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

Sheryl Johnson[1], James Murray[1], Johnathan Carr[1], Marco Laackmann[2], Daniel-Jakub Wilhelm[2], Tony Clark[3], Cristino Ruano[3].

[1]Koura Global, Pool lane, Ince, Cheshire, CH2 4NU, UK
[2]Harro Höfliger, Helmholzstraße 4, 71573 Allmersbach i.T., Germany
[3]Pharmatec solutions ltd, Timberly, Gyfelia, Wrexham. LL13 0YH, UK

Summary

Due to the present tightening of environmental legislations governing medical propellants, there is more emphasis than ever on understanding the manufacturing steps required in handling of low global warming potential (GWP) propellants. This paper explores one such approach that aims to mitigate safety concerns at the formulation manufacturing stage, brought about by the flammability of the novel propellants. By first proving the adaptability of dry powder filling equipment in filling pMDI cans at the bench scale, the ability to separate the drug dosing and propellant filling stages can be assessed. The use of such technology to dispense a high fill weight API, resulted in data that met precision limits outlined (±10%). Optimised trial dosages all fell within 6% of the target weight with low RSD values of 1.7-2.1%. The next step is to determine if formulations manufactured using this technique are of equivalent in-vitro performance to those made using traditional bench filling techniques.

Key Message

Bench scale dry powder filling equipment can be effortlessly adapted to dispense Salbutamol Sulphate for pMDI formulations with accurate and precise results. This could help to adapt how the industry approaches pMDI filling at manufacturing scale, particularly for low global warming potential (GWP) propellants and goes some way to mitigate the risks associated with flammability.

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 that appear to meet the industry's requirements. Despite this, there are still some hurdles to overcome before the adoption of one of these next generation propellants, due to their flammability. The main control measures needed to mitigate flammability are the installation of ATEX rated manufacturing equipment and the decoupling of the formulation manufacture from the filling line into two distinct purpose-built areas. [1] An alternative pMDI API filling technique using technology very similar to that used for Dry Powder Inhalers (DPIs) and other capsule products was studied. If proven successful, this 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.

As proof-of-concept study, applicability of current dry powder filling technology to dispensing APIs into pMDI cans at the bench scale was investigated. Traditionally at this scale, pMDI cans are filled using a microbalance by hand. This technique has proven to be both time consuming and arduous given the inherent small masses of powder involved. Additionally, static interferences when dealing with moisture sensitive APIs in a humidity-controlled environment such as a glovebox can cause further interferences. With the aim of improving efficiency and precision the adaptability of a commercially available bench scale dry powder filling machine capable of dispensing at the desired scale was investigated using a relevant high dosage formulation. To be adaptable for most pMDI formulations the technique would need 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), this ability will be assessed after initial proof of concept.

Materials and Methods

Harro Höfliger's (HH) compact bench filling machine, Drum TT, capable of dosing at the micro scale was used for this adaptability assessment. The Drum TT laboratory table-top device enables the dosing of

powders according to the drum principle. Given that the equipment is normally used for dry powder filling applications, the machine required a modest amount of temporary adaptation to allow filling of pMDI cans. The spacing between the drum and the machine platform had to be increased by 25 mm to accommodate the height of a large pMDI can. Two acrylic spacers were inserted between the handwheel and the platform to allow the filling of both aluminium and glass pMDI cans, drawings of this modification along with a schematic of the original Drum TT are detailed in Figures 1 and 2.

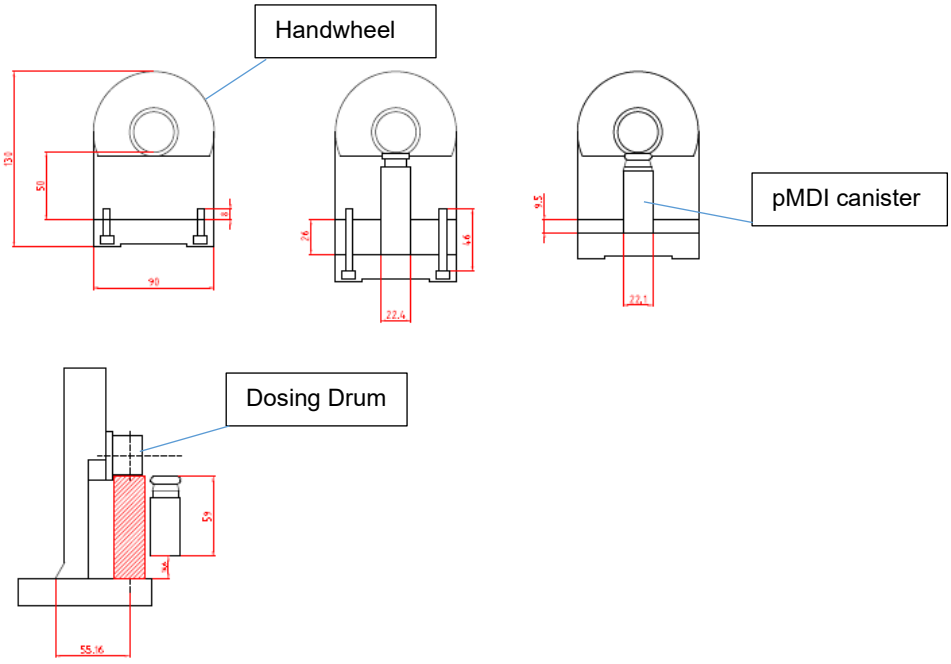

Figure 1- Engineering Drawings of Modified Drum TT

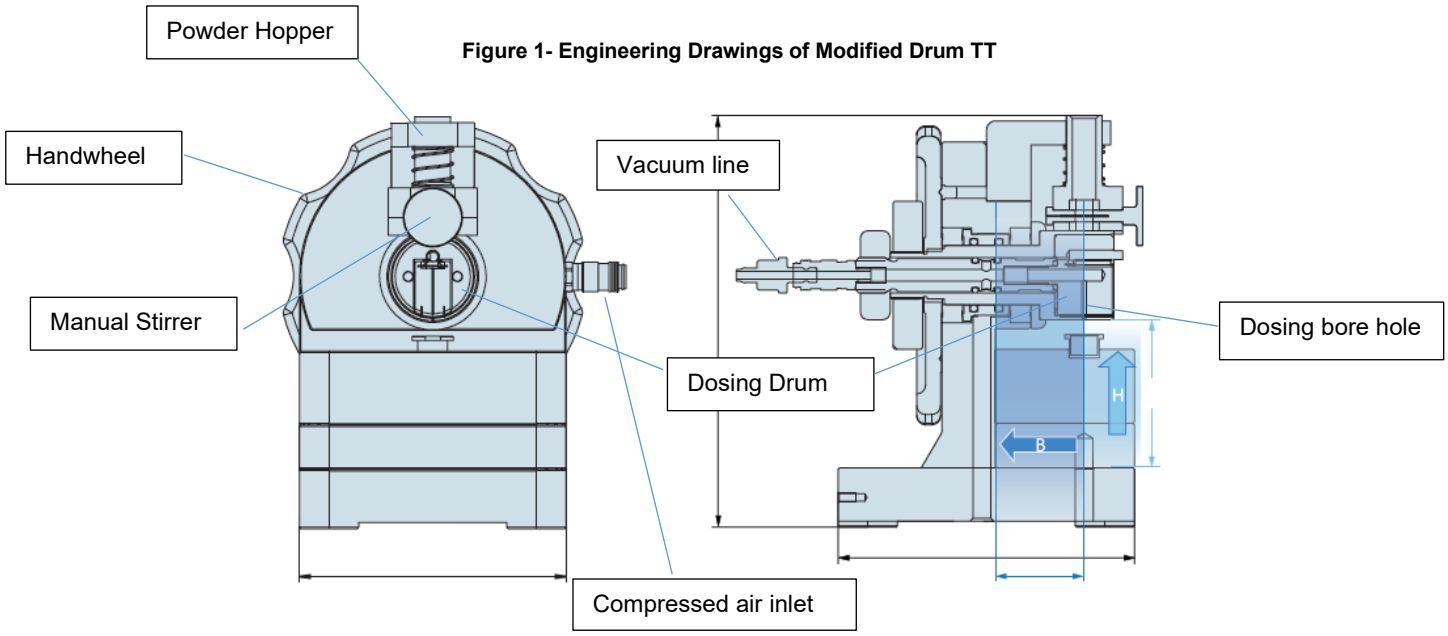

Figure 2- Schematic of Original Drum TT

The modified Drum TT was placed in a Sicco anti-static glovebox equipped with a hygrometer (temperature and humidity) and supplied with Nitrogen. A Mettler Toledo 5 d.p. balance was placed in the glovebox, to enable check weighing of the material dispensed in milligrams. For an initial proof of concept Salbutamol Sulphate (SS) was chosen as the API of choice given its high fill weight in formulations such as Ventolin and Pro-Air. Commercially available EP inhalation grade SS was sourced for the study and stored in a desiccator prior to use. An additional sample of the material was characterised by HH to allow specification of the potential drum sizes needed to deliver the chosen target weight of 30mg. Two drum sizes of 30mm^3 and 50mm^3 were specified for the trials, each with different multi-dosing requirements.

The Drum TT system comprises of a machine attached to a pneumatic unit that controls the vacuum and compressed air. Manipulation of the vacuum and compressed air pressure can control the dispensed mass of API and impact on the form of the plug ejected. The machine was commissioned using typical reference powders (lactohale-200 (D90<149µm)[2] and micronised lactohale-300 D90<10µm)[3] sourced from DFE Pharma to ensure the system was working adequately and to provide baseline of data for comparison between the two powder forms. Initial tests from optimising vacuum and blow out pressures, indicated that for a 50mm^3 drum, 600mbar and 700mbar dispensed a two-plug SS weight close to the target of 30mg. The same assessment for the 30mm^3 drum indicated parameters of 500mbar and 700mbar dispensed a three-plug weight closest to the target weight. All API was dosed into Presspart 19ml plain aluminium pMDI cans.

Results

Commissioning studies with Lactose

Commissioning experiments were performed on the Drum TT once in-situ, using two inhalation grade lactose reference powders of differing particle sizes (lactohale-200 and micronised lactohale-300), a summary of the results is provided in Table 1.

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

Table 1- A summary of the average weights obtained for lactose reference standards dispensed on the Drum TT

Initial Drum TT trials with Salbutamol Sulphate using 50mm^3 drum

Working at a vacuum and blow out pressure of -600mbar and 700mbar respectively, three separate trials were performed to assess the overall precision and accuracy of the data for Salbutamol Sulphate. All results are summarised in Figure 3 and Table 2 below.

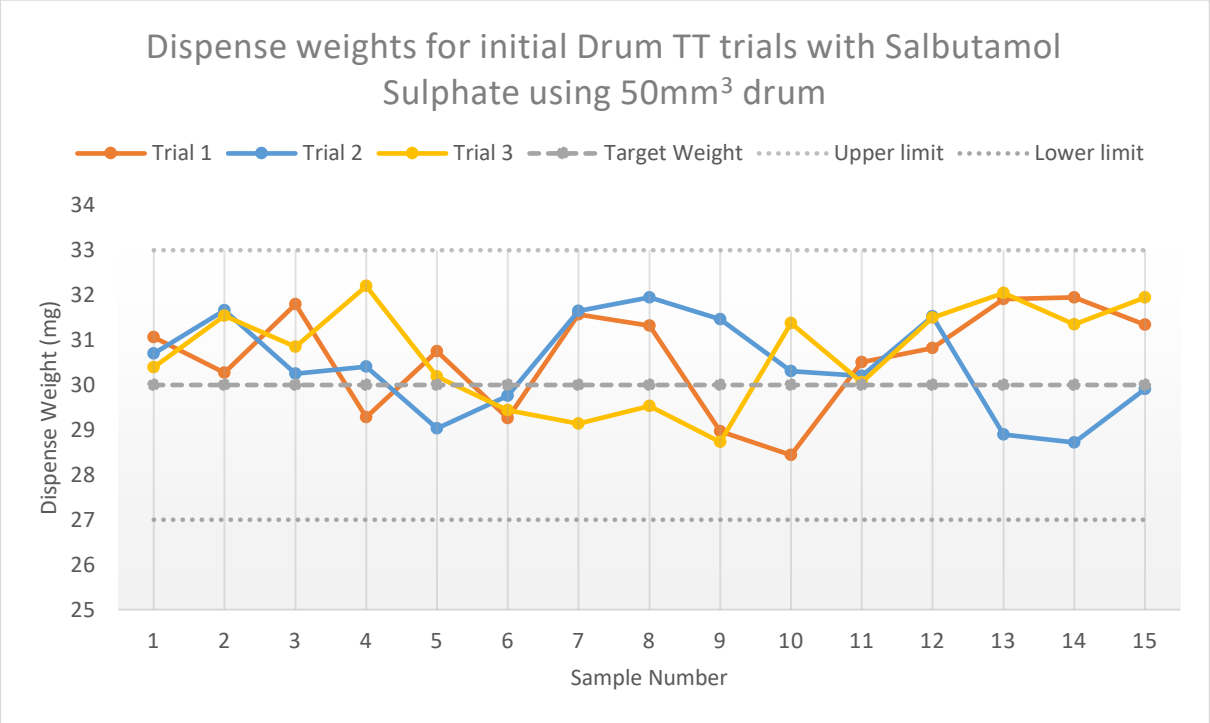

Figure 3- Graph summarising the combined two-dose SS dispense weights obtained from initial successive Drum TT trials using 50mm^3 drum

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

Table 2- A summary of the average weights obtained for multi dosed SS from a 50mm^3 drum on the Drum TT

Initial Drum TT trials with Salbutamol Sulphate using 30mm^3 drum

Working at a vacuum and blow out pressure of -500mbar and 700mbar respectively, 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. All results are summarised in Figure 4 and Table 3 below.

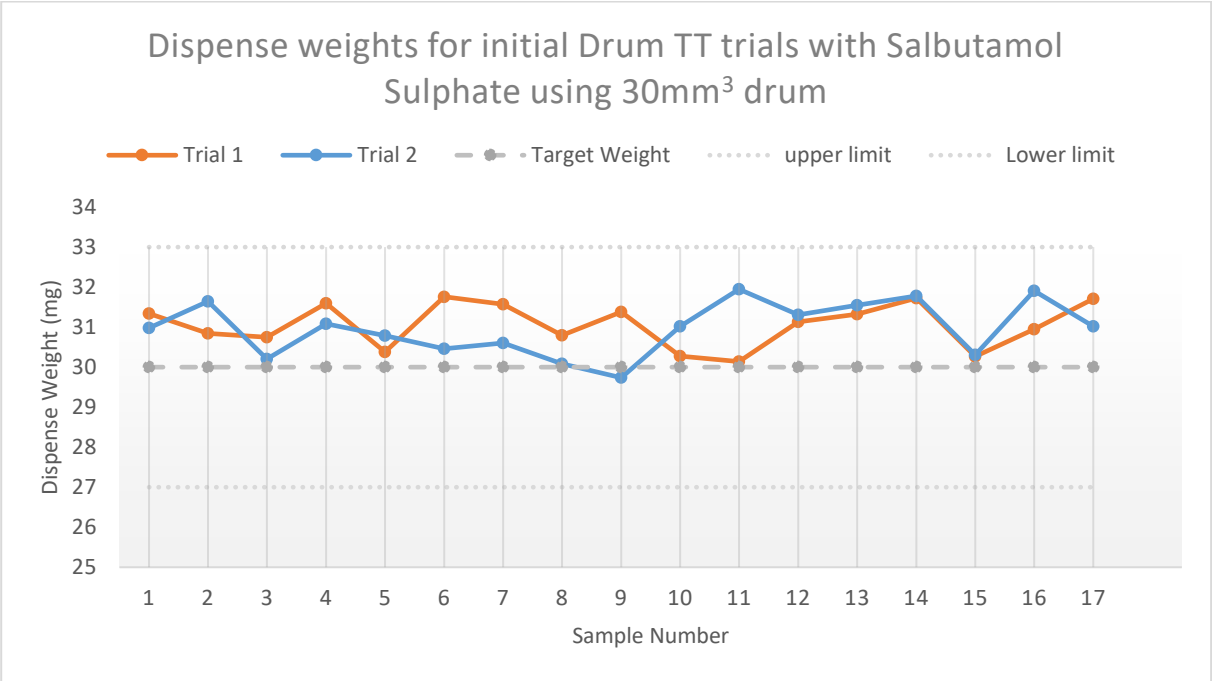

Figure 4- Graph summarising the combined three-dose SS dispense weights obtained from initial successive Drum TT trials using 30mm^3 drum

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

Table 3- A summary of the average weights obtained for multi dosed SS from a 30mm^3 drum on the Drum TT

Discussion

Commissioning study results show that the Drum TT was operating within the expected limits, the desired RSD of 1% for lactohale-200 was obtained. The micronised lactohale-300 reference sample proved more difficult to handle, resulting in an RSD of 5.08% across a similar sample size. Powders of smaller particle size can exhibit reduced flowability because of an increase in particle cohesiveness [4], in this case this is thought to be the cause of the increased RSD. The reference trials were deemed

adequate and met the specified target of ≤5% RSD, set by the manufacturer, so the decision to proceed to API trials was made.

Initial Drum TT trial data from the larger drum size, across all three batches, indicates that the desired target weight can be obtained with a high degree of accuracy and good degree of precision (3.4-3.6% RSD). A goal of ±10% of the target weight was initially set, which all individual data points comfortably fell within the boundaries of. The trial data for the smaller drum size showed some improvement in the precision (1.7-2.4% RSD) thought to be mainly due to the change in drum size. When comparing data against results from commissioning trials, it is evident that Salbutamol Sulphate is more difficult to dispense precisely than lactohale-200 (0.60% RSD Vs 1.7-3.6% RSD) which could be expected given the reduced particle size. With decreasing particle size, there tends to be a corresponding increase in inter-particle cohesion, which can adversely affect flowability, fill ability and dispersibility of the powder [5].

Alternatively, when compared against the data obtained from the micronised lactose reference sample (lactohale-300), Salbutamol Sulphate gave results with seemingly improved precision especially during the smaller drum size trial (RSDs of 1.7-2.1% Vs 5.08%), this possibly being a fairer comparison given their similar particle size (D90<10µm Vs D90<5µm).

Although initial results look promising, 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 [6]. As it stands the can content uniformity would be equivalent to other dry powder filling approaches for Salbutamol Sulphate like Respitab® (RSD 1.4-2.7 %) found in the literature [7]

Conclusion

Harro Höfliger's drum TT equipment 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. The values obtained seem plausible for a high fill weight API, however the impact of this will need to be determined at the next stage by use of an in-vitro stability study of the formulations manufactured. Further work is underway to assess the performance of lower fill weight API formulations and to confirm the overall proof of concept.

References

[1] Corr S, Watkinson P. *HFA-152a from the laboratory to commercial production; a guide*. RDD 2022.

[2] Lactohale® 200 (dfepharma.com)

[3] Lactohale® 300 (dfepharma.com)

[4] U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). *Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Products - Quality Considerations Guidance for Industry.* April 2018 Revision 1. p11

[5] Hao Shi, Rahul Mohanty, Somik Chakravarty, Ramon Cabiscol, Martin Morgeneyer, Harald Zetzener, Jin Y. Ooi, Arno Kwade, Stefan Luding and Vanessa Magnanimo. *Effect of Particle Size and Cohesion on Powder Yielding and Flow*. Powder and Particle 2018, issue 35

[6] U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). *Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Products - Quality Considerations Guidance for Industry.* April 2018 Revision 1. p6

[7] Taylor, Glyn, Warren S, Tran Cuong & Cardiff Scintigraphics Limited 2015*, Pressurised metered dose inhalers and methods of manufacture,* WO2015121653