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Dynamic properties of adsorption layers of pulmonary surfactants. Influence of matter exchange with bulk phase

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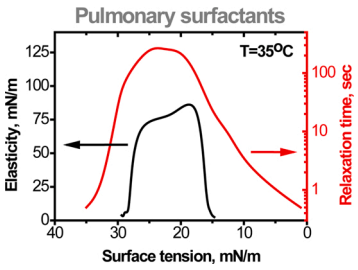
GRAPHICAL ABSTRACT



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ABSTRACT

The dynamic surface properties of solutions of pulmonary surfactant (PS) were investigated at various temperatures and in a broad range of surface tensions. The efficient dynamic surface elasticity was determined for the first time in case when the characteristic adsorption time is comparable with the period of surface area oscillations. The mechanical relaxation in the PS adsorption layer is accelerated strongly not only in the course of compression, but also in the course of expansion due to the formation of a sublayer. The harmonic oscillations of the surface area induce stationary oscillations of the surface tension if the characteristic adsorption time does not exceed the oscillation period and the sublayer formation is sufficiently fast. The information on the dynamic properties of the PS adsorption layer allows estimation of the PS efficiency in medical applications.

1. Introduction

Pulmonary surfactant (PS) is a complex mixture of lipids and proteins. The PS solution covers the inner surface of lungs and provides functionality of the respiratory system [1]. The lack of PS leads to the neonatal respiratory distress syndrome of premature infants [2–6]. The PS extracted from animal lungs has been applied for medical treatment of these patients since the end of the twentieth century [7,8]. The main component of PS is 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC), which can form a dense monolayer at the air/water surface [3,3,4,5,6,9]. The compression of this monolayer leads to extremely low surface tensions, which are presumably the main factor preventing the

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alveoli from collapse under exhalation. It was also shown that surface active proteins (SP-B and SP-C) and unsaturated lipids, in particular palmitoyl-oleoyl-phosphatidylglycerol, promote PS transfer from the subsurface to the surface layer in the course of the expansion step, thereby providing the low surface tension and energy required for breathing [10–15]. These findings have stimulated recently studies of mixtures of synthetic lipids and some protein analogs of SP-B and SP-C as alternatives of PS from natural sources [10,11,16–18]. Note that the application of simple analogs of natural PS to treat adult patients with acute respiratory distress syndrome (ARDS) can be inefficient in some cases [4,19,20]. At the same time, the use of natural PS in combination with surgical treatment of ARDS can decrease mortality for of patients with coronaviruses [21].

The composition and properties of the surface layer of PS solutions were investigated by Brewster angle microscopy [22], atomic force microscopy [23], fluorescence microscopy [24], small angle x-ray scattering [15], infrared reflection-absorption spectroscopy [25]. Most of these studies were devoted to the investigation of equilibrium surface properties because measurements of the dynamic surface properties in the range of extremely low surface tensions are a difficult experimental task. Only the surface tension has been measured rather frequently in dynamic conditions. A few methods have been developed to measure the low dynamic surface tension in the course of periodic surface dilation, for example, the modified Langmuir trough [2], the captive bubble surfactometer [26] and the constrained sessile drop [27]. Note that the use of the minimum surface tension of the compressed state of a PS layer is not sufficient to characterize the layer. Besides, this value depends on the measurement procedure, in particular, the rate and degree of compression [28,29].

It is known that the surface tension oscillations in the course of periodic surface compressions and expansions can give additional information on the dynamics of PS adsorption layers [30,31]. Notter et al. showed the importance of the hysteresis of compression and expansion isotherms for the air penetration in the maximal number of alveoli [30]. Sosnowski et al. indicated connections of the hysteresis with dynamic surface properties of PS solutions [32]. Bae et al. and Choi et al. have shown recently, that the dynamic surface properties can be used to estimate the efficiency of synthetic PS [33,34]. Saad et al. proposed to characterize the response of a PS layer to periodic deformations by the dilational elasticity for compression and expansion steps, and by kinetic coefficients of relaxation [28,29]. Meantime this approach cannot be applied to the case of large deformations when the surface properties change significantly in the course of compression and expansion. Another approach has been proposed recently to estimate the dynamic surface elasticity in a broad range of the surface tension from a nonlinear response of the system to large harmonic deformations [35]. Recently the dynamic surface properties have been investigated for spread monolayers of DPPC and solutions of PS with slow adsorption [36]. These systems are considered as simple models of PS and their mixtures with nanoparticles of different chemical natures [37–40]. However in lungs the exchange between the adsorbed layer and bulk phase plays a significant role for maintaining of lung functionality.

The main goal of this work is to estimate the dynamic surface elasticity of PS layers and the rate of mechanical relaxation in these systems in a relatively broad range of temperatures and bulk concentrations in case when the characteristic adsorption time does not exceed the oscillation period. Special attention is paid to changes of the dynamic surface properties in the course of long oscillations of the surface area. This information is crucial for the estimation of PS efficiency, since numerous studies showed that the influence of transitional processes on surface tension oscillations can lead to the impairment of PS functionality [10,15,18,34,41–44].

2. Materials and methods

Curosurf® suspension was obtained from CHIESI FARMACEUTICI (Italy) with the concentration of active components of 80 mg/mL, which corresponds to that in the alveoli. Triply distillated water was used to prepare solutions. The least two distillations were implemented in an apparatus made entirely of glass. NaCl (Merck) was preliminary heated at 750 °C to eliminate any organic impurities. NaH_2PO_4 and Na_2HPO_4 (Sigma-Aldrich) were used as received. The Curosurf® suspension was dissolved in a phosphate buffer at pH 7 and contained NaCl to increase the ionic strength to 0.15 M. The Concertation of investigated PS solutions changed from 0.04 to 1.25 mg/mL. Although these concentrations are lower than in lungs, they allow investigation of the influence of adsorption rate on the dynamic surface properties [45]. The temperature was controlled during all the measurements and changed from 25 to 35 °C. The Langmuir trough was placed into a plexiglass box to increase the air humidity.

The surface tension was measured by the Wilhelmy plate method. After the solution had been poured into the trough, the solution surface was cleaned by a moving barrier and an aspirator. After that the Wilhelmy plate touched the almost pure surface and measurements of the dynamic surface tension started in one minute.

The dynamic dilational surface elasticity was measured by the oscillating barrier method using an instrument from KSV NIMA, Finland. The Langmuir trough was equipped with leakage-proof barriers to exclude the undesirable leakage of the investigated substance under the barriers [46]. For this purpose, a flexible Teflon film was fixed along the trough perimeter, giving the possibility to reach extremely low surface tensions. The two barriers oscillated in counter phases at given amplitudes. Although, the frequency of breathing is in the range from 0.5 to 0.1 Hz, the frequency of surface area oscillations was changed from 0.005 to 0.03 Hz due to the device limitations. Therefore, the comparison of the obtained results with those for conditions in lung alveoli can be done only with caution. The harmonic oscillations of the surface area with amplitudes from 3.9 to 39% induced oscillations of the surface tension, which were measured by the Wilhelmy plate method. The plate from filter paper with a width of 1 cm was positioned parallel to the barriers in the middle of the through to minimize the influence of surface shear deformations [47–49]. Standard roughness for measurements of dynamic surface elasticity does not exceed 10 %.

The analysis of a non-linear system response to large surface deformations and estimation of the efficient dynamic surface elasticity (ε_{ef}), which characterizes the response, was described previously [35,36,46,50,51]. This quantity is determined by the following relation (cf. Fig. 1S of supporting information)

$$\varepsilon_{ef} = \frac{(\Delta\gamma^2 - \Delta\gamma^1)}{(\Delta A^2 - \Delta A^1)/(A_0 \pm \Delta A^1)} \quad (1)$$

where $\Delta\gamma^1$ and $\Delta\gamma^2$ are the surface tension amplitudes corresponding to the surface area amplitudes ΔA^1 and ΔA^2, A_0 is the initial surface area, and the different signs before ΔA^1 correspond to expansion and compression. If the difference between ΔA^1 and ΔA^2 approaches zero ε_{ef} characterizes the elasticity of the adsorption layer at large compressions and expansions, which are determined by $\Delta A^1 \approx \Delta A^2$, and thereby at two corresponding values of the surface tension $\gamma \approx \gamma_0 \pm \Delta\gamma^1 \approx \gamma_0 \pm \Delta\gamma^2$, where γ_0 is the surface tension of the unperturbed state. This approach allows estimation of the surface elasticity in a broad range of surface tensions by changing the amplitudes of surface area oscillations.

If $\Delta A^2 = 0$ and ΔA^1 approaches zero, ε_{ef} reduces to the dynamic surface elasticity for infinitesimal perturbations of equilibrium ε

$$\varepsilon = \frac{\Delta\gamma}{\Delta A/A_0} \quad (2)$$

where ΔA is the surface area increment, A_0 is the initial surface area, $\Delta\gamma$ is the surface tension increment [52].

ε_{ef} can be determined easily for arbitrary deformations even in the region of low surface tensions, while ε cannot be measured in this region

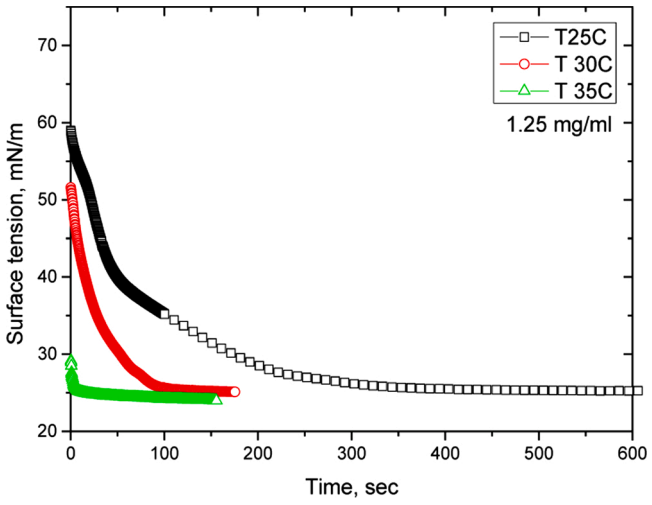

Fig. 1. Kinetic dependencies of the surface tension of PS solutions with concentration 1.25 mg/mL at temperatures 25 (black squares), 30 (red circles) and 35 °C (green triangles).

using standard procedures and is not a convenient characteristic of the adsorption layer in this case [36,50,51]. At high deformations, it is difficult to estimate the phase shift between the oscillations of surface tension and surface area, which is necessary for the determination of the real and imaginary parts of the dynamic surface elasticity. Therefore, only the modulus of ε_{ef} is determined in this work. The most of measurements of εef were repeated at least two times.

The static surface elasticity can be estimated by differentiation of the quasi-equilibrium compression isotherms according to Eq. (2), when the deformation rate tends to zero and the system is at equilibrium at any steps of deformation. If the deformation rate increases, the modulus of the dynamic surface elasticity estimated from the quasi-equilibrium isotherms can deviate from the static elasticity modulus. In this case, the corresponding dynamic surface elasticity was denoted as E_v, where v is the rate of deformation. The compression/expansion isotherms were measured after equilibration of the adsorbed layer using a modified Langmuir trough at a constant rate of relative deformations (in the range from 5 to 200 %/min). ε_{ef} and E_v coincided in error limits at the same surface tensions and the same rates of relative surface deformations [36].

The morphology of adsorption films was investigated by Brewster angle microscopy using BAM1 microscope (Nanofilm Technology, Germany). The ellipsometric angles were measured by the null ellipsometer Multiskop (Optrel, Germany) at the wavelength of 632.8 nm and at the incidence angle of 49°. The changes of polarization of the laser beam at the reflection from the solution surface depend on the adsorbed amount and are characterized by two ellipsometric angles Ψ and Δ.

3. Results and discussions

3.1. Adsorption kinetics

The results of this work relate to concentrations of the natural PS from 0.04 to 1.25 mg/mL and to temperatures of 25, 30 and 35 °C. It is accepted, that the PS adsorption consists of two steps – the diffusion of vesicles from the solution bulk to the subsurface and the transfer of lipid molecules from the vesicles to the surface layer [3–6,53–56]. The adsorption kinetics is usually investigated by measuring the dynamic surface tension. The increase of temperature leads to a significant acceleration of the adsorption (Fig. 1 and 2S), which can be connected with the diffusion acceleration or a decrease of the adsorption barrier [53]. Schram et al. showed that the adsorption barrier in PS solutions has an entropic origin, because the transition of lipid molecules from vesicles to the air/water interface occurs through the aqueous phase, where hydrophobic acyl groups are surrounded by water molecules [53]. The hydrophobic interactions are reduced by the increase of temperature and the adsorption barrier decreases. Moreover, it was shown that SP—B and SPC— proteins decrease the adsorption barrier and accelerate the PS adsorption [3–6,54,54,55,56]. Loney et al. showed that the adsorption acceleration close to equilibrium occurs if the lipid adsorption is higher than a certain critical value (Fig. 2S) [55]. SP-B and SP-C proteins promote the formation of a highly curved structural intermediate between the vesicles and the interfacial layer, which accelerates the destruction of the film between a vesicle and the interface [14, 20,55,57,58].

3.2. Dynamic surface properties

The whole PS concentration range under investigation can be divided into three zones according to the adsorption rate

3.3. Low concentrations

In the first concentration range (C < 0.6 mg/mL at 25 °C, C < 0.2 mg/mL at 30 °C, C < 0.05 mg/mL at 35 °C) the surface tension reaches equilibrium values later than 600 s after surface formation (Fig. 2S). In

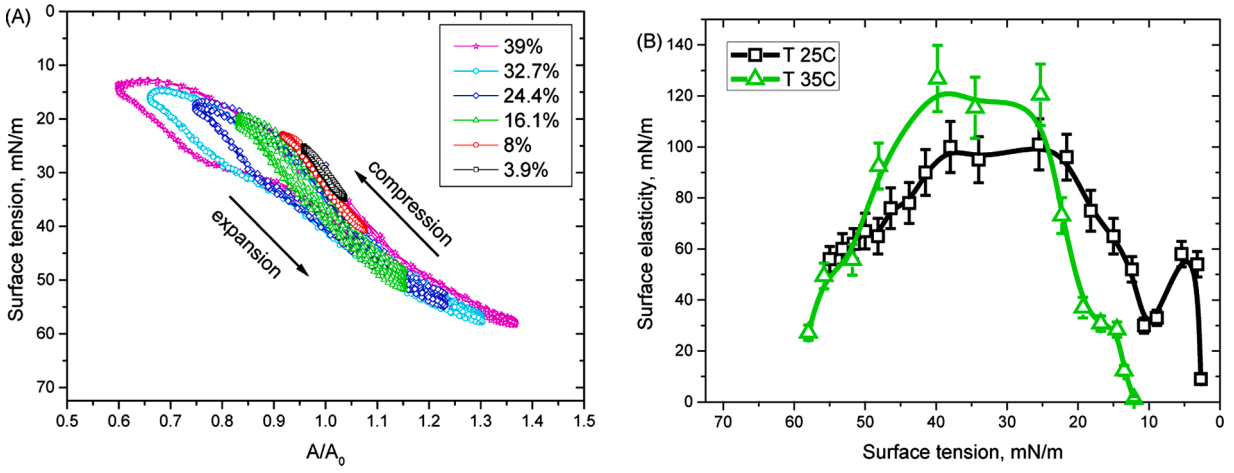

Fig. 2. (A) Dependencies of the surface tension on relative deformation (Lissajous plots) measured at different amplitudes of the area oscillations, as indicated on the Figure, for PS solutions at a concentration of 0.04 mg/mL at 35°. (B) Dependencies of ε_{ef} on the surface tension for PS solutions in the region of low concentrations at temperatures 25 (black squares) and 35 °C (green triangles).

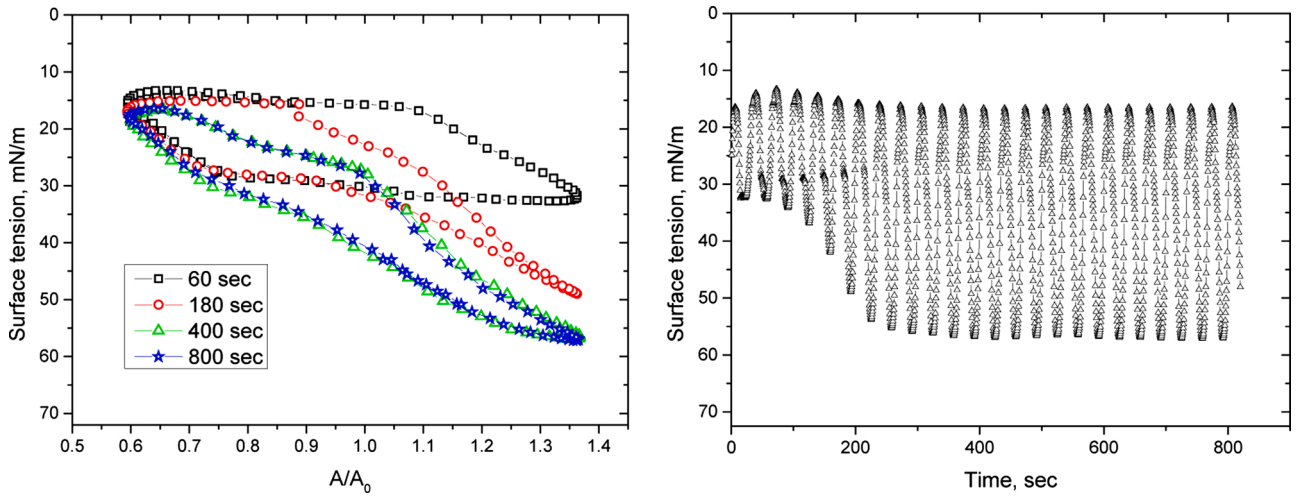

Fig. 3. Dependencies of the surface tension of PS solutions on the relative deformation after 60 (black asterisks), 180 (red squares), 400 (green circles) and 800 s (blue asterisks) (A) and surface age (B) at a concentration of 0.2 mg/mL at 35°.

this case, the surface tension changes in the course of harmonic oscillations of the surface area after equilibration resemble corresponding changes in the case of an insoluble monolayer, since the period of oscillations is much shorter than the equilibration time. The dynamic surface properties of PS solutions in this region at 25 °C have been discussed previously [36]. It was shown that the oscillations of the surface area with high amplitude led to significant changes of the surface tension as in the case of spread DPPC monolayers, and the matter exchange between the surface layer and the bulk phase only slightly decreased the maximum surface tension when the oscillation frequency decreased from 0.03 to 0.005 Hz. The main difference between PS adsorbed layers and spread DPPC monolayers at low surface tensions and at 25 °C consisted in lower ε_{ef} and faster relaxation processes in the former case presumably due to the influence of proteins on the equilibration at the interface [36]. This behavior agrees with the concept of "squeeze-out" of PS components during surface compression [3,5,6,59].

The Lissajous plots at high temperatures proved to be similar to those at low temperatures (Fig. 2A and 3S). At the same time, the temperature increase leads to a decrease of ε_{ef} in the range of higher surface tensions (Fig. 2B). At 25 °C the surface elasticity proves to be relatively high until the surface tension becomes lower than 2 mN/m, while at 35 °C ε_{ef} decreases to zero at a surface tension of about 12 mN/m indicating a decrease of the main relaxation time at low surface tensions (< 10 mN/m) in the latter case. The acceleration of the mechanical relaxation with a temperature increase reasonably agrees with the results on the influence of temperature on the dynamic surface properties of spread DPPC monolayers. It has been shown recently that the increase of temperature from 25 to 35 °C leads to a decrease of the main relaxation time in the region of low surface tensions presumably due to the disordering of the lipid monolayer structure [50]. It is possible to assume that the increase of temperature beyond the melting temperature for some lipids in case of PS layers also results in the disordering of the monolayer structure facilitating the PS transfer between the surface and subsurface layers at high compressions.

3.4. Middle concentrations

In the second concentration range (1.25 ≥ C > 0.6 mg/mL at 25 °C, 1.25 > C > 0.2 mg/mL at 30 °C, 0.2 > C > 0.05 mg/mL at 35 °C) the surface tension reaches equilibrium values within 100–500 s after the surface formation. In this case, the shape of the Lissajous plots and the amplitude of the surface tension oscillations change with the surface age (Fig. 3). The surface tension at expansion does not exceed 35 mN/m at the beginning of oscillations. After that the maximum surface tension at

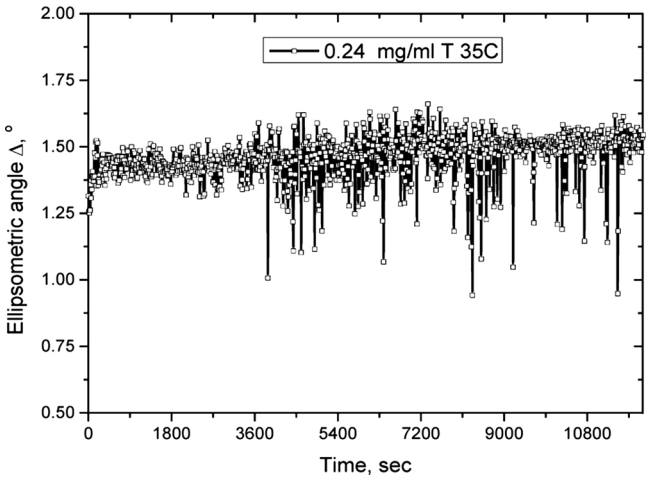

Fig. 4. Kinetic dependencies of the ellipsometric angle Δ for PS solutions at a concentration of 0.2 mg/mL and at a temperature of 35 °C.

expansion starts to increase and finally reaches a constant value. These stationary oscillations of the surface tension resemble the corresponding data in the first concentration region (Figs. 2 and 3A).

At the same time, the changes of the surface tension amplitude with the surface age depend on the amplitude of surface area oscillations (Fig. 4S). The surface tension amplitude does not change if the surface area amplitude is less than a certain critical value, approximately 8% at 35 °C. This means that the changes of the surface layer structure in the course of compression and expansion are reversible in this case. If the amplitudes of the surface area oscillations are higher, the surface tension amplitude starts to change with time. Probably, when the surface tension is lower than a certain critical value, the collapse of the adsorption layer leads to the irreversible displacement of some molecules from the interface. The irreversible collapse of the PS adsorption layer has been observed earlier and led to a partial loss of the functional properties of lipids [10,36,50,60]. Moreover, the surface tension starts to increase in the course of expansion long after, if the surface area oscillations are switched on in two hours after the surface tension takes an equilibrium value (Fig. 4S). To explain this behavior, one has to take into account the formation of a sublayer accumulating lipid molecules [3–6]. This process presumably occurs much slower than the establishment of equilibrium surface tension, and the sublayer can compensate the loss of lipid during 600 s of surface area oscillations only in approximately two

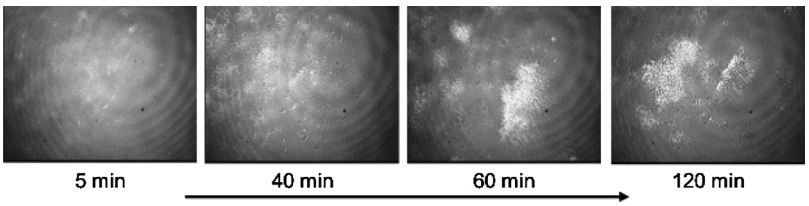

Fig. 5. BAM images for surface layers of PS solutions at a concentration of 0.2 mg/mL and at a temperature of 35 °C.

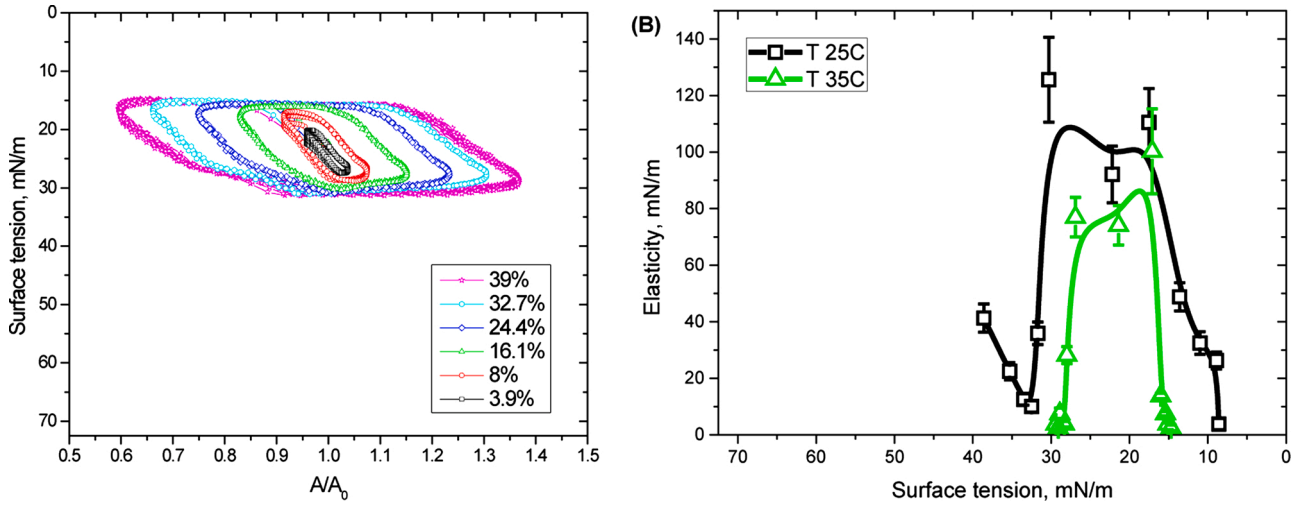

Fig. 6. (A) Dependencies of the surface tension of PS solutions on the relative deformation (Lissajous plots) at different amplitudes of the surface area oscillations at a concentration of 1.25 mg/mL and at 35°. (B) Dependencies of ε_{ef} at a frequency of 0.03 Hz on surface tension for PS solutions in the range of high concentrations at 25 (black squares) and 35 °C (green triangles).

hours. The results of ellipsometry and BAM (Figs. 4 and 5) agree with this assumption. One can observe strong chaotic fluctuations of the ellipsometric angle indicating the inhomogeneity of the adsorption layer in one hour after the surface tension coincides in error limits with the equilibrium value. BAM images also demonstrate the layer heterogeneity approximately after the same time.

3.5. High concentrations

In the third concentration range (C ≥ 1.25 mg/mL at 30 °C, C ≥ 0.6 mg/mL at 35 °C) the surface tension reaches equilibrium values close to 25 mN/m in approximately 100 s after the layer formation. In this case, the transitional processes are shorter than the oscillation period and one can observe only stationary surface tension oscillations (Fig. 5S). The analysis of surface tension oscillations at different amplitudes shows that the surface elasticity abruptly decreases when the surface tension is lower than approximately 15 mN/m and higher than 32 mN/m (Fig. 6). This indicates fast relaxation processes not only at compression, but also at expansion (Figs. 2B and 4 B).

ε_{ef} and E_ν at different frequencies and rates of relative deformations were measured to estimate the main relaxation time at 35 °C. In the range of surface tensions from 25 to 18 mN/m ε_{ef} is relatively high

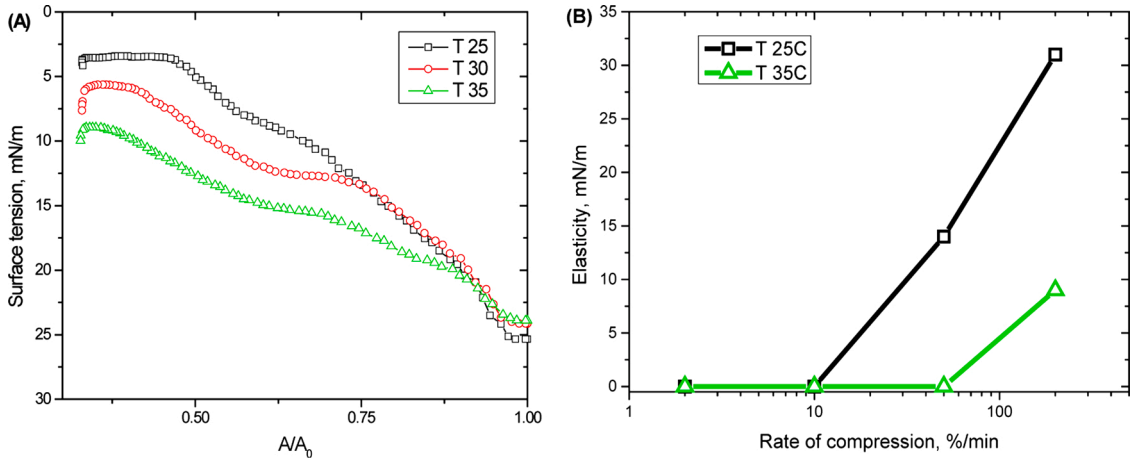

Fig. 7. (A) Compression isotherms of PS adsorption layers at the bulk concentration of 0.6 mg/mL and at the rate of relative deformation of 200 %/min and at 25 (black squares), 30 (red circles) and 35 °C (green triangles), respectively. (B) Dependencies of E_ν on the rate of relative deformation for the same system at a surface tension of 12 mN/m and at 25 (black squares) and 35 °C (green triangles).

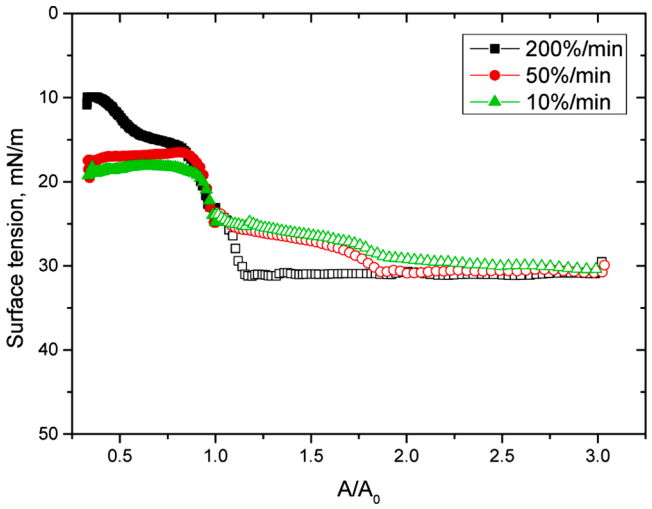

Fig. 8. Compression (closed symbols) and expansion (open symbols) isotherms for PS solutions at a concentration of 1.25 mg/mL at 35 °C and at deformation rates of 200 %/min (black squares), 50 %/min (red circles) and 10 %/min (green triangles).

(Fig. 4B) and does not depend on the oscillation frequency, indicating that the main relaxation is much longer than the oscillation period. At lower surface tensions ε_{ef} abruptly decreases and the surface tension at compression increases from 15 to 18 mN/m with a frequency decrease from 0.03 to 0.005 Hz (Fig. 6S). It means that in the range of surface tensions between approximately 20 and 10 mN/m the main relaxation time in the course of compression becomes comparable with the oscillation period and, consequently, decreases from several hundreds to several tens of seconds. At the same time, the surface tension decreases down to 9 mN/m at the highest rate of relative deformation in the course of compression (Fig. 7) indicating a decrease of the relaxation time from a few dozens of seconds to a few seconds with a decrease of the surface tension below 10 mN/m.

Measurements of the compression isotherms at different temperatures show, that the increase of temperature from 25 to 35 °C leads to lower surface tensions at the same compression rate (Fig. 5A and 7S). At surface tensions close to 12 mN/m and at 35 °C E_ν deviates from zero at deformation rates almost one order of magnitude higher than at 25 °C (Fig. 5B). It means that the temperature increase leads to the acceleration of relaxation and the main relaxation time at compression is close to several tens of seconds at the surface tension around 10 mN/m and temperature of 25 °C. These results agree with the data for lower concentrations in Ref. [35] where it was shown that main relaxation time at the low temperature was several tens of seconds at surface tensions below 10 mN/m. These results agree with the data of the captive bubble surfactometer and the constrained sessile drop where the surface tension oscillations were measured at frequencies around 0.1 Hz [10,11,28,29,61].

The comparison of the results for adsorbed layers of PS and spread DPPC monolayers in the range of low surface tensions at 35 °C indicates that other components in the mixture of natural PS, in particular proteins, accelerate the mechanical relaxation [36,50]. The increase of the PS concentration in the bulk leads to a shift of the surface elasticity at compression to slightly higher surface tensions (Fig. 2B and 6 B). Probably, this slight increase of the critical surface tension value is connected with an increase of the protein surface concentration, facilitating a transition from a monolayer to a multilayer.

The increase of bulk concentration leads to a significant acceleration of the relaxation process at expansion in case of periodic deformations. In the range of high concentrations at 35 °C the surface tension during late phase of surface expansion is almost the same at different frequencies (Fig. 6S). Moreover, the surface tension does not increase higher than approximately 33 mN/m even at the highest rate of expansion (Fig. 8). It means that the characteristic time of the matter exchange between surface layer and sublayer is few seconds or even less. Note that the relaxation in the course of expansion starts only after the surface tension increases up to 30−33 mN/m. To estimate the impact of adsorption on this process the surface tension oscillations were measured when the PS solution was replaced by the pure buffer solution after formation of the equilibrium adsorption layer (Fig. 8S). The oscillations during the first 300 s proved to be similar to the corresponding surface tension changes before the replacement, due to the preservation of the sublayer for some time after the subphase exchange. Thus, the adsorption does not influence the relaxation process in the course of expansion. At the same time, the adsorption from the bulk phase has to be sufficiently fast to compensate the decrease of surface concentration due to the irreversible collapse and provide stationary oscillations of the surface tension.

Investigations of the surface properties of PS solutions at different temperatures and concentrations give us a possibility to estimate the characteristics of the relaxation processes in the adsorption layer. The displacement of the surfactant into the sublayer in the course of compression is accelerated with the increase of temperature. At temperature of 35 °C the main characteristic time of the mechanical relaxation decreases from several hundreds to several tens of seconds with a decrease of surface tension from 20 to 10 mN/m and from several tens to few seconds at the further surface tension decrease to 1 mN/m. In spite of this relaxation process, the compression of the surface layer higher than 10 % leads to a loss of the functionality for some molecules in the adsorbed layer. The recovery of the surface layer composition proceeds in the course of expansion at the expense of the sublayer, when the surface tension increases up to around 33 mN/m. The characteristic time for the matter transfer from the sublayer to the interface is a few seconds or even less. This fast process helps to preserve low surface tension in the course of expansion. However, the low surface tension can be maintained only if the sublayer concentration is high enough. Therefore, stationary oscillations of the surface tension occur, when the characteristic adsorption time is comparable with the period of surface area oscillation and the sublayer formation is sufficiently fast.

4. Conclusion

The efficient dynamic surface elasticity of PS solutions was determined for the first time at low surface tensions (< 20 mN/m), at different temperatures and concentrations up to 1.25 mg/mL, when the characteristic adsorption time is comparable with the period of surface area oscillations. The determination of the surface elasticity at different frequencies and rates of deformation gives a possibility to estimate the characteristic time of mechanical relaxation in PS adsorption layers. At 35 °C the characteristic time is a few seconds, when the surface tension is lower than 10 mN/m at compression and higher than 33 mN/m at expansion. At relative deformations higher than 10 % the amplitude of surface tension oscillations changes in the course of a transitional process, presumably, due to the collapse of the adsorption layer, when the adsorption rate is much slower than the deformation rate. The harmonic oscillations of the surface area induce stationary oscillations of the surface tension when the PS concentration is higher than 1 mg/mL at 35 °C and the characteristic adsorption time does not exceed the oscillation period.

CRediT authorship contribution statement

A.G. Bykov: Conceptualization, Investigation, Writing - original draft. **O.Yu. Milyaeva:** Investigation. **N.A. Isakov:** Investigation. **A.V. Michailov:** Investigation. **G. Loglio:** Validation. **R. Miller:** Writing - review & editing. **B.A. Noskov:** Writing - original draft.

Declaration of Competing Interest

The authors report no declarations of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.colsurfa.2020.125851.

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