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PHYSICOCHEMICAL MECHANISMS OF MINERAL NANOPARTICLES EFFECTS ON PULMONARY GAS/LIQUID INTERFACE STUDIED IN MODEL SYSTEMS

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Abstract: Inhaled mineral nanoparticles which are deposited on the lung surface may influence the gas/liquid barrier and the pulmonary surfactant (PS) which constitutes the vital element of the respiratory system. This research is focused on the physicochemical effects caused by selected clay nanoparticles (bentonite, halloysite, montmorillonites) interacting with PS and changing its original surface activity. Using three measuring methods (pulsating bubble technique, Langmuir balance and drop shape analysis), we demonstrated the influence of different mineral nanoparticles on the dynamic surface tension of animal-derived PS material (Survanta®) and main surfactant phospholipid (DPPC). The results which are dependent on material properties and concentration allow to hypothesize possible pathways of health effects from inhalation of mineral nanoparticles. This may help to set the guidelines in defining occupational safety standards and methods of protection of the respiratory system against inhaled mineral dusts.

Keywords: *inhalation, nanoparticles, gas/liquid interface, dynamic surface tension*

Introduction

Inhalation of dusts formed of mineral materials may contribute to respiratory symptoms and undesired health effects. Aerosol deposition in the respiratory system is a complex problem governed by airflow pattern and particle dynamics in a complicated geometrical structure of the upper airways and bronchial tree (Zhang et al., 2003; Rostami, 2009; Sosnowski, 2011; Longest and Holbrook, 2012). Depending on size and shape, inhaled particles can penetrate to deep lungs with different efficiency. It is recognized that compact (spherical-like) particles larger than 10 μm have a low chance to get to the bronchial tree as they are primarily deposited in the

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mouth and throat (e.g. Sosnowski et al., 2006). On the other hand, elongated (needle-like) particles, such as of asbestos, easily penetrate deeply into lungs even if their length exceeds 20 μm. It is due to reorientation of needles during flow via curved airways and narrowings, which allows to avoid the deposition in upper airways and bronchi (Zhang et al., 1996). Health effects from inhaled nano-sized or nano-structured particles attract much attention nowadays (Oberdorster, 2001; Maynard and Kuempel, 2005; Marijnissen and Gradon, 2010; Bakand et al., 2012). Due to small size and low inertia nanoparticles can be effectively transported to the pulmonary (alveloar) region with inhaled air.

Particles which are deposited in deep lungs come into contact with the pulmonary surfactant (PS) which constitutes an important component of the respiratory system (Zuo et al., 2008; Rugonyi et al, 2008). PS has the extraordinary dynamic surface activity which is expressed during variations of pulmonary gas-liquid surface area caused by breathing. PS is responsible for a significant reduction of the surface tension during surface contraction (related to air exhalation from the lungs), what reduces the effort of lung inflation. Surface tension hysteresis observed during periodic interfacial area variations is important for the stability of the alveolar network of the lungs. In addition, the local variations of the surface tension result in Marangoni effects and superficial flows - these phenomena are important for the mass transfer in the respiratory system (Gradoń and Podgorski, 1989; Sosnowski et al., 1998). All the mentioned facts indicate the necessity of maintaining the specific composition and surface activity of the pulmonary surfactant, and, accordingly, any notable disturbances of surfactant quality should be expected as harmful to the lungs (Sosnowski et al, 2000).

Within this work we focus on mechanisms of direct physicochemical interactions between selected inhalable mineral nanoparticles and the pulmonary surfactant, which can be studied using selected *in vitro* experimental systems.

Materials and Methods

Nanoparticles

Five types of mineral nanoparticles have been tested in this study. All selected nanopowders are commercially available aluminosillicates (Sigma Aldrich) being used as mineral nanofillers in polymer industry. They are of natural origin, however they are standardized regarding the purity, and some of them are chemically modified to produce surface hydrophobicity required in technological applications. The list of used nanomaterials is given in Table 1, together with the indications of nanoparticle morphology, characteristic size and the specific surface area, which were determined in the separate study (Kondej and Sosnowski, 2013).

Table 1. Mineral nanoparticles used in the study

Particle designation	Material name, morphology and characteristic particle size	Specific surface area [m^2/g]
HN	HALLOYSITE Morphology: needles (nanotubes), diameter <100 nm, length - up to a few μm	25.5
PGV	BENTONITE Morphology: nanoplates, thickness < 200 nm	67.3
I.28.E	MONTMORILLONITE modified by trimethyl stearyl ammonium: Morphology: flakes, thickness < 200 nm	9.6
I.30.E	MONTMORILLONITE modified by octadecylamine Morphology: flakes, thickness < 200 nm	14.0
I.31.PS	MONTMORILLONITE modified by octadecylamine and aminopropyltriethoxysilane Morphology: flakes, thickness < 200 nm	13.5

Pulmonary surfactants

Two types of pulmonary surfactant models have been used:

a) pure 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC – Sigma Aldrich) – the predominant natural phospholipid found in the natural PS. It is recognized as a key surface-active component of the pulmonary fluid.

b) Survanta® (Abbott Laboratories, France) – an animal-derived standardized whole PS which is used to treat surfactant deficiencies in humans (surfactant replacement therapy – e.g. Lam et al., 2005; Engle et al., 2008).

Measuring methods and procedures

Experiments have been done using three independent techniques allowing to study different aspects of the influence of mineral nanoparticles on the interfacial activity of model pulmonary surfactants. A Langmuir-Wilhelmy film balance (model Mini – KSV, Finland) was used to study surface-tension effects induced by nanoparticles interacting with PS phodphilipid at air-liquid interface. The measurements were done for gradually decreased interfacial area mimicking the behavior of the lung surface during air exhalation. The gas-liquid area was compressed by two barriers sliding in the predefined manner on the top of the saline (0.9%) covered by DPPC monolayer – a model of physiological lung fluid, Figure 1.

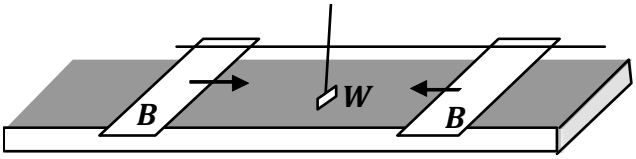

Fig. 1. The schematic of the Langmuir-Wilhelmy film balance. Two movable barriers (*B*) compress the interface while the surface pressure (eq. 2) is measured by Wilhelmy plate (*W*) connected to an electronic sensor

To study the effects of nanoparticles on the surfactant phospholipid, the liquid phase was prepared as a suspension of the known amounts of particles determined by calculations of lung deposition of dusts inhaled at occupational environments (Kondej and Sosnowski, 2013). Several nanoparticles concentrations (0.1-1 mg/cm^3) in the saline were used in measurements conducted at physiological temperature (37 ± 0.5 °C).

A more realistic representation of the pulmonary surfactant system is available in the oscillating bubble tensiometry (PBS device - Electronetics Corp., USA). These experiments rely on measuring a pressure difference Δp during continuous pulsations of an air bubble (diameter 0.8–1.1 mm) submerged in Survanta® (concentration: 1.25 mg/cm^3; volume: 30 mm^3). The pulsation were done at the frequency corresponding to the breathing rate (15 min^{-1}). The instantaneous, dynamic surface tension at the interface of a bubble with radius r, is found from the Young-Laplace equation:

$$\sigma = \frac{r\Delta p}{2} \tag{1}$$

The experimental system and measuring procedure have been described in details recently (Kondej and Sosnowski, 2013). Nanoparticles concentrations used in this study were similar to the ones tested in the Langmuir-Wilhelmy balance experiments. The temperature of measurements was set to 37 ±0.5 °C.

The third method used in this study to characterize the physicochemical interactions between nanoparticles and the pulmonary surfactant was the drop shape analysis (DSA – using the equipment made at the Faculty of Chemistry, Warsaw University of Technology). The dynamic surface tension of tested suspensions was determined in this case from the pending drop profile (Figure 2).

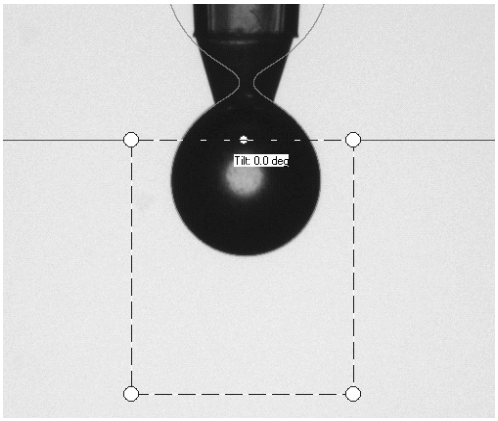

Fig. 2. An example of a picture of pending drop (volume of approximately 3 mm^3) in DSA method

This type of measurements allows to monitor the long-time evolution (up to several hours) of the dynamic surface tension, so it helps to study slow adsorption of surface-active material on a gas-liquid interface. It should be noted, however, that the system offers an incomplete analogy to the physiological system. Firstly, the experimental interface is stationary, secondly – the ratio of liquid volume to the interfacial area is much higher in the measuring system than in the real pulmonary fluid, and finally, the available observation times are much longer than a duration of a single breathing cycle. Therefore, these data can be used only as a supportive information during recognition of mechanisms by which nanoparticles interact with PS in the dynamic system. In DSA experiments we used the same concentrations of mineral nanomaterials as in the two other studies. However, due to technical limitations, the measurements were done only at room temperature (23 ± 0.5 °C) although the samples were pre-thermostated at 37 °C.

Results and data analysis

The methods of reduction of raw experimental data obtained with different techniques need additional explanation before results are presented and discussed. In all experimental systems the dynamic surface tension, σ (or surface pressure, π), is found as a function of either time, τ, or the time-dependent interfacial area, $A(\tau)$. Let us note that the surface pressure is defined as:

$$\pi = \sigma_w - \sigma \tag{2}$$

where σ_w denotes the surface tension of water (70 mN/m at 37 °C).

Univocal comparison of the dynamic surface tension evolution requires data reduction and defining some numerical indicators. For data obtained with the oscillating bubble method (an outline of a typical result is shown in Figure 3) it will be informative to find the minimum surface tension, σ_{min}, during pulsations as a measure of the highest surface activity at the tested surface oscillations. It is obvious that σ_{min} depends on the total surfactant concentration but also on its composition which governs the surface activity. For comparative purposes done in this study, when it is essential to assess the σ_{min} deviation after surfactant contact with nanomaterials, it is convenient to indicate the percent change of σ_{min}, defined as:

$$\Delta\sigma_{\min\%} = \left(\frac{\sigma_{\min}}{\sigma_{\min}^{*}} - 1 \right) 100\% \tag{3}$$

where σ_{min}^{*} denotes the minimum surface tension of the control surfactant sample (no particles). Positive values of $\Delta\sigma_{\min\%}$ indicate the increased minimum surface tension when compared to the control case, i.e. a loss of surface activity, while negative values suggest a stronger lowering of the surface tension (increased interfacial activity).

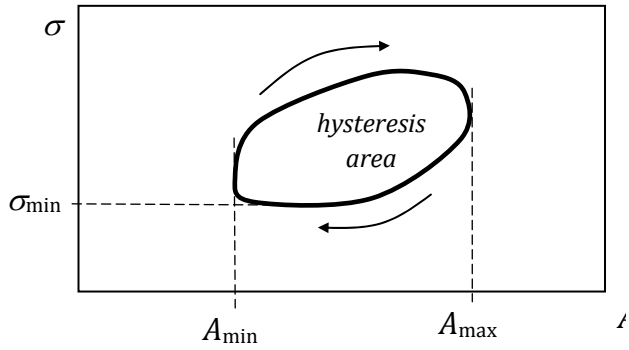

Fig. 3. A sketch of a characteristic result from oscillating bubble experiments

Another indicator of dynamic surface activity in this measurement is the size (area) of surface tension hysteresis, schematically drawn in Fig. 3. The hysteresis reflects dissipative processes during surface area cycling. It is recognized that the hysteresis for physiologically active pulmonary surfactant remains higher than in case of surfactant inactivation caused by lung diseases (Clements et al., 1961; Notter et al., 1982). The mathematical formula to find the area confined size by the σ-hysteresis loop is given by:

$$HA = \left[\int_{A_{\min}}^{A_{\max}} \sigma dA\right]_{\text{expansion}} - \left[\int_{A_{\min}}^{A_{\max}} \sigma dA\right]_{\text{contraction}} \tag{4}$$

HA should be normalized against the applied surface compression (e.g. Notter at al., 1982), however for all oscillating bubble measurements in this study, the compression was always the same ($A_{\min}/A_{\max} = 0.53$), so the additional calculation is not needed.

By analogy to eq. (3), the relative percent change of *HA* induced by nanoparticles added to PS can be expressed as:

$$\Delta HA_{\%} = \left(\frac{HA}{HA^{*}} - 1\right) 100\% \tag{5}$$

where HA^{*} denotes the hysteresis area in the control surfactant sample (no particles). Here, the decrease of dynamic surface activity will be indicated by negative values of $\Delta HA_{\%}$.

Experimental results from the oscillating bubble studies were obtained for the complete pulmonary surfactant under physiological conditions (dynamic breathing-like surface pulsations). These results are the most informative, but simultaneously the most difficult to interpret on the physicochemical basis. The values of two parameters defined by eqs. (3) and (5) at nanoparticles concentration of 0.5 mg/ml is presented in Fig. 4.

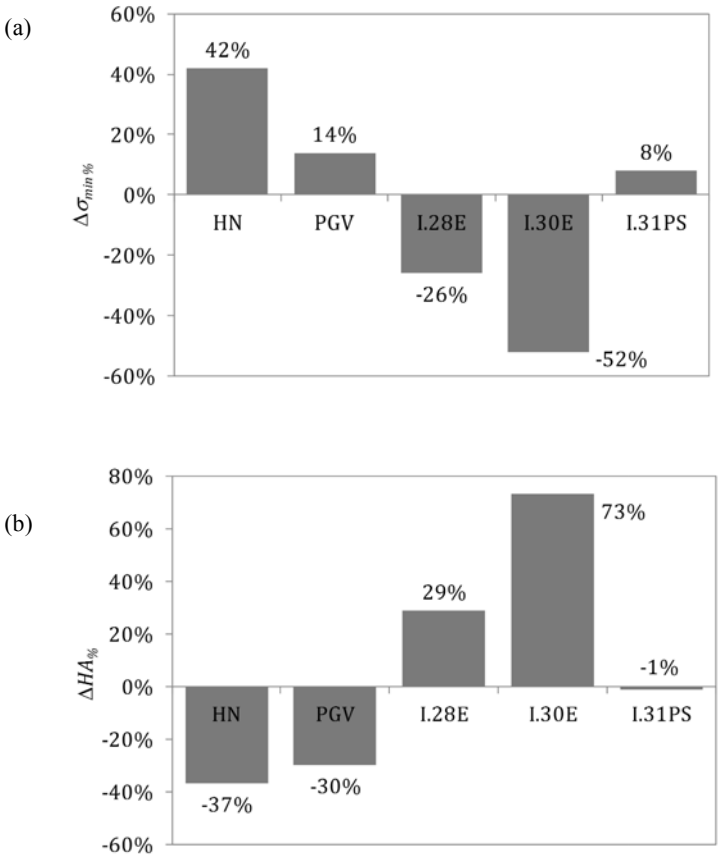

Fig. 4. Relative change of (a) – the minimum surface tension ($\Delta\sigma_{min\%}$) and (b) – the hysteresis area ($\Delta HA_{\%}$) for different mineral nanoparticles at concentration of 0.5 mg/cm^3

It is visible that the response of the system depends on type of nanoparticles. For three kinds of minerals (HN, PGV and 1.31 PS) there is an increase of the minimum surface tension and a decrease of the surface tension hysteresis, suggesting an evident decline of the original PS surface activity. For montmorillonites 1.28E and 1.30E there is a reduction of the minimum surface tension and a simultaneous increase of the hysteresis. In this case the surface activity of the PS is changed in the opposite way than for the other mineral particles. Similar responses of model PS system can be observed for lower (down to 0.1 mg/cm^3) and higher (up to 1 mg/cm^3) dust contents, and the extent of change of discussed parameters is well correlated with nanoparticles concentration.

Studies done with the Langmuir–Wilhelmy balance support the results obtained with the oscillating bubble method. In these experiments, the compression isotherms for DPPC at 37 °C were obtained - an example in the presence of bentonite

nanoparticles (PGV) is presented in Figure 5. To facilitate the comparison of all data obtained for different mineral nanoparticles at variable concentrations, we propose to derive a single parameter as an indicator of the surface tension reduction effectiveness in each tested system. Here we define MA_{30} to denote the molecular surface area at which the initial surface tension in the system is reduced by 30 mN/m (i.e. the surface pressure is increased by the same value – Figure 5). Higher values of MA_{30} indicate that smaller surface compressions are required to obtain low surface tensions, that is the interface contains a more active surfactant.

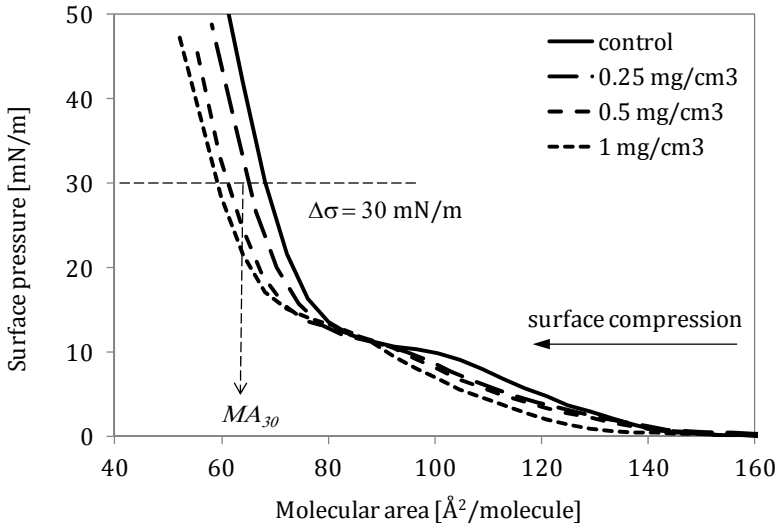

Fig. 5. Compression isotherms (37°C) for DPPC in the presence of bentonite (PGV) nanoparticles. Dashed line illustrates the meaning of MA_{30} parameter

From Fig. 5 it is visible that the compression isotherms are deformed due to surfactant interactions with the particles. It can be also seen that the phospholipid without particles exhibits the highest value of MA_{30} what means that low surface tension is attained already at a low degree of surface compression. The surface needs to be more compressed when PGV nanoparticles are added to the system.

The comparative results of MA_{30} for all tested nanoparticles at different concentrations are shown in Fig. 6.

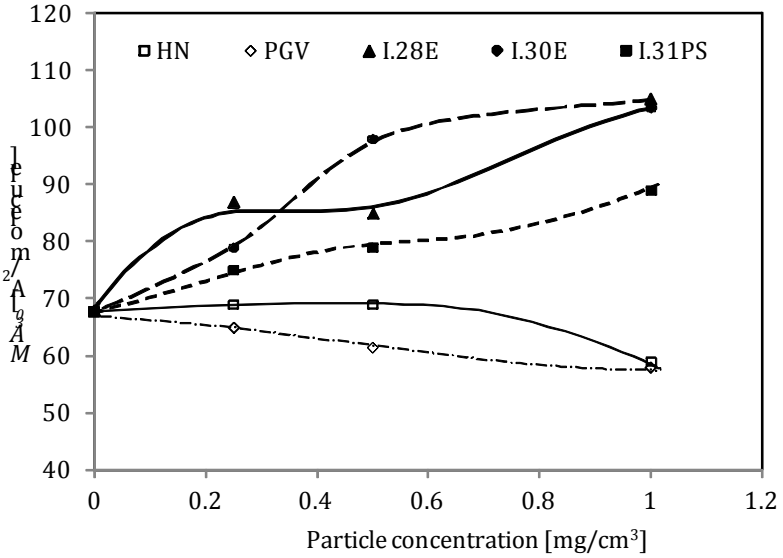

Fig. 6. The dependence of MA_{30} on particle type and concentration

In case of HN or PGV particles added to the system, the molecular area parameter is equal or smaller than for the pure phospholipid monolayer, and it implies that a higher compression of the interfacial area is required to obtain the expected low surface tension value. This reveals an impairment of DPPC surface activity by these two types of nanoparticles. On the contrary, if I.28E, I.30E and I.31PS particles are present in the system, they promote an increase of MA_{30}, suggesting an additional surface-active effect allowing to reduce surface tension at a lower interfacial compression. The mechanism of the observed effect remains unclear unless additional surface-visualization studies are done (e.g. Guzman et al. 2011). However, one can postulate that an improved surface activity observed for surface-modified montmorillonites results from an extra surface tension lowering properties of either these nanoparticles themselves or the compounds that are released (washed out) from the nanomaterials. Such conclusions correspond to the data from the oscillating bubble experiments, where also two different types of system response was found – a decrease of the surface activity by HN or PGV nanoparticles, and its moderate increment by modified montmorillonites: I.28E or I.30E. Moreover, such a correlation suggests that DPPC is indeed the most important compound in the regulating the dynamic surface tension of the whole PS.

In the DSA method of testing PS surface activity in the presence of mineral nanoparticles, the parameter $\Delta\sigma_{\tau\%}$ is used by analogy to the parameter defined by eq. (3). It represents the temporary change of the dynamic surface tension in the given system, $\sigma(\tau)$, in respect to the temporary surface tension of the pure surfactant, $\sigma^*(\tau)$:

$$\Delta\sigma_{\tau\%} = \left(\frac{\sigma(\tau)}{\sigma^*(\tau)} - 1 \right) 100\% \tag{6}$$

The interpretation of $\Delta\sigma_{\tau\%}$ values is similar to that of $\Delta\sigma_{\min\%}$ in the discussion presented earlier. Figure 7 shows the comparison of $\Delta\sigma_{\tau\%}$ averaged in the first 10 minutes of monitoring the dynamic surface tension of Survanta® containing different mineral nanoparticles (concentration 0.5 mg/cm^3).

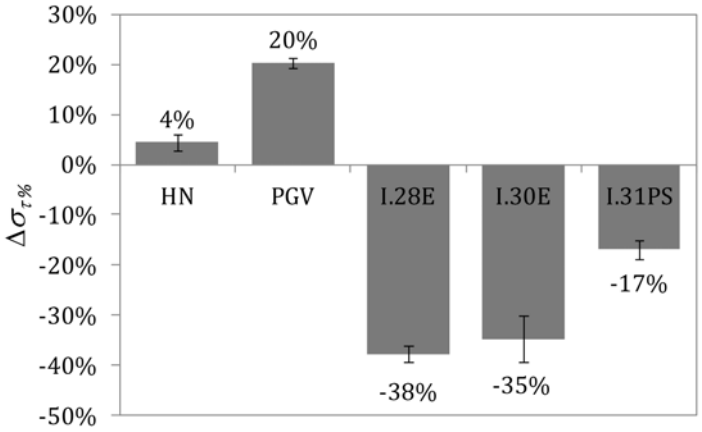

Fig. 7. Comparison of $\Delta\sigma_{\tau\%}$ value for PS with different mineral nanoparticles (0.5 mg/cm^3).

Interestingly, data obtained with DSA studies are also supportive for the findings from two other experimental approaches. Both HN and PGV nanoparticles decrease the activity of the surfactant while each of three modified montmorillonites (I.28E, I.30E and I.31.PS) acts in synergy with the surfactant in lowering the surface tension. The changes are different numerically than the ones found in the oscillating bubble studies, however it should be reminded that these two experimental systems differ in a few essential aspects, as discussed earlier. It is striking however, that the overall trend of changes of the surface activity in the PS-nanoparticles system remains similar to the obtained in two other sets of experimental data.

Discussion

Our results provide an apparent support that mineral nanoparticles influence the properties of the pulmonary surfactant due to physicochemical interactions related either to changes in adsorption dynamics at a gas-liquid interface or altering the surface tension lowering capabilities of the adsorbed compounds. However, at dynamic conditions which are indispensable associated with the breathing cycle, the mechanisms interfacial phenomena become more difficult to trace and identify. There is a vast number of published data recognizing that different micro- and nanoparticles,

as well as gaseous contaminants, influence surface processes in the model PS systems (e.g., Sosnowski et al., 2000; Podgórski et al., 2001; Wallace et al., 2007; Bakshi et al, 2009; Kondej and Sosnowski, 2010; Harishchandra et al. 2010; Fan et al. 2011; Guzman et al. 2011). Some theoretical interpretations employ also mathematical modeling of mass transfer phenomena (e.g. Sosnowski, 2001) or molecular dynamics analysis (Choe et al., 2008; Sosnowski et al., 2012), still giving only partial explanation of the observed effects. Several studies confirm that ultrafine particles present in the PS system provide an additional interface for adsorption, so PS components can be collected on solids. In this way the concentration, and – consequently – the surface activity of PS at gas-liquid interface may be reduced. In our studies this mechanism can feasibly elucidate the influence of HN and PGV particles on the surfactant. Other types of particles produce the opposite effects and this may be explained rather by a synergy in dynamic surface activity between the PS and the particles or the compounds they transport into the system.

The fundamental question which needs to be answered during discussion of the results is if the effects revealed in the specialized *in vitro* experimental systems are indeed taking place in the real physiological system. It is known that homeostatic biological environment of the lungs is equipped with specialized mechanisms which protect against the elevation of the concentration of deposited inhaled nanomaterials in the pulmonary fluids (e.g. mucociliary clearance, chemotactic activity of alveolar macrophages). This environment is also effectively buffered and continuously refreshed by surfactant production and turnover – such processes are absent in all laboratory settings. So, keeping in mind that tensiometric approaches tested within this work should be considered only as simplistic models of physiologically-related systems, they allow to speculate that accidental or repetitive overdosing of inhaled mineral nanoparticles (e.g. at the workplace) may cause a runaway of the physiological system from a natural dynamic equilibrium. In such a situation, the initiated biological response can lead to a pulmonary dysfunction or disease.

Conclusions

It was demonstrated that the evaluation of dynamic surface activity of a model pulmonary surfactant (PS) or its main phospholipid constituent (DPPC), obtained from three different tensiometric techniques, allow to investigate the plausible interactions of inhaled mineral nanoparticles in the liquids covering lung surface. It was shown that the response of the model system depends on particle type and concentration, and that different nanoparticles may decrease or increase the surface tension of the PS. The exact physiological implication of these findings cannot be straightforwardly interpreted, however it may be expected that alteration of the original surface activity of the surfactant in the lungs can initiate a biological response which will lead to undesired health effects. As the surfactant also regulates pulmonary defense mechanisms against inhaled aerosol deposits, the induced changes of PS properties

may result in an increased susceptibility to lung infections or allergies. This conclusions confirms that it is essential to minimize the breathing with air contaminated with mineral dusts. It can be achieved by using personal protection equipment (filtering facial masks or respirators) which must be properly designed to collect airborne nanoparticles.

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