Understanding How the Manufacturing Process Affects the Quality of Spray-dried Phospholipid Porous Particles for Inhalation

Yang Yang[1], Apipa Wanasathop[1], Yuan Zhang [1,2], Jafrin Jobayer Sonju[1,2], Abhinav Mohan[2], Susan Boc[2], Sneha Dhapare[3], Elizabeth Bielski[2], Bryan Newman[2], Muhammad Ashraf[1], Xiaoming Xu[1]
[1]Division of Pharmaceutical Quality Research V, Office of Pharmaceutical Quality Research, Office of Pharmaceutical Quality, Center for Drug Evaluation and Research, Food and Drug Administration, MD, USA.
[2]Division of Therapeutic Performance I, Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, Food and Drug Administration, MD, USA.
[3]Division of Inflammation and Immune Pharmacology, Office of Clinical Pharmacology, Office of Translational Sciences, Center for Drug Evaluation and Research, Food and Drug Administration, MD, USA.

Disclaimer: This poster reflects the views of the authors and should not be construed to represent the views or policies of the U.S. Food and Drug Administration.

Abstract

Spray-dried phospholipid porous particles (PPPs) are lipid-based microparticles with relatively low density attributed to their nanosized porous structure. PPPs are increasingly used as excipients in orally inhaled drug products (OIDPs) for higher drug loading and improved dose uniformity and lung deposition as compared to OIDPs formulated with traditional drug-excipient (e.g., lactose) mixtures. Understanding the manufacturing process to identify critical process parameters that affect critical quality attributes (CQAs) of PPPs is crucial for informing the development of product-specific guidances (PSGs) for generic drug development. A design-of-experiment (DoE) approach was used to systematically analyze the effect of spray drying process variables on the quality of PPPs.

Introduction

- Spray drying was utilized to manufacture dry powders for inhalation as the residual moisture content and particle size distribution (PSD) can be controlled by the solidification process parameters. From nanoemulsions or nanosuspensions, spray drying can create microparticles with the ideal particle size and morphology for lung administration (1, 2). PPPs are spray-dried microparticles with a special nano porous morphology.
- In our preliminary study, spray drying process parameters, including inlet and outlet temperature, air flow rate, feedstock flow rate, etc. could significantly impact product yield, morphology, moisture content, particle size distribution, brittleness, and pore density of PPPs.
- A systematic analysis of the effect of manufacturing process variables on the CQAs of PPPs would help identify the critical process parameters (CPPs) of the spray drying process. Therefore, a DoE approach was adopted in this study.
- After the manufacturing process, solid-state characterization, morphological characterization and PSD studies were performed on the in-house PPPs.
- The study enhanced our understanding of the manufacturing process of PPPs, which may aid in the assessment of product quality and performance for generic products referencing RLDs containing PPPs. In addition, this study will support the development of PSGs to facilitate bioequivalence assessment of generic products using this platform.

Materials

Table 1. Formulation composition of in-house manufactured PPPs

Excipient Composition	Vendor
Calcium Chloride	Sigma-aldrich
DSPC (1,2-Distearoyl-sn-glycero-3-phosphocholine)	Lipoid GMBH
Perflubron (Perfluorooctyl Bromide)	Fluoryx Lab
Water	In-house

Methods

Manufacturing process of PPPs

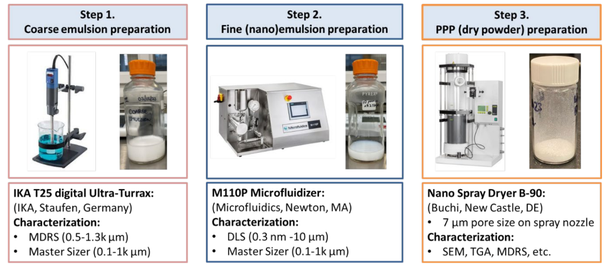


Figure 1. Diagram of the manufacturing process of in-house PPPs (w/o active ingredients).

Manufacturing process variables

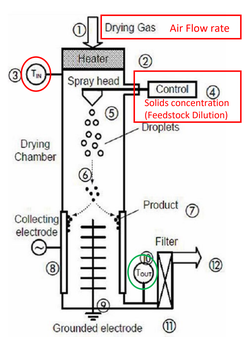
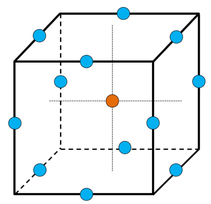


Figure 2. Diagram of the Nano spray dryer.



- 3 independent variables
- With 3 center point replicates
- 15 total experiments

Figure 3. Box-Behnken response surface design.

Table 2. Manufacturing process parameters and CQAs

Independent Variables	Level (-)	Level (0)	Level (+)
1. Air Flow (L/min)	100	110	120
2. Inlet Temp. (°C)	115	130	145
3. Dilution factor (dilution of original feedstock @ 4% SC)	5	7.5	10
Response Variables (CQAs)	**%Moisture Particle Size Distribution (D10, D50, D90)**		

Design of Experiment (DoE)

Box-Behnken response surface design (Figure 3) was adopted to study the effects of three independent manufacturing process variables (inlet temperature, air flow, dilution factor/solids concentration) on CQAs of in-house manufactured spray dried PPPs.
DoE and data analysis of variance (ANOVA) were conducted by JMP software (SAS, Cary, NC) to determine the significance of the models and the effect of each variable.

Results and Discussion

Characterization of emulsions

	Emulsion 1 (250 mL) 11/27/2023 Used for F1-F7	**Emulsion 2** (250 mL) 12/04/2023 Used for F8-F15
I. Coarse emulsion (MasterSizer, MDRS)	Ave. diameter: 6.72 μm Span: 1.434	Ave. diameter: 6.61 μm Span: 1.363
II. Fine emulsion (DLS)	Z-Ave diameter: 141 nm PdI: 0.197 178 nm	Z-Ave diameter: 142 nm PdI: 0.178 172 nm

Figure 4. Characterization of emulsions prepared for spray drying.

Characterization of PPPs

Table 3. Summary of recorded CQAs in the DoE series.

Experiment	Batch	Pattern	%Moisture[a]	#particle	D10 (μm)[b]	D50 (μm)[b]	D90 (μm)[b]
F1	DOE1	0−−	11.93	5358	0.59	1.66	3.68
F2	DOE2	+0+	11.26	1296	0.64	1.97	4.37
F3	DOE1	+0−	9.87	3202	0.61	1.95	5.89
F4	DOE1	000	11.53	3315	1.13	2.64	5.31
F5	DOE1	0++	11.39	5000	0.72	1.93	4.13
F6	DOE1	−0−	8.76	5000	0.71	2.56	4.95
F7	DOE1	++0	9.52	5000	1.58	3.06	6.10
F8	DOE2	−+0	10.37	5000	0.91	2.00	3.44
F9	DOE2	000	10.30	5000	0.76	2.10	3.98
F10	DOE2	−0+	14.19	4602	0.68	1.89	3.49
F11	DOE2	−−0	13.67	5000	0.60	1.78	3.76
F12	DOE2	0−+	12.09	3781	0.61	1.80	3.82
F13	DOE2	+−0	12.44	5000	0.72	2.62	4.72
F14	DOE2	000	12.72	4015	0.60	1.87	4.61
F15	DOE2	0+−	9.79	5000	0.61	2.02	5.00

[a] determined by TGA analysis. [b] determined by MDRS automated particle image analysis.

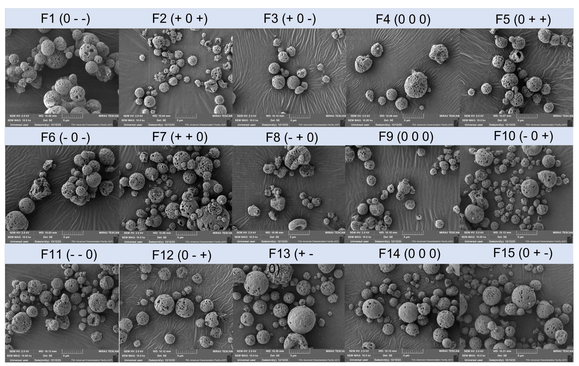


Figure 5. SEM images of in-house manufactured PPPs.

ANOVA analysis

To enhance the fitting, a linear model was utilized to fit the DoE data since no pure quadratic curvature was observed from the response and the design space includes the limit of process settings.

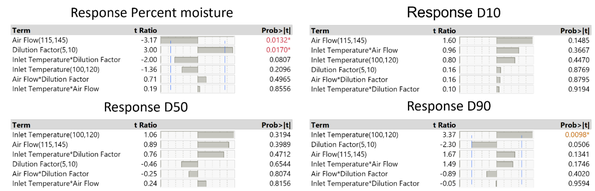


Figure 6. Pareto chart of sorted parameter estimates based on t-ratio (high to low) for CQAs of in-house spray dried PPPs.

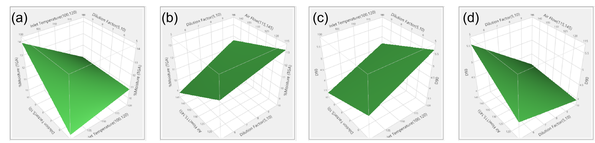


Figure 7. Surface profilers showing effect of (a) inlet temperature, dilution factor on percent moisture of PPPs; (b) air flow rate, dilution factor on percent moisture of PPPs; (c) inlet temperature, dilution factor on D90 of PPPs; (d) air flow, dilution factor on D90 of PPPs.

Key findings: The moisture of the PPPs decreases with increasing air flow rate and increases with increasing dilution factor. The D10 and D50 of the particle size distribution did not show statistically significant correlation ($p<0.05$) with the manufacturing process variables according to the ANOVA analysis. However, the D90 of the in-house spray dried PPPs showed positive correlation with inlet temperature.

Conclusions

- All three main effects (inlet temperature, air flow, dilution factor) proved to have a significant effect on the CQAs of the in-house spray dried PPPs and therefore were identified as CPPs.
- The study enhanced our understanding of the effect of manufacturing process on the quality of PPPs.

Reference

1. Malamatari M. et al. *Processes*. 2020;8(7):788.
2. Meenach SA. et al. *Int J Nanomedicine*. 2013;8:275-93.

Acknowledgement

1. FDA Office of Chief Scientist CORES Grant
2. ORISE fellowship appointments (Apipa Wanasathop, Yuan Zhang)