Spray Dried Porous Lipid Particles for Pulmonary Drug Delivery

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Introduction

Porous lipid particles have long been used as drug carriers in pressurized metered dose inhalers and dry powder inhalers for respiratory drug delivery because of their excellent physical stability, content uniformity, and aerosolization efficiency [1]. However, the production of such porous particles is a multi-step, time-consuming process that also requires the use of a scarce oil as a pore-forming agent [2]. In this study we present an alternative method of producing similar porous lipid particles to be used for pulmonary drug delivery.

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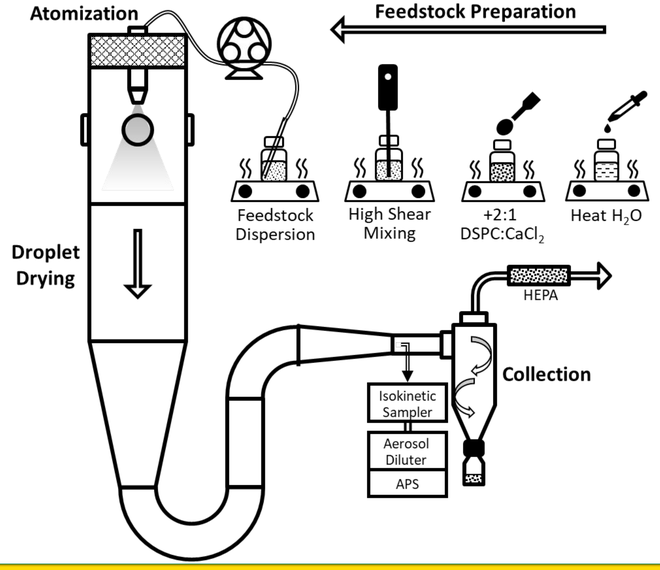
Spray Drying of Porous Lipid Particles

Materials

- Calcium chloride dihydrate ($CaCl_2 \cdot 2H_2O$; CAS 10035-0408, Sigma-Aldrich, ON, Canada)
- 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC; CAS 816-94-4, Avanti Polar Lipids Inc., AL, USA)

Spray Drying

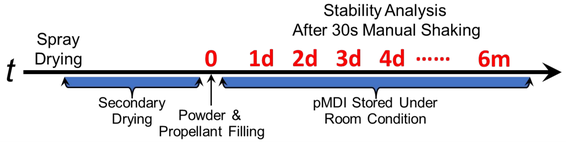
- HPLC grade water was first heated close to the main phase transition temperature of DSPC [3]
- $CaCl_2$ and DSPC lipid were then added at a molar ratio of 1:2 to a total solids concentration of 20 mg/mL
- The feedstock was dispersed by a high shear mixer at 25 krpm for 3 minutes
- Spray drying parameters: T_{feed}=53±0.5°C T_{inlet}=50°C Q_{feed}=2.5mL/min Q_{dry}=600SLPM ALR=10



Stability Study

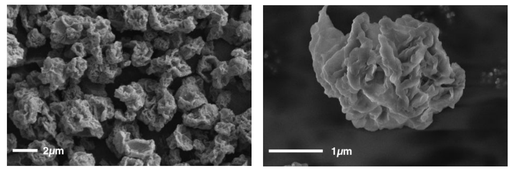
Stability Study in pMDI

- Fresh lipid particles were characterized by SEM and BET for morphology and specific surface area
- Particles were suspended in HFA134a and characterized at different time points by shadowgraphic imaging and SEM for change of colloidal stability and morphology
- Shadowgraphic imaging [4] for 30min immediately after 30s of manual shaking of the pMDI canister, instability index (0 - 1) used for quantitative comparison: 0 for extremely stable samples, 1 for extremely unstable samples



3 mg/mL suspension

Results and Discussion

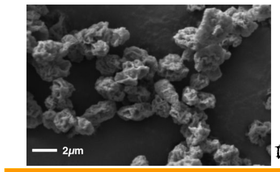


- Spray dried lipid particles showed highly rugose surface and porous structure (SSA=8.6 m^2/g rugosity f_r=3.7) → good dispersibility
- Critical conditions for producing the lipid porous particles

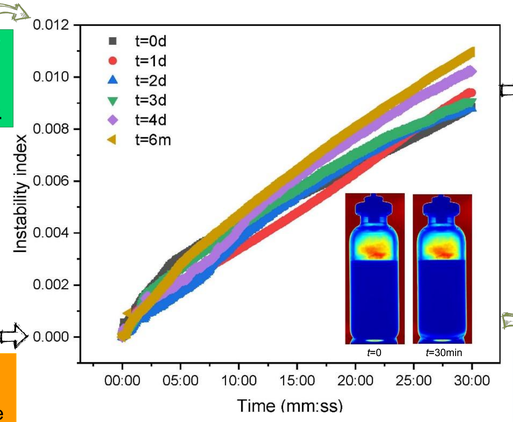
$$T_{feed} \approx T_m \qquad T_{out} < T_m$$

- DSPC lipids dispersed to nanoparticles during high shear mixing and initiated diffusion-controlled particle formation process
- Applicable to lipids with different main transition temperatures (DAPC, DBPC) [5]

Instability index increased slightly to ~0.01 after 30min post manual shaking, demonstrating excellent dispersibility and colloidal stability.



Porous structure and rugose surface feature retained after 6m, proving compatibility of the lipid particles with HFA134a.



No significant change in colloidal stability detected for up to 6m, proving stability of the lipid particles in HFA134a.

Inset shows representative initial (left) and final (right) status of suspension, indicating extremely stable suspension for >30min.

Conclusions

- A novel spray drying method produced highly rugose porous lipid particles suitable for respiratory drug delivery.
- Simplified processes: no pore-forming agent, no organic solvent, aqueous suspension-based feedstock.
- Demonstrated compatibility with propellant HFA134a and potential in other pMDI formulations.
- The lipid microparticles show potentially promising attributes including good dispersibility, high drug loading capacity, and physicochemical stability for use as an inhalation formulation platform.

References

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