Physicochemical and Aerosolization Performance Stability of an Excipient Enhanced Growth (EEG) Synthetic Lung Surfactant Powder Formulation

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INTRODUCTION

- Neonatal respiratory distress syndrome (NRDS) remains one of the single major causes of infant death.
- Surfactant replacement therapy (SRT) is the standard therapy for infants with NRDS. Despite frequent use, liquid bolus instillation of SRT has some challenges and delivery issues [1].
- Surfactant administration as a powder aerosol could eliminate some of these problems. However, efficient delivery of dry powder aerosols also faces a number of challenges due to the breathing pattern of the neonates including low tidal volumes and short inhalation times [2].
- We have developed highly dispersible spray-dried formulations and positive-pressure air-jet inhalers that are ideal for aerosol administration to these infants with small actuation air volumes and low air flow rates [3-4].

OBJECTIVE

This study presents the formulation and characterization of a synthetic lung surfactant EEG powder, along with its short-term and in-use aerosol performance and stability under different storage conditions.

METHODS

Powder Preparation and Storage

- Feed dispersions containing DPPC, B-YL, mannitol, sodium chloride and l-leucine (25:3:42:10:20% w/w) were spray dried [5].
- Powders were filled in size 0 HPMC capsules, packaged in Al-Al blister strips and stored at 40±5%RH and 25±2ºC, 5±2ºC and −20±2ºC for 3 months (3M). For in-use aerosolization stability, powders were exposed to 22ºC/45%RH and 30ºC/75%RH following device loading for 0.5 – 2 hrs.

Physicochemical properties

- Liquid chromatography–mass spectrometry (LC-MS), laser light diffraction particle sizing, powder X-ray diffraction (PXRD) and bubble pressure tensiometry were performed for stability assessments.

Aerosolization performance

- An infant air-jet DPI connected to a preterm nose-throat (NT) model was used to test realistic *in vitro* aerosol performance [5] (Fig. 1).

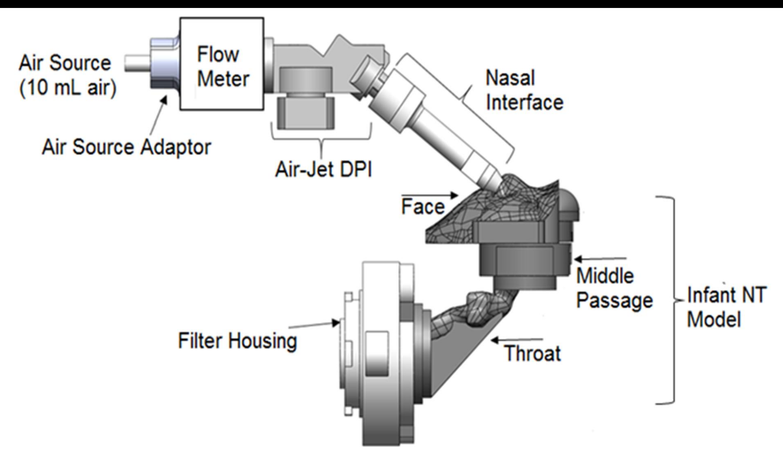

Fig. 1. **Infant air-jet DPI platform attached to preterm nose-throat (NT) model [5].**

RESULTS

- Compared to the initial value, there were no significant differences observed in the DPPC content after 3 months storage under the study conditions.
- The surface activity also remained unchanged following 3 months storage at the three study temperatures.
- The micrometer sized powder remained unchanged following storage at 5ºC and -20ºC, with a small increase in primary particle size observed at 25°C. Small changes in the particle fractions (<1 µm and/or <5 µm) were observed during storage, suggesting limited primary particle aggregation during storage.
- PXRD (Fig. 2) showed evidence of crystalline structure in the synthetic lung surfactant powder formulation both initially and following 3 months storage suggesting no change in the solid-state stability of the powder during storage.

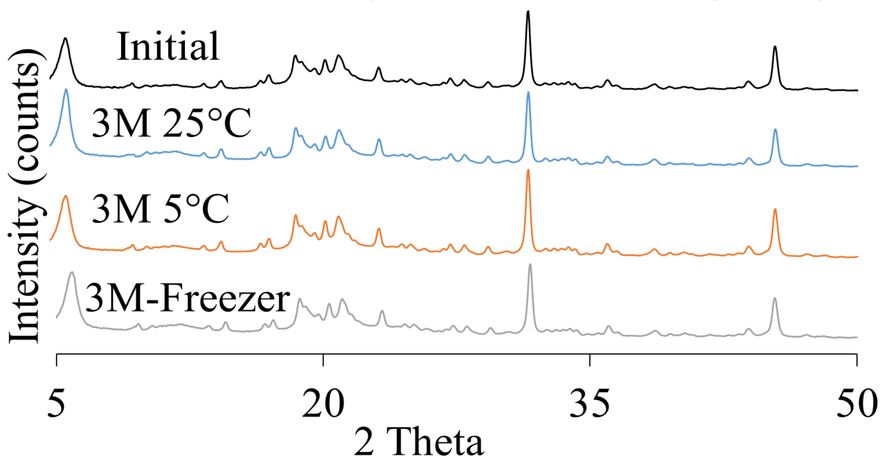

Fig. 2. **X-ray diffractograms of spray-dried synthetic lung surfactant powder.**

- Emitted dose of formulation during realistic *in vitro* testing was high (>95%) and it remained unchanged (P>0.05) during storage (Fig. 3).
- Lung delivery efficiency was high (~50%), however there was a significant reduction (P<0.05) of ~10% compared to initial following storage under all temperature conditions but there was no difference between the three temperatures (Fig. 3).
- There was no change in lung delivery efficiency following 30 min in device exposure to 22°C/45% RH but increasing the exposure time to 120 min resulted ~10% decrease in efficiency. Exposure to 30°C/75%RH for 120 min did not further significantly reduce the lung delivery efficiency compared to storage at 22°C/45% RH (Fig. 4).

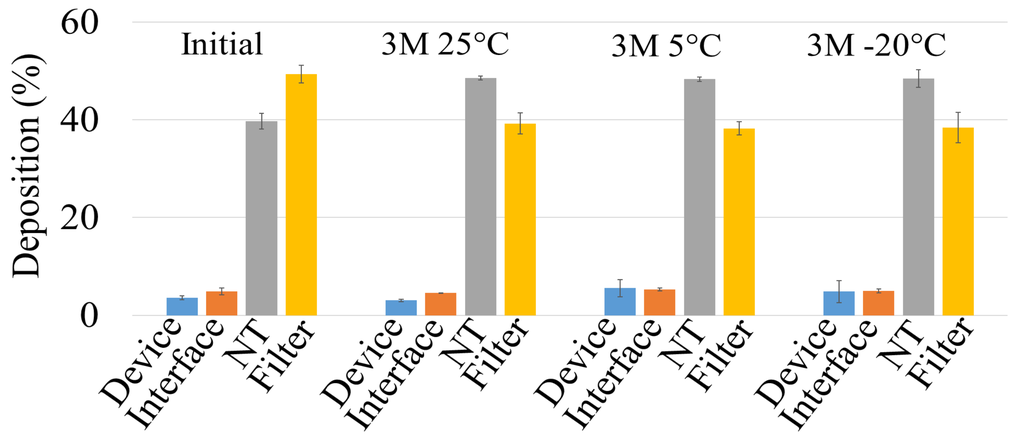

Fig. 3. **Initial aerosol performance of spray-dried synthetic lung surfactant powder and after 3 months storage.**

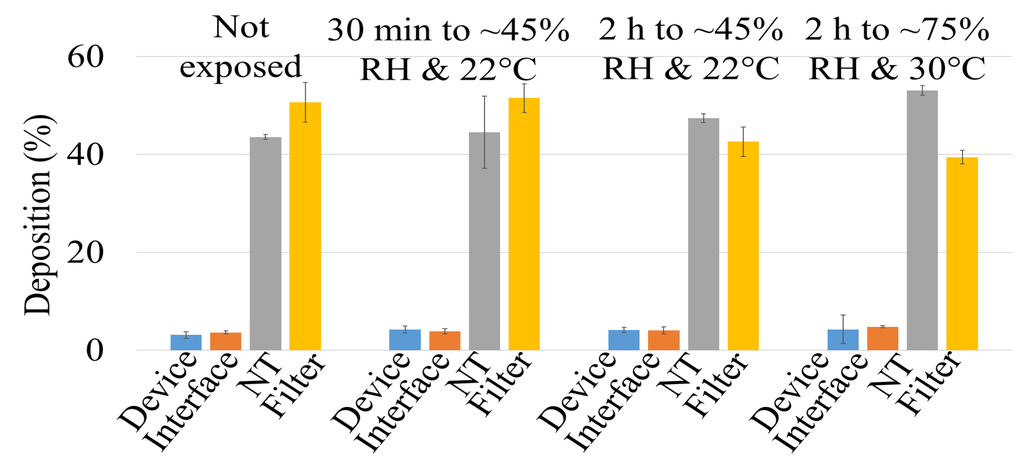

Fig. 4. **Aerosol performance of the spray-dried synthetic lung surfactant powder following in use environmental exposure.**

CONCLUSIONS

- Solid-state stability and surface activity remained unchanged after 3M storage, with only small changes in the primary size observed after storage at 25°C.
- The realistic *in vitro* lung delivery efficiency (50%) was high for dry powder delivery to a simulated neonatal airway and decreased by ~10% following storage but remained acceptable for this challenging delivery route.
- In-use testing indicated some changes in lung delivery efficiency (~40% vs ~50%) under simulated exposure environmental conditions.

ACKNOWLEDGEMENTS

This study was funded by the Bill and Melinda Gates Foundation [INV-029019]. The funding body was not involved in the collection, analysis, and interpretation of data and in writing the abstract.

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