Interfacial dynamics of the pulmonary surfactant model in the presence of glycerol/propylene glycol mixtures

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Introduction and Objectives

Electronic cigarette (EC)

- ECs are the common type of electronic nicotine delivery systems, existing in a variety of electronically powered devices used to evaporate a liquid mixture (e-liquid) (Farsalinos & Le Houezec, 2015).
- E-liquid is typically composed of varying flavors, with or without nicotine, diluted in aerosol formers like propylene glycol (PG) and/or glycerol (VG) and containing water.
- Aerosol in ECs is generated by heating the e-liquid to form supersatured vapors, which nucleate and condense, forming an aerosol mixture, after mixing with the external air.
- The aerosol mixture is composed of liquid particles and vapors and is inhaled by the user in a process commonly called “vaping.”
- ECs rapidly evolved from the first-generation disposable or rechargeable units to new devices with built-in tank systems, large batteries, and integrated circuits, allowing users to control the amount of delivered aerosol by adjusting the heating power (Brandon et al., 2015; Farsalinos & Polosa, 2014).

Lung surfactant (LS)

- LS is a sensitively structured pulmonary (alveolar) lipid–protein complex directly exposed to the inhaled aerosol mixture.
- LS is responsible for the homogeneous lung inflation and minimization of breathing effort.
- Inhaling high doses of aerosol leads to acute severe pulmonary dysfunction, which is at least partially caused by a disturbance in the lung surfactant system.
- The large surface area of the pulmonary region (up to 100 m^2 in adult humans) requires a considerable mechanical energy (work) for expansion during inhalation from the minimum lung volume and surface area (A_{min}) to the maximum (A_{max}) (Figure 1).

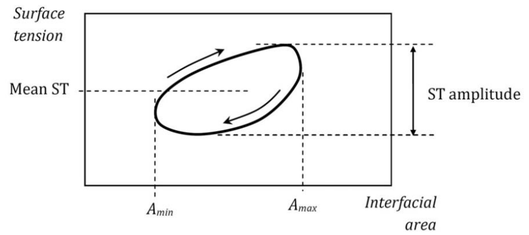

Figure 1. Definition of the mean ST and the ST amplitude in the experimental relationship (hysteresis loop).

Surface tension (ST)

- ST is the elastic tendency of a fluid surface that makes it acquire the least surface area possible.
- ST is a function of the LS surface concentration at the air/liquid interface of the pulmonary liquid.
- By dynamic adsorption, LS decreases the ST, diminishing the work of breathing.
- Dynamic ST gradients are produced during variations of the alveolar area during breathing.
- These gradients are responsible for the micro-flows of pulmonary fluid (Marangoni effects), which facilitate the mass transfer in the lungs.
- Alveolar flows contribute to the lung clearance of insoluble deposits and can also affect the gas exchange rate in the lungs.

Importance

- Deficiency or inactivity of LS leads to severe health consequences.
- These include life-threatening conditions, such as acute lung injury or acute respiratory distress syndrome, that often occur as an outcome of inhaling aggressive agents,
- The capability to modulate ST in alveolar fluid during respiration is the most essential feature of LS in view of its physiological functions related to lung mechanics and clearance.
- The ST-lowering properties of LS can be studied experimentally under specialized *in vitro* settings that mimic the natural dynamic conditions of the lungs during a breathing cycle.
- One of the most important indicators of dynamic surface-active properties of LS is the hysteresis of ST observed during periodic, breathing-like variations in the air/liquid area (compression/expansion).
- This hysteresis that is also related (together with the elastic properties of the pulmonary tissue) to the well-known p-V hysteresis during lung ventilation, a very sensitive feature of the LS system (Banerjee & Bellare, 2001).

The aim of this study was to establish the effects of adding PG and VG as essential components of e-liquids on the interfacial dynamics of LS. The measurements were conducted under simulated physiological conditions corresponding to human breathing.

Materials and Methods

Dose estimation

- To estimate the total mass of liquid particles deposited in the lung alveoli, data on their size distribution, density, and the efficiency of deposition were used (Sosnowski & Kramek-Romanowska (2016).
- Regional deposition values were calculated for measured particles in the respiratory system for various breathing parameters using the Multiple-Path Particle Dosimetry model (MPPD, 2015).
- The calculated average pulmonary dose deposited in the e-cigarette user’s alveoli after the average puffing session should be between 3.5 and 4.3 mg of PG/VG mixture. This mass is called the nominal dose delivered per session (NDDS).
- The exact value depends on the composition of e-liquid, as the aerosol formers have different densities.
- It is assumed that this amount of deposited e-liquid is homogeneously distributed throughout all of the pulmonary fluid.

LS and aerosol mixture compositions

- The LS model used in the studies was based on the Survanta product (Beractantum, Abbott Labs., Abbott Park, IL), a commercially available LS substitute derived from calf lungs (Figure 2).
- Survanta was diluted with ultra-pure water to obtain a final phospholipid concentration equal to 2.5 mg/mL, which corresponds to the one naturally found in humans.
- The amount of each mixture component was precisely calculated for five different e-liquid compositions to be used in the planned experiments containing the LS: PG/VG v./v. 100/0 (pure PG), 80/20, 50/50, 20/80, and 0/100 (pure VG).
- The approach allows determination of the possible effects of the composition of inhaled e-liquid on LS properties. NDDS and pulmonary liquid concentration data for the different compositions of e-liquid are shown in Table 1.

Figure 2. Survanta LS product (picture adopted from www.survanta.com).

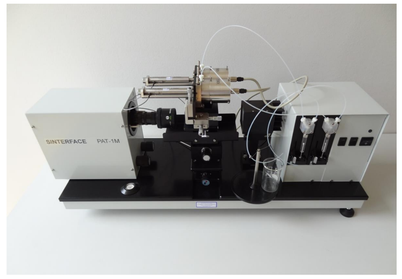

Figure 3. PAT-1M tensiometer (picture adopted from www.sinterface.com).

Measurement method

- Test e-liquid mixtures were prepared without nicotine and flavorings by mixing PG and VG at known volumetric proportions. These aerosol former compositions were used in mixtures including LS at various concentrations corresponding to 1x, 10x, 100x, 200x, 1000x, and 2500x NDDS to scan for the effects that may appear even at hypothetically ultra-high inhaled doses of deposited EC aerosols.
- Dynamic ST was measured using the drop shape method implemented in a commercial PAT-1M tensiometer (Sinterface, Berlin, Germany) (Figure 3).
- Dynamic ST at each instant of harmonic variation of the air/liquid interfacial area was determined by solving the Young-Laplace equation to approximate the shape of a small droplet (12 mm^3) formed at the tip of a capillary tube.
- The droplet was continuously pulsated at physiological temperature (36.8 ± 0.2 ºC), with the adjusted frequencies corresponding to the breathing rate at various levels of activity.
- Based on time profiles of dynamic ST, the essential numerical parameters needed to characterize the interfacial properties of the LS under breathing-like oscillations were evaluated (mean ST, ST amplitude, dilatational surface elasticity, and dilatational surface viscosity).
- Surface elasticity and viscosity were determined from the fast Fourier transform analysis of a time series of the ST and surface area.

Table 1. Nominal deposited dose per session (NDDS) and the corresponding mixture concentrations in the pulmonary fluid for different propylene glycol/vegetable glycerin (PG/VG) ratios in the inhaled aerosolized e-liquid.

PG/VG ratio (%)	100/0	80/20	50/50	20/80	0/100
NDDS (mg)	3.54	3.67	3.91	4.15	4.29
Concentration in pulmonary liquid (mg/mL)	0.117	0.122	0.130	0.137	0.142

Results

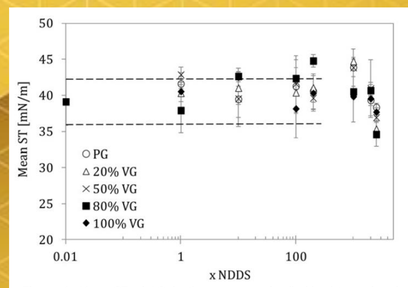

Figure 4. Mean ST of LS in the presence of e-liquid mixture of various compositions and concentrations (NDDS: estimated nominal deposition dose per session). Data for the normal rate of breathing (0.25 Hz). Dashed lines show the control range (pure LS).

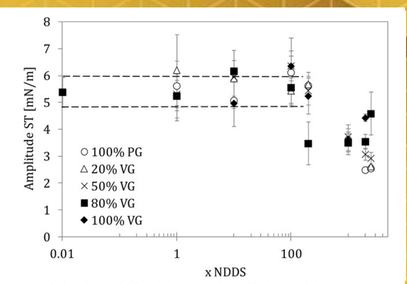

Figure 5. Amplitude of ST variations (amplitude ST) in the LS in the presence of e-liquid mixture of various compositions and concentrations (NDDS: estimated nominal deposition dose per session). Data for the normal rate of breathing (0.25 Hz). Dashed lines show the control range (pure LS).

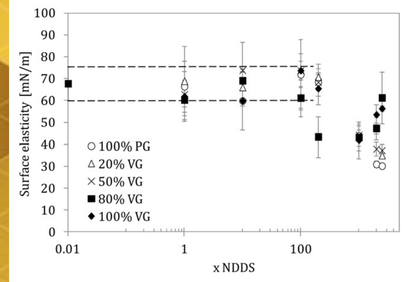

Figure 6. Surface dilatational elasticity of the LS liquid interface in the presence of e-liquid mixtures of various compositions and concentrations (NDDS: estimated nominal deposition dose per session). Data for the normal rate of breathing (0.25 Hz). Dashed lines show the control range (pure LS).

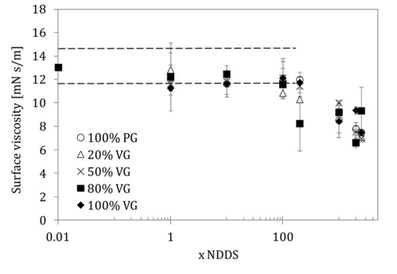

Figure 7. Surface dilatational viscosity of the LS liquid interface in the presence of e-liquid mixtures of various compositions and concentrations (NDDS: estimated nominal deposition dose per session). Data for the normal rate of breathing (0.25 Hz). Dashed lines show the control range (pure LS).

Conclusions

- The computed total relative average deviation of the mean ST, surface elasticity, and surface viscosity with respect to the control values show that concentrations up to 10x NDDS have practically no effect on the interfacial activity of the LS.
- 20%–30% deviation from the control state (i.e., pure LS) was observed when the mixture concentration approached 200x NDDS. At this concentration, the mixture with a 20/80 PG/VG composition had the most striking effect.
- Ultra-high concentrations (>1000x NDDS) clearly changed the dynamic surface-active properties.
- Pure PG and mixtures with a high PG content had a greater influence on total deviation than VG alone and mixtures with high VG content.

Details published in

“Physicochemical studies of direct interactions between lung surfactant and components of electronic cigarettes liquid mixtures”, Tomasz R. Sosnowski, Katarzyna Jablczynska, Marcin Odziomek, Walter K. Schlage, and Arkadiusz K. Kuczaj, INHALATION TOXICOLOGY, 2018, VOL. 30, NO. 4-5, 159-168

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