W0930-08-52

Method Development for the Evaluation of Orally Inhaled Drug Products Containing Spray-Dried Phospholipid Porous Particles

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PURPOSE

Spray-dried phospholipid porous particles (PPPs) are increasingly used in orally inhaled drug products (OIDPs) such as dry powder inhalers (DPIs) and meter-dosed inhalers (MDIs). PPPs enable higher drug loading, improved dose uniformity and lung deposition as compared to OIDPs formulated with traditional drug-excipient (e.g., lactose) mixture. The PPP's distinctive nano-sized (200–500 nm) pore structure creates an ultra-low density that minimizes particle sedimentation and allows for deeper lung penetration. Identifying suitable techniques for the characterization of PPP-containing OIDPs is important for understanding how differences in PPP formulation and manufacturing process may affect product quality and performance that may impact bioequivalence (BE).

OBJECTIVE

This study aims to develop techniques for material characterization of OIDPs containing spray-dried PPPs, which may aid the assessment of product quality and performance for these OIDPs.

METHODS

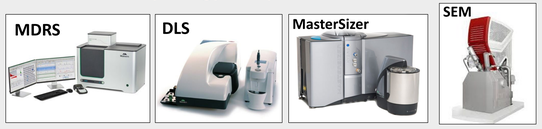
Model Drug Products:

- One DPI and two MDIs (MDI-1 and MDI-2) containing PPPs

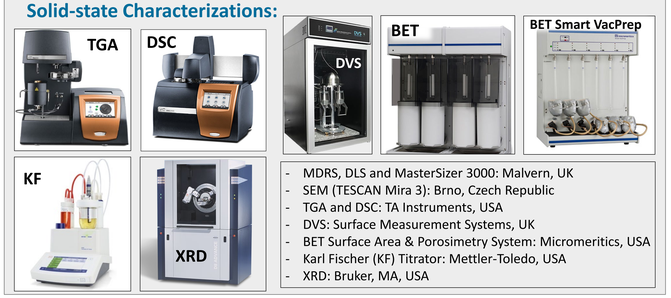
Sample Collection Methods:

- **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., PTFE, PVDF, and glass fiber) and at various air flow rates (i.e., 8-28 L/min). (**Figure 1**)

Particle Size and Morphology Analysis:



Solid-state Characterizations:



- MDRS, DLS and MasterSizer 3000: Malvern, UK
- SEM (TESCAN Mira 3): Brno, Czech Republic
- TGA and DSC: TA Instruments, USA
- DVS: Surface Measurement Systems, UK
- BET Surface Area & Porosimetry System: Micromeritics, USA
- Karl Fischer (KF) Titrator: Mettler-Toledo, USA
- XRD: Bruker, MA, USA

METHODS (Continued)

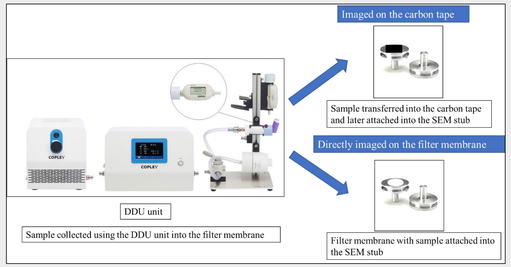


Figure 1. *Schematic diagram for collecting samples of MDI particles for scanning electron microscope (SEM)*

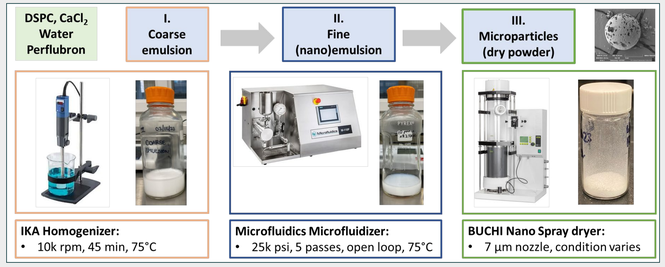


Figure 2. *Diagram of the manufacturing process of in-house PPPs (w/o API)*

- **Coarse emulsion:** IKA T25 digital Ultra-Turrax (IKA, Staufen, Germany)
- **Fine emulsion:** M110P Microfluidizer (Microfluidics, Newton, MA)
- **PPP dry powder:** Nano Spray Dryer B-90 (Buchi, New Castle, DE)

RESULTS

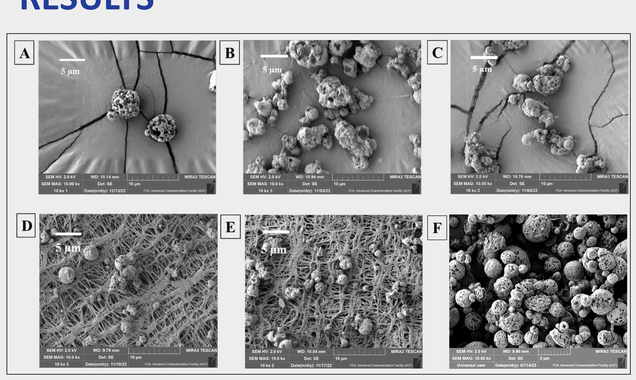


Figure 3. *SEM images of PPPs from (A) DPI; (B) MDI-1 and (C) MDI-2; (D) MDI-1 on PTFE 0.45 µm filter membrane; (E) MDI-1 on PVDF 0.45 µm filter membrane; and (F) In-house manufactured PPPs (all images are at 10kx magnification).*

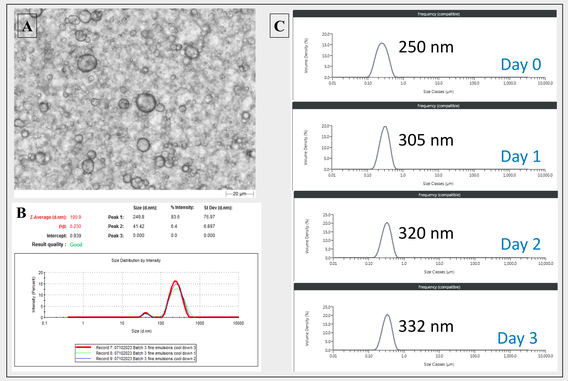


Figure 4. *Evaluation of in-house emulsions before spray drying (A) MDRS image of coarse emulsion at 20x magnification; (B) Dynamic Light Scattering size distribution of fine emulsion; (C) Stability indicated by globule size of the fine emulsion monitored by Master Sizer.*

Solid-state Properties		DPI	MDI-1	MDI-2	In-house PPPs
Particle size (µm) (MDRS)	D10	3.1	0.8	0.8	0.5
	D50	3.7	3.4	5.2	3.4
	D90	4.9	6.3	12.3	13.3
Water content (TGA)		9.3%	5.5%	6.5%	12.3%
Moisture absorption @ 40% RH (DVS)		9.0%	5.8%	3.3%	4.8%
Moisture content (KF)		5.1%	-	-	-
Surface area (BET)		4.6-5.6 m^2/g	-	-	-
Surface porosity (BET)		58-63 %	-	-	-
Pore width (BET)		2.1 to 4.1 nm	-	-	-

RESULTS (Continued)

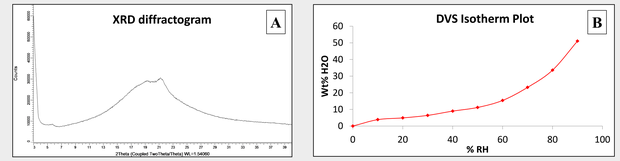


Figure 5. (A) *XRD diffractogram of DPI indicating amorphous pattern.* ***(B)*** *DVS isotherm moisture absorption plot of DPI at 25° C.*

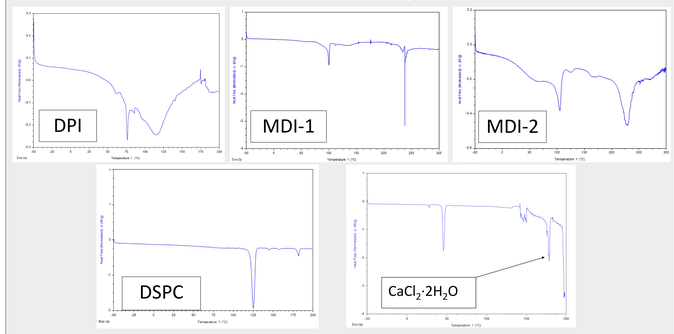


Figure 6. *Differential Scanning Calorimetry thermographs of the model drug products and major excipients in PPPs. Results revealed that API in DPI is amorphous and in MDIs are crystalline. DSPC: Distearoylphosphatidylcholine*

CONCLUSIONS

- The sample preparation technique and material characterization methods were successfully developed to evaluate different OIDPs containing spray-dried PPPs.
- The sample collection technique was shown to be critical in minimizing particle aggregation when evaluating the PPP morphology from the MDI products.
- In-house spray-dried PPPs were successfully manufactured and characterized.

ACKNOWLEDGEMENTS

Funding for this work was made possible, in part, by the U.S. Food and Drug Administration through an FDA Office of Chief Scientist CORES Grant. Abhinav Mohan was supported by a fellowship program administered by the Oak Ridge Institute for Science and Education (ORISE) through an interagency agreement between the U.S. Department of Energy and the U.S. FDA. This poster reflects the views of the authors and should not be construed to represent FDA's views or policies.

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