich in negative ions and the charge decays exponentially towards neutrality in the bulk (Fig. 4). The combination of "Stern layer" and "diffusion layer" is called "double layer".

⁷Initially, this theory was formulated for two identical interfaces (i.e., aggregation of identical particles), but later, it was extended to particles with different size, including a flat surface. Reader interested in the DLVO theory is referred to textbooks (e.g., Russel et al., 1989; Elimelech et al. 1995; Israelachvili 2011) for more detailed treatment

Section 3 Adsorption of biomolecules to lower the surface energy: Corona formation

The objective of this section is to familiarize the reader with the idea that corona formation with bio-molecules is another way for the ENPs to reduce surface energy, rather than to simply review corona formation in detail. Readers interested in the detailed events involved in the formation of corona with bio-molecules around ENPs can find excellent articles elsewhere (e.g., Nel et al., 2009; Gehr et al., 2011; Monopoli et al., 2012; Kreyling et al., 2014; Lynch 2015).

The concept of particles adsorbing serum proteins on their surface (“opsonization”) was first suggested in 1903 (Wright et al., 1903). The binding of proteins to particle surface is a dynamic process, it occurs through sequential adsorption and desorption cycles –called the “Vroman effect” (Vroman, 1962). This basic concept has recently resurfaced in the emerging field of nanotechnology (Lundqvist et al., 2008), since the relative importance of surface atoms to the bulk atoms increases (i.e. an increase of asymmetric force field, surface energy) as the size of particles decreases into the nanometer range (see Figs. 1 & 2). As described in Section 1, lowering surface energy is a natural process. Thus, once the ENPs enter an organism (biological milieu), they spontaneously adsorb biomolecules (e.g., Ruge et al., 2012; Dawson et al., 2007). Thermodynamically, this is expressed as $\Delta G_{ads} < 0$ where ΔG_{ads} the net change of Gibbs free energy by binding; the change is negative showing that the adsorption process occurs spontaneously (Norde 2003).

The ENPs entering a bio-fluid encounter a mixture of a variety of biomolecules (e.g. proteins, lipids, ions, and enzymes), and are evolving systems that are changing by exposure to different biomolecule-rich environments. This review article focuses on ENPs in the lungs because 1) the lungs are one of the major organs where ENPs interact with bio-fluids, 2) the lungs could be considered to have two compartments; the conducting airways in the proximal part of the respiratory tract and the gas exchange region in the distal part of the respiratory tract. Inhaled ENPs mainly deposit in the gas exchange region due to their small size, and 3) the encounter of ENPs with the lungs is unique due to the presence of pulmonary surfactant. Thus, in the following we briefly cover the topic of corona formation with the constituents (proteins and phospholipids) of the pulmonary surfactant (e.g., Gasser et al., 2012).

On the lung surface, inhaled particles first encounter pulmonary surfactant layer which reside the top layer of the alveolar lining fluid. (Bastacky et al., 1995) (Fig. 5). Pulmonary surfactant comprises 85–90% w/w phospholipids and 10 % w/w proteins (Goerke 1998). The saturated lipid dipalmitoyl phosphatidylcholine (DPPC) is the most abundant component, followed by monoenoic phosphatidylcholine, cholesterol, and anionic phospholipids (Clements and Avery 1998). Among the surfactant-associated proteins, hydrophilic surfactant proteins SP-A (90% w/w of the total surfactant proteins) and SP-D (~3% w/w of SPs) are the major proteins (McCormack and Whitsett, 2002; Pastva et al., 2007), but hydrophobic surfactant proteins SP-B and SP-C are also present (Perez-Gil 2008a, Perez-Gil 2008b). Although the amount of SP-B and SP-C is much smaller than SP-A, these hydrophobic proteins play a critical role in surfactant function, namely, they lower

the surface tension and avoid alveolar collapsing (Parra et al. 2013). Indeed, studies in mice lacking expression of SP-B have shown that these mice suffered from lethal neonatal respiratory distress (Melton, et al. 2003).

Landing on the lung surface, the ENPs adsorb phospholipids and proteins of the alveolar lining fluid, especially of the pulmonary surfactant⁸; and this takes place almost instantly (Ruge, et al. 2012). Therefore, it is reasonable to assume that the subsequent interactions of ENPs with cellular structures of the lung occur mostly via the phospholipid/protein-nanoparticle complex and not with bare nanoparticle surfaces (Lynch et al., 2007; Lynch & Dawson 2008; Schleh and Hohlfeld 2009; Walczyk et al., 2010).

There are many reported studies on corona formation with surfactant-associated proteins on ENPs. Beck-Broichsitter and his colleagues extensively studied how corona formation with SP-B and SP-C proteins on ENPs affects surfactant function, such as dynamic surface tension behavior (e.g., Beck-Broichsitter et al. 2011, 2014a, 2014b). Using two polystyrene ENPs of the same size (~100nm diameter) but with opposite zeta potential (−46 mV vs. +60 mV), they demonstrated that the negatively charged ENPs adsorbed positively charged SP-B and SP-C proteins (Possmayer et al., 2001; Zhang et al., 2011), leading to the alteration of surfactant function due to the formation of SP-B/SP-C coronas around ENPs. Also, using *Infasurf* which contains only the hydrophobic components of natural surfactant (Notter et al., 2002; Zhang et al., 2011), Zuo' group studies the effects of hydrophobicity and surface charge of ENPs on hydrophobic, positively charged SP-B and SP-C (Fan et al., 2011; Hu et al., 2013). Molecular dynamic simulations by Hu et al. (2013) clearly showed detailed effects of hydrophobicity and the surface charge of ENPs on forming SP-B/SP-C coronas around ENPs which in turn influence particle translocation across the pulmonary surfactant and demonstrated their delicate interplay. Note that since natural surfactant possesses both hydrophobic (SP-B & SP-C) and hydrophilic (SP-A & SP-D) components, testing the effects of hydrophobicity and surface charge of ENPs with *Infasurf* is not sufficient; further studies focusing on SP-A and SP-D are necessary which is discussed in the next few paragraphs.

Without mucociliary clearance⁹ mechanisms, the alveolar macrophages (AM) represent the sole means of particle clearance in the lung periphery (Konduru et al., 2014). Forming corona on the ENPs, the hydrophilic surfactant proteins, SP-A and SP-D, enhancing phagocytosis of ENPs by AMs, play an important role in the immune defense of the lungs (Malloy et al. 2002, Reid et al. 2005). Similarly to studies on the bio-interactions of ENPs with SP-B and SP-C, there are many reports addressing the bio-interactions of ENPs with SP-A and SP-D. For instance, using magnetite NPs (mNPs) with various coating, Lehr's group studied the effects of SP-A and SP-D on AM clearance (Ruge et al., 2012). They

⁸In the 1990's Schürch and colleagues developed the idea that surfactant displaces particles toward the epithelium in the airways and alveoli (e.g., Schürch et al., 1990; Geiser et al., 2003). However, Mijailovich et al. (2010) demonstrated that particles smaller than the thickness of the hypophase cannot reach the cell layer only by the forces described by Schürch and colleagues.

⁹Epithelial cells of the conducting airways possess cilia which are surrounded by an epithelial lining fluid (i.e., mucus) to maintain the airway wall moisturized and clear inhaled particles and pathogens landed on the conducting airways. As the cilia beat toward the mouth, the mucus containing the inhaled particles and pathogens moves toward the mouth and gets cleared from the lungs. This is called mucociliary clearance. On the other hand, the epithelial cells in the gas exchange region do not possess cilia. Thus, the alveolar macrophages (AM) represent the sole means of particle clearance in the lung periphery. About ten years ago, Rothen-Rutishauser's group suggested that interplay between AMs and dendritic cells is involved in the transport of particles across the epithelial cell wall barrier (e.g., Rothen-Rutishauser et al. 2005).

found that coating of mNPs with hydrophilic starch (ST-mNP) strengthens corona formation with SP-D, while coating the mNPs with hydrophobic phosphatidylcholine (PL-mNP) enhances corona formation with SP-A. Since the binding forces between proteins and ENPs are likely to be determined by the sum of physicochemical interactions (e.g., electrostatic or hydrophobic interaction) and the material-specific molecular interactions, they interpreted the observed difference in SP-A and SP-D binding as SP-D showing interaction with more polar substrates, whereas SP-A would preferably bind to lipophilic molecules since SP-A is more hydrophobic than SP-D.

So far, we have only discussed surfactant-associated proteins (SP-A, SP-B, SP-C, and SP-D), but the pulmonary surfactant is a complex mixture composed of both lipids and proteins, thus, the inhaled ENPs also encounter surfactant lipids. Compared with the abundance of reports about protein-corona formation on ENPs, corona formation with lipids is less studied. Among the relatively few studies, we will discuss two reports – both from the Lehr laboratory. Ruge et al (2012), while reporting an important role for surfactant lipids in the clearance of ENPs by AMs, demonstrated that surfactant lipids also modulate protein-mediated particle agglomeration. Recently, performing proteomic and lipidomic analyses of coronas formed on ENPs with porcine pulmonary surfactant, Raesch et al. (2015) showed that whereas the formation of protein corona significantly depends on the surface characteristics of ENPs, the formation of lipid corona is not determined by the particle surface properties. As there are abundant lipids in bio-fluids which ENPs encounter before making contact with cells, and lipid coronas can modulate particle aggregation, it is important to study the interactions between lipids and ENPs in order to elucidate ENP behavior in bio-fluids,

Much of the current knowledge of bio-interactions of ENPs is generated by lung cell culture studies (Cohen et al., 2013; Deloid et al., 2014), therefore we need to discuss protein-corona formation in *in-vitro* cell culture systems. Incubating silver nanoparticles of two different sizes (20 nm vs. 110 nm diameter) in cell culture medium (DMEM supplemented with 10 % fetal bovine serum) Shannahan et al (2013) investigated corona formation. Proteomic analyses of the corona formed on ENPs showed that the complexity of the protein corona (number of protein components) bound to the larger particles was 1.7 times higher than that of bound to the smaller particles. Remarkably, the protein corona constituents of the smaller particles were significantly more hydrophobic than those of the larger particles. Moreover, the variety of proteins (number of distinct constituents) bound per unit surface area of the particles was more than 3 times higher in the case of the smaller particles than the larger ones.

The concepts of “hard corona” and “soft corona” (Cedervall et al., 2008; Walczyk et al., 2010; Monopoli et al., 2011; Milani et al., 2012; Pyrgiotakis et al., 2013, 2014) are important to consider when we envision the race between particle agglomeration and corona adsorption in order to reduce surface energy. The “hard corona” represents a strongly bound layer, driven by high affinity toward the surface of the ENPs. The “soft corona”, on the other hand, represents a loosely bound layer, having low affinity to the ENP surface and a high exchange rate with other proteins. In addition to protein corona¹⁰, the formation of lipid corona also needs to be considered, since lipid coronas may modulate protein-mediated

particle agglomeration (Ruge et al., 2012). In the race between particle agglomeration and corona formation to reduce the surface energy of the ENPs, a crucial factor which needs to be also considered is the time. Agglomeration and corona (hard and soft, protein and lipid) formation are both dynamical processes, each depend on many factors (physicochemical properties of the particles, characteristics of the surrounding environment, etc.) and are finely orchestrated in time. Thus, it is an exceedingly formidable task to investigate these complex processes using only experimental approaches. We suggest, therefore, that a systematic approach based on molecular dynamic simulations can complement experimental studies, and we will discuss this approach next.

Section 4 Molecular Simulation

To supplement and complement experimental work on nano-toxicology, one would like a theoretical framework that might allow interactions of ENPs with biological molecules and tissues to be understood and categorized, as quantitatively as possible. However, ENPs by definition lie between molecular and continuum realms and their interactions with each other and with bulky amphiphilic and amphoteric biological molecules such as lipids and proteins are so complex that conventional continuum descriptions are rendered impotent (Batista et al. 2015). This motivates pursuit of understanding through molecular simulations, the most common of which is molecular dynamics (MD). MD simulations can be carried out with atomistic resolution, or with “coarse-grained” (CG) resolution, where in the latter 3 or 4 “heavy” atoms (i.e., non-hydrogen atoms) are lumped into each spherical bead. Molecular dynamics simulations solve Newton’s equations of motion for all beads, as they interact with each other through semi-empirical force fields that described the hard-core repulsion, van der Waals attraction, and electrostatic interactions. Simulations containing hundreds of thousands and even millions of atoms are becoming routine, encompassing systems 10s of nanometers in size, and with simulation times ranging into the microseconds (Bjellmar et al. 2009; Dror et al. 2009) or even milliseconds with the aid of specialized hardware and software (e.g., the computer “Anton”) (Dror et al. 2010). In addition, well designed CG simulations now allow runs to be speeded up a thousand-fold, with some loss of resolution (Monticelli et al. 2008). With ever-faster computers such simulations will become routine, and promise to revolutionize our ability to predict nanoparticle interactions. MD simulations have been shown to be capable of predicting nanoparticle interactions at least qualitatively; for example the unusual stability of charged nanoparticles in the presence of large counterions, which has long been observed experimentally, has recently been predicted by molecular simulations (Guerrero-García et al., 2013). There is now a large literature demonstrating that molecular dynamics simulations can accurately predict a wide variety of association phenomena, if the force field is chosen carefully (see for example, Tang et al 2014). Thus, there is good reason to be optimistic about the potential for MD simulations to greatly improve our understanding of the interactions of ENPs with biological molecules.

Many MD simulations of ENPs to date have focused on interactions of ENP’s with lipid membranes and proteins, but the interest has primarily focused on application to bio-medicine, such as bio-imaging or the delivery of a drug payload through a cell membrane

¹⁰The topics of “hard corona” and “soft corona” are usually regarding protein corona.

(Makarucha et al. 2011). In particular, MD studies have been conducted on the interactions of cell membranes and several types of nanoparticles including fullerenes (Bedrov et al. 2008; Li et al. 2007; Qiao et al. 2007; Wong-Ekkabut et al. 2008), carbon nanotubes (Shi et al. 2008; Wallace and Sansom 2008) and gold nanoparticles (Ghorai and Glotzer 2007). Most of the simulation work to date has focused on hoped for efficacious effects of ENPs on human health through predicted binding of cargo to the ENP and transport through the lipid membrane, which can now be simulated directly. However, there is also a rapidly growing interest in applying molecular simulation tools to the field of nano-toxicology, which is the study of undesired effects of ENPs resulting either from the deliberate introduction of ENPs into the body for therapeutic reasons, or from inadvertent exposure to toxic ENPs manufactured for non-medical purposes.

A recent review by Yanamala et al. (2013) describes a number of recent MD and molecular docking simulations that show that fullerene and single-walled carbon nanotubes can interfere with the binding sites of enzymes such as glutathione-s-transferase, can block ion channels, and can interact with actin and DNA, with possible negative consequences. There has been some recent work on the binding of proteins to hydrophobic ENPs, primarily fullerene and carbon nanotubes, shown to be due to pi-pi interactions between the ENP and the aromatic residues in proteins (Ge et al. 2011; Sasidharan et al. 2011; Zuo et al. 2010). Simulations have also revealed that positively charged amino acids can play a role in the adsorption of proteins onto ENPs (Hung et al. 2013), and thus formation of a biological “corona” on such ENPs. Despite this work, and the evident importance of corona formation on the biological outcome of exposure to ENPs (Monopoli et al. 2012), little to no simulation work seems to have been carried out to date on the corona formation on common inorganic ENPs, such as metal oxide titanium oxide, or cerium oxide. Such work can, in fact, now be carried out, at atomic resolution on flat surfaces of ENP material or on very small (< 10 nm diameter) NPs, or on somewhat larger (< 30 nm) ENPs with CG simulations. While length and time scales accessible to such methods are still very limited, it should be possible to determine the relative strength of interaction of lipids, peptides, and eventually whole proteins to such ENPs using MD simulations and to correlate this with ENP properties, such as wettability, charge, polarity, size, shape, etc. A deeper understanding of the relationship between ENP composition and corona formation, assisted by MD simulations, would provide a vital element in the development of “taxonomy” of nano-toxicology. This in turn, could help us to anticipate better the health risks of various types of ENPs.

Future directions

The behavior of ENPs in biological environments is highly complex. It depends on their physicochemical properties, such as size, shape, surface chemistry, charge, hydrophobicity, etc. as well as characteristics of the environment, such as ionic strength, constituents of the solution, the amount of constituents in the solution, etc. ENPs may aggregate first and then form corona around the aggregate or ENPs may form corona around individual particles first and then aggregate. Although both processes lower the surface energy of ENPs, the order of these two events is likely to be very important for the cells which encounter the ENPs. The elucidation of these processes requires knowledge of many different fields (e.g., chemistry,

physics, material science, biology), and it is a formidable task (at least experimentally) as many factors influence or determine them. Witnessing rapid advancement in computer science, such as dramatic increases in the speed of calculations, handling of large data sets with a new hardware design (e.g. dataflow computer architectures), we suggest that molecular dynamic simulations based on multidisciplinary knowledge, may represent a promising alternative approach to experimental research on the behavior of nanoparticles.

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Highlights

- The surface chemistry of engineered nanoparticles becomes more crucial as their size decreases
- The agglomeration of engineered nanoparticles reduces the surface energy
- The formation of corona (proteins and lipids) around engineered nanoparticles reduces the surface energy
- Pulmonary surfactant plays an important role to form coronas around engineering nanoparticles
- Molecular dynamic simulations are a promising approach to study bio-interaction between engineered nanoparticles and the lungs

Figure 1. Surface atoms vs. bulk atoms. As the size of particles decreases and enters the nanometer-range, the particle components (atoms) start to be seen more like individual entities. (a) The atoms in the interior of the ENPs are surrounded by similar ones in all directions. (b) The atoms at the surface have neighbor atoms only on one side of the interface.

Figure 2.
 A/V ratio as a function of particle diameter. The A/V ratio rapidly increases as d decreases.

Figure 3. The DLVO theory. The total interaction between two particles is a combination of electrostatic repulsion and van der Waals attraction shown in red line.

Figure 4. Electrical double layer. The double layer [the Stern layer and the diffusion (Gouy) layer] is formed around a charged particle.

Figure 5.

Alveolar walls are covered with fluid (called “hypophase”). The top layer of hypophase is the pulmonary surfactant layer, which contains phospholipids and proteins (SP-A, B, C, D). On the lung surface, the inhaled ENPs first encounter this layer, and adsorb bio-molecules of the surfactant layer almost instantly. Therefore, the subsequent interactions of ENPs with the body (e.g, lung cells, blood, etc.) are assumed to occur mostly via the phospholipid/protein-nanoparticle complex and not with bare nanoparticle surfaces.