MANUFACTURING DPIS: AN ENGINEERING PERSPECTIVE

In this article, Pietro Pirera, Product Manager, and Stefano Crivellaro, Process Development R&D Laboratory Technologist at IMA Group's IMA Active division, discuss the rising prominence of the DPI in inhalable drug delivery, how this has been facilitated by industrial filling technologies and how dosators in particular provide high-precision industrial-scale filling.

INTRODUCTION

In 1948, the first commercial dry powder inhaler (DPI) was launched. This first technology seems archaic by today's standards, using a mechanism whereby a deep inward breath would cause a ball to strike a cartridge containing powder and shake the powder into the airstream. Since then, changes in the drug delivery market and regulatory pressures have driven innovation of DPIs forward. Firstly, the introduction of capsules has meant standardised filling technologies can be incorporated into the manufacturing process, thus meeting the need for industrial-scale filling of such devices. With the availability of accurate filling technologies, it is possible to manufacture DPIs on a large enough scale to meet worldwide volume needs at acceptable costs. In addition, the 1987 Montreal Protocol, which called for minimising the use of chlorofluorocarbons (CFCs), diverted market interest away from CFC-propelled metered dose inhalers (MDIs) to DPIs. In the end, healthcare reforms in fast-growing economies did the rest. The availability of low-cost, patient-friendly DPI options also encouraged their use in Asia and Latin America, where MDIs are often still preferred because they are generally considered more cost-effective.

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It is estimated by the WHO that, worldwide, some 300 million people suffer from asthma and 240 million people suffer from chronic obstructive pulmonary disease (COPD). DPIs take 50% of the total asthma/COPD market by value worldwide. Recent patient-focused studies using DPIs have indicated that the expectations regarding this technology have evolved; patients and pneumologists are now increasingly focusing on convenience and ease of use, favouring a compact design. Indeed, DPIs have shown great promise in their ability to deliver drugs reliably and effectively, and novel designs can ensure that future cost, compliance and safety challenges are overcome.

Some of the performance characteristics essential to DPIs are related to dose delivery, fine-particle fraction (FPF) and performance levels at varying airflows. These characteristics can differ from one powder formulation to another, and some fine tuning of either device, formulation or a combination of both may be necessary to achieve optimal performance. Micro-dosing DPIs takes this challenge to

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extremes. IMA Group draws on extensive expertise to provide the most advanced solutions for DPI processing and assembly.

CASE STUDY: INVESTIGATING OPTIMAL PROCESS PARAMETERS FOR LOW-DOSE DRY POWDER INHALERS

The aim of the study was to explore the best process parameters to achieve a 5.5 mg dose of a powder mix including one type of lactose as the carrier and another (4% in concentration) as an API simulator, using micro-fine lactose. The process was carried out as a first approach in IMA's Minima table-top capsule filling device (Figure 1) and then up-scaled to IMA's Adapta industrial-scale capsule filling machine, with 100% gravimetric fill-weight control (Figures 2 & 3). Two types of lactose were compared from different suppliers: Inhalac 251 (Meggle, Germany) and Respitose SV003 (DFE, Germany). Table 1 shows some technological characteristics of the two kinds of powder mixes.

Figure 1: IMA's Minima table-top capsule filling device.

The target dosage of 5.5 mg was achieved step-by-step after preliminary work on the Minima machine, starting from 25 mg, and then 15 mg, with both formulations. Tables 2 & 3 show the results of this first screening, including machine setting, net weight achieved, tolerances, range between minimum and maximum sample weight obtained and relative standard deviation. It was demonstrated that both formulations gave good results in terms of machinability and tolerance obtained. No significant difference was observed by the operator.

Figure 2: IMA's Adapta industrial-scale capsule filling machine.

The second step of the study was to up-scale the experience gained on the

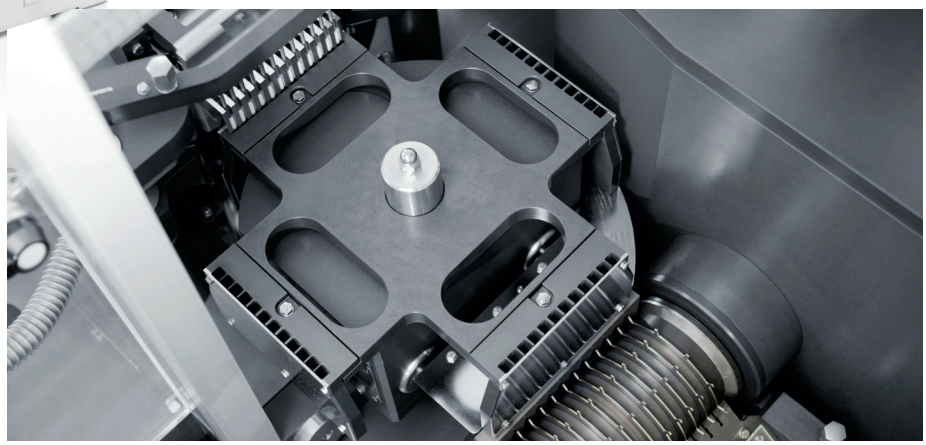

Figure 3: Adapta has 100% gravimetric fill-weight control.

Powder Mix	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr Index (%)	Loss on Drying (%)
Inhalac 251 + 4% lactose microfine	0.593	0.780	23.9 (poor flowability)	0.04
Respitose SV003 + 4% lactose microfine	0.658	0.812	18.9 (fairly good flowability)	0.08

Table 1: Inhalac 251 (Meggle, Germany), Respitose SV003 (DFE, Germany).

Average Net Weight (mg)	Doser Internal Diameter (mm)	Min-Max Weight Sample Deviation (mg) *	Tolerance Obtained (%) *	Relative Standard Deviation (%) *
25.9	3.0	1.48	+3.3/-2.3	2.03
14.6	2.5	0.74	+1.6/-3.4	1.48
5.4	2.0	0.70	+8.0/-6.1	3.0

Table 2: Inhalac 251+ 4% Lactose microfine, Minima trials. * Values calculated over the gravimetric fill-weight of the 100% of processed capsules.

Average Net Weight (mg)	Doser Internal Diameter (mm)	Min-Max Weight Sample Deviation (mg) *	Tolerance Obtained (%) *	Relative Standard Deviation (%) *
25.5	3.0	1.75	+3.4/-3.4	2.24
14.6	2.5	0.46	+1.5/-1.6	0.90
5.5	2.0	0.67	+4.8/-8.1	2.9

Table 3: Respitose SV003 + 4% Lactose microfine, Minima trials. * Values calculated over the gravimetric fill-weight of the 100% of processed capsules.

Lactose Type	Average Net Weight (mg)	Doser Internal Diameter (mm)	Relative Standard Deviation (%)	Machine Speed (caps/h)
Inhalac 251 + 4% lactose microfine	5.5	2.0	2.52	85,000
Respitose SV003 + 4% lactose microfine	5.5	2.0	2.52	85,000

Table 4: Powder mixes Adapta trials.

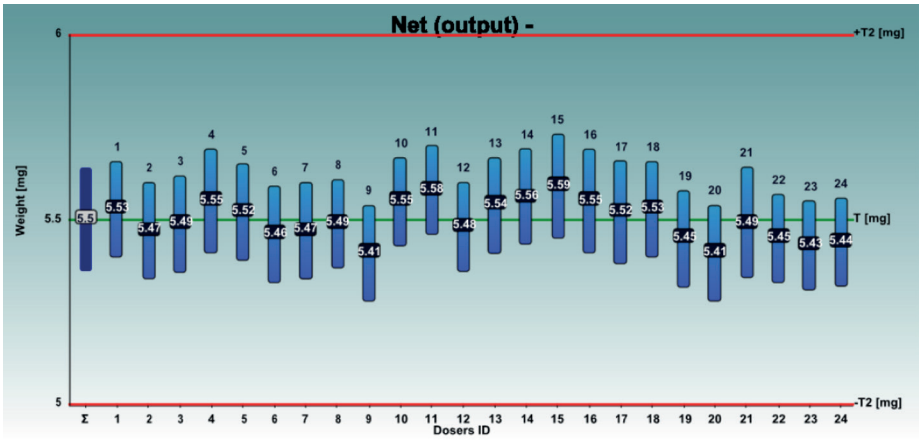

Figure 4: Inhalac 251 + 4% Lactose microfine, behaviour of the 24 dosators on Adapta.

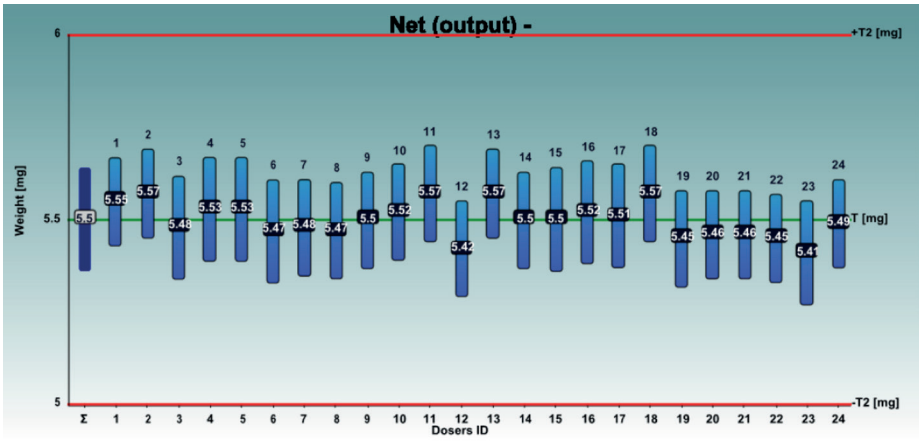

Figure 5: Respitose SV003 + 4% Lactose microfine, behaviour of the 24 dosators on Adapta.

bench-top machine to the production equipment. Since the target dose was 5.5 mg the main work was concentrated on this target with both preparations. Again, both formulations demonstrated good behaviour in the machine without any particular problems (e.g. no seizing, no empty capsules produced). This can be also seen in the final results that are summarised in Table 4, the machine settings for the powder mixes are reported, including net weight achieved and relative standard deviation for an easy evaluation.

It was confirmed that, for 5.5 mg dosing, the range between the minimum and maximum weight value in the table-top capsule filler always came to below 1.0 mg. The results obtained once formulations were tested in the industrial-scale capsule filling machine were even better. For both formulations the relative standard deviation was confirmed to be below 3%. Figures 4 & 5 show the net weights of all 24 dosators of the Adapta.

> "A major advantage of using dosator technology for processing low-dose DPIs is that the system can dose very small amounts of powders into capsules with very high precision."

CONCLUSION

As shown by this study, a major advantage of using dosator technology for processing low-dose DPIs is that the system can dose very small amounts of powders into capsules with very high precision. This powder dosing technology does not require powder compaction to transfer the powder to the capsule, thus ensuring that the powder within the capsule is less likely to form aggregates and is maintained as a free-flowing powder. Maintaining the free flowing properties of the dispensed powder within the capsule ensures the release of powder from the capsule into

the inhaler when the capsule is pierced, thereby better controlling both the emitted dose and the FPF of the dose discharged from the DPI.

ABOUT THE COMPANY

IMA Group is a leader in the design and manufacture of automatic machines for the processing and packaging of pharmaceuticals, cosmetics, tea, coffee and food. IMA Active, one of the three pharmaceutical divisions of IMA Group, partners with pharma for each solid dose processing phase: granulation, tableting, capsule filling and banding, weight checking, coating, handling and washing.

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ABOUT THE AUTHORS

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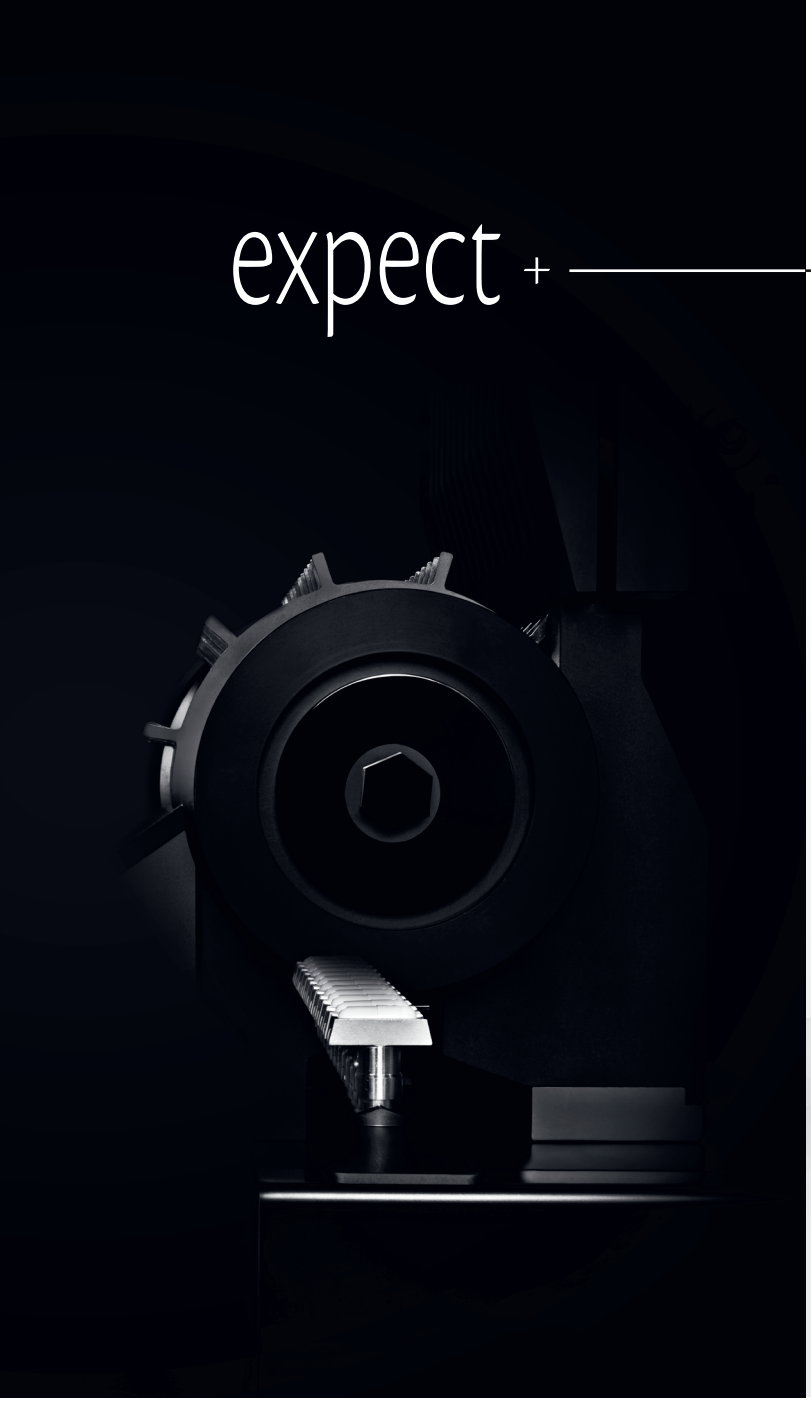

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