

A Platform Technology for Developing Dry Powder Inhalation Formulations of New Chemical Entities from Feasibility Evaluation to Clinical Batch Manufacturing – A Case Study

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Summary

A case study is presented to demonstrate a platform technology for developing dry powder inhalation formulations of new chemical entities (NCE) from formulation feasibility evaluation through to clinical manufacturing. The process, applicable to both R&D laboratory and clinical manufacturing, involves processes for manufacturing uniform NCE carrier dry powder formulations and accurate filling of small quantities, in this case, 25 mg formulation into HPMC inhalation size 3 capsules using a semi-automatic Quantos™ Perfect Dosing System. The capsules, filled with both low (0.4% w/w) and high (3.2% w/w) strength formulations gave consistent fill weight (RSD < 1%, n=35) and drug content uniformity (RSD < 1%, n=6). The fine particle fraction (< 5 µm) measured by the Next Generation Pharmaceutical Impactor was 38% to 40% for the low and 39% to 46% for the high strength formulations when delivered from a Monodose capsule based dry powder inhaler device. The filling technology applied in the case study demonstrated excellent fill reproducibility, no segregation and no powder compaction as evidenced by the acceptable aerosolization performance. Investigation continues on the applicability of this approach at the extremes of fill weights for inhalation products with powders having various flow characteristics.

Introduction

Increasing demands and rapid growth of the asthma and COPD market have led to a greater effort in searching for novel therapeutic agents delivered via inhalation route¹. One of the key challenges facing most pharmaceutical and biotech companies developing formulations in dry powder inhalation format is to establish a process suitable for both formulation screening in the R&D laboratory and clinical batch manufacturing as well as an appropriate device filling method which provides acceptable dose uniformity with no powder segregation or compaction and does not negatively impact product performance.

At Catalent, we have developed a platform technology, which enables rapid screening/development of the NCE formulations suitable for formulation feasibility evaluation through to the Ph I and II clinical batch manufacturing.

Methods

In this study, an NCE was used as a model compound.

To manufacture the dry powder formulations, the micronized NCE was blended with Lactohale™ LH200 (Friesland Foods Domo, The Netherlands) at 400 g scale using the Turbula® Shaker-Mixer (Glen Mills Inc., USA). Intermediate sieving steps were introduced to facilitate dispersion of the micronized compound and form uniform blends. A time course study was carried out to establish the process conditions and a low (0.4% w/w) and high (3.2%, w/w) strength dry powder formulations were manufactured. Formulations were assayed for content uniformity (CU) at 15, 30, 60, 90 and 120 minute mixing time points.

Formulations produced at 60 and 120 minutes were selected for a subsequent filling trial, dose uniformity and aerosolization performance evaluation.

For the filling trial, thirty-five HPMC inhalation size 3 capsules were filled with 25 mg of powder formulation for both low and high strength formulations using a semi-automatic Quantos™ Perfect Dosing System (Mettler Toledo, Switzerland) in the first trial and an additional ten capsules were tested in the second trial. The capsules were weighed before and after filling to determine the mean fill weight, variability and verify the fill weight performance of the Quantos unit. Six capsules were assayed for each formulation strength to determine the dose uniformity.

To evaluate the aerosolization performance, the aerodynamic particle size distribution of formulations delivered from a RS-01 Monodose dry powder inhaler device (Plastiapi, Italy) was measured using the Next Generation Pharmaceutical Impactor (NGI) at a flow rate of 100 L/min.

Results and Discussion

Dry powder blend uniformity

Ten CU samples (20-30 mg each) were taken from different locations in the bulk blend at each time point and assayed for drug content using the HPLC. The results are presented in Table 1. Recovery was calculated based on the weight of the input materials. The results gave an RSD of less than 2% for the low strength and less than 1% for the high strength formulations which demonstrated acceptable blend content uniformity.

The recovery of the samples from all time points was close to 100% and no high content values were determined from fifty samples measured from each formulation, suggesting absence of the "hot spots" within the dry powder formulations.

Filling trial

Target fill weight of 25 mg was selected for this study.

In the first trial, thirty-five capsules were filled for both the low and high strength blends. The target fill weight was set at 25 mg \pm 5% for the first four capsules for the low strength blend, which was then adjusted to 25 mg \pm 2.5% for the remaining capsules in order to reduce the fill weight variability. The fill weight of individual capsules was close to the target value of 25 mg with an RSD less than 1% (Table 2).

In the second trial, ten capsules were filled, with the target fill weight set at 25 mg \pm 2.5%. The fill weight was close to the target and the RSD was less than 0.5%.

The filling process was very efficient and can be readily scaled to support clinical manufacturing.

Capsule content uniformity

For the content assay, six filled capsules were dissolved in separate volumetric flasks and assayed by HPLC after being diluted to the volume. The mean drug recovery (%) and RSD (%) calculated based on the blend strength, fill weights and assay values of individual capsules were 97.0% and 1.2% the 0.4% w/w formulation and 100.0% and 0.8% for the 3.2% w/w formulation (Table 3) suggesting acceptable content uniformity of the capsules and no drug loss during filling.

Formulation aerosolization performance

Aerodynamic particle size distribution of the formulation delivered from the RS-01 Monodose dry powder inhaler device was measured in triplicate using the NGI at a flow rate of 100 L/min. The fine particle fraction (FPF, < 5 μ m) was calculated using the Copley CITDAS software (Version 2.0). The FPF (< 5 μ m) was between 38% to 40% for the low strength formulation and 39% to 46% for the high strength formulation (Table 4). Percentage drug deposition at each stage was consistent between the tests for both formulations (Figure 1).

Conclusions

To conclude, the platform technology established at Catalent provides a rapid solution for developing NCE dry powder inhalation formulations from laboratory feasibility studies through to clinical manufacturing.

The filling technology applied in the case study demonstrated excellent fill reproducibility, no segregation and no powder compaction as evidenced by the acceptable aerosolization performance. Investigation continues on the applicability of this approach at the extremes of fill weights for inhalation products with powders having various flow characteristics.

The process used in this case study not only provides a cost effective approach for formulation development in the R&D laboratory but also enables direct transfer of the process to clinical manufacturing which accelerates the development cycle by avoiding the delays due to additional scale up and/or process transfer activities.

Table 1 Content Uniformity (% w/w) Results from Blending Time Course Study

Formulation	Low strength formulation (0.4 % w/w)					High strength formulation (3.2 % w/w)				
	15	30	60	90	120	15	30	60	90	120
CU sample 1	0.393	0.397	0.402	0.386	0.388	3.158	3.164	3.165	3.196	3.178
CU sample 2	0.391	0.399	0.404	0.393	0.404	3.208	3.167	3.192	3.156	3.175
CU sample 3	0.409	0.400	0.410	0.402	0.395	N/A	3.195	3.164	3.164	3.131
CU sample 4	0.411	0.412	0.400	0.393	0.393	3.188	3.190	3.165	3.128	3.122
CU sample 5	0.399	0.410	0.406	0.389	0.386	3.174	3.193	3.161	3.091	3.119
CU sample 6	0.395	0.394	0.397	0.389	0.392	3.191	3.184	3.160	3.157	3.186
CU sample 7	0.389	0.396	0.390	0.391	0.391	3.181	3.150	3.187	3.179	3.156
CU sample 8	0.393	0.396	0.393	0.396	0.390	3.188	3.156	3.167	3.170	3.112
CU sample 9	0.386	0.410	0.400	0.396	0.386	3.204	3.166	3.184	3.175	3.130
CU sample 10	0.397	0.394	0.400	0.389	0.388	3.151	3.183	3.116	3.101	3.135
Mean (%)	0.40	0.40	0.40	0.39	0.39	3.18	3.17	3.17	3.15	3.14
RSD (%)	2.0	1.7	1.5	1.1	1.4	0.6	0.5	0.7	1.1	0.9
Recovery (%)	99.4	100.5	100.4	98.5	98.2	100.3	100.0	99.8	99.3	99.1

Table 2 Fill Weight Uniformity

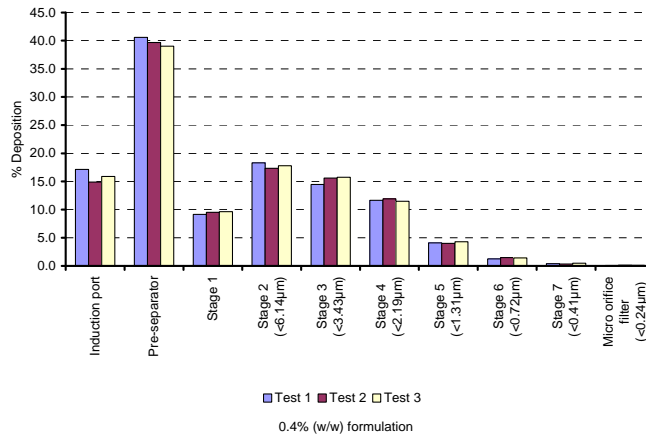
Trial	Formulation	Fill weight (mg)					Mean (mg)	RSD (%)
One	0.4% w/w	23.82	24.36	24.44	24.24	24.62	24.34	0.9
		23.88	24.37	24.64	24.45	24.57		
		23.77	24.43	24.34	24.52	24.29		
		23.86	24.37	24.36	24.54	24.33		
		24.17	24.42	24.52	24.40	24.33		
		24.20	24.48	24.08	24.44	24.55		
		24.24	24.31	24.45	24.55	24.53		
	3.2% w/w	24.16	24.54	24.61	24.56	24.51	24.52	0.7
		24.30	24.44	24.99	24.46	24.46		
		24.42	24.52	24.33	24.59	24.79		
		24.49	24.40	24.65	24.56	24.49		
		24.43	24.43	24.82	24.28	24.70		
		24.62	24.57	24.57	24.50	24.33		
		24.61	24.62	24.42	24.65	24.52		
Two	0.4% w/w	24.43	24.64	24.73	24.70	24.60	24.65	0.4
		24.71	24.68	24.59	24.72	24.68		
	3.2% w/w	24.84	24.66	24.91	24.79	24.88	24.80	0.4
		24.84	24.77	24.84	24.62	24.81		

Table 3 Recovery (%) of the Individual Capsules Calculated Based on the Blend Strength, Fill Weight and Content Assay

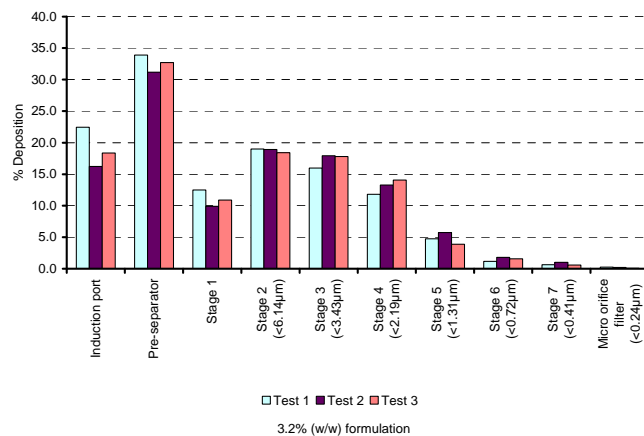
Formulation	0.4 % w/w	3.2 % w/w
Capsule No 1 (%)	98.1	101.1
Capsule No 2 (%)	97.8	100.7
Capsule No 3 (%)	98.1	98.9
Capsule No 4 (%)	95.3	100.1
Capsule No 5 (%)	96.3	99.7
Capsule No 6 (%)	96.5	99.5
Mean (%)	97.0	100.0
RSD (%)	1.2	0.8

Table 4 Aerosolization Performance

Formulation	0.4 % w/w			3.2 % w/w		
	1	2	3	1	2	3
Test						
% deposition on pre-separator	34.6	34.5	33.7	27.7	26.8	27.6
% deposition on induction port	14.6	13.0	13.7	18.3	14.0	15.5
% deposition on stage 1	7.8	8.3	8.3	10.2	8.5	9.2
% deposition on stage 2 (<6.14 µm)	15.6	15.1	15.4	15.5	16.3	15.6
% deposition on stage 3 (<3.43 µm)	12.3	13.6	13.6	13.0	15.4	15.0
% deposition on stage 4 (<2.19 µm)	9.9	10.4	9.9	9.7	11.4	11.9
% deposition on stage 5 (<1.31 µm)	3.5	3.5	3.7	3.9	4.9	3.3
% deposition on stage 6 (<0.72 µm)	1.1	1.3	1.2	0.9	1.5	1.3
% deposition on stage 7 (<0.41 µm)	0.3	0.3	0.4	0.5	0.9	0.5
% deposition on the micro orifice filter (<0.24 µm)	0.1	0.1	0.1	0.2	0.2	0.1
Fine particle fraction < 5 µm (%)	38.2	39.7	39.6	38.9	46.0	42.9
Mass median aerodynamic diameter (µm)	3.2	3.1	3.1	3.3	3.0	3.1
Geometry standard deviation	1.9	1.9	2.0	2.1	2.0	1.9



a



b

Figure 1 Percentage Deposition of the Low (a) and High (b) Strength Formulations Delivered from the RS-01 Monodose Dry Powder Inhaler Devices

References

1. Datamonitor Pipeline Insight: COPD/Asthma Targeted Therapies on the horizon Nov 2006

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