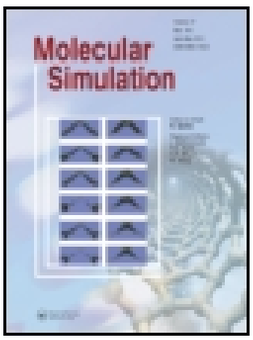

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Effect of the surface charge density of nanoparticles on their translocation across pulmonary surfactant monolayer: a molecular dynamics simulation

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ABSTRACT

Interaction between nanoparticles (NPs) and pulmonary surfactant monolayer plays a very significant role in nanoparticle-based pulmonary drug delivery system. Previous researches have indicated that different properties of nanoparticles can affect their translocation across pulmonary surfactant monolayer. Here we performed coarse-grained molecular dynamics simulation aimed at nanoparticles' surface charge density effect on their penetration behaviours. Several hydrophilic nanoparticles with different surface charge densities were modelled in the simulations. The results show that NPs' surface charge density affects their translocation capability: the higher the surface charge densities of NPs are, the worse their translocation capability is. It will cause the structural changes of pulmonary surfactant monolayer, and inhibit the normal phase transition of the monolayer during the compression process. Besides, charged NPs can be adsorbed on the surface of the monolayer after translocation as a stable state, and the adsorption capability of NPs increases generally with the increase of surface charge densities. Our simulation results suggest that the study of nanoparticle-based pulmonary drug delivery system should consider the nanoparticles' surface charge density effect in order to avoid biological toxicity and improve efficacy.

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KEYWORDS
Surface charge density; nanoparticles; translocation; pulmonary surfactant monolayer; molecular dynamics simulation

1. Introduction

It is well known that inhaled nanoparticles (NPs) have obtained intense interests for their extensive biomedical applications, such as specific targeting, bio-imaging, drug delivery, etc. For example, using inhaled NPs as pulmonary drug delivery carrier has showed comprehensive promises for treating lung diseases due to NPs' good administration, higher bioavailability and low side effects [1,2]. Besides, NPs are able to enter the respiratory system because of the large surface area, abundant vascular tissue and low acidity in the human lungs. However, accumulating researches show that some inhaled NPs may cause serious adverse effect to the human beings, such as blood disease, pneumonia and nephrotic syndrome, presumably similar to the toxicological effect of ultrafine particulate matters [3,4]. Therefore, understanding the interaction between NPs and pulmonary surfactant monolayer has attracted great attention for improving the nanoparticle-based pulmonary drug delivery system and avoiding NPs' potential toxicological effect.

As mentioned above, inhaled NPs are an excellent drug carrier to the pulmonary drug delivery system. Hence, much attention should be paid to the translocation mechanism of NPs across the lung barrier and the relative side effects of NPs. In the present work, the most studied lung barrier is the pulmonary surfactant. The pulmonary surfactant bathes the inner surface of the lung, which lines the entire alveolar surface and is considered to be the first line of lung defense. It can reduce alveolar surface tension at the air–liquid interface in order to maintain the normal respiratory mechanics characteristics, hence it can effectively prevent the collapse of the alveolar structure during the respiration process [5]. Moreover, as a complicated network of extracellular membranes that overlies the alveolar epithelium and alveolar macrophages, pulmonary surfactant can also defend against inhaled pathogens and protect against injury to be an anti-inflammatory and antioxidant. Therefore, lack of pulmonary surfactant, whether caused by premature birth, lung injury, or mutations in genes critical to surfactant production or function, causes respiratory failure [6]. The pulmonary surfactant is a lipoprotein complex consisting of approximately 90% lipids and 10% proteins [7]. Among them, dipalmitoyl phosphatidylcholine (DPPC) is the main component of lipids [5,8], therefore, DPPC in the gas–liquid interface is often used to simulate the pulmonary surfactant. Both experiments and computer simulations [6,8], the normal phase transition of the lipid monolayer has been proved to play a quite important role in regulating the biophysical function of the pulmonary surfactant. During the expansion process, the lipid monolayer becomes a liquid-expanded (LE) phase from a liquid-condensed (LC) phase. During the compression process, the lipid monolayer changes the direction of its phase transition and becomes an LC phase from an LE phase. The normal phase transition continues throughout the entire respiratory system cycles.

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Previous researches [9–11] have indicated that different properties of NPs can affect their translocation across pulmonary surfactant monolayer, including size, hydrophobicity, shape, surface charge density. Surface charge density has an important impact on the interaction between NPs and pulmonary surfactant monolayer [12,13]. It can determine the behaviour of NPs in the cellular or extracellular environment [14,15]. For example, Lin et al. [16] have indicated that NPs with different surface charge densities can be adsorbed on the surface of cell monolayer after they have an interaction. Hong et al. [17] have showed that charged NPs can penetrate the lipid bilayer and cause an irreparable hole. Though many researchers have studied how surface charge density affects the interaction between NPs and a lipid bilayer [18,19], few works focus on the effects of charged NPs on pulmonary surfactant monolayer, regardless of simulations or experiments.

Currently, the studies of the interactions between NPs and pulmonary surfactant monolayer are mainly *in vitro* experiments. However, the results in different laboratories sometimes cannot achieve absolute consensus due to the difficulty in controlling experimental parameters that affect the behaviour of NPs and pulmonary surfactant monolayer. Hence, there is a need to use theory or simulations to compensate for the disadvantages of experiments [20]. Moreover, it is impossible for traditional experiments to explore various related properties of the complex system in the molecular level due to the limitation of time or space scale [21]. As an important research tool in many fields, molecular dynamics simulation can build the similar models of the real experiments on the computer and generally improve the size of space according to research needs. Besides, it has been successfully used to study the interactions between NPs and cell membranes [22,23]. Therefore, it is necessary and also effective to research NPs' surface charge density effect on their translocation across pulmonary surfactant monolayer with molecular dynamics simulation and these research studies can promote the design, the optimisation and the applications of the nanoparticle-based pulmonary drug delivery system.

In this paper, we study the effect of the surface charge density of NPs on their translocation across pulmonary surfactant monolayer with molecular dynamics simulation. Simulation details are given in the methods, and simulation results and analysis are given in the results and discussion.

2. Methods

2.1. Coarse-grained model

In this paper, the coarse grained (CG) force field was performed in all the molecular dynamics simulation. Compared to atomistic models, CG models can allow simulations undergo a larger length scale and a longer time period because they map several atoms into one interaction site. The CG force field, MARTINI, is one of the most popular CG models, which can be used to study for lipids, peptides and proteins at the level of time and space [24,25].

MARTINI can build the model according to four main types of interaction sites: Polar (P), nonpolar (N), apolar (C) and charged (Q). Particles of type N and Q contain four subtypes (0, d, a, da), which are used to distinguish the hydrogen-bonding capabilities. Particles of type C and P contain five subtypes (1–5), which are used to indicate the degree of polarity. Besides, a coulomb interaction potential energy function and a Lennard-Jones (LJ) potential energy function are applied for the non-bonded interactions. A weak harmonic potential function is used to describe the bonded interactions. The CG DPPC and water models can be downloaded from http://md.chem.rug.nl/cgmartini/.

2.2. Simulation details

The simulated symmetric system consisted of 784 DPPC molecules and 47,040 water molecules with the box dimensions of $14.72 \times 14.72 \times 70.00$ nm^3, including a gas slab sandwiched by two non-interacting surfactant monolayers with individual waterside, and the nanoparticle was introduced from the air layer (Figure 1(a)). Moreover, we added Na^+ or Cl^- into the simulated system to neutralise the surface charge of the nanoparticles in order to keep the system in a neutral state. Many recent researches have experimentally proved that similar simulated symmetric systems can be used to simulate certain biological properties of the pulmonary surfactant monolayer, such as the surface activities [26], outflow of phospholipids during the compression [27]. In the CG force field, DPPC molecule model is comprised of 12 beads including the headgroup (NC3, PO4), glycerol ester linkage (GL1, GL2) and two tails (C1A-C2A-C3A-C4A, C1B-C2B-C3B-C4B) (Figure 1(b)). Besides, water molecule model is comprised of four polar beads (P4). More details can be found in the paper of Marrink et al. [28].

We established several hydrophilic NPs with different surface charge densities, and all the NPs were the face-centred cubic structure. The surface charge densities of NPs were, respectively, 0 e/nm^2, ±4.0 e/nm^2, ±10.0 e/nm^2 and ±18.6 e/nm^2 and all the NPs (diameter: 5 nm) were consisted of 856 CG beads (Figure 1(c)). The CG bead type P2 was used for constructing the neutral hydrophilic NPs and Qda was used to modify the surface charge of the particle [29]. Cationic, anionic and neutral beads were shown in yellow, blue and black, respectively. Besides, to restrict bonds and bond angles among beads of NPs, the force constants applied to NPs equalled to what was used for DPPC molecules [30].

To facilitate the following discussion, we defined mid-plane of DPPC layer as x–y plane, with z axis perpendicular to the layer. The system was kept same and had only single NP in each simulation. All simulations were performed with GROMACS 4.5.4 simulation package [31]. A cutoff of 1.2 nm was used for van der Waals interactions. The default value of relative dielectric constant was 15 and the system temperature was set at 310 K with a coupling constant 1 ps. Berendsen coupling schemes for both pressure (semi-isotropic, coupling constant of 4.0 ps, compressibility in the x–y plane of 3e-5 bar^{-1} and in the z axis of zero bar^{-1}) were used to establish a NPT ensemble.

After energy minimisation, an equilibration of 50 ns was performed, and the final equilibrium configuration was used as the starting state for the next simulation. Then 120 ns molecular dynamics (MD) simulations have been performed to obtain a stable configuration.

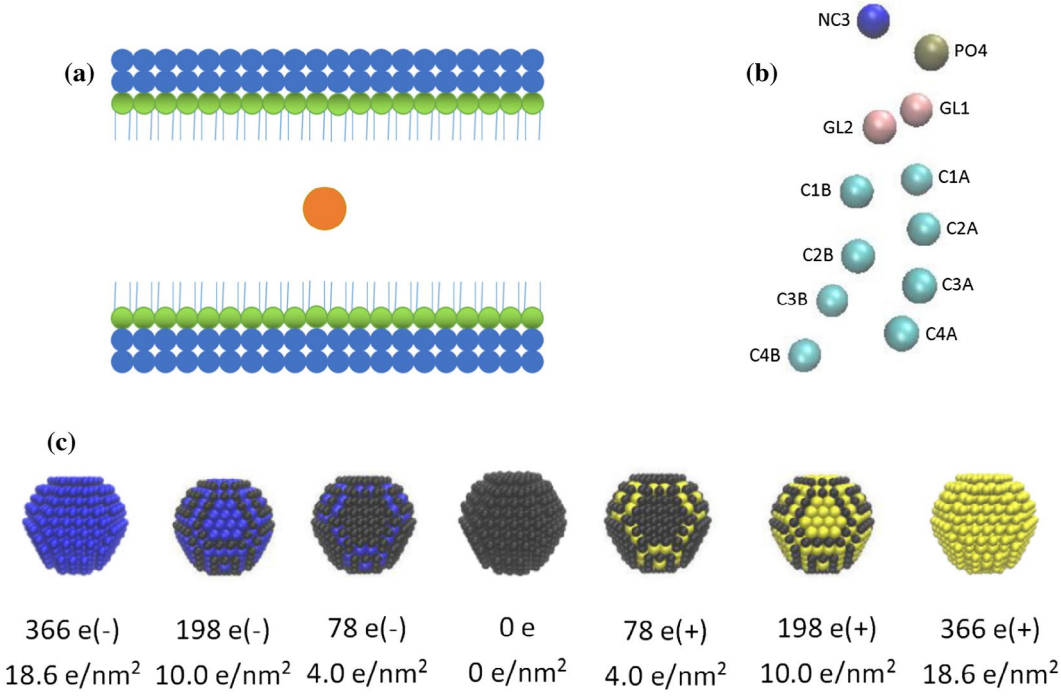

Figure 1. (Colour online) Initial set-up of the molecular dynamics simulation system. (a) The simulated symmetric system with a gas slab sandwiched by two non-interacting surfactant monolayers with individual waterside, and the nanoparticle was introduced from the air layer. (b) CG model of DPPC. A DPPC molecule contains 12 beads, including the headgroup (NC3, PO4), glycerol ester linkage (GL1, GL2) and two tails (C1A-C2A-C3A-C4A, C1B-C2B-C3B-C4B). (c) The snapshots of the model set-up for NPs with different surface charge densities. The surface charges of NPs are, respectively, 0 e, ±78 e, ±198 e and ±366 e and the surface charge densities are 0, ±4.0, ±10.0 and ±18.6 e/nm^2.

Notes: Colour code used in NPs: the neutral CG beads in black, the cationic CG beads in yellow and anionic CG beads in blue.

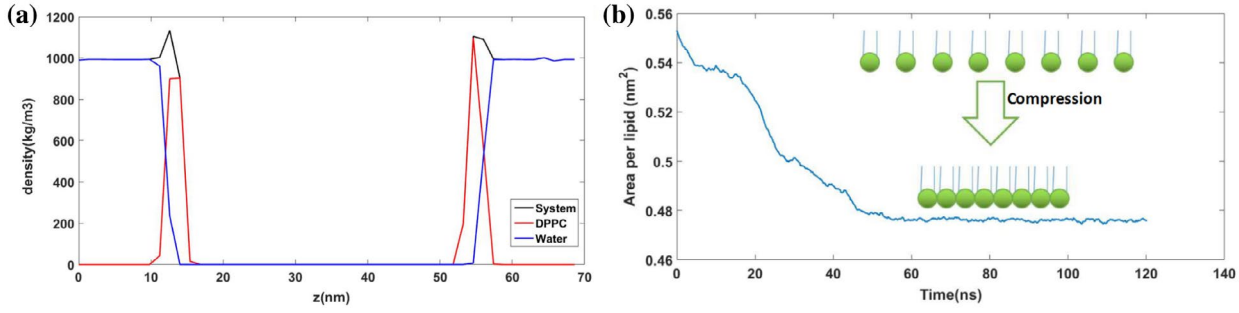

Figure 2. (Colour online) Density profile of DPPC layer along *z* axis (a) and area per lipid of the simulation system under the compression process over time (b).

3. Results and discussion

After 120 ns molecular dynamics simulations, we analysed the simulation trajectory for getting the density profile of DPPC layer along *z* axis and area per lipid of the simulation system under the compression process over time. As shown in Figure 2(a) and (b), the thickness of lipid layer is about 2.05 nm, and the area per lipid decreases gradually until stability under the compression process over time, which can be found that the area per lipid is about 0.552 nm^2 in the expansion state and about 0.471 nm^2 in the compression state, corresponding to the results with the given methods in Ref. [32].

3.1. Surface charge densities of NPs affect their translocation across pulmonary surfactant monolayer

We first experimentally compared the effects of neutral NPs and charged NPs on their translocation across pulmonary surfactant monolayer. As shown in Figure 3(a) and (b), the NP without surface charges can penetrate the monolayer easily, but the NP completely coated by surface charges was only wrapped by lipids partially instead of penetrating the monolayer in both of expanded and compressed states. Besides, all the NPs did not leave the surface of the pulmonary surfactant monolayer or cause a lipid pore on the pulmonary surfactant monolayer in the stable state. It is that pulmonary surfactant monolayer has the ability to heal [33]. Therefore, surface charges of NPs might determine their fate of translocation. Lee et al. [34,35] have reported that PAMAM dendrimer can induce pore formation in DPPC bilayer, which is similar to the results in this paper that NPs completely coated by surface charges have the poor translocation ability and will cause the monolayer to appear a disturbance more easily.

To understand the interaction mechanism between pulmonary surfactant monolayer and NPs on the different surface charge densities, we then established some partial charged MD

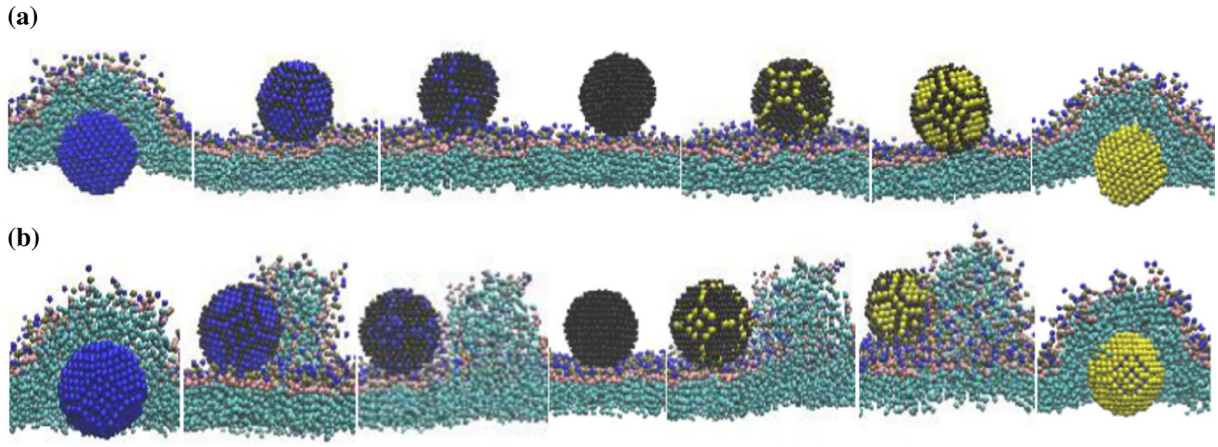

Figure 3. (Colour online) Simulated results of a hydrophilic NP with different surface charge densities (positive charge and negative charge) and different compression states through a pulmonary surfactant monolayer. (a) is the expanded state, (b) is the compressed state.
Notes: Each column shows the final structure of translocation corresponding to surface charge density, and the upper side of the monolayer is water and the lower side of the monolayer is air.

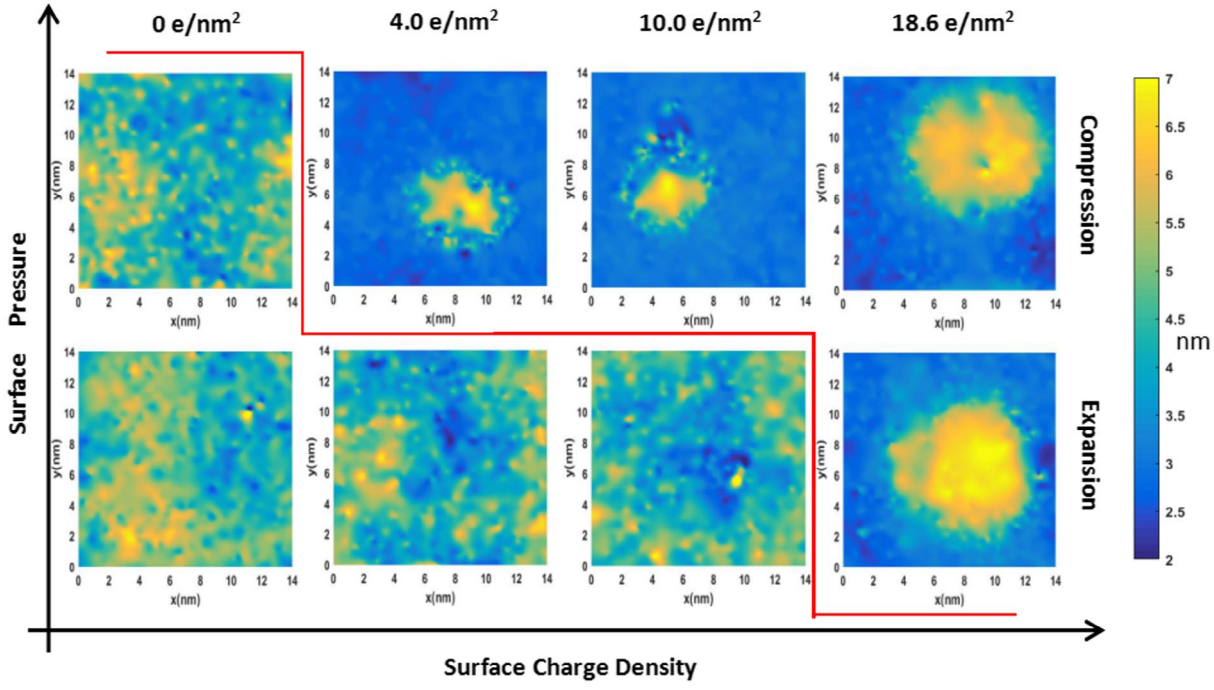

Figure 4. (Colour online) Local membrane thickness distribution under the different stable systems.
Notes: The four columns show the local membrane thickness distribution of different surface charge densities, respectively. In each column, there are two kinds of different surface pressure stages, which are expansion state and compression state. The eight photos are divided into two parts by the red line. Photos in the above part have an apparent contrast, which represents a disturbance on the monolayer, and photos in the below part represent that the monolayers are relatively smooth.

models to simulate NPs' translocation with different surface charge densities. As shown in Figure 3, all the NPs with different surface charge densities (except for NPs completely coated by surface charges) can penetrate the monolayers in spite of the expanded state or the compressed state. And all the NPs are adsorbed on the surface of pulmonary surfactant monolayer instead of entering the water phase. These results are in line with the results of the experiment [36,37]. Besides, it is worth noting that these above results will not change, although NPs switched the surface charge. In other words, positive or negative charge will not make any difference to the translocation results, which can be considered that DPPC is a zwitterionic molecule and it will not cause any apparent differences for cationic or anionic NPs to cross through the pulmonary surfactant monolayer. Hu et al. [29] have reported that cationic NPs can adsorb more palmitoyl-oleoyl phosphatidylglycerol (POPG) than DPPC compared anionic NPs or neutral NPs on their translocation through pulmonary surfactant monolayer, which is similar with our simulation results.

Moreover, NPs with different surface charge densities can cause a disturbance to the monolayer during their translocation across pulmonary surfactant monolayer, but it is not permanent and will tend to heal slowly. Besides, it is more or less bucking or folding due to curvature of the NPs in contact with the soft monolayer only in the compressed state even if the system has been stable. Figure 4 shows local membrane thickness distribution

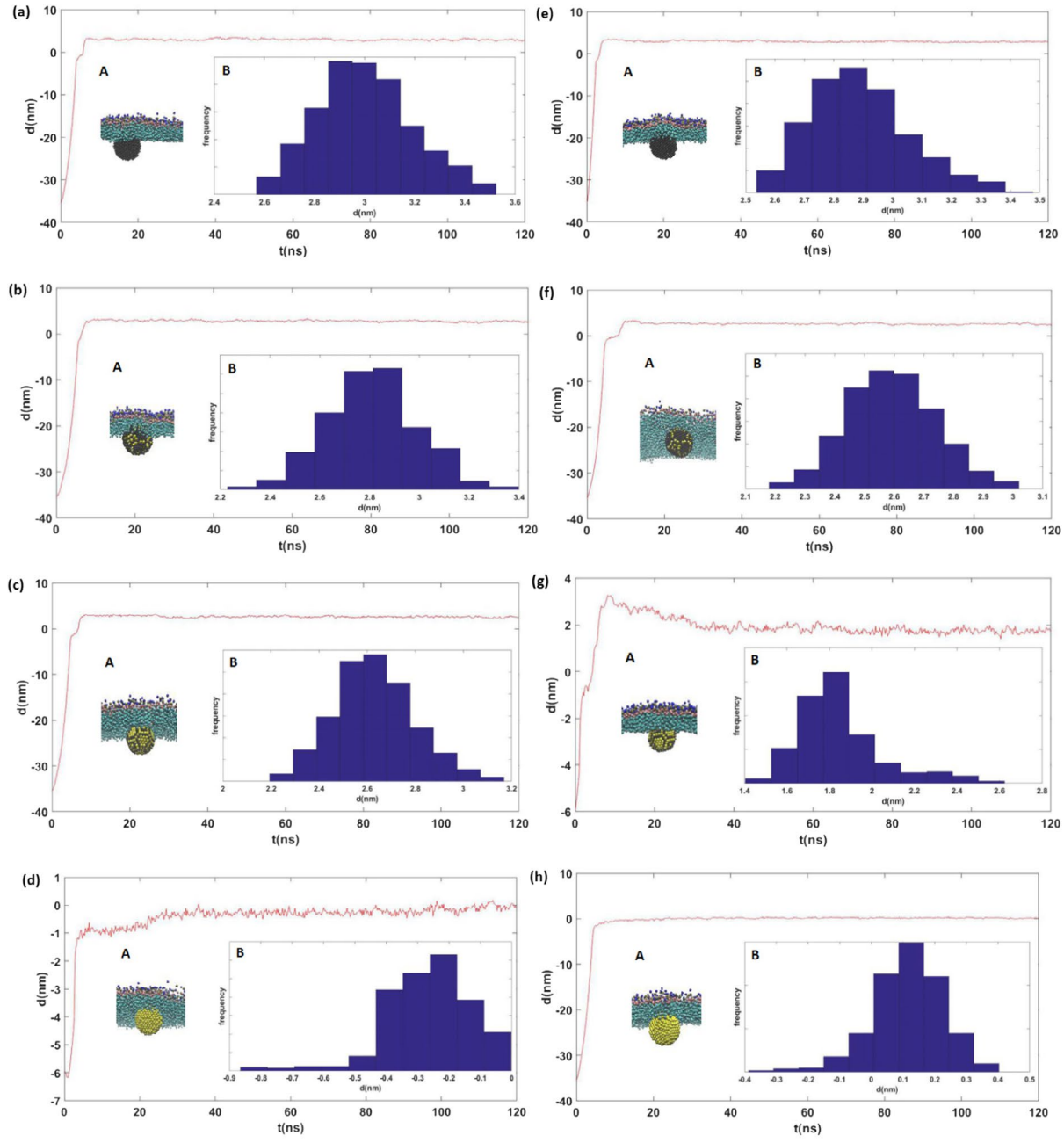

Figure 5. (Colour online) Trajectories of NPs with different surface charge densities along *z* axis through a pulmonary surfactant monolayer under the different compression states.

Notes: The left and right columns are corresponding to the expansion state and compression state, respectively. The four rows from top to bottom represent the translocation process of NP with 0, 4.0, 10.0 and 18.6 e/nm^2 surface charge densities. Inset (A) shows the side view of the simulation system when NPs just touched the monolayers, and the upper side of the monolayer is water and the lower side of the monolayer is air. Inset (B) shows the histogram of the distance distribution between NPs and the monolayer after NPs enter the monolayer.

under the different stable systems, and a red line has divided them into two parts. It can be found that there is a striking contrast on the photos of the above part, which represents a disturbance on the monolayer, and photos in the below part represent that the monolayers are relatively smooth. The results exactly agree with the results in Figure 3, which is said that NPs with different surface charge densities can cause the structural changes of pulmonary surfactant monolayer when they cross through the monolayer. Besides, the huge disturbance to the monolayer might cause DPPC out of the gas–liquid interface and further affect the dynamic equilibrium of pulmonary surfactant monolayer [38]. Therefore, NPs without surface charges might be more suitable to nanoparticle-based pulmonary drug delivery system.

3.2. Surface charge densities of NPs cause NPs' adsorption on the pulmonary surfactant monolayer

Lipids usually have different interactions with NPs, such as adsorption [39,40], insertion [41], translocation [42,43] and aggregation [44]. Among them, surface charge properties play an important role on the NPs' adsorption on the lipid layer [45]. We have known that all the NPs are adsorbed on the surface of pulmonary surfactant monolayer instead of entering the water

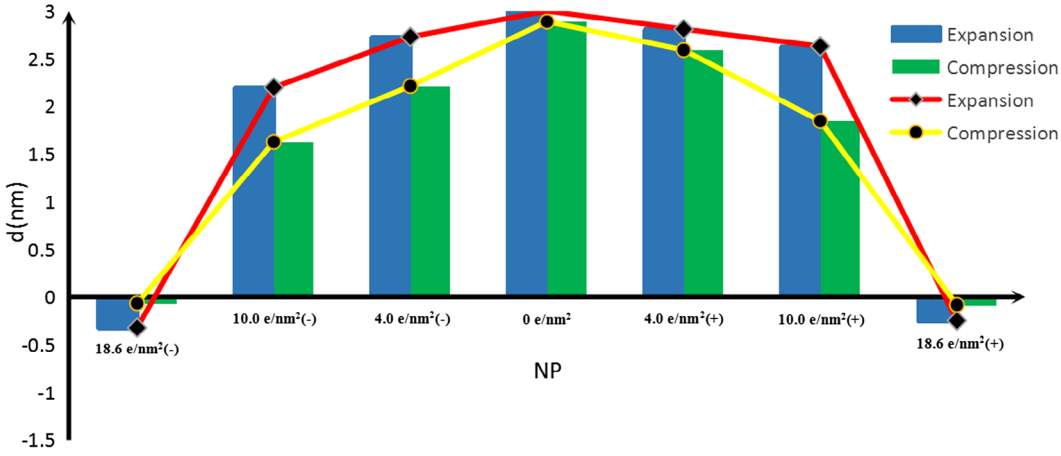

Figure 6. (Colour online) The NPs' average distance from the monolayer in the *z* axis in the stable state.
Notes: *X* axis represents NPs with different surface charge densities. *Y* axis represents the distances between NPs and the monolayers, and the positive or negative value means the two sides of the monolayer.

phase when the systems are stable in Figure 2. Then, we compared the simulation trajectory to study the adsorption capability of NPs with different surface charge densities.

We have counted the distances between NPs with different surface charge densities and the monolayers in the *z* axis during the time of each simulation. As shown in Figure 5, inset (A) shows the side view of the simulation system at the first time of interaction between the NP and the monolayer, inset (B) shows the histogram of the distance distribution between NPs and the monolayer after NPs enter the monolayer. From the curves in Figure 5, it can be observed that the distance decreased sharply at the beginning of translocation, which means the NP moved very fast until it got close to the monolayer. When the NP crashed on the monolayer, the distance reduced slowly but its velocity sharply declined, corresponding to the transition region in the curve. After the NP went through the monolayer from gas phase to liquid phase completely in several nanoseconds, it would be adsorbed on the head groups of lipids as a stable state. While NPs are able to cross through the monolayer, two obvious turning points in each line illustrate the process clearly: one represents the moment that the NP just contacted with lipids (Figure 5 inset (A)) and the other represents that the NP achieved a stable state immediately after penetration through the monolayer. Otherwise, there is only a turning point in the curve which means the moment that the NP just contacted with lipid.

In Figure 5 inset (B), we observed that the equilibrium distances between NPs and the monolayer are also different in (a)-(h) systems, corresponding to ~2.9 nm (a), ~2.85 nm (b), ~2.65 nm (c), ~–0.25 nm (d), ~2.85 nm (e), ~2.55 nm (f), ~1.85 nm (g), ~0.15 nm (h), respectively. It can be found that the equilibrium distances between NPs and the monolayer seem to be affected by the surface charge densities of NPs. For the sake of more accurate analysis, the histogram about the distances between NPs and the monolayer in the stable system was plotted. As shown in Figure 6, each NP has a different final distance from the monolayer in the stable stage and the positive and negative values represent, respectively, the two sides of the monolayer. The increase of the surface charge density of NP leads to the decrease of distance generally (Figure 5 inset (B) and Figure 6), which means the surface charge of NPs might enhance the adsorption ability of NPs. In addition, the slightly shorter distances for anionic NPs than cationic NPs denote that the adsorption ability of anionic NPs is stronger. It might be resulted from the positive charged head group of the DPPC molecule exposed to the outside can attract the anionic NPs more easily [24,32]. It is also remarkable that the distances in the expansion state are longer than those in the compression state. The main reason is that charged NPs cause more or less structural changes of lipids in the compression, which leads to the increase of the average thickness of the monolayer (Figure 3(b)) and the decrease of the average distances between NPs and the monolayer. All the results are very consistent with previous researches [16]. Besides, our results suggest that surface charge densities of NPs not only affect their absorption ability but also play an important role in regulating subsequent biomolecular exchange and designing the nanoparticle-based pulmonary drug delivery system.

3.3. Surface charge densities of NPs inhibit the normal phase transition of pulmonary surfactant monolayer during the compression process

NPs' nonspecific adsorptions may induce the change of pulmonary surfactant monolayer in thickness, therefore there is a large possibility to affect the monolayer's related properties, such as order parameter [46]. To better understand the NP–PS interaction mechanism, we analysed the order parameter of the monolayer in the different NP's translocation process over time.

As shown in Figure 7, in the expansion process, the order parameter values of NPs with different surface charge density have a sharp depression, but the order parameter values of NPs with 0, 4.0 and 10.0 e/nm^2 surface charge density keep stable generally, and only the order parameter value of the NP with 18.6 e/nm^2 surface charge density decreases and finally becomes stable over time. It is that only the NP with 18.6 e/nm^2 surface charge density cannot penetrate through the monolayer. Respectively, in the compression process, the order parameter values of NPs with different surface charge density also have a sharp depression, and then only the order parameter value of the NP with 0 e/nm^2 surface charge density increases generally and finally keeps stable over time, others decrease firstly and

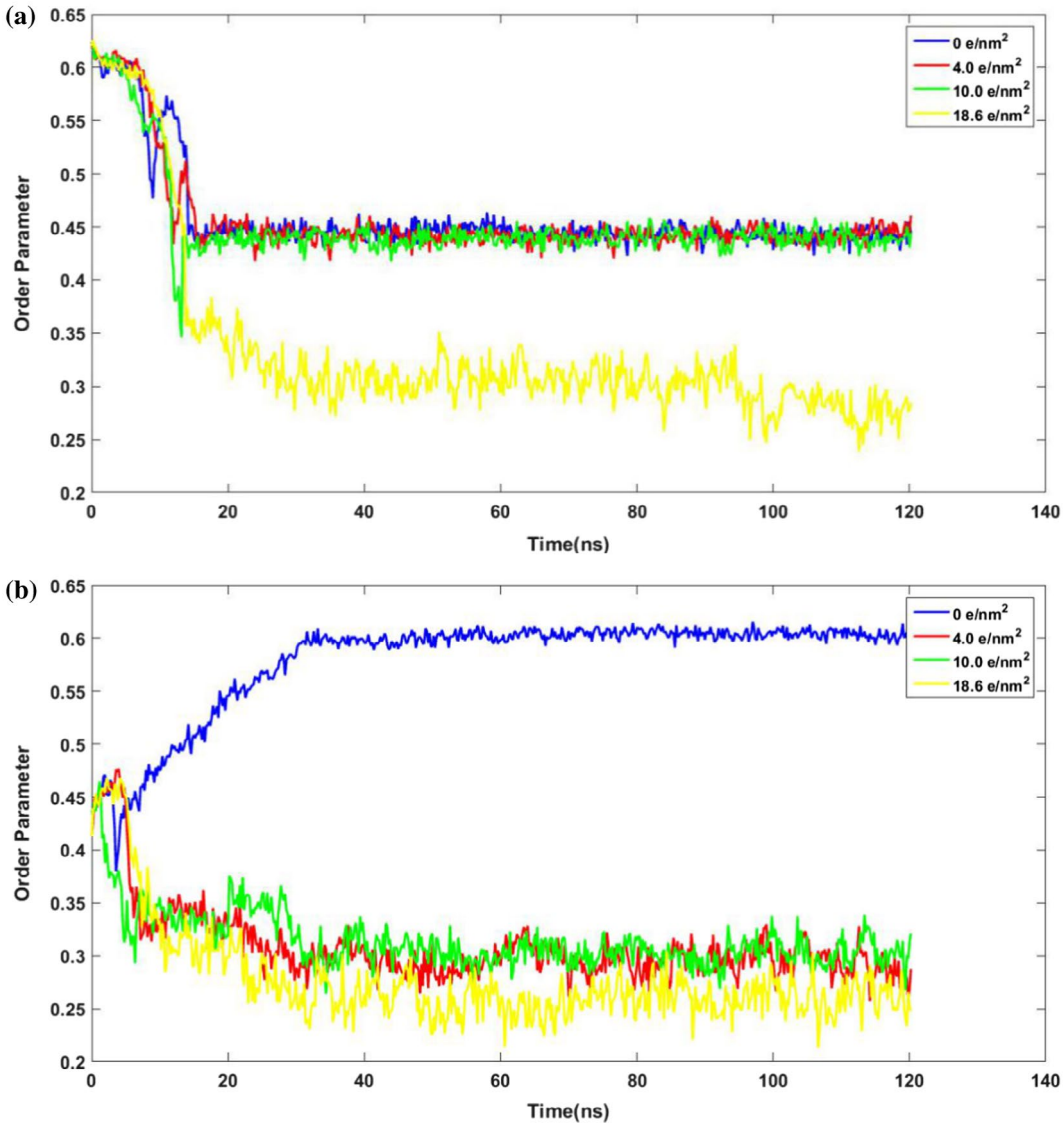

Figure 7. (Colour online) Order parameter of the pulmonary surfactant monolayer under the expansion process (a) and the compression process (b) over time.
Notes: The red, blue, green yellow lines represent the NP with 0, 4.0, 10.0 and 18.6 e/nm^2 surface charge density, respectively.

then get stable. By analysing the entire shown curve, the order parameter value of the NP with 0 e/nm^2 surface charge density is about 0.45 in the expanded state and 0.60 in the compressed state. It can be clearly found that compression can promote the order parameter value of the monolayer in the normal phase change, corresponding to the previous researches [47,48]. However, the order parameter values of NPs with 4.0 e/nm^2, 10.0 and 18.6 e/nm^2 surface charge density don't agree with the result and it represents that NPs with the surface charge can inhibit the normal phase change of the pulmonary surfactant monolayer, which is similar to the previous results [49]. It is worth noting that 0 e/nm^2 surface charge density NP started to penetrate the monolayer before 4.0 e/nm^2, 10.0 e/nm^2 or 18.6 e/nm^2 surface charge density NP, and it still needs to be more considered in order to analyse whether it is the reason of surface charge density.

The normal phase transition of pulmonary surfactant monolayer is very important to maintain the normal respiratory mechanics characteristics [50,51]. Therefore, inhibition of the normal phase transition will not only disrupt the normal phase transition of pulmonary surfactant monolayer, but also affect the structural stability of the gas–liquid interface. Our results show that neutral NPs might be the safest for pulmonary drug delivery.

4. Conclusion

With coarse-grained molecular dynamics simulations, we investigated NP's surface charge density effect on translocation across the DPPC layer. Several NPs with different surface charge densities were considered in our simulations. The results show that NPs' surface charge density affects their translocation capability: higher surface charge density NPs inhibit the translocation capability and facilitate more structural changes of pulmonary surfactant monolayer, especially disrupt the normal phase transition of pulmonary surfactant monolayer during the compression process. Besides, charged NPs can be adsorbed on the surface of the monolayer after translocation as a stable state, and the adsorption ability becomes stronger generally as NPs' surface charge densities increase. Our data therefore suggest that any *in vitro* study of inhalation nanotoxicology or NP-based pulmonary

drug delivery system should consider the nanoparticle's surface charge density effect.

Disclosure statement

No potential conflict of interest was reported by the authors.

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References

[1] Bailey MM, Berkland CJ. Nanoparticle formulations in pulmonary drug delivery. Med Res Rev. 2009;29(1):196–212.
[2] Patton JS, Byron PR. Inhaling medicines: delivering drugs to the body through the lungs. Nat Rev Drug Discovery. 2007;6(1):67–74.
[3] Nel A, Xia T, Mädler L, et al. Toxic potential of materials at the nanolevel. Science. 2006;311(5761):622–627.
[4] Oberdörster G, Oberdörster E, Oberdörster J. Nanotoxicology: an emerging discipline evolving from studies of ultrafine particles. Environ Health Perspect. 2005;113(7):823–839.
[5] Zuo YY, Veldhuizen RA, Neumann AW, et al. Current perspectives in pulmonary surfactant – inhibition, enhancement and evaluation. Biochim Biophys Acta. 2008;1778(10):1947–1977.
[6] Serrano AG, Pérezgil J. Protein-lipid interactions and surface activity in the pulmonary surfactant system. Chem Phys Lipids. 2006;265(141):105–118.
[7] Kuroki Y, Takahashi M, Nishitani C. Pulmonary collectins in innate immunity of the lung. Cell Microbiol. 2007;9(8):1871–1879.
[8] Fan Q, Wang YE, Zhao X, et al. Adverse biophysical effects of hydroxyapatite nanoparticles on natural pulmonary surfactant. ACS Nano. 2011;5(8):6410–6416.
[9] Gliga AR, Skoglund S, Wallinder IO, et al. Size-dependent cytotoxicity of silver nanoparticles in human lung cells: the role of cellular uptake, agglomeration and Ag release. Part Fibre Toxicol. 2014;11(1):1–17.
[10] Monopoli MP, Aberg C, Salvati A, et al. Biomolecular coronas provide the biological identity of nanosized materials. Nat Nanotechnol. 2012;7(12):779–786.
[11] Fröhlich E, Meindl C, Pieber TR. Important issues in the cytotoxicity screening of nano-sized materials. EURO-NanoTox-Lett. 2012;1(1):1–6.
[12] Duro N, Gjika M, Siddiqui A, et al. POPC bilayers supported on nanoporous substrates: specific effects of silica-type surface hydroxylation and charge density. Langmuir. 2016;32(26):6766–6774.
[13] Yang Y, Gao N, Hu Y, et al. Gold nanoparticle-enhanced photodynamic therapy: effects of surface charge and mitochondrial targeting. Ther Deliv. 2015;6(3):307–321.
[14] Fröhlich E. The role of surface charge in cellular uptake and cytotoxicity of medical nanoparticles. Int J Nanomed. 2012;7(11):5577–5591.
[15] Liu S, Qiao S, Li L, et al. Surface charge-conversion polymeric nanoparticles for photodynamic treatment of urinary tract bacterial infections. Nanotechnology. 2015;26(49):495602.
[16] Lin X, Wang C, Wang M, et al. Computer simulation of the effects of nanoparticles' adsorption on the properties of supported lipid bilayer. J Phys Chem C. 2012;116:17960–17968.
[17] Hong S, Leroueil PR, Janus EK, et al. Interaction of polycationic polymers with supported lipid bilayers and cells: nanoscale hole formation and enhanced membrane permeability. Bioconjug Chem. 2006;17(3):728–734.
[18] Hyldgaard KL, Thomas F, Dong M. Mapping surface charge density of lipid bilayers by quantitative surface conductivity microscopy. Nat Commun. 2016;7:12447.
[19] Kim JA, Åberg C, Salvati A, et al. Role of cell cycle on the cellular uptake and dilution of nanoparticles in a cell population. Nat Nanotechnol. 2012;7(1):62–68.
[20] Eslami M, Nikkhah SJ, Hashemianzadeh SM, et al. The compatibility of Tacrine molecule with poly(n-butylcyanoacrylate) and Chitosan as efficient carriers for drug delivery: a molecular dynamics study. Eur J Pharm Sci Off J Eur Federation Pharm Sci. 2015;82:79–85.
[21] Lindorff-Larsen K, Trbovic N, Maragakis P, et al. Structure and dynamics of an unfolded protein examined by molecular dynamics simulation. J Am Chem Soc. 2012;134(8):3787–3791.
[22] Sachan AK, Galla HJ. Understanding the mutual impact of interaction between hydrophobic nanoparticles and pulmonary surfactant monolayer. Small. 2014;10(6):1069–1075.
[23] Proctor EA, Dokholyan NV. Applications of discrete molecular dynamics in biology and medicine. Curr Opin Struct Biol. 2016;37:9–13.
[24] Marrink SJ, Risselada HJ, Yefimov S, et al. The MARTINI force field: coarse grained model for biomolecular simulations. J Phys Chem B. 2007;111(27):7812–7824.
[25] Monticelli L, Kandasamy SK, Periole X, et al. The MARTINI coarse-grained force field: extension to proteins. Methods Mol Biol. 2013;924(924):533–565.
[26] Bakshi MS, Zhao L, Smith R, et al. Metal nanoparticle pollutants interfere with pulmonary surfactant function in vitro. Biophys J. 2008;94(3):855–868.
[27] Zhang H, Fan Q, Wang YE, et al. Comparative study of clinical pulmonary surfactants using atomic force microscopy. Biochim Biophys Acta. 2011;1808(7):1832–1842.
[28] Marrink SJ, Tieleman DP. Perspective on the Martini model. Chem Soc Rev. 2013;42(16):6801–6822.
[29] Hu G, Jiao B, Shi X, et al. Physicochemical properties of nanoparticles regulate translocation across pulmonary surfactant monolayer and formation of lipoprotein corona. ACS Nano. 2013;7(12):10525–10533.
[30] Lin X, Li Y, Gu N. Nanoparticle's size effect on its translocation across a lipid bilayer: a molecular dynamics simulation. J Comput Theor Nanosci. 2010;7(1):269–276.
[31] Sun D, Lin X, Gu N. Cholesterol affects C_{60} translocation across lipid bilayers. Soft Matter. 2014;10(13):2160–2168.
[32] Marrink SJ, de Vries AHD, Mark AE. Coarse grained model for semiquantitative lipid simulations. J Phys Chem B. 2004;108(2):750–760.
[33] Chiu C, Shinoda W, Devane RH, et al. Effects of spherical fullerene nanoparticles on a dipalmitoyl phosphatidylcholine lipid monolayer: a coarse grain molecular dynamics approach. Soft Matter. 2012;8(37):9610–9616.
[34] Lee H, Larson RG. Molecular dynamics simulations of PAMAM dendrimer-induced pore formation in DPPC bilayers with a coarse-grained model. J Phys Chem B. 2006;110(37):18204–18211.
[35] Lee H, Larson RG. Lipid bilayer curvature and pore formation induced by charged linear polymers and dendrimers: the effect of molecular shape. J Phys Chem B. 2008;112(39):12279–12285.
[36] Schulz M, Olubummo A, Binder WH. Beyond the lipid-bilayer: interaction of polymers and nanoparticles with membranes. Soft Matter. 2012;8(18):4849–4864.
[37] Huynh L, Perrot N, Beswick V, et al. Reply to "Comment on 'Structural properties of POPC monolayers under lateral compression: computer simulations analysis'". Langmuir ACS J Surf Colloids. 2014;30(2):564–573.
[38] Perez-Gil J, Weaver TE. Pulmonary surfactant pathophysiology: current models and open questions. Physiology. 2010;25(3):132–141.
[39] Aramrak S, Flury M, Harsh JB, et al. Does colloid shape affect detachment of colloids by a moving air-water interface? Langmuir. 2013;29(19):5770–5780.
[40] Chatterjee N, Flury M. Effect of particle shape on capillary forces acting on particles at the air-water interface. Langmuir. 2013;29(25):7903–7911.
[41] Hess B, Kutzner C, van der Spoel D, et al. GROMACS 4: algorithms for highly efficient, load-balanced, and scalable molecular simulation. J Chem Theor Comput. 2008;4(3):435–447.
[42] Huang C, Zhang Y, Yuan H, et al. Role of nanoparticle geometry in endocytosis: laying down to stand up. Nano Lett. 2013;13(9):4546–4550.
[43] Li Y, Yue T, Yang K, et al. Molecular modeling of the relationship between nanoparticle shape anisotropy and endocytosis kinetics. 2012;33(19):4965–4973.

[44] Kolhar P, Anselmo AC, Gupta V, et al. Using shape effects to target antibody-coated nanoparticles to lung and brain endothelium. Proc Nat Acad Sci. 2013;110(26):10753–10758.
[45] Li Y, Gu N. Thermodynamics of charged nanoparticle adsorption on charge-neutral membranes: a simulation study. J Phys Chem B. 2010;114(8):2749–2754.
[46] Savarala S, Ahmed S, Ilies MA, et al. Stabilization of soft lipid colloids: competing effects of nanoparticle decoration and supported lipid bilayer formation. ACS Nano. 2011;5(4):2619–2628.
[47] Zhang Y, Lervik A, Seddon J, et al. A coarse-grained molecular dynamics investigation of the phase behavior of DPPC/cholesterol mixtures. Chem Phys Lipids. 2014;185:88–98.
[48] Baoukina S, Tieleman DP. Computer simulations of phase separation in lipid bilayers and monolayers. Methods Mol Biol. 2015;1232(1232):307–322.
[49] Lin X, Bai T, Zuo YY, et al. Promote potential applications of nanoparticles as respiratory drug carrier: insights from molecular dynamics simulations. Nanoscale. 2014;6(5):2759–2767.
[50] Baoukina S, Mendez-Villuendas E, Tieleman DP. Molecular view of phase coexistence in lipid monolayers. J Am Chem Soc. 2012;134(42):17543–17553.
[51] Baoukina S, Monticelli L, Risselada HJ, et al. The molecular mechanism of lipid monolayer collapse. Proc Nat Acad Sci. 2008;105(31):10803–10808.