Characterization of Spray-dried Phospholipid Porous Particles for Inhalation Drug Delivery

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Background

Spray-dried phospholipid porous particles (PPPs) are lipid-based microparticles with low density attributed to their nanosized porous structure [1, 2]. PPPs are increasingly used in orally inhaled drug products (OIDPs) for higher drug loading, improved dose uniformity and lung deposition as compared to OIDPs formulated as traditional drug-excipient (e.g., lactose) mixtures. In formulations comprised of PPPs, dry powder inhaler (DPI) drug products have demonstrated increased drug loading and uniformity with superior lung deposition due to the PPPs' optimal aerodynamic diameter (1-5 μm), while metered dose inhaler (MDI) drug products containing drug crystals co-suspended with the PPPs have demonstrated improved dose consistency. Identification of suitable techniques for the characterization of PPPs in OIDPs [3] is necessary to understand their effects on product quality and performance that may impact bioequivalence (BE).

Objective

This study aims to develop techniques for morphological and solid-state characterization of OIDPs containing spray-dried PPPs, as part of an alternative BE approach to the comparative clinical endpoint or pharmacodynamic BE studies.

Materials and Methods

Model Drug Products:

- One DPI drug product and two MDI drug products (MDI-1 and MDI-2) containing spray-dried PPPs were used as model reference listed drugs (RLDs).

Sample Collection Methods:

- **DPI:** Solid dispersion unit (SDU) integrated in Morphologically Directed Raman Spectroscopy (MDRS, Malvern, UK)
- **MDIs**: A dosage unit sampling apparatus (DUSA, Copley, UK) with different types of filter membranes [i.e., polytetrafluoroethylene (PTFE), polyvinylidene fluoride (PVDF), and glass fiber] at various air flow rates (i.e., 8-28 L/min).

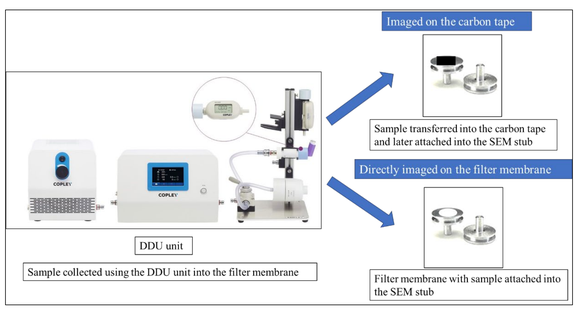

Figure 1. Schematic diagram for collecting samples of MDI particles for scanning electron microscope (SEM) using Copley delivered dose uniformity (DDU) setup.

Materials and Methods (continued)

Figure 2. Characterization methods for model drug products.

Results

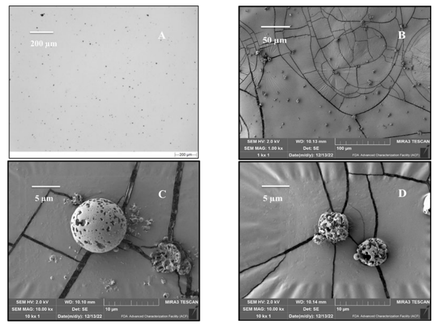

Figure 3. Images of DPI particles obtained using MDRS at 5x magnification (A) and SEM at 1 kx (B) and 10 kx magnification (C) and (D).

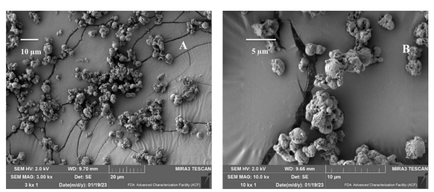

Figure 4. SEM images of MDI-1 particles at 3 kx (A) and 10 kx magnification (B).

Results (continued)

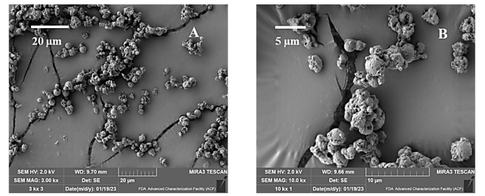

Figure 5. SEM images of MDI-2 particles at 3 kx (A) and 10 kx magnification (B).

Figure 6. SEM images of PPPs from MDI-1 on PTFE 0.45 μm filter membrane (A) and MDI-1 on PVDF 0.45 μm filter membrane (B).

Table 1. DPI Drug Product Characterization Results

Tests on DPI	Results
PSD Dn50	3.7 μm
DSC	Amorphous characteristics
Karl Fisher	5.1% water in DPI
TGA	9.3% weight loss from DPI
DVS @ 10% RH, 25°C	DPI absorbed 5% moisture
DVS @ 40% RH, 25°C	DPI absorbed 9% moisture
BET surface area	4.6-5.6 m^2/g of DPI
BET porosity	58-63% in DPI
XRD	Amorphous pattern in DPI

Dn50 = median PSD for number distribution

Table 2. MDI Drug Products Characterization Results

Tests on MDIs	Results
PSD Dn50 (MDI-1)	3.4 μm
PSD Dn50 (MDI-2)	5.2 μm
DSC of both MDIs	Crystalline characteristics
TGA (MDI-1)	5.5% weight loss
TGA (MDI-2)	6.5% weight loss
DVS @ 40% RH, 25°C	MDI-1 absorbed 5.8% moisture
DVS @ 40% RH, 25°C	MDI-2 absorbed 3.3% moisture

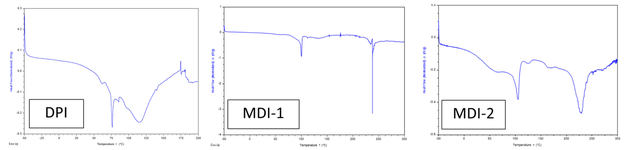

Figure 7. DSC thermograms of DPI, MDI-1 and MDI-2.

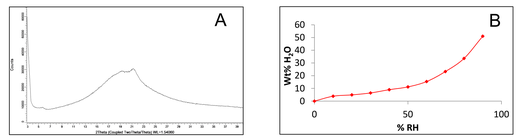

Figure 8. (A) XRD diffractogram of DPI. **(B)** DVS isotherm moisture absorption plot of DPI at 25° C.

Conclusions

- In this study, morphological evaluation and physicochemical characterization methods were identified and developed to evaluate three RLD OIDPs containing spray-dried PPPs.
- The developed methods were effective at characterizing PPPs from either DPI or MDI formulations.
- Additional characterization methods under development will further assist the evaluation of RLDs and the comparison between RLD and generic products.
- Studying the effect of manufacturing processes, including the preparation of emulsions and spray drying, on the product quality and performance will further enhance our understanding of this emerging drug delivery platform.

References

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