

## Review article

# 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 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. These series of events occur even before the ENPs reach the cells. Furthermore, for systematic and mechanistic understanding of such interactions at atomic scale, we suggest that molecular dynamic (MD) simulations can represent a promising future direction for research of the behavior of inhaled ENPs, complementing the experimental approaches. MD simulations may provide important insights into the nature of ENP-biomolecular interactions at the alveoli. In this review, we want to draw attention of biologists working on ENPs to the importance of the relationship between ENP surface energy and particle size.

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## Contents

1. Introduction . . . . .	38
2. Surface vs. core of the particles: thermodynamical considerations . . . . .	39
3. ENPs' aggregation in water . . . . .	40
4. Adsorption of biomolecules to lower the surface energy: Corona formation . . . . .	41
5. Molecular simulation . . . . .	42
6. Future directions . . . . .	43
Acknowledgement . . . . .	43
References . . . . .	43

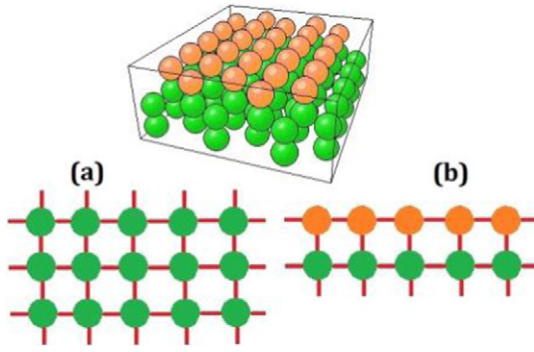
## 1. Introduction

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 nanoparticles<sup>1</sup> (ENPs) (e.g., 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.

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<sup>1</sup> According 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).



**Fig. 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.

ii) Quantum effects which are discontinuous behavior of the ENPs, and these are associated with the dislocation of electrons.

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

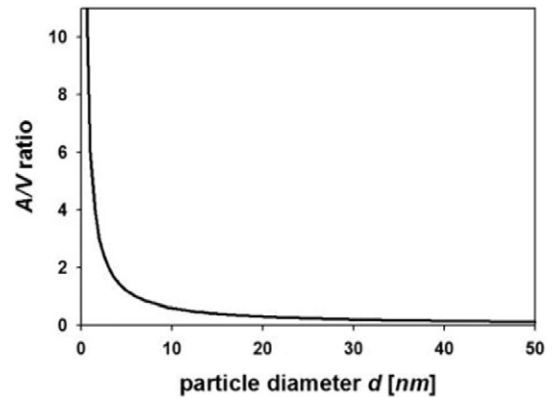
In the following sections, we first explain why surface atoms have higher energy (i.e., energy needed to break bonds between atoms to create a surface) than the atoms at the interior and why this difference increases as the size of particles gets smaller. We also describe the difference in energy levels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

## 2. 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 experience 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 is called surface energy (e.g., Roduner, 2006; Somorjiaj and Li, 2010; Cao and Wang, 2011). It is important to note that higher<sup>2</sup> surface energy means an energetically unfavorable/unstable condition (otherwise, the bulk would tend to break into many pieces and would create more surfaces in order to achieve more energetically favorable state).

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



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

given as:

$$\frac{A}{V} = \frac{4\pi\left(\frac{d}{2}\right)^2}{\frac{4}{3}\pi\left(\frac{d}{2}\right)^3} = \frac{6}{d} \quad (1)$$

As the ratio<sup>3</sup>  $A/V$  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 Somorjiaj and Li's excellent argument (Somorjiaj 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 entropy<sup>4</sup> 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:

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

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

where  $A$  is surface area. Similarly, Gibbs total free energy<sup>5</sup> ( $G_{total}$ ) of the ENP may be expressed as:

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

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

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

<sup>3</sup> The 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  $F$  (Roduner, 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  $N^{1/3}$ .

<sup>4</sup> Entropy 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.

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

<sup>2</sup> The high surface energy of nanoparticles can be used for catalytic activity (Somorjiaj and Li, 2010).

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