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Assessing the adaptability of bench scale dry powder technology for filling of an pMDI can with a high fill weight API

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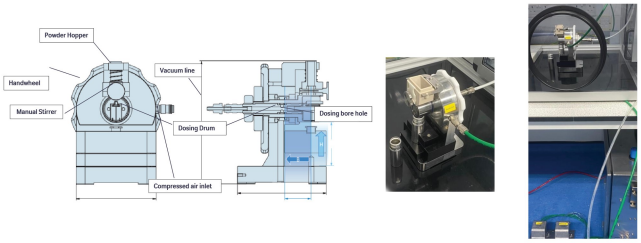
Introduction

Present fluorinated gas propellants used for pressurized metered dose inhalers (pMDIs) have a high GWP, given their environmental impact, legislation governing the use of these propellants is tightening. Two potential low GWP alternatives P152a and P1234ze(E) have been identified which are flammable. To mitigate the flammability, installation of ATEX rated manufacturing equipment and the decoupling of the formulation manufacture from the filling line into two distinct purpose-built areas is advised.

An alternative pMDI API filling technique based on Dry Powder technology, could eliminate the need of a mixing vessel at both development and manufacturing scales and pave the way for a reconfiguration of the current pMDI supply chain to suit low GWP propellants. Applicability of this dry powder filling technology to dispensing APIs, firstly a high dosage API into pMDI cans at the bench scale was investigated. To be adaptable for most pMDI formulations the technique needs to be capable of accurately dosing at a range of typical fill weights, from tens of milligrams (e.g., salbutamol formulations) to hundreds of micrograms (e.g., formoterol formulations), with no effect on formulation stability.

Materials and Methods

Harro Höfliger's (HH) compact bench filling machine, Drum TT, was used for this adaptability assessment, the machine required a modest amount of temporary adaptation to allow filling of pMDI cans. pictures of this modification along with a schematic of the original Drum TT are detailed in figures below.



- Salbutamol Sulphate (SS) was chosen as the API of choice given its high fill weight in formulations such as Ventolin and Pro-Air.
- The material was characterised by HH to specify drum sizes (30 and 50mm³) for the chosen target weight of 30mg.
- The machine was commissioned using typical reference powders lactohale-200 (D90<149µm) and micronised lactohale-300 (D90<10µm) to ensure the system was working adequately and to provide baseline of data for comparison between the two powder forms.
- Dosed into Presspart 19ml plain aluminium pMDI cans.
- Operating pressures (Vacuum and blow out) for the SS trials.
  - 50mm³ drum, 600mbar and 700mbar dispensed a two-plug SS weight.
  - 30mm³ drum 500mbar and 700mbar dispensed a three-plug SS weight.

Results

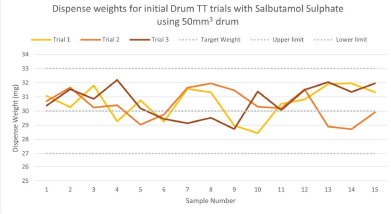
Commissioning studies with Lactose

Commissioning experiments were performed on the Drum TT using two inhalation grade lactose reference powders of differing particle sizes (lactohale-200 and micronised lactohale-300).

Reference	D90 (µm)	No. of samples	Average Weight (mg)	Std D (mg)	RSD (%)	Vacuum (mbar)	Blow out pressure (mbar)
Lactohale - 200	149	30	40.07	0.24	0.60	-600	600
Lactohale - 300	10	23	21.40	1.09	5.08	-400	600

Initial Drum TT trials with Salbutamol Sulphate using 50mm³ drum

Three separate identical trials were performed to assess the overall precision and accuracy of the data for Salbutamol Sulphate.

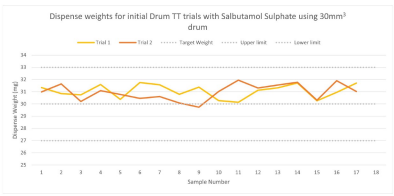


Sample	Salbutamol sulphate weight (mg)		
Average	30.6	30.4	30.7
Std.D	1.1	1.0	1.1
RSD (%)	**3.6**	**3.4**	**3.6**

Initial Drum TT trials with Salbutamol Sulphate using 30mm³ drum

Two separate trials were performed to assess the overall precision and accuracy of the data for Salbutamol Sulphate. Slightly lower vacuum pressure was used to reduce strain on the filter and to reduce the risk of carry over between doses.

Sample	Salbutamol sulphate weight (mg)	
Average	31.05	30.97
Std.D	0.5	0.7
RSD (%)	**1.7**	**2.1**



Results continued

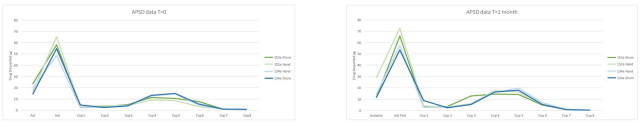
Stability Studies

Initial stability data (30°C/65%RH) on salbutamol formulations filled via this technique have been analysed by DDU and APSD at T=0 and T=1 month, post quarantine.

Shot weight

Delivered Dose Uniformity (DDU through life)

Aerodynamic Particle Size Distribution (APSD)



	152a Drum Actual µg	152a Hand Actual µg	134a Hand Actual µg	134a Drum Actual µg
CDD (exc act)	99.833	98.839	91.196	100.389
FPD	**33.407**	**24.648**	**35.829**	**36.786**
FPF%	**33.463**	**24.937**	**39.288**	**36.643**
MMAD	2.429	2.814	2.334	2.407
GSD	2.44	2.8	2.11	2.56

	152a Drum Actual µg	152a Hand Actual µg	134a Hand Actual µg	134a Drum Actual µg
CDD (exc act)	119.755	126.56	112.851	110.873
FPD	**41.441**	**43.92**	**47.464**	**39.177**
FPF%	**34.605**	**34.703**	**42.059**	**39.177**
MMAD	3.804	2.579	2.248	2.626
GSD	1.951	2.143	2.041	4.087

Discussion

Commissioning study

- Drum TT was operating within the expected limits, <1% RSD (lactohale-200), RSD of 5.08% (micronised lactohale-300).
- The micronised lactose reference sample proved more difficult to handle due to its smaller particle size.

Initial Drum TT trials

- Large drum (3.4-3.6% RSD) and small drum (1.7-2.4% RSD) weights both fell within goal of ±10% of the target weight.
- Effect thought to be mainly due to the change in drum size.
- Powder precision hierarchy can be explained by particle size and cohesivity. Lactohale-200 (0.60%RSD) >SS (1.7-3.6%RSD, D90<10µm) > Lactohale-300 (5.08%RSD, D90<5µm).
- With decreasing particle size, there is a corresponding increase in inter-particle cohesion, which can adversely affect flowability, fill ability and dispersibility of the powder, increasing RSD.
- Additional trials are planned to fully optimise the filling procedure by refining the vacuum and blow out pressures and studying the effects of mixing and inline sieving or sonication to further reduce the RSD.
- Further work to understand the effects of API CQAs such as moisture content, morphic form and morphology on dosing data may also be beneficial.
- Can content uniformity is equivalent to other dry powder filling approaches for Salbutamol Sulphate like Respitab® (RSD 1.4-2.7 %).

In-vitro stability

- Filled formulations have shown to be stable for at least one month, irrespective of propellant or filling technique.
- Current studies are planned to assess the formulation stability for up to 6 months post quarantine.

Conclusion

The Drum TT can be adapted to dispense Salbutamol Sulphate for pMDI formulations with very good accuracy and good precision. This confirmation is the first step in determining the suitability of such equipment at development and manufacturing scales. The levels of precision seen around the target weight, fall within limits outlined at the onset of the study and within those seen for other dry powder filling techniques.

Initial stability data indicates that formulations manufactured are stable for at least one month but work is ongoing to assess this longer term. The performance of the technique for lower fill weight API formulations is also underway, which will help to confirm the overall proof of concept.

Harro Höfliger

Pharmatec Solutions Ltd.