A New Dosing System to Fill Dry Powder Inhaler Discs

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Summary

Several multi-unit dose dry powder inhalers on the market or in the development phase contain injection-molded annular rings, which carry the single powder doses in closed cavities. These pockets can be round or oblong shaped and may be arranged in symmetric or asymmetric circles or even spirals. Current micro dosing systems such as dosator, vacuum drum or membrane filler, which are suitable for dosing powders for inhalation, possess certain limitations when being used to fill inhaler discs, like insufficient robustness, inadequate output or limited flexibility regarding filling level. Based on the membrane filling technology a new dosing system to fill such discs has been developed. Discs with any number or shape of cavities can be filled in one process cycle, and only two format parts have to be exchanged to adapt the filler to new discs. The system can be integrated into automated machines to fill, assemble and package disc-based DPI and it can be up-scaled by simply increasing the number of filling heads.

The dosing system described in this paper has been tested using different lactose monohydrate powder blends with moderate to very poor flow properties, characterized by Carr's indices of 14% to 42%. The fill weights achieved using 12mm³ dosing chambers were in the range of 6,3mg to 9,1mg, the relative standard deviation ranged between 1,7% and 4,8%. The compaction of the powder during the dosing step was low which qualifies the disc filler for processing inhalation powders.

Introduction

The global inhalation device market is growing continuously, as pulmonary drug delivery is ideal to treat airway diseases but is also an attractive alternative to oral and parenteral delivery methods. As dry powder inhalers (DPI) offer advantages over other types of inhaler, there are currently many development projects in this field, using either single dose or multiple dose devices. Current multiple dose DPI contain the powder either as bulk material in a reservoir, or pre-metered into discrete compartments. In a reservoir-based inhaler the powder dose to be inhaled is confined by the device itself during actuation by the patient, whereas in a multi-unit dose device the powder portions are dosed by special machines in the course of the industrial filling and assembly process. The dosing and packaging of single powder portions using special machinery is advantageous regarding the dosing accuracy and the protection of the powders from moisture.

A portable multi-unit dose DPI should have a handy size to be carried everywhere but contain as many doses as possible. Numerous concepts have been developed to meet these conditions, marketed DPIs today work either with blister strips or with injection-molded sealed discs. Disc-based solutions have been described in several patent applications and may carry up to 60 pockets of variable size, shape and geometric arrangement [1- 5]. In order to place a maximum number of powder cavities on a smallest possible disc, their volume is minimized and their shape adapted accordingly. As a result the powder doses have to be transferred into pockets with small cross section or of extreme narrow oblong shape, which is always a challenge for the dosing system.

Today there are three different technologies available on the market which can be utilized for industrial automated microdosing of powders for inhalation, namely dosator, vacuum drum and membrane filler (Figure 1). In principle these systems could also be used to fill inhaler discs, but each one will show certain restrictions: The dosator system is limited to the filling of more or less circular cavities, and the dosing accuracy is rather poor when doses are below 5mg or the powders are very cohesive. The vacuum drum system shows excellent dosing accuracy compared to dosator [6] and can handle nearly every type of powder formulation, but the dosing cavities are arranged in a straight line along the drum axis. Thus the filling of a disc is slow, as a maximum two opposite cavities per disc can be filled in one machine cycle (if there is an even number of cavities), for example requiring 30 cycles to fill a 60-up disc. The membrane filling system can be well adapted to dose into annular arranged cavities in a single machine cycle. However, the filling level is limited to 95 – 100% of the target cavity volume, as the cavity itself is acting as the dosing chamber.

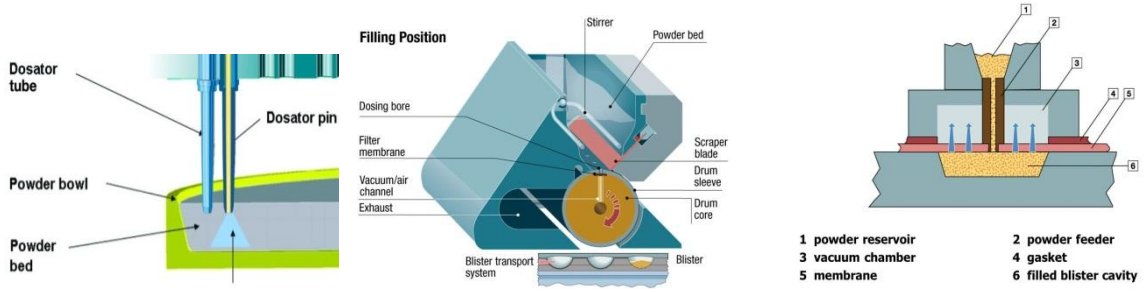

Figure 1: Common microdosing systems to fill powder into inhaler disc cavities

The new dosing system to fill dry powder inhaler discs has been designed to meet the following requirements:

- Filling of inhaler discs containing annular arranged cavities with variable powder doses in one step
- Suitability to process most of the present powder formulations
- Safe transfer of powder doses into small circular but also extremely oblong shaped cavities
- Acceptable dosing accuracy (e.g. CV < 5%), even at fill weights below 10mg
- Cycle time < 2s
- Capable of being integrated into machines to automatically fill, seal and assemble inhaler discs.

Experimental Methods

Materials

The new dosing system has been developed using lactose monohydrate, inhalation grades, having different mean particle size (Table 1): Lactohale LH200 (DFE Pharma, Goch. Germany) have been used as delivered. Inhalac 120, Inhalac 250, and Inhalac 400 (Meggle Group, Wasserburg, Germany) has been used pure or as blends, prepared by mixing the coarse lactose types (Inhalac 120 or 250) with microfine inhalac 400 (5% or 20% W/W respectively).

Equipment and methods

Particle size distribution: Laser light diffraction (Helos/BF, Sympatec, Clausthal-Zellerfeld, Germany); dry dispersion (Rodos/L): 0.5 bar.
Bulk and tapped density, Carr's index (CI): Ph. Eur. 8.0 (2.9.36)
Powder blending: Sandwich method. Batch size 750 g. Turbula blender T2F (Willy A. Bachofen Maschinenfabrik, Muttenz, Switzerland): 30 min at 72 rpm.
Determination of fill weight: Automated disc weighing system (Harro Höfliger, Allmersbach, Germany)

Sample or blend (carrier type / % Inhalac400)		Lactohale LH200	Inhalac 400	Inhalac 120/0	Inhalac 120/5	Inhalac 120/20	Inhalac 250/0	Inhalac 250/5	Inhalac 250/20
PSD	X_{10} [µm]	10	5	84	17	4	13	8	4
	X_{50} [µm]	73	200	131	128	110	51	46	36
	X_{90} [µm]	147	317	174	177	177	95	89	88
Bulk density [g/l]		540	650	730	720	640	590	600	540
Tapped density [g/l]		930	850	850	890	890	850	880	850
CI [%]		42	24	14	19	28	31	32	36

Table 1: Powder samples used for development and testing of the new filling system

Results and Discussion

Description of the filling process (Figure 2)

The starting point for the development of the filling system was the available membrane technology [7], which allows for a variable arrangement of the dosing cavities, especially in an annular design. The powder is contained in an annular hopper which may be combined with a stirrer, actuated by a planetary drive. The base plate of the hopper is equipped with small capillaries, which are adapted to the flow properties of the powder: The powder particles cannot pass through by gravity alone, but will flow when a pressure drop is generated. To increase the dosing range and to avoid the limitation of 100% filling degree, an annular plate with intermediate dosing cavities is integrated into the process. The cavities are connected to a vacuum system, separated by a membrane filter, which acts as the base of each cavity. The number and position of the powder hopper's capillaries correspond to the cavities of the plate, which for their part relate to the pockets of the inhaler disc. The base of the powder hopper and the plate with the intermediate dosing chamber are the only format parts needing to be exchanged for filling different discs (Figure 3).

To fill the intermediate dosing cavities, the plate is brought in close contact to the powder hopper from beneath and a negative pressure is generated inside the cavities through the membrane filter. This will cause the powder to flow from the hopper down through the capillaries into the dosing chambers. In the next process step, the plate with the filled cavities is separated from the hopper (Figure 4), rotated by 180° and is then positioned on top of the inhaler disc to be filled (Figure 5). Using a short positive air pulse, the powder is discharged into the target pockets of the disc.

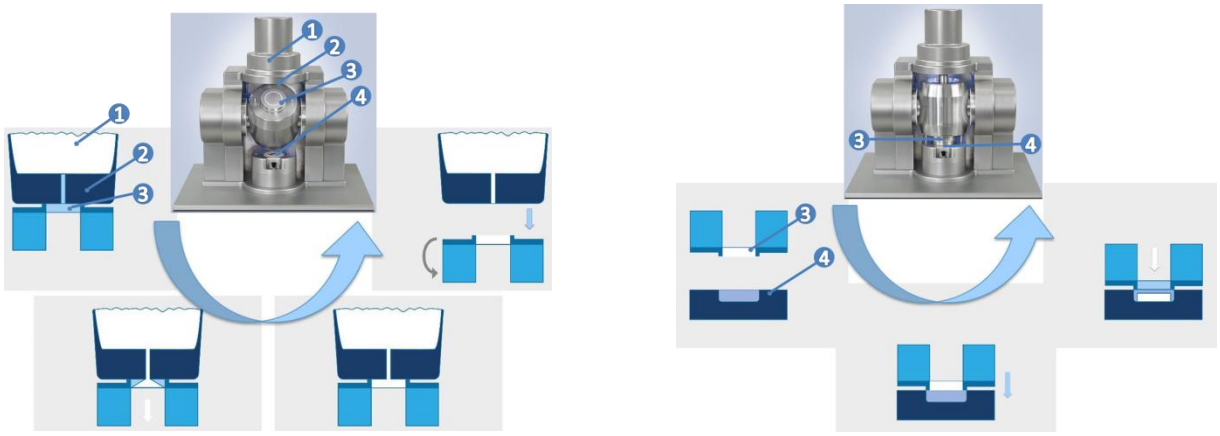

Figure 2: Filling process; Left: filling of dosing chamber; right: Powder transfer to disc pocket
❶ Powder bed ❷ Base plate powder hopper ❸ Dosing plate ❹ Inhaler disc

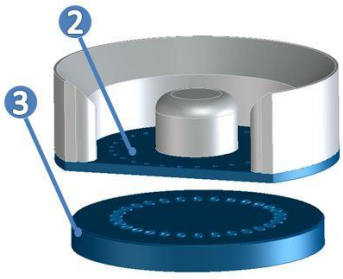

Figure 3: Format parts

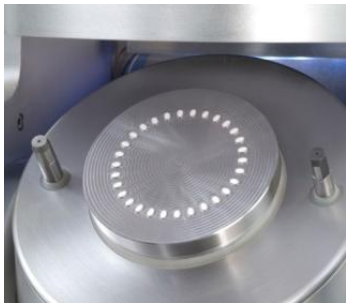

Figure 4: Filled dosing plate

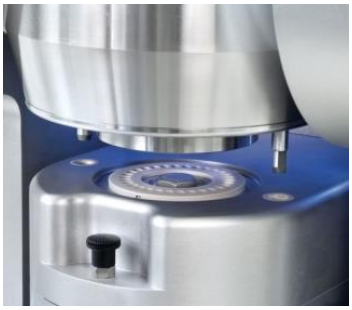

Figure 5: Powder discharge into inhaler disc

Dosing results

The following dosing results (Table 2) have been achieved using a set of format parts to fill an inhaler disc with 30 oval shaped cavities, the volume of the 30 dosing chambers was 12mm³, the combined cycle time for generation and transfer of the powder dose was 2s. For comparability reasons the internal diameter of the capillaries of the powder hopper base plate was 1,6mm for all dosing tests. The optimization of the process parameters by means of a DOE experiment was performed using the Inhalac 120/5 blend, because it is a good model for lactose-based API formulations.

Analysis of the main effect diagrams showed that the fill weight is predominantly influenced by the pressure drop: The lower the negative pressure, the higher the fill weight and the better the dosing accuracy. Increasing the stirrer speed in the powder hopper and the height of the powder bed also produced a slightly higher fill weight. The setting leading to the lowest variance of fill weight as target parameter was used to run all other powder blends, without further individual optimization.

All powders could be processed with an acceptable dosing accuracy, regarding the low fill weight of 6,3mg to 9,1mg. The dosing density was always far below the tapped density, indicating only moderate densification during the process, which is important for good powder performance in the inhaler.

Dosing Results	Lactohale LH200	Inhalac 400	Inhalac 120/0	Inhalac 120/5	Inhalac 120/20	Inhalac 250/0	Inhalac 250/5	Inhalac 250/20
Average weight [mg]	8,8	6,3	9,1	8,9	8,7	9,0	8,7	8,3
Min. weight [mg]	8,2	5,5	8,3	8,4	7,9	8,1	7,8	7,4
Max. weight [mg]	9,2	6,9	9,7	9,4	9,5	9,4	9,3	9,1
Standard deviation [mg]	0,15	0,30	0,19	0,17	0,25	0,19	0,27	0,32
Rel. Standard deviation [%]	1,7	4,8	2,1	1,9	2,8	2,1	3,1	3,8
Sample number [pockets]	390	510	660	600	450	450	450	450

Table 2: Summary of dosing results

Conclusion

A new powder dosing system to fill inhaler discs with multiple cavities in one step has been developed and tested with various lactose monohydrate powder blends, characterized by Carr's indices between 14% and 42%. All test powders could be dosed with acceptable dosing accuracy. The cycle time was below 2min, which is sufficient for integration of the system into assembling and packaging lines.

References

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