# OPTIMIZING LIPOSOME PRESERVATION THROUGH SPRAY-DRYING: ATOMIZATION PARAMETER ADJUSTMENT AND ANALYSIS OF LIPOSOME COMPOSITION AND LIPOSOME-TO-CARBOHYDRATE RATIOS VIA EXPERIMENTAL DESIGN

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**INTRODUCTION**: Dry powder inhalers (DPIs) are advanced delivery systems for respiratory diseases that enhance drug stability and eliminate propellants. 'Particle engineering' through spray-drying (SD) optimizes powder properties, improving aerodynamic characteristics [1]. Moreover, incorporating liposomal drug formulations into DPIs protects active pharmaceutical ingredients (APIs), reduces toxicity, and enhances bioavailability, ultimately improving therapeutic efficacy [2].
This study aims to optimize drying parameters and formulation variables to improve liposomal DPI formulations. An initial Design of Experiments (**DOE A**) optimizes drying parameters and carbohydrate type to preserve liposome integrity and achieve desirable particle properties for lung deposition. Subsequently, **DOE B** explores the effect of API polarity, lipid composition, and carbohydrate-to-liposome ratios during SD, aiming to improve the understanding of liposome drying for stable, inhalable powders and effective pulmonary drug delivery.

**METHODS**: Liposomes were produced using supercritical fluid extraction with $CO_2$, composed of SPC/CHOL/DSPE-$PEG_{2000}$ in varying molar ratios [3]. SD was performed with a Procept 4 M8-Trix Formatrix SD, atomizing 5% solid content (w/V) liquids. Powders were analyzed for particle size, moisture content, and morphology, with liposome integrity assessed post-rehydration by DLS and API quantification by HPLC, after dialysis.
**DOE A** optimized carbohydrate type (trehalose and HPβCD) and variables like atomization temperature, pump feed rate, nozzle gas pressure, and cyclone gas pressure. Initial suspensions had a 1:99 lipid-to-carbohydrate ratio and 5 mM empty liposomes. **DOE B** studied the effect of API type (Budesonide (BUD) and salbutamol (SAL)), DSPE-$PEG_{2000}$ content, and liposome-to-carbohydrate ratios.

**RESULTS AND DISCUSSION: DOE A** identified HPβCD as more effective than trehalose for preserving liposome integrity during SD. HPβCD's high Tg (220°C) prevents powder collapse, enhancing stability. Optimized drying parameters yielded powders with suitable inhalation properties and preserved liposomal integrity, including a particle size of 2.83 ± 0.24 µm, moisture content of 4.60 ± 0.42%, and a rehydrated liposomal size ratio of 0.91 ± 0.03, with a PdI below 0.3. **DOE B** results with BUD-encapsulated liposomes revealed a clear link between high DSPE-$PEG_{2000}$ levels and BUD release during drying. Indeed, higher DSPE-$PEG_{2000}$ content reduced the membrane's transition temperature (Tm), increasing fluidity and enhancing BUD release due to increased susceptibility to atomization. However, atomized liposome quantity (up to 10%) had minimal impact on DPI properties and liposomal integrity.

**CONCLUSION**:
Experimental design validated SD parameters and identified HPβCD as an effective liposomal protectant, highlighting the impact of liposomal composition on API release and membrane stability. Ongoing research focuses on optimizing co-encapsulation of SAL and BUD using PGSS-based liposome production and SD technology, with future PK/PD studies in asthmatic mice and rats via PreciseInhale® equipment.

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