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Thin liquid films from a new synthetic pulmonary surfactant preparation

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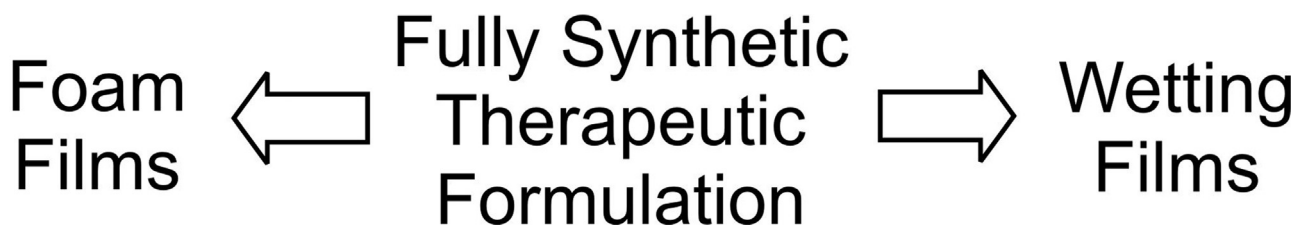
GRAPHICAL ABSTRACT



HIGHLIGHTS

- Thin liquid films from fully synthetic therapeutic surfactant.
- Foam and wetting films at physiological electrolyte concentrations.
- Wetting behaviour at hydrophobic silica surface.
- Surface forces acting in thin liquid films.

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ABSTRACT

A new pulmonary surfactant with synthetic analogs of surfactant proteins SP-B and SP-C (CHF5633) was studied by the method of thin liquid films (foam and wetting films). For foam films dependences such as probability W for formation of black foam films vs. surfactant concentration (C_s), disjoining (capillary) pressure isotherms ($\Pi(h)$) and film thickness (h) were studied. The minimum CHF5633 concentration for a black foam film formation was established in 75 μg/cm^3 (after 30 min). The results obtained were compared with those of therapeutic pulmonary surfactant preparations and in particular to Curosurf®, the one that showed the best profile among the tested animal-derived surfactants with respect to black film formation, stability and homogeneity. It was shown that with respect to stability surfactant CHF 5633 (from W/C curves) was very close to Curosurf®. The differences involved black foam film thicknesses which for the synthetic surfactant (at 200 μg/cm^3) were h = 14.7 nm and for Curosurf® (at 200 μg/cm^3), h = 12.6 nm, i.e. film thickness of the synthetic surfactant was larger, probably due to the larger quantities of surfactant protein analogs SP-B and SP-C contained in it and/or to the different phospholipid composition. The same was observed for $h(C_s)$ dependence. For wetting films equilibrium thickness vs. degree of hydrophobicity on a solid surface was measured as well as wetting contact angles.

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Practically no significant difference in the wetting behaviour of the aqueous suspensions of natural surfactant preparation Curosurf® and CHF 5633 was established, however about 25% less Curosurf® was needed to achieve almost the same wetting behavior.

1. Introduction

Respiratory distress syndrome (RDS) in preterm infants is caused by a pulmonary surfactant deficiency. Today, RDS is treated effectively with therapeutic surfactants produced from animal lungs. Medical practice has proven them to be beneficial and products such as Curosurf®, Infasurf®, Survanta®, Alveofact®, etc. are largely used in preterm infants.

The recent years have marked an increased interest towards developing a new generation of fully synthetic pulmonary surfactants with SP-B and/or SP-C surfactant protein analogs [1–4]. Recent research has led to formulate advanced SP-B and SP-C peptides in a lipid mixture that mimics the composition of native lung surfactant. Several companies are attempting to develop new synthetic surfactants based on simple mixtures of phospholipids and synthetic or recombinant peptides. Most of them have been tested only in pre-clinical trials and animal models of RDS. CHF5633 is the first synthetic surfactant that contains analogs of both surfactant proteins SP-B and SP-C. It has been shown to be more resistant to inactivation than the animal derived surfactants in preterm lambs [5,6].

Most frequently therapeutic surfactants are described by characteristics associated with the adsorption layer at the liquid/air interface. A common approach to physicochemical characterization involves establishing surfactants surface tension or surface pressure [7–10]. In vitro methods can rapidly provide information about surface activity of experimental surfactant preparations.

It is of interest to identify other physicochemical parameters describing pulmonary surfactant. In that respect, black foam film studies prove to be particularly relevant. We have introduced them as a method for investigation of alveolar surface structure and stability [11–16]. In comparison with the largely used 'monolayer' model, the black foam film accounts not only for lateral intermolecular interactions between first neighboring molecules in the adsorption layer, but also for the interactions in the bi-dimensional ordered system such as the bilayer film being the thinnest black film or the so-called Newton black film [13,15]. Further, such an in vitro model considers alveolar surface and stability via a microscopic black film set under the conditions of lung alveolus, in terms of capillary pressure, film radius, and electrolyte concentration. This represents an additional advantage of the method. The capillary pressure ranges within 0.03–3.0 kPa, which falls within the lung capillary pressure interval during inhaling and exhaling. The values of capillary pressure required for inhalation/exhalation are dictated by the surface tension and radii of the alveoli and this "breathing pressure range" could be estimated approximately between 0.3 and 3 kPa [15]. The introduction of the 'black foam film' model affords new opportunities in the study of pulmonary surfactant behaviors in vitro [13,16], providing possibilities to measure dependences such as film thickness vs. electrolyte concentration, probability for black foam film formation vs. alveolar surfactant concentration, interaction forces (disjoining pressure) vs. film thickness, etc. This approach has been already used for characterising therapeutic preparations [16].

On the other hand many observations show that the breathing function can be strongly affected by air pollution—fine and ultrafine particles from the atmospheric air can be conducted to the air spaces of the lung [17]. There these particles interact with the pulmonary surfactant layers in the alveoli. Obviously the wetting properties of the solid particles with respect to the pulmonary surfactant suspensions are very important for these interactions. Recently we studied [18] the wetting contact angles as well as the film thickness of wetting thin liquid films on solid surface from aqueous suspensions of the therapeutic surfactant. Here we extend these studies to aqueous suspensions of the synthetic surfactant CHF5633.

2. Materials and methods

2.1. Materials

CHF5633 is a sterile saline suspension of dipalmitoylphosphatidylcholine (DPPC), phosphatidylglycerol (POPG) and synthetic analogs of SP-B and SP-C at the concentration of 80 mg/ml [6], provided by Chiesi Farmaceutici (Parma, Italy). The original product contains DPPC and POPG in the ratio of 1:1 (98.3%), surfactant protein SP-C analogue (1.5%), and SP-B analogue (0.2%) [5]. CHF5633 was appropriately diluted with 0.15 mol/dm^3 NaCl to obtain the required C_s concentrations. Tri-distilled water was used in all solutions; NaCl (Merck, Germany) was preheated at 550 °C to remove eventual surfactant contamination.

2.2. Microinterferometric method for formation and study of thin liquid films

Foam films of about 100 μm radius were studied at a capillary pressure P_σ = 0.03 kPa and temperature of 23 °C. Film thickness h values as well as probability (W) of film formation obtained at this temperature did not differ significantly from those obtained at 37 °C [19,20]. Microscopic foam films were studied by means of the microinterferometric apparatus of Scheludko-Exerowa [15]. The method has been employed for the study of pulmonary surfactants and amniotic fluid, as well as for some model mixtures of phospholipids and pulmonary surfactant components [21–23].

Fig. 1a depicts a detail of the measuring cell used in the thin liquid films study. A microscopic foam film of radius r was formed in a biconcave drop in a tube-holder of radius R. Capillary pressure was determined by the surface tension (σ) and R, $P_\sigma = 2\sigma/R$. Film drainage (Fig. 2a) took place under constant pressure and continued until a jump-like formation of black spots occurred, and gradually spread across the entire film (see Fig. 2b–d). A microscopic black foam film of constant radius and capillary pressure was formed.

Disjoining pressure $\Pi(h)$ isotherms were depicted by means of the Pressure Balance Technique, described previously [24,25]. The Exerowa-Scheludko porous plate cell was used to monitor the $\Pi(h)$ isotherm. Fig. 1b shows a detail of the porous plate cell. The foam film was formed in a little hole drilled into a porous plate soaked with the solution. The gas pressure inside the glass chamber was increased (up to 10^5 Pa) with a membrane pump. The pressure difference measured was the capillary pressure which equals disjoining pressure at equilibrium. In all cases the film thickness is monitored by measuring the reflection of monochromatic light using the microinterferometric method [15,25].

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