SYNSURF - SYNTHETIC LUNG SURFACTANT

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Brief Description

A Pulmonary surfactant is a surface-active lipoprotein complex having both hydrophilic and hydrophobic properties. The surfactant facilitates gaseous exchange by adsorbing to the air-water interface of lung alveoli thereby reducing its surface tension. Surfactants are therefore essential for the breathing process and the absorption of oxygen in alveoli. Respiratory diseases may be treated with surfactants in order to avoid a decline in respiratory function.

This invention is a synthetic surfactant formulation consisting of a combination of readily accessible phospholipids and synthetic peptides which may be administered as either a liquid or in a nebulised/aerosolised form. It offers several advantages over currently available surfactants.

Problem Statement

Common problems associated with most of the current commercially available surfactants are that many of them contain surfactant proteins with varying efficacies in patients and also that the majority of them contain surfactant proteins derived from animals.

The manufacture of animal-derived surfactant proteins can be a relatively expensive exercise requiring multiple purification processes which impact on the efficiency of the protein extraction and add to the expense of manufacturing surfactants. The use of animal-derived surfactant proteins has the added potential risk of transmitting animal diseases to humans.

Another challenge associated with commercially available surfactants is that the therapeutic application of these surfactants has primarily been associated in HMD/RDS in premature infants, and therefore its scope of application has always been limited.

Target Market

Respiratory diseases affect a significant part of the world's population. Disease complexes such as respiratory distress syndrome (RDS) have serious repercussions and can be life threatening. RDS typically affects mainly premature born infants (~ 50% of infants born before 32 weeks) whilst acute RDS (ARDS or "lung injury"), affects young infants, children and adults.

Our novel surfactant, "Synsurf", can potentially be used in the treatment of RDS, asthma, chronic obstructive pulmonary disease (COPD), adult respiratory syndrome, HIV/AIDS related lung diseases (PJP infection), tuberculosis, severe acute respiratory distress syndrome, near-drowning events and hydrocarbon poisoning.

Furthermore, Synsurf can also play an important role in the administration of pulmonary drugs as a carrier for active pharmaceutical ingredients (API's) such as immuno suppressants, glucocorticosteroids, vasodilators, β-sympathomimetics, antibiotics, short interfering RNA's and monoclonal antibodies in pulmonary and other conditions.

Value proposition/ Benefits

Synsurf is an entirely synthetic formulation that mimics the action of naturally occurring surfactant protein. The advantages of this product are that it:

- shows superior efficacy as a surfactant compared to leading commercially-available surfactants, showing better oxygenation values in preclinical trials;
- is inexpensive to manufacture as the formulation contains readily available components;
- is less complicated to manufacture since it does not rely on protein purification and harvesting from animal sources;
- reduces the risk of the transmission of animal-derived pathogens;

- decreases the potential of allergenic responses because its components are not animal-derived;
- can be administered by means of a nebuliser or aerosol device; and
- it is a potential drug carrier and/or permeation-enhancing agent for various API's.

Unique Characteristics

Synsurf's unique characteristics are that it:

- is completely synthetic and devoid of possibly animal protein contamination, therefore eliminating the possibility of transmitting animal-associated diseases;
- is supplemented with spreading agents and polypeptides, mimicking SP-B function;
- allows for scalable production;
- consists of simple commercially available polypeptides which form a peptide complex in vivo that mimics an essential surfactant protein for enhanced pulmonary function;
- has superior surface tension lowering ability; and
- has demonstrable drug carrier capacity.

Technical Description

Synsurf comprises a lipidaceous carrier and a peptide complex consisting of a mixture of poly-L-lysine and poly-L-aspartic acid or pharmaceutically acceptable salts of these peptides.

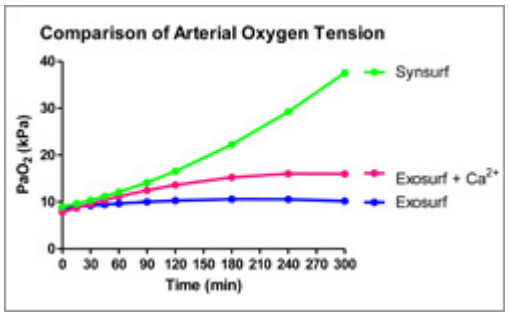
The poly-L-lysine is predominantly positively charged and the poly-L-glutamic acid is predominantly negatively charged. The poly-L-lysine is longer than the poly-L-glutamic acid by which means that, when permitted to complex with one another, they form a peptide complex comprising a substantially charge-neutralised region and a positively-charged region. The substantially charge-neutralised region of the peptide complex is therefore capable of interacting with the lipidaceous carrier, while the positively-charged region is available to interact with an aqueous and/or polar environment.

In addition, the formulation comprises pharmaceutical excipients suitable for pulmonary administration in liquid form or by nebulisation. The composition is administered into the lungs to temporarily substitute for natural pulmonary surfactant. The surfactant reduces surface tension at alveolar interfacial surfaces, thereby facilitating expansion of the alveolar spaces.

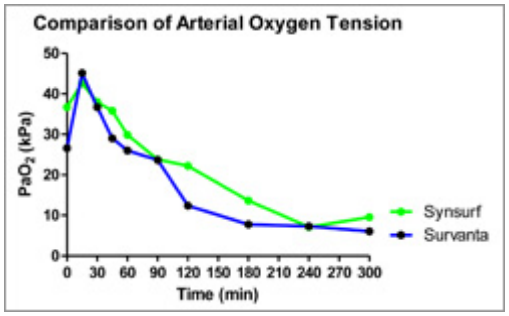
Innovation Status

The efficacy of Synsurf has been demonstrated and used in both vivo trials and in vitro permeability studies using animal and human tissue specimens.

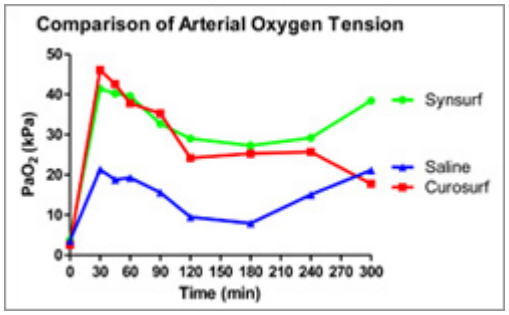
Three sets of in vivo trials were conducted. The first in vivo trial was conducted on adult rabbits, which were made surfactant-deficient by repeated pulmonary lavage. The trials showed that a group of animals treated with our product demonstrated an improvement in oxygenation and lung histology, far superior to that of a group of animals treated with a commercially available surfactant.



The second in vivo trials were conducted on pre-term lambs. The aim of the trial was to assess the efficacy of our product compared with bovine-derived surfactant as early rescue surfactant treatment for HMD/RDS. The main objective of the study was to compare systemic oxygenation and lung mechanics in the pre-term lambs during administration of either our product or one of the bovine-derived surfactants 30 minutes after birth. The results were indistinguishable based on gas exchange, dynamic respiratory compliance and lung histology, meaning that our surfactant was capable of competing against other bovine-derived surfactants.



The third study was a randomized trial in which our product was evaluated against a porcine-derived surfactant in pre-term lambs before first breath. We assessed systemic oxygenation and lung mechanics in preterm lambs during instillation of saline (control), our product or a porcine-derived lung surfactant. A significant improvement in oxygenation was shown by both our product and the porcine-derived surfactant, but the oxygenation was sustained for longer period over 5 hours compared to the porcine derived surfactant.



In vitro thermodynamic, inactivation and interfacial rheology studies were performed in which our product was compared with two mammalian-derived surfactants. The outcomes of these studies showed that equilibrium surface pressures, as an indication of adsorption behaviour, were similarly dependent on concentration and temperature for all three surfactants. The equilibrium surface pressures for the three surfactants varied between 30 - 40 mN/m and those of the Hill coefficient, which is a measure of cooperativity in the adsorption behaviour of surfactant molecules, between 1.24 - 4.6.

Surfactant Type	Surfactant Concentration	Surface Pressure (mN/m) 23 °C	37 °C
Survanta®	400 µl	19	–
	800 µl	21	–
	1600 µl	23	43.2
	4.44 X 10^{-4} ml/ml	–	40
Curosurf®	50 µl	27.5	–
	200 µl	32	–
	400 µl	41	39.7
	4.44 X 10^{-4} ml/ml	–	40
Synsurf®	400 µl	19.5	–
	800 µl	24.5	–
	1600 µl	29.5	30.6
	4.44 X 10^{-4} ml/ml	–	30

With regard to the behaviour of the above three surfactants during the breathing cycle, compression-expansion experiments (mimicked by variation of the surface area of the Langmuir trough) were performed, the adsorptions of all three surfactants are slow. Both Curosurf® and Survanta® reached surface pressures of about 40 mN/m while that of Synsurf® was about 30 mN/m. Considering the kinetics, Curosurf® (containing 1% - 2% of SP-B & SP-C), adsorbed the fastest followed by Survanta® (containing ~ 1% SP-B) followed by Synsurf® (containing ~ 4% protein). Similar surface pressure-area isotherms were found for all three surfactants studied.

For all three surfactants it was demonstrated that albumin, released into alveoli during pathological processes, interfered with the respreading mechanism of surfactant molecules, inhibiting the activity of these preparations. Furthermore, it was shown that cholesterol, which is elevated in conditions such as ARDS, stabilised maximum surface pressures at ~51 mN/m for all three surfactants. However, the rate at which this stabilisation occurred differed for each surfactant studied and it was found that it occurred slowest in our product. To retain surfactants in the alveoli it is desirable that these mixtures should have fairly high viscosities at high surface pressures, while at low surface pressures the reverse is true. This facilitates the respreading of the constituent molecules after compression. To assess the rheological properties of the surfactants at the air-water interface, shear viscosity and elasticity of the surfactant monolayer for these preparations were measured. Overall the in vitro studies demonstrated that our product showed a physico-chemical behaviour non-inferior, and sometimes superior, to that of the mammalian-derived surfactants.

Regulatory acceptable toxicity studies have not been conducted and such studies need to be conducted in order to bring the product closer to commercialisation. The components of the surfactant are all readily available and have had some sort of FDA or equivalent approval in other products.

National phase applications has been filed for this invention. The experiments mentioned above demonstrate that preclinical efficacy experiments have been conducted and the results have shown our product to be favourable as a surfactant and/or potential drug delivery carrier. Toxicity trial studies are still outstanding and need to be conducted in conjunction with a commercialisation partner.

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