ADSORPTION AND CO-ADSORPTION OF POLYALDEHYDE DEXTRAN NANOPARTICLES AND NONIONIC SURFACTANT AT AN AIR–WATER INTERFACE: POTENTIAL IMPLICATIONS FOR PULMONARY DRUG DELIVERY

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Dedicated to Prof. Leon Gradoń on the occasion of his 70th birthday

Measurements of dynamic surface tension were carried out in aqueous systems (water or 0.1 mM Triton X-100) comprising nanoparticles formed from chemically modified polyaldehyde dextran (PAD). The nanostructures, considered as potential drug carriers in aerosol therapy, were obtained from biocompatible polysaccharides by successive oxidation and reactive coiling in an aqueous solution. The dynamic surface tension of the samples was determined by the maximum bubble pressure (MBP) method and by the axisymmetric drop shape analysis (ADSA). Experiments with harmonic area perturbations were also carried out in order to determine surface dilatational viscoelasticity. PAD showed a remarkable surface activity. Ward-Tordai equation was used to determine the equilibrium surface tension and diffusion coefficient of PAD nanoparticles ($D = 2.3 \times 10^{-6}$ m$^2$/s).

In a mixture with Triton X-100, PAD particles showed co-adsorption and synergic effect in surface tension reduction at short times (below 10 s). Tested nanoparticles had impact on surface rheology in a mixed system with nonionic surfactant, suggesting their possible interactions with the lung surfactant system after inhalation. This preliminary investigation sets the methodological approach for further research related to the influence of inhaled PAD nanoparticles on the lung surfactant and mass transfer processes in the respiratory system.

Keywords: polysaccharide nanoparticles, lung surfactant, dynamic surface tension, surface viscoelasticity, hysteresis

1. INTRODUCTION

Lung surfactant (LS) present in the liquid phase which covers the inner surface of pulmonary alveoli is responsible for lowering the surface tension during breathing cycle and assures proper functioning of the respiratory system (Goerke, 2001). As proposed by Gradoń and co-workers (Gradoń et al., 1996; Gradoń and Podgórski, 1989; Podgórski and Gradoń 1993), the LS is responsible for Marangoni-type convection in the alveolar fluid, generating flows which influence mass transfer processes in the respiratory system. Several studies confirmed that dynamic surface tension gradients produced due to periodic variation of pulmonary air/liquid surface area during breathing, create the driving force for removal of inhaled particles from deep lungs (‘pulmonary clearance’) and possibly facilitate the respiratory gas exchange (Grotberg, 2001; Sosnowski et al., 1998). The characteristic feature found in the LS during periodically compressed and expanded air/liquid surface area, $A$, (i.e. in the situation characteristic for breathing) is the hysteresis of surface tension, $\gamma$. It is related to the correct
physiological functionality of LS but from physical viewpoint - it can be considered as a measure of the amount of surface energy which is used to produce convective effects (Notter et al., 1982; Podgórski and Gradoń, 1989; Sosnowski, 2006). Therefore, reduction of this hysteresis is often used as an indication of a decrease of LS functions, particularly those related to the pulmonary mass transfer (Kondej and Sosnowski, 2013; Podgórski et al., 2001; Sosnowski et al., 2000). \(\gamma\)-A hysteresis can be analyzed in the framework of surface dilatational rheology, assuming that the observed time shift between surface tension and surface area reflects overall visco-elasticity of the interfacial region (Lyklema, 2000; Sosnowski, 2006).

Changes in the surface activity of the LS, which may occur due to interactions with particular drugs or drug carriers delivered by inhalation, can lead to abnormal physiological function of LS and, eventually, even to a respiratory failure (Kramek-Romanowska et al., 2015; Rosenberg et al., 2016; Zhang et al., 2012). On the other hand, the surface activity of administered drugs may have a supplemental effect if lung surfactant does not (e.g. due to its lack or damage) sufficiently lower the surface tension during the breathing cycle (Ellyett et al., 1996). Therefore, both the determination of surface activity of newly developed inhalable drug carriers and the evaluation of their interactions with LS are a very important step in safety assessment of aerosol therapy.

Recently, a new type of drug carrier for aerosol delivery was proposed in the form of modified polyaldehyde dextran (PAD) nanoparticles (NPS) (Jabłczyńska et al., 2015). It is known from the literature that some polymeric nanoparticles can adsorb at air/liquid interface and reduce the surface tension (Okubo, 1995). On the other hand, different types of polymeric and non-polymeric NPS have been demonstrated to inhibit the biophysical function of LS in vitro in a material- and concentration-dependent manner (Beck-Broichsitter et al., 2014; Kondej and Sosnowski, 2013). Until now, no data regarding surface activity of PAD nanoparticles are available, therefore the current paper is focused on this issue. In this first analysis, the interactions of PAD nanoparticles with a model nonionic surfactant (instead of LS) are also investigated in order to determine possible NPS-surfactant interactions in aqueous environment.

2. MATERIALS AND METHODS

The following reagents have been used in the synthesis of nanoparticles: dextran (MW = 75 kDa, Pharmacosmos, Denmark), dodecylamine hydrochloride, sodium periodate and alanine (Sigma Aldrich). Water used in all experiments was purified in a reverse osmosis system (Puricom, USA) and characterized by low conductivity of 3.8±1.0 µS. Nanoparticles were synthesized by successive oxidation and reactive coiling in an aqueous solution, according to a protocol described by Wasiak et al. (2016). Briefly, dextran was dissolved in water to gain the concentration of 5%, and sodium periodate was added in the molar ratio of 1:10 (IO\(_4\)-/ glucose units). The solution was stirred for 1 h in the dark at the room temperature and subsequently dialyzed against water for 3 days (Carl-Roth membrane bag with MWCO 12-14 kDa). The obtained polyaldehyde dextran (PAD) was dried in a laboratory drying oven at the temperature of 40°C for 24 h. For the coiling step 10% w/v aqueous solution of PAD was prepared, and 5% dodecylamine hydrochloride solution was added in the amount providing 33% degree of substitution of aldehyde groups. The rest of aldehyde groups were substituted by alanine which was added after 45 minutes of reaction. The reaction was carried out for 1.5 hours at 30°C and the pH of the mixture was gradually increased to 10. Finally the pH was adjusted to pH 7.4. pH adjustment was made by the addition of 1M NaOH or 2M HCl (Sigma Aldrich). The resultant suspension of nanoparticles was dialyzed for 30 min against water. Nanoparticles were spontaneously formed due to self-organization of polysaccharide chains in aqueous environment because of hydrophobicity of the attached coiling agent.
The nanosuspension of PAD was dried in a B-290 laboratory spray dryer (Büchi, Switzerland) directly after synthesis in order to obtain inhalable powder and increase the stability of the preparation. As demonstrated recently, the resultant micrometer-sized powder has very good properties for products typically used in aerosol therapy, moreover after rehydration it transforms to nanosuspension (Jablcyńska et al., 2015). The precursor was pumped at the volumetric rate of 3 cm³/min to the atomizing nozzle (diameter 0.7 mm) where it was mixed with compressed air (flow rate = 12 dm³/min). Drying air was supplied with the rate of 20 m³/h and inlet temperature of 200°C. Produced powder was separated in a high performance cyclone and collected in a product container.

For the evaluation of the surface activity, the powder was rehydrated to gain three values of concentration of reassembled nanoparticles: 1, 5 and 10 mg/cm³. In addition to systems based on pure water, similar nanosuspensions were prepared with a model nonionic surfactant Triton X-100 (0.1 mM; Sigma Aldrich). The resultant dispersion was shown to reconstruct the size distribution of PAD nanoparticles from the precursor suspension as demonstrated by Jabłczyńska et al. (2015). The dynamic surface tension (DST) of each sample was determined by the maximum bubble pressure (MBP) method using a BP2 tensiometer (Krüss, Germany) and by the axisymmetric drop shape analysis (ADSA) with a profile analysis tensiometer (model PAT-1M, Sinterface, Germany). The accuracy of both tensiometers was 0.1 mN/m. BP2 tensiometer allows to measure DST in relatively short time-scales (0.01-50 s), while PAT-1M device gives an opportunity to study adsorption in longer times (1-10³ s).

The latter apparatus was also used in our work to perform experiments with harmonic perturbations of interfacial area carried out in order to determine rheological parameters of the interface (dilatational visco-elasticity). All surface tension measurements were performed at the temperature of 36.6 ± 0.2 °C. Both tensiometers were calibrated using pure water for which surface tension was taken to be 70.14 mN/m at the temperature of experiments. Experimental results were discussed on the basis of Ward-Tordai equation (Ward and Tordai, 1946), which allowed to evaluate the equilibrium surface tension and the diffusion coefficient of NPS. Details of this approach are given in the following section.

2.1. Adsorption theory

Since PAD nanoparticles were recognized as surface-active we decided to employ Ward-Tordai model of the diffusion-controlled mechanism for quantitative description of NPS adsorption at the air/liquid interface. NPS diffusion is considered to be a two-step process where particles diffuse from the bulk into the subsurface and then they are adsorbed at the interface. For diffusion-controlled mechanism, the time scale of adsorption is much faster than the diffusion step. The classic solution for this process is given by Eq. (1) (Ward and Tordai, 1946):

\[ \Gamma(t) = 2c_0 \sqrt{D t / \pi} - 2 \sqrt{D / \pi} \int_0^\sqrt{t} c_s d \left( \sqrt{t} - \tau \right) \]  

(1)

This equation cannot be solved analytically, but two asymptotic solutions: for very short or very long surface ages, can be applied in order to estimate diffusion coefficient of surface active agent.

For short time approximation (t → 0), the limiting surface tension (\( \gamma \)) value is given by (Eastoe and Dalton, 2000):

\[ \gamma_{t \to 0} = \gamma_0 - 2nRTc_0 \sqrt{D t / \pi} \]  

(2)

where \( n = 1 \) for non-ionic surfactants, and \( n = 2 \) for ionics. The long time approximation (t → ∞) takes the form:

\[ \gamma_{t \to \infty} = \gamma_{eq} + \frac{nRTc^2}{c_0} \frac{\pi}{4Dt} \]  

(3)
For the purpose of calculations we treat nanoparticles as non-ionic surface-active macromolecules and we assume, according to Wasiak et al. (2016) that each nanoparticle consists of 10 dextran chains so it has molecular weight of around 750 kDa. It is also claimed that NPS content in the suspension is sufficiently low to assume that thermodynamic activity of particles is equal to their concentration, hence the diffusion coefficient of NPS is independent of their concentration in the examined range.

2.2. Surface visco-elasticity

To fully describe systems with dynamically changing interface such as the surface of alveolar fluid where the area changes harmonically during breathing cycle, the rheological approach can be useful (Sosnowski, 2006). The surface elasticity modulus $E$ expresses the response of the surface tension, $\Delta \gamma$, to the change in the surface area (surface dilatation), $\Delta A$. This parameter, also called surface dilatational (dilational) modulus, was defined by Gibbs (1961) as:

$$E = \frac{d\gamma}{d \ln A}$$

When some relaxation processes occur, for example reorientation of the molecules at the surface or diffusional exchange of the molecules/particles with the subsurface, the elasticity modulus becomes a complex number. The elasticity modulus consists then of a real part equal to the surface elasticity $E'$ and an imaginary part $E''$, related to surface viscosity $\eta_d$ (Miller, 2009):

$$E = E' + i E'' = E' + i\omega \eta_d$$

Where $\omega$ is the angular frequency of periodic changes of surface area.

3. RESULTS AND DISCUSSION

Data obtained by the axisymmetric drop shape analysis (ADSA) were plotted in the coordinates $\gamma$ versus $t^{-\frac{1}{2}}$ (as a consequence of long time approximation - Eq. 3) and the linear portions of the dynamic tensiograms were extrapolated to the intersection with the ordinate axis as presented in Fig. 1. The estimated values of equilibrium surface tension $\gamma_{eq}$ of PAD nanoparticles obtained for the $t^{-\frac{1}{2}} \rightarrow 0$ are shown in Table 1. Values of the derivative $(d\gamma/dt)^{-\frac{1}{2}} \rightarrow \infty$ were used for the calculation of the equilibrium surface excess $\Gamma_{eq}$ which is also listed in Table 1.

![Fig. 1. Dynamic surface tension of PAD nanoparticle suspensions of different concentration as a function of $t^{-\frac{1}{2}}$. Straight lines are used for the determination of $d\gamma/dt^{-\frac{1}{2}}$ and $\gamma_{eq}$ for $t \rightarrow \infty$.](image-url)
The results of measurements of the surface tension as a function of surface age show a good agreement of both applied methods as presented in Fig. 2. Both methods are complementary since they are operative in different time-scales. The concentration of PAD nanoparticles strongly affects both the rate of surface tension reduction and the equilibrium value of the surface tension, $\gamma_{eq}$. For the highest tested concentration of 10 mg/ml and very long adsorption time (3000 s), NPS reduce surface tension down to 35.7 mN/m. Extrapolation according to the long time approximation ($t \rightarrow \infty$) of Ward-Tordai equation indicates an even lower value of $\gamma_{eq}$ (32.4 mN/m). NPS at concentrations of 1 mg/ml and 5 mg/ml lowered surface tension to 46.1 mN/m and 38.3 mN/m, respectively, and extrapolated values of the equilibrium surface tensions were 35.1 and 33.3 mN/m, respectively. The obtained values indicate that the magnitude of adsorption (and surface tension reduction) was proportional to nanoparticle concentration in the bulk.

![Fig. 2. Dynamic surface tension of PAD nanoparticles in aqueous suspensions at different concentration as a function of surface age - results obtained by MBP (grey markers) and ADSA (black markers). Lines represent theoretical prediction of surface tension changes.](image-url)

Results obtained by the maximum bubble pressure method (for relatively short times of adsorption) were used to determine the diffusion coefficient. For each set of measurements, the diffusion coefficient providing the best fit to the experimental data was found according to Eq. (2). These values are collected in Table 1. Lines shown in Fig. 2 depict the theoretical surface tension calculated from Eqs. (2) and (3) for the averaged diffusion coefficient $D = 2.3 \times 10^{-10} \pm 0.6 \times 10^{-10}$ m$^2$/s. They allow to extrapolate the results for very long adsorption times which are not feasible experimentally.

| PAD NPS concentration [mg/ml] | $\gamma_{eq}$ [mN/m] | $(d\gamma/dt^{-1/2})_{t \rightarrow \infty}$ [mN$^{-1/2}$/m] | $D \cdot 10^{10}$ [m$^2$/s] | $\Gamma_{eq} \cdot 10^5$ [mol/m$^2$] |
|-------------------------------|----------------------|--------------------------------------------------|------------------|------------------|
| 1                             | 35.1                 | 593.4                                            | 2.1              | 7.3              |
| 5                             | 33.3                 | 262.2                                            | 1.9              | 10.8             |
| 10                            | 32.4                 | 180.7                                            | 3.0              | 12.7             |

* Estimated error value for calculated parameters is below 2%.

Dynamic surface tension results in an aqueous system with the non-ionic surfactant Triton X-100 (0.1 mM) and PAD nanoparticles (concentrations: 1, 5 and 10 mg/ml) are plotted in Fig. 3. Again, the series obtained by MBP and ADSA methods are complementary. As seen from Fig. 3, PAD nanoparticles...
affect the DST of Triton X-100. For short adsorption times, NPS immediately decrease the surface tension, and the range of this effect is greater than that of any single component which suggests synergic interactions between surfactant molecules and PAD nanoparticles. The reduction of surface tension is stronger when NPS concentration increases. However, for surface age longer than 100 seconds, nanoparticles seem to have negative impact on surface-activity of Triton X-100 ($\gamma_{eq}$ of the solution of pure surfactant has the lowest value). Almost no effect of NPS is observed for time-scales relevant for dynamics of breathing (1-10 s), where the nonionic surfactant itself controls the DST value. It must be stressed though that presented results show only one type of specific interactions between NPS and surface-active compound. Since Triton X-100 cannot be considered as a realistic model of the LS, the actual impact of tested NPS on the lung surfactant can be different.

Fig. 3. Dynamic surface tension of mixture of Triton X-100 (0.1 mM aq.) and PAD nanoparticles (NPS) at different concentrations as a function of surface age – results obtained by MBP (grey markers) and ADSA (black markers) methods.

Fig. 4. Dynamic surface tension of mixtures of Triton X-100 (0.1 mM aq.) and PAD nanoparticles (NPS) as a function of $t^{-1/2}$. Straight lines given as an example for the determination of $dy/dt^{-1/2}$ and $\gamma_{eq}$ for $t \to \infty$. 
Equilibrium surface tension values in mixed systems (surfactant + NPS) were calculated again from the long-time approximation of Ward-Tordai equation. It should be noted though, that in this case none of the physical parameters of this equation (bulk concentration, surface excess, diffusion coefficient) should be considered as real values since we deal with the co-operative or competitive adsorption of two surface-active components. Extrapolation done for \( t \to \infty \) is shown in Fig. 4 and the obtained values of \( \gamma_{eq} \) and \( (dy/dt^{1/2})_{t \to \infty} \) are listed in Table 2. It is seen that presence of NPS increases \( \gamma_{eq} \) which suggests that surface activity of PAD nanoparticles is really important only for processes with a short time scale. From the comparison of \( (dy/dt^{1/2})_{t \to \infty} \) for 1 mg/ml PAD particles in Triton X-100 (second row in Table 2: 145.5 mN·s\(^{1/2}\)/m) and for 1 mg/ml PAD particles in water (first row in Table 1: 593.4 mN·s\(^{1/2}\)/m) it is seen that this co-adsorption lowers the rate of surface tension reduction close to the equilibrium value of the surface tension (31.1 and 35.1 mN/m, respectively).

Table 2. The most essential data for measurements derived from DST for mixtures of Triton X-100 / PAD nanoparticles.

| PAD NPS concentration [mg/ml] | \( \gamma_{eq} \) [mN/m] | \( (dy/dt^{1/2})_{t \to \infty} \) [mN·s\(^{1/2}\)/m] |
|-----------------------------|-----------------|------------------|
| 0                           | 25.0            | 263.8            |
| 1                           | 31.1            | 145.5            |
| 5                           | 29.6            | 127.7            |
| 10                          | 28.0            | 145.5            |

* Estimated error value for calculated parameters is below 2%.

The results of surface visco-elasticity measurements in PAD aqueous nanosuspensions during air/liquid surface oscillations are shown in Fig. 5. Applied oscillation periods were in the range of human lung function: 2 seconds for fast, 4 seconds for moderate, and 8 seconds for slow breathing.

With increasing oscillation frequency, the dilatational elasticity, \( E' \) raises while dilatational viscosity, \( \eta_d \) - decreases. It is evident that surface elasticity of the air/liquid interface noticeably decreases with increasing concentration of nanoparticles, which suggests that the presence of NPS reduces the amplitude of surface tension variations during harmonic perturbations of air-liquid interface. This effect can be easily explained by fast exchange (mass transfer) of surface-active NPS between the surface and the adjacent liquid subphase during periodic variations of the interface. On the contrary, the
concentration effect on the surface dilatational viscosity is very small, at least for most typical physiologically, i.e. relatively quick surface oscillations (period of 2 and 4 s). It means that time-lag between surface perturbation (contraction/expansion) and surface tension variation, which is reflected by $\gamma$-A hysteresis, remains similar independent of NPS concentration in the liquid phase.

The result obtained set the ground for a preliminary discussion on possible effects of inhaled PAD nanoparticles (used as drug carriers) in the lungs. The tested NPS are evidently surface-active under dynamic conditions which is in line with several other results regarding nanoparticle behavior in aqueous environment (Bizmark et al., 2014; Kondej and Sosnowski, 2016). Consequently, NPS can either compete or cooperate (synergic effect) with other surface-active components of the system, leading to increased dynamics of surface tension reduction at short time-scales, as shown in the experiments done for the mixtures of Triton X-100 and NPS. In a physiological situation, high surface-activity of these NPS may interfere with the balanced surface-tension variations caused by the activity of the natural components of the LS. Competitive adsorption of NPS may decrease the mass of phospholipids and proteins exchanged with the interface during surface variations (breathing). As a consequence, their physiological function and their role in effects dependent on the adequate surface-tension dynamics (e.g. mass transfer in the pulmonary region) may be altered. Such hypothesis is supported by literature data which confirm that inhalation of potent surface-active compounds can be detrimental for the LS and respiratory functions (Hall et al., 1985; Rao and Das, 1994). It must be noted though, that NPS concentrations tested in our experiments were intentionally very high, since they were used to highlight the potential physicochemical effects. In real inhalation it is not probable that the concentration of 1 mg/ml can be attained in the pulmonary liquid because it would require inhalation of more than 30 mg of fine (< 5 $\mu$m) powder particles at a time (Sosnowski et al., 2000). It is highly improbable since typical inhalation drugs contain less than 500 $\mu$g of active compounds (e.g. corticosteroids), while even for an inhaled systemic drug like insulin, the inhaled mass does not exceed 9 mg of powder per dose (Santos and Edelman, 2014).

Another important observation is related to surface tension hysteresis during harmonic surface perturbation, which is known to occur in the LS system. Our study shows that such hysteresis is also produced by PAD nanoparticles themselves, as demonstrated by the visco-elastic surface response. However, a more detailed analysis of these effects is needed to assess their possible physiological consequences for LS and the respiratory system dynamics.

4. CONCLUSIONS

Experimental results show high surface activity of the studied PAD nanoparticles in the aqueous environment. The equilibrium surface tension of systems which contain NPS decrease to the value of 30-odd mN/m in the concentration-dependent manner. The concentration affected the rate of surface reduction, as well as the time in which the equilibrium was reached. The Ward-Tordai equation was used to calculate the diffusion coefficient of NPS and predict the asymptotic, equilibrium surface tension value in studied systems. The average value of the diffusion coefficient of PAD nanoparticles in water was determined as $D = (2.3 \pm 0.6) \times 10^{-10}$ m$^2$/s.

DST in aqueous systems which contain a model nonionic surfactant is determined mainly by activity of this surfactant. However, the effect of additional surface tension reduction by NPS present in such systems is the most significant for a very short adsorption time and it depends on particle concentration. This suggest a co-adsorption mechanism in mixed NPS-surfactant system. However, for surface ages similar to the timescale of breathing cycle (several seconds) the impact of nanoparticles is not very high. Our measurements showed that PAD nanoparticles influence surface dilatational elasticity but do not cause significant changes in surface dilatational viscosity in the tested ranges of surface oscillation rates and NPS concentrations.
As stated earlier, at this stage it is possible only to speculate on the mechanisms of interactions of inhaled NPS in the lungs. Their co-adsorption on the air-liquid interface may influence the dynamic surface tension during breathing. The most important is concentration-dependent reduction of surface elasticity which is related to the shape of surface tension hysteresis recognized as a marker of lung surfactant activity (Sosnowski, 2006). However, to fully evaluate the safety of PAD nanoparticles as potential carriers of drugs delivered by inhalation it will be necessary to study their adsorption and effect on surface rheology of the realistic model of the lung surfactant, e.g. the one based on commercial medicines such as Survanta, Curosurf, Infasurf or other suitable multi-component systems under investigation (Sosnowski et al., 2016).

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SYMBOLS

\[ A \] air/liquid surface area, \( \text{m}^2 \)
\[ c_0 \] bulk concentration, \( \text{mol/m}^3 \)
\[ c_s \] concentration in the subsurface, \( \text{mol/m}^3 \)
\[ D \] diffusion coefficient, \( \text{m}^2/\text{s} \)
\[ E \] surface dilatational modulus, \( \text{N/m} \)
\[ E' \] real part of complex surface dilatational modulus (surface elasticity), \( \text{N/m} \)
\[ E'' \] imaginary part of complex surface dilatational modulus (loss modulus), \( \text{Ns/m} \)
\[ n \] constant (eq. 1)
\[ R \] gas constant, \( \text{J/(mol K)} \)
\[ t \] time (surface age), s
\[ T \] temperature, K

Greek symbols

\[ \gamma \] surface tension, \( \text{N/m} \)
\[ \gamma_0 \] surface tension at \( t = 0 \), \( \text{N/m} \)
\[ \gamma_{eq} \] equilibrium surface tension, \( \text{N/m} \)
\[ \Gamma \] surface excess, \( \text{mol/m}^2 \)
\[ \eta_d \] surface dilatational viscosity, \( \text{Ns/m} \)
\[ \tau \] dummy variable of integration (eq. 1), \( \text{s} \)
\[ \omega \] angular frequency of periodic changes of surface area, \( \text{1/s} \)

Abbreviations

ADSA axisymmetric drop shape analysis
DST dynamic surface tension
LS lung surfactant
MBP maximum bubble pressure
MW molecular weight
NPS nanoparticles
PAD polyaldehyde dextran

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