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Comparative *in vitro* performance evaluation of the Novopulmon® 200 Novolizer® and Budesonid-ratiopharm® Jethaler: two novel budesonide dry powder inhalers

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A special single dose collector and a multi stage liquid impinger were used to assess the consistency of delivered dose and fine particle fraction respectively, of the Novopulmon® 200 Novolizer® (Viatris, Frankfurt, Germany) and Budesonid-ratiopharm® Jethaler (Ratiopharm, Ulm, Germany). The obtained average delivered dose from the Jethaler at 4 kPa is 199 μg (99.5% of the label claim) versus 219 μg (109.6%) for the Novolizer (mean of 90 doses from the same device). The corresponding relative standard deviation (RSD) for the Jethaler is on average 14.05% (maximal and minimal dose are 289 and 148 μg respectively), versus an RSD of 5.56% for the Novolizer (max. is 240; min. is 187 μg). It can be shown that the rather extreme spread in the delivered dose from the Jethaler is caused by a variation in metered mass, and to less extent by a poor content uniformity of the drug-lactose compact. The fine particle fractions (FPFs, as percent of label claim, for particles <5.1 μm) of both devices show an increase with increasing pressure drop across the inhalers, although at 4 kPa already 62% (Jethaler), respectively 72% (Novolizer) of the 'maximal' value (at 8 kPa) is achieved. FPF from the Novolizer is highest at all pressure drops and varies between 23.2% (at 2 kPa) and 54.3% (at 8 kPa). The difference in FPF between both devices increases with decreasing upper class for the FPF: the ratio of FPF from Novolizer to that from Jethaler (at 4 kPa) is 1.42 for particles <5.1 μm versus 2.14 for particles <1.8 μm, suggesting that the aerosol produced by the Novolizer has much greater potential for deep lung deposition.

1. Introduction

Budesonide is a glucocorticosteroid used to control inflammatory processes in asthma. Since its patent protection for dry powder inhalation elapsed, many generic formulations have been introduced to the market with this type of drug. In Germany alone, six different budesonide DPI's are currently available: Pulmicort Turbuhaler® (AstraZeneca), Budes® Easyhaler® (Hexal), Miflonide® Aerolizer® (Novartis), Novopulmon 200 Novolizer (Viatris), also known as Budecort® Novolizer (Fujisawa), Budesonid Cyclocaps® for Cyclohaler® (Jenapharm) and Budesonid-ratiopharm Jethaler (Ratiopharm), also marketed by Ct-Arzneimittel. These devices differ from each other in type of powder formulation and inhaler design, and therefore, it is not self-evident that they are equivalent in their performance. Currently, the budesonide Novolizer and Jethaler are among the most successful generic multi-dose devices on the market. However, relatively few comparabale *in vitro* evaluations of these inhalers are known. Newman et al. (2002) obtained a fine particle fraction (FPF) of 46.7% (derived from the stages 3 to 5 of a high-precision multistage liquid impinger) from the salbutamol MAGhaler at 60 l/min, which is the same device as the Jethaler. They also reported dose consistency results for only small dose numbers from this device: RSD is on average 8.5% at 60 l/min, respectively 8.4% at 30 l/min ($n = 10$ per device). Fyrnys (1999) showed that less than 20 out of 2000 doses (from 10 different multi dose cartridges) are beyond the $\pm 25\%$ specification limit for the Novolizer, whereas FPF from this device collected in the Erweka MSLI increases from 10 to 30% between 30 and 90 l/min. The aim of our study was to evaluate consistency of delivered dose and fine particle fractions (of different size classes within the total range between 0 and 5.1 μm) from the budesonide Novolizer and Jethaler at different pressure drops, using exactly the same test equipment and circumstances for both devices.

2. Investigations, results and discussion

2.1. Inhaler designs

Figs. 1 and 2 show the relevant inhaler parts for dose measuring and fine particle generation of the Novolizer and Jethaler respectively. The Novolizer has a reservoir

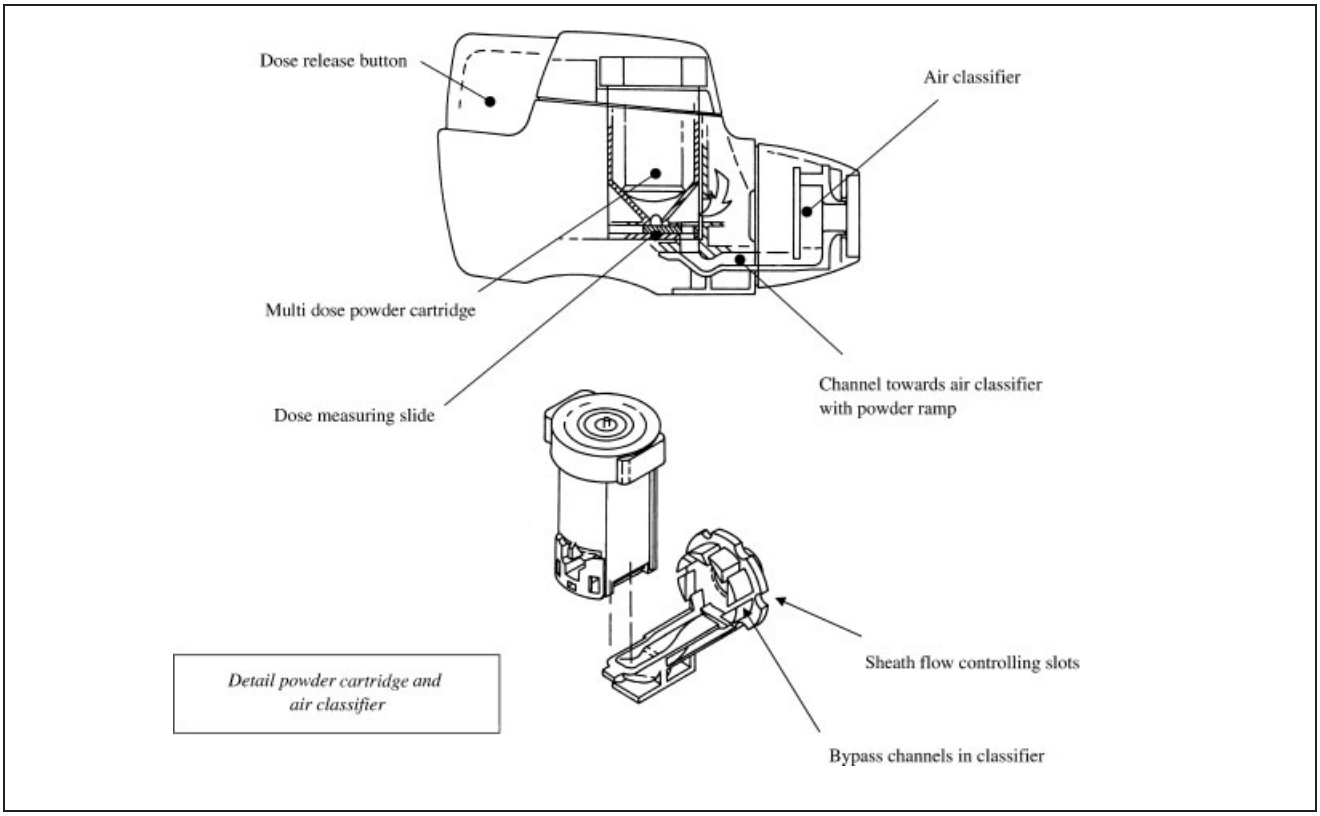

Fig. 1: Technical drawing of the Novolizer showing the Novopulmon powder cartridge and the powder de-agglomeration principle (air classifier)

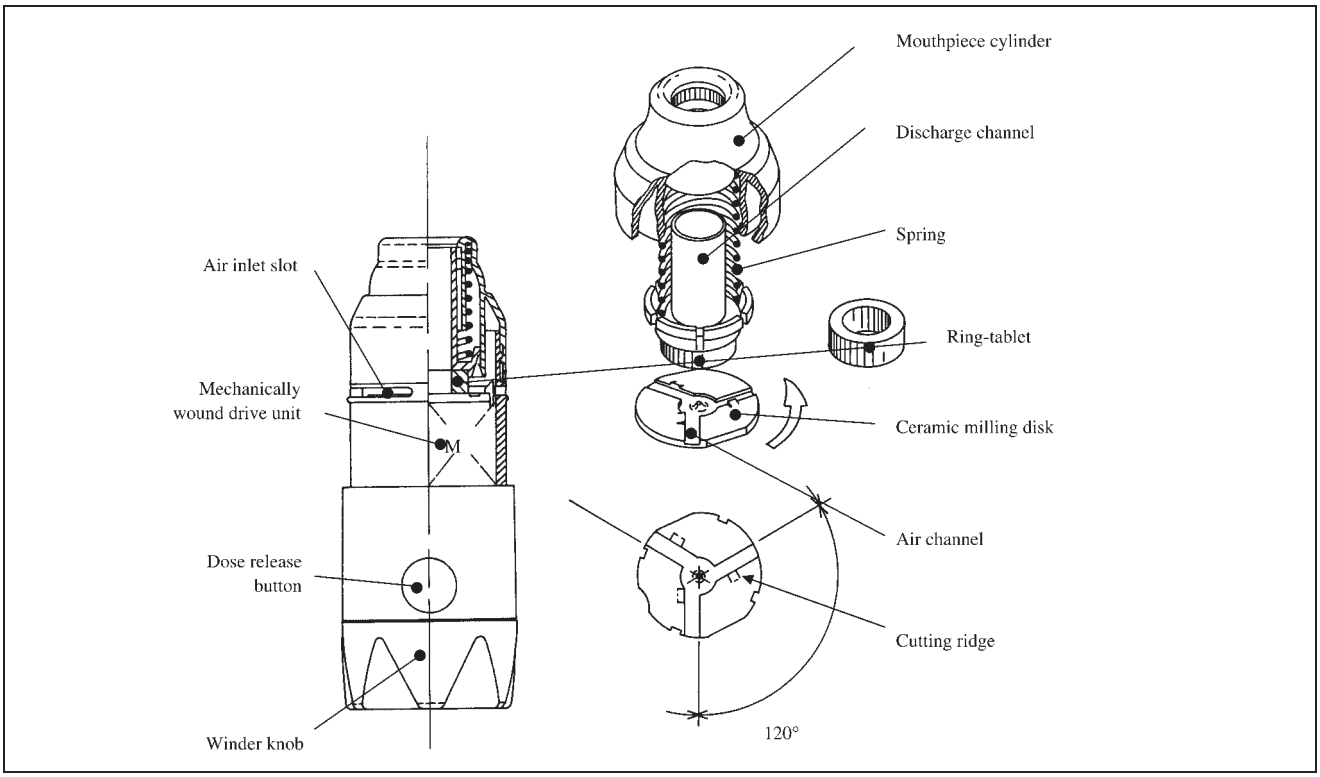

Fig. 2: Technical drawing of the Jethaler showing the scraper disk with three dissimilar cutting ridges adjacent to shallow air channels and a spring loaded drug-lactose tablet inside the mouthpiece

for the powder formulation (multi dose cartridge with 100 or 200 doses) with a slide mechanism that contains a measuring chamber for isolation of a single dose (Fig. 1). Fine particle redispersion from the powder formulation occurs in an air classifier of which the mechanism of action has been described previously (de Boer et al. 2003). The classifier in the Novolizer has a special design that discharges the carrier crystals in the powder formulation after preceding detachment and emission of the drug particles. The Novolizer also has several signalling and safety functions

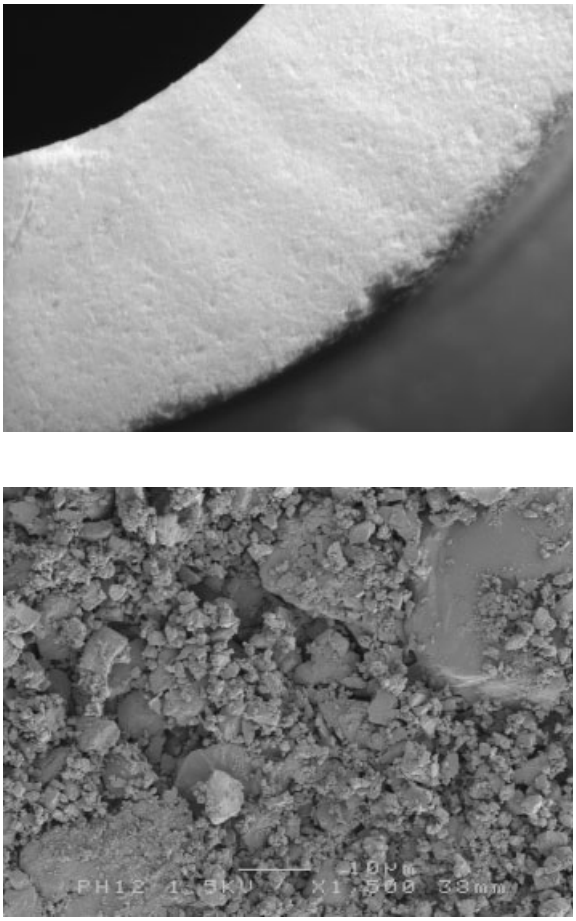

Fig. 3: Light microscopic photograph (A) and scanning electron micrograph (B) of the front surface of the drug-lactose tablet inside the mouthpiece cylinder of the Jethaler

that help optimising the inhalation therapy, such as a dose counter, showing the residual number of doses in the powder cartridge and a window, changing colour from red to green upon dose actuation, and from green to red again when during inhalation the minimally required flow rate for powder de-agglomeration is achieved. The Jethaler in Fig. 2 has been described previously by Rymsa (1998) and Newman et al. (2002), in a period when this device was still referred to as MAGhaler. The device has a design unlike all other currently marketed dry powder inhalers, since the drug-lactose mixture has been processed into a relatively soft ring-shaped tablet from which small amounts are grated with a ceramic milling disk. The front surface of the tablet from which doses are derived (light microscopic photograph) and its structure (SEM photograph) are shown in Figs. 3A and B at two different magnifications. In contrast to the Novolizer, dose measuring by the Jethaler is independent of the inhaler position, but the complete dose is lost if not a flow through the inhaler is generated simultaneously when pressing the dose release button, since the counter action of the drag flow is required to prevent that the particles are discharged through the air inlet slots by centrifugal action. For both types of devices, two different batches were investigated, being 2G068 (Batch 1: 100 dose Novopulmon cartridge) and 3D088 (Batch 2: 200 dose cartridge) for the Novolizer. For the Jethaler (200 dose), batches C14448 (Batch 1) and C22796 (Batch 2) were tested.

2.2. Inhaler resistances

It was observed that the air flow resistance (R) of the Jethaler decreases with increasing flow rate (Φ) up to approximately 40 l_N/min. At higher flow rates, R is rather constant for this type of DPI. For three Jethalers, the calibrations were replicated following delivery of a (variable) number of doses (Table 1). It was observed that the resistance of this device may change due to grating of the ring tablet. Without grating (dose delivery) between the series (device 6 in Table 1), repeatability is the same as for the Novolizer. For the Novolizer, a difference in resistance before and after reset of the slide was found, which is the result of a valve in the central air inlet channel opening at sufficient kinetic pressure from the inspiratory air flow. The switchpoint of the valve (equals reset point of the slide) is between 1.5 and 2 kPa. As for the Jethaler, the resistance of the Novolizer decreases with increasing flow rate up to valve switch point (as the valve gradually opens) and is constant above 50 l_N/min. For the Novolizer, no change in resistance was observed during use, but there is a minor difference in resistance between devices from different batches (Table 1). The good proportionality between kPa and Φ at flow rates above 40–50 l_N/min, allowed single point calculation of R at 60 l_N/min. Table 1 also shows the extremes (range) of the individual series per experiment, except for the Novolizer, for which the intradevice variation is confined to differences in the fourth decimal. For the cascade impactor and dose delivery experiments in this study, only Novolizers of Batch 1 have been used.

Table 1: Air flow resistance (R; $kPa^{0.5} \cdot min \cdot l_N^{-1}$) and flow rate at 4 kPa (Φ: l_N/min) for five different inhalers from two different batches

Device (Batch)	Novolizer		Jethaler			Jethaler after release of X doses			
	R	Φ at 4 kPa	R	Range	Φ at 4 kPa	X	R	Range	Φ at 4 kPa
1 (1)	0.028	70.5	0.038	0.037 –0.038	53.2	180	0.035	0.033 – 0.037	57.7
2 (1)	0.028	72.0	0.034	0.033 – 0.036	58.6	90	0.033	0.033 – 0.033	60.8
3 (1)	0.028	72.0	0.037	0.036 – 0.038	53.9				
4 (2)	0.029	68.2	0.038	0.037 – 0.040	52.2	30	0.037	0.034 – 0.039	54.4
5 (2)	0.029	67.4	0.035	0.035 – 0.036	56.6				
6 (1)			0.035	0.035 – 0.035	54.2				
Overall mean*	0.028	70.0	0.036		55.7				
Max.	0.028	72.5	0.040		49.7				
Min.	0.028	67.3	0.033		60.8				

* Overall mean is for all series, including the experiments after release of X doses for Jethaler
Range indicates the extremes per experiment. Only for device 6 (Jethaler) no dose was delivered between the individual series

Table 2: Mean drug content of 30 samples having the same order of magnitude as the metered mass of Novolizer (10.9 mg) and Jethaler (2.2 mg)

	Novolizer		Jethaler	
Batch	1	2	1	2
Mean drug content (%)	1.87	1.89	9.12	9.21
RSD	1.046	1.046	5.171	2.200
Max.	1.92	1.85	9.77	9.66
Min.	1.83	1.96	7.18	8.70

2.3. Content uniformity

The results from content uniformity testing are summarised in Table 2. The spread in drug content is highest for the Jethaler samples, which could be a consequence of different factors, including a higher drug concentration in the powder blend (compared to the Novolizer), the use of a much finer lactose (having poor flow and mixing properties) and the isostatic compression technique that may cause some redistribution of drug in the compact due to air expelling from the pores. On the basis of minimal and maximal values and nominal metered masses (10.9 mg for the Novolizer and 2.2 mg for the Jethaler), dose variation between the extremes of 199 and 209 μg (Batch 1), respectively 202 and 214 μg (Batch 2) may be expected for the Novolizer, versus 158 and 215 μg (Batch 1), respectively 191 and 213 μg (Batch 2) for the Jethaler.

2.4. Consistency of delivered dose

Several Jethalers and Novopulmon cartridges from both batches were investigated on consistency of delivered dose

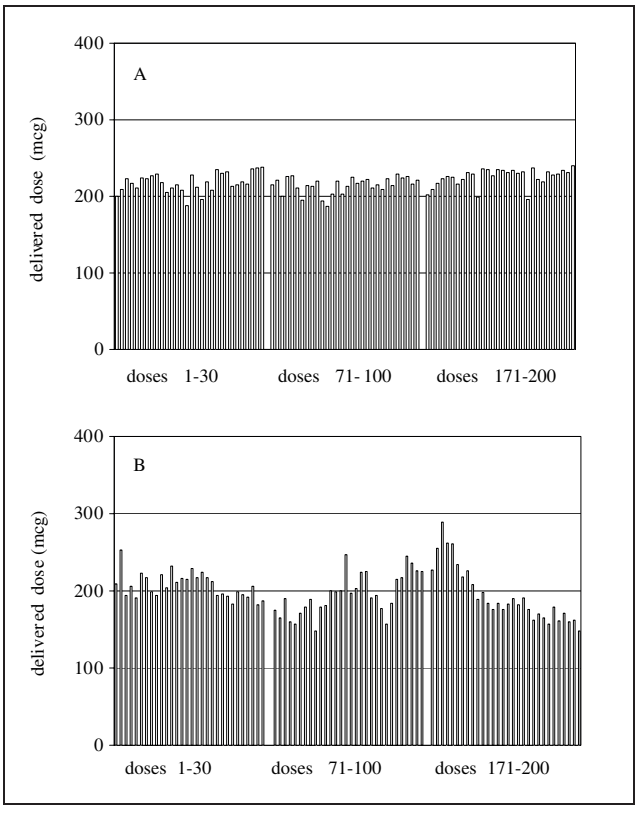

Fig. 4: A. Consistency of delivered dose (in μg) at 4 kPa from the Novolizer with 200 dose Novopulmon cartridge (Batch 2)
B. Consistency of delivered dose (in μg) at 4 kPa from the (200 dose) Jethaler (Batch 1)
For both devices, mean and RSD for the doses 1–30, 71–100 and 171–200 are given in Table 3

Table 3: Mean values for delivered dose (Novolizer and Jethaler) and metered mass (Novolizer) and their relative standard deviations (RSDs) for the doses presented in Figs. 4

Delivered dose

	Novolizer (Batch 2)		Jethaler (Batch 1)	
	Mean (μg)	RSD (%)	Mean (μg)	RSD (%)
Doses 1–30	218	5.7	207	7.8
Doses 71–100	214	4.9	195	13.8
Doses 171–200	225	5.0	195	18.2
Overall (n = 90)	219	5.6	199	14.1
Label claim	200		200	

Corresponding metered mass

	Novolizer (Batch 2)	
	Mean (μg)	RSD (%)
Doses 1–30	12.59	4.0
Doses 71–100	12.67	4.5
Doses 171–200	13.19	3.3
Overall (n = 90)	12.81	4.4
Label claim	10.9	10.9

at 4 kPa, using different procedures. The standard procedure was the same for both DPIs: the doses 1–30; 71–100 and 171–200 were analysed individually and the doses in between were either wasted, averaged (per series of 10) or used for cascade impactor analysis. A typical result is shown in Figs. 4A (Novolizer) and 4B (Jethaler). Other devices from both investigated batches show the same trends of a relatively large spread in delivered dose for the Jethaler and a much more constant output for the Novolizer. Mean values and RSD for the doses 1–30; 71–100 and 171–200 in Figs. 4A and B are given in Table 3. For the results in Figs. 4A and B, not more than ten doses per day were taken from the inhalers in order to avoid possible effects from tribocharge (both DPIs) and stressing of the Jethaler tablet. The standard procedure included also determination of corresponding metered masses for the Novolizer (derived from weight loss of the Novopulmon cartridge), which show the same low RSD as the delivered dose (Table 3). For the Jethaler, metered mass determination was excluded in order not to damage the ring tablet during repeated (dis)mounting of the mouthpiece (disassembling of mouthpiece and inhaler body would be necessary, because the whole device is too heavy for accurate weighing).

On theoretical grounds, high metered doses from the Novolizer are extremely unlikely, which minimises the risk of overdosing. The reasons are the fixed metering volume of the slide (20.07 mm^3) and the rather narrow size distribution of the carrier in the powder mixture. The lactose carrier particles have a granule-like structure, that yields a stable adhesive mixture (Staniforth 1987), and contain a fixed intraparticular porosity that can not be changed unless the granules are exposed to extreme forces. The large mean carrier diameter (X_{50} from laser diffraction analysis is approximately 250 μm) and the relative narrow size distribution (X_{10} is 130 μm and X_{90} is 375 μm) guarantee good flow properties and set limits to the interparticular porosity inside the measuring slide. Therefore, the metered mass varies within a narrow range, as shown in Fig. 5, presenting the cumulative number percent curve as func-

tion of metered mass for 150 doses from two different batches of Novopulmon cartridges. To produce this figure, the obtained (150) metered masses have been arranged into subsequent weight classes increasing by 0.25 mg. The number of doses in each class has been counted and expressed as percent of 150, and the percentages of subsequent classes have been added to yield a cumulative number percent curve as function of the mean class weight. The range has an upper limit of 13.81 mg (which is only 108% of the mean value of 12.74 mg) containing 260 μg budesonide (at 1.88% drug content), and a lower limit of 11.24 mg (88% of mean). The experimental data in Fig. 5 confirm what is theoretically expected: the range of higher (than average) porosities, due to incomplete filling of the measuring slide, is wider than that of lower porosities. This, because there exists a minimum value for the total porosity (approximately 0.50 for the carrier used, as can be derived from intra- and interparticular ordering) which makes metered masses of 15.5 mg or more virtually impossible. This confines the theoretically highest possible dose (at 1.88% drug content) from the Novolizer to 290 μg (145% of label claim).

The RSD values for delivered dose from the budesonide Jethaler (Table 3) are much higher than those (for small dose numbers) presented by Newman et al. (2002) for the salbutamol Jethaler. They cannot solely be explained by the variations in drug content (paragraph 2.3). Neither does the frequency of dose delivery from the Jethaler seem to have influenced the results. This can be concluded from the first ten doses in Fig. 4A (Jethaler from Batch 1: ten doses per day) having a mean of 211 μg (105% of label claim) with an RSD of 8.9%. The mean of the first ten doses taken individually from a device of Batch 2, now only one dose per day, is 306 μg (153% of label claim) with an RSD of 18.1%. Whereas the mean of the first ten doses from another device of Batch 2 (Table 4) taken with only a few minutes interval time (analysed together) is 265 μg (133% of label claim). These results suggest that stressing (weakening) of the tablet as the result of frequent dosing is very unlikely to occur.

Light microscopic investigation of the tablet revealed that even careful assembling of the mouthpiece and inhaler body in most cases leads to some minor scratching of the tablet front surface. Such scratches could be the reason for irregular grating of the tablet over a certain number of doses. In this respect, the recommendation in the instructions for use to clean the mouthpiece with a dry cloth after each inhalation, is rather arguable. This may lead to physical contact with the top of the discharge channel which, initially, is only 0.8 mm below the rounded top of the mouthpiece cylinder. Pressure on this channel inevitably leads to some damage of the front surface of the ring tablet. Not only is this top of the discharge channel easily accessible. It is also the place where most powder accumulates during inhalation and thus, a part of the mouthpiece likely to be wiped. It must also be expected that damage of the front surface of the tablet repeatedly occurs during its lifetime even without making physical contact (otherwise than during intentional use with the milling

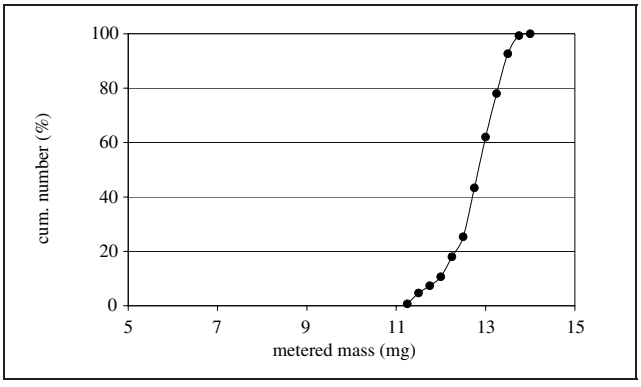

Fig. 5: Cumulative number percent distribution of 150 metered masses from the Novolizer with Novopulmon cartridge (devices from Batches 1 and 2): see text

Table 4: Mean metered mass and delivered dose (n = 10) for two Jethalers derived from the same batch (first 100 doses from device 1, and doses 100–170 from device 2)

Jethaler, device 1 (Batch 2)			Jethaler, device 2 (Batch 2)		
Doses	Metered mass (mg)	Delivered dose (μg)	Doses	Metered mass (mg)	Delivered dose (μg)
1–10	3.486	265.10	101–110	3.033	221.00
11–20	3.209	245.29	111–120	2.638	195.72
21–30	3.379	269.52	121–130	3.800	275.89
31–40	2.886	221.61	131–140	3.517	260.02
41–50	3.020	242.87	141–150	3.412	271.68
51–60	2.682	201.97	151–160	3.181	246.82
61–70	2.862	223.06	161–170	3.151	254.12
71–80	2.550	187.45			
81–90	2.861	213.93			
91–100	2.483	183.44			
Mean	2.942	225.42		3.247	246.46
RSD	11.40	13.33		11.50	11.67

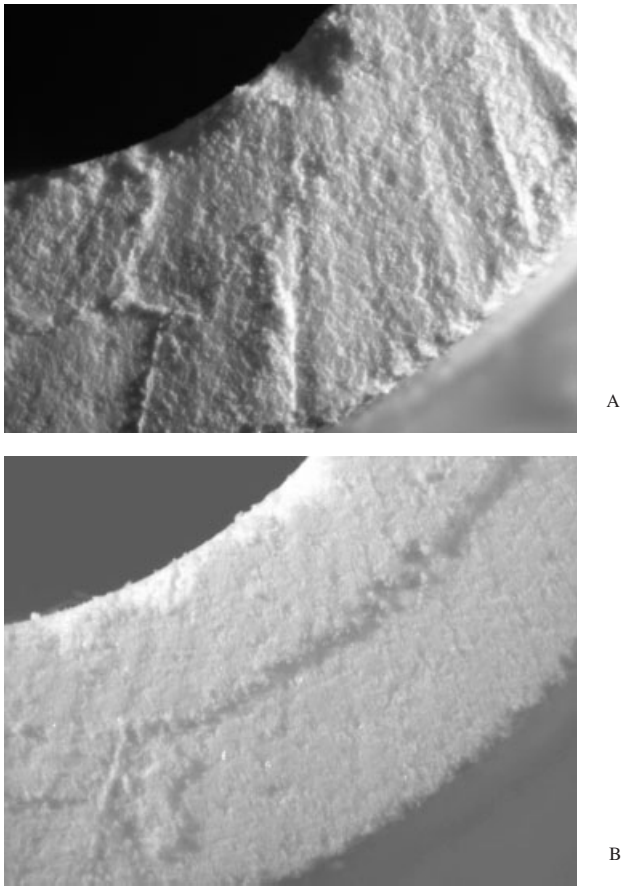

Fig. 6: Micrographs of the front surface of drug-lactose ring tablets for two different Jethalers (from different batches) after release of different numbers of doses

disk). A strong indication for this is obtained from the RSD in delivered dose (Table 3), which is even higher for the doses 71–100 and 171–200 than for the first doses (1–30) after placement of the mouthpiece. Also the observed variation in air flow resistance between released doses (paragraph 2.2) supports this expectation. The cross section for air flow between the front surface of the tablet and the milling disk is quite scanty. Therefore, a minor irregularity already has a strong effect on the inhaler resistance. Figs. 6A and B show tablet front surfaces after different numbers of doses were taken. Both photographs do not reveal small local scratches (as from assembling of the mouthpiece and inhaler body), but much larger damages along the inner circumference (6A) and the results of irregular grating (6A and B). The different levels in the front surface of the tablet in Fig. 6B are from scraping at different depths by the cutting ridges on the milling disk. This could be the result of imperfect plane parallel alignment between the tablet and milling disk. Both photographs show tablet conditions that have also been observed for other devices (from both batches) after different numbers of doses taken.

Figs. 7A and B give an impression of the size (distribution) of released particles from the Jethaler, showing an isolated fragment of more than 700 μm. Such large fragments are unwanted, because they are deposited in the throat where the drug inside the fragment contributes to adverse local side effects instead of contributing to the desired therapy. Laser diffraction analysis of the aerosol cloud from the Jethaler at 4 kPa revealed that release of such large fragments is not an incident and confirmed that the size of such fragments may exceed even 1000 μm. It was furthermore observed that the number of inhalations with extremely large particles decreases with increasing pressure drop across the DPI (from 1 to 4 kPa). This suggests that some tablet shavings with sufficient kinetic energy at least partially de-agglomerate into smaller particles by collisions inside the discharge channel, which could explain why the fine particle fraction from the Jethaler increases with increasing flow rate. This observation makes the instructions for use of the Jethaler in respect of recommending 'slow and constant inhalation' rather arguable.

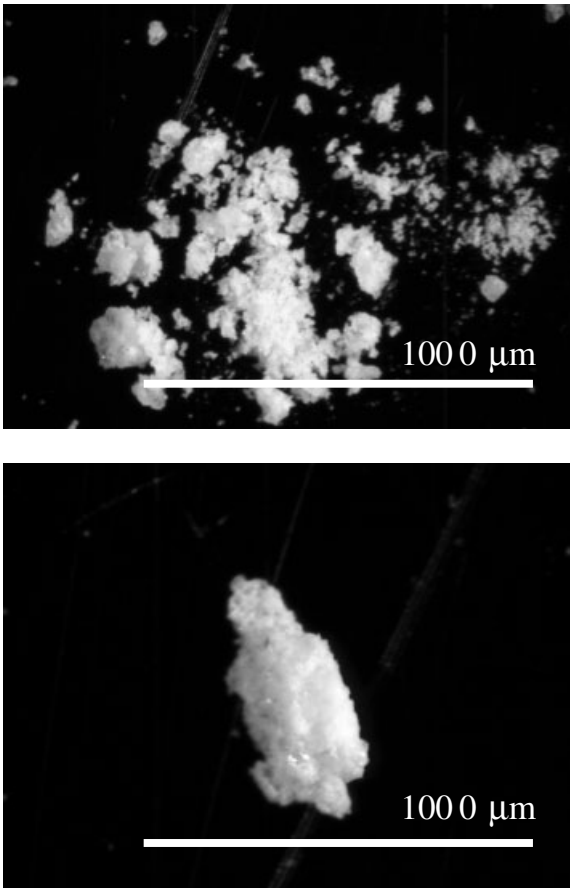

Fig. 7: Micrographs of shavings from the Jethaler drug-lactose tablet showing the size distribution of the released particles (A). The isolated large tablet fragment on Fig. 7B is from the outer circumference of the ring tablet

The possible damages of the front surface of the tablet make it likely that the span of the range of higher (than average) metered masses from the Jethaler is much wider than that from the Novolizer. Particles of 1000 μm (or more) in the aerosol cloud from the Jethaler, contribute approximately 20% to a single dose. In contrast with the Novolizer, there is no theoretical upper limit for the metered mass from the Jethaler, unless tablet weight is considered as such. In order to get an impression of the metered mass from the Jethaler, the weight loss of a ring tablet was measured after (and averaged for) every ten doses taken from the device (mouthpiece removed and replaced after weighing). This may have resulted in some scratching of the tablet front surface after every tenth dose. The results are summarised in Table 4, suggesting that repeated (dis)mounting of the mouthpiece does not have a dramatic effect. At least, the average delivered dose (for all 170 doses in Table 4) is 234.09 μg, with an RSD of 13.04% (for the 17 mean values), which is not really different from the RSD-values (without metered mass determination) in Table 3. This suggests that the effect of scratches created during (dis)mounting of the mouthpiece is negligible compared to that of the severe tablet damages occurring during use (Figs. 6A and B). As expected, the ratio of highest (mean of 10) to average (overall) metered mass from the Jethaler in Table 4 is 1.24, versus 1.08 for the Novolizer (Fig. 5). This may explain why during other experiments with the Jethaler (e.g. the duplicate cascade impactor experiments at 4 kPa) occasionally delivered doses of 300 μg or more were found.

2.5. Fine particle fractions

Figs. 8A (for the Novolizer) and 8B (Jethaler) show the fine particle fractions as percent of the label claim at four different pressure drops across the inhalers for devices derived from the same batches (Batch 1). Control measurements were performed only at 4 kPa (marked with an asterisk) with devices from the other batches (Batch 2). Bars on top indicate the spread (in FPF < 5.1 μm) between the duplicate measurements with the same device at the same pressure drop. The results show an increasing FPF with increasing kPa for both devices. At all flow rates FPF is highest for the Novolizer. The results seem to confirm that 2 kPa is more or less the threshold value for successful use of such types of DPIs. This is the reason, why the previously explained valve switch point of the Novolizer has been set between 1.5 and 2 kPa. Above 4 kPa, the increase in FPF tones down. For the Novolizer, already 72% of the 'maximal' FPF < 5.1 μm (equals 54.3% of label claim at 8 kPa) is obtained at 4 kPa. For the Jethaler, this is 62% (of 44.2% at 8 kPa). An increase in FPF may compensate for more substantial losses in the upper tract at higher inspiratory flow rates, so as to obtain a constant central and peripheral lung deposition.

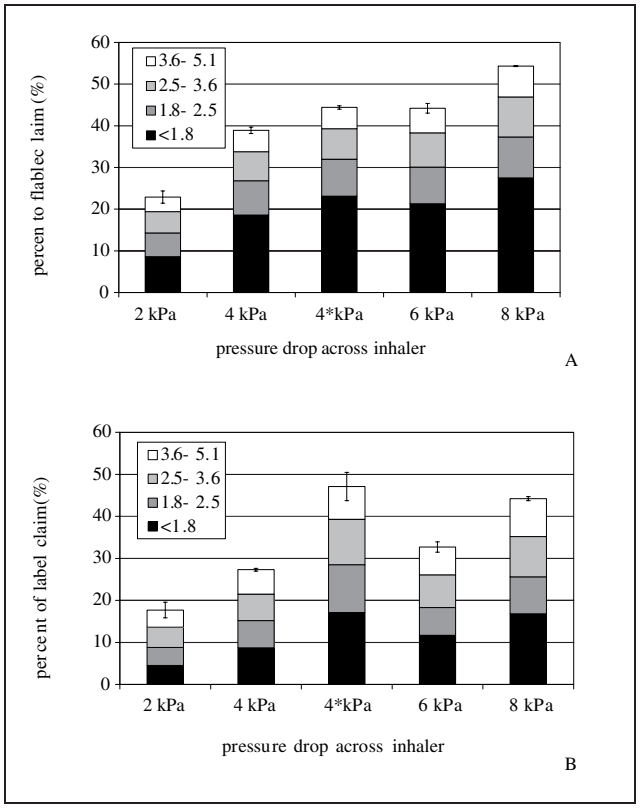

Fig. 8: A. Fine particle fractions as percent of the label claim for the Novolizer with 100 dose Novopulmon container (Batch 1) at four different pressure drops across the inhaler
B. Fine particle fractions as percent of the label claim for the Jethaler (Batch 1) at four different pressure drops across the inhaler
Each value given in the Figs. A and B is the mean of two series of ten inhalations each. Bars at 4 kPa with an asterisk represent inhalers from Batches 2. Bars on top indicate the spread (in FPF < 5.1 μm) between the duplicate measurements with the same device at the same pressure drop

There is a great difference between the Novolizer and Jethaler in the drug distribution over the subclasses within the range up to 5.1 μm. For the Novolizer, on average 49% of FPF (for particles < 5.1 μm) is within the size range up to < 1.8 μm between 4 and 8 kPa. For the Jethaler, this is only 35%, suggesting that the Novolizer aerosol has greater potential for deep lung penetration and deposition, as can be derived from deposition modelling in the human respiratory tract (e.g. Gerrity 1990; Clark and Egan 1994). The difference in FPF < 5.1 μm at 8 kPa between both devices is reflected by the difference in total lung deposition at maximal inspiratory effort for budesonide (35.7% for Novolizer) and salbutamol (26.4% for Jethaler), as reported by Newman et al. (2002). The ratios of percent lung deposition to % FPF are 0.66 for the Novolizer and 0.60 for the Jethaler respectively. The duplicate experiments at 4 kPa with devices from Batch 2, suggest a great variation in FPF for the Jethaler. The reason is the variation in the delivered dose for this type of DPI (as discussed in paragraph 3.4) which for the duplicate measurements was rather extreme (on average 280.1 μg, equals 140% of label claim). When a correction is made for the overdosing, the fraction of particles < 5.1 micron is 33.2% (instead of 47.1% in Fig. 8), which yields a much better duplicate value.
The increasing fine particle fraction with increasing pressure drop across the DPI has already been discussed for the Jethaler in paragraph 2.4. Partial de-agglomeration of released large clusters by particle-particle collisions inside the discharge cylinder is most likely to occur and an increase in air (and particle) velocity increases the particle momentum during collision. The working principle of the fine particle disperser (air classifier) in the Novolizer has been discussed previously (de Boer et al. 2003). In this study, it has been shown that the ratio of removal forces to adhesive forces (applied to drug particles on carrier crystals in adhesive mixtures during inhalation) increases with increasing flow rate through the classifier.
In conclusion, there are relevant differences between the Novolizer and Jethaler referring to design, handling and performance. Overdosing from the Novolizer is highly unlikely, whereas use of the inhaler by patients that are unable to generate sufficient flow rate through a DPI (1.5 to 2 kPa) is excluded. In contrast with the Novolizer, the Jethaler performs independently of how the device is held during dose activation, but it requires good coordination between dose release and inhalation. The difference between the devices is most pronounced for the consistency of delivered dose, which is clearly better for the Novolizer. Moreover, fine particle fractions, at all flow rates, are higher for the Novolizer too, particularly the fraction < 1.8 μm that has the potential of deep lung penetration and deposition.

3. Experimental

3.1. Flow rate versus pressure drop calibration

Pressure drops (kPa) across the inhaler were recorded at nine different flow rates (Φ) between 0 and 90 l_N/min for five different Novolizers and Jethalers, freshly taken from two different batches. Each experiment with a particular device existed of three to four duplicate series. Air flow resistances (R) were calculated at all flow rates from the mean of the corresponding kPa-values, according to the simplified equation $R = kPa^{0.5} \cdot \Phi^{-1}$ for an orifice type of air flow resistance. Pressure drops were measured with a differential pressure gauge HBM, type PD1 with Messkonverter MC2A (HBM, Darmstadt, Germany) and corresponding flow rates (in l_N/min, at 2730 K and 1013 mbar) were read from a thermal mass flow meter Brooks, type 5863S with readout panel type 0154 (Brooks, Veenendaal, The Netherlands).

3.2. Content uniformity testing

Content uniformity was measured in 30 samples taken randomly (with a spatula) from the formulation in the Novopulmon multi dose powder cartridge of the Novolizer and (with a scalpel) from the front surface of the ring tablet in the Jethaler (after preliminary investigations revealed that the variation in drug content throughout the whole tablet is not greater than that at the front surface). For each type of DPI, two copies derived from two different batches were investigated. The size (weight) of the samples was chosen to be of the same order of magnitude as the metered masses given by the suppliers: 2.2 mg for the Jethaler and 10.9 mg for the Novolizer. The samples (weighed on a five decimal analytical balance, Mettler AT261, Greifensee, Switzerland) were allowed to dissolve in approximately 15 ml 100% ethanol of analytical grade for at least one hour. Next, non dissolved lactose particles were removed with a Rotana 3500 centrifuge at 3 000 rpm during 5 min rotation (Hettich, Tuttlingen, Germany) and the clarified solutions were measured at a wavelength of 243 nm with a Unicam UV500 spectrophotometer (Unicam, Cambridge, UK).

3.3. Determination of fine particle fraction

A four stage liquid impinger, described as apparatus C in the Eur. Pharmacopoeia, 3rd edition, 1977 (Erweka, Heusenstamm, Germany) was used for assessment of fine particle fractions from the Novolizer and Jethaler at 2, 4, 6 and 8 kPa (3 s inhalation time). Pressure drops across the Novolizer were adjusted with an empty classifier, using the same dP-meter as described in paragraph 3.1, since it is known that the presence of powder in this classifier reduces the inhaler resistance. Ethanol of analytical grade was used as solvent for the fractions deposited on the impactor stages. The solutions were treated before measurement of the drug concentrations according to the procedures described in paragraph 3.2. At all pressure drops, two duplicate experiments of 10 inhalations each were performed. Cumulative stage mass fractions (SMFs, as percent of label claim) were plotted as function the experimental cut-off diameters (ECDs) presented by Asking and Olsson (1997) for the stages 1 to 4. Flow rates in l_N/min corresponding with the adjusted pressure drops (from Φ– dP calibration; para-

graph 3.1) were first recalculated into l_A/min (at room temperature) and next into l_S/min (at system pressure) through the impactor, taking account of the pressure drops across the inhaler. From the SMF-ECD plots, cumulative fine particle (mass) fractions (FPFs) in the subclasses < 1.8; 1.8–2.5; 2.5–3.6 and 3.6–5.1 μm were derived by graphic intrapolation and presented in the Figs. 8A and B.

3.4. Measurement of delivered dose and metered mass

A special single dose collector was used for the assessment of delivered doses at 4 kPa. The collector is a multi-jet impinger with sustained centrifugal action, having a high collection efficiency. The impinger was filled with 10 ml ethanol of analytical grade and connected to the same vacuum system with flow controller and solenoid valve (with timer set to 3 s) as used for the cascade impactor analyses. Delivered doses (not more than 10 per day, in order to avoid tribocharge and stressing of the Jethaler tablet) were collected individually and allowed to dissolve in the ethanol for at least one hour, before the solutions were clarified with a centrifuge and measured spectroscopically at 243 nm (see par. 3.2 for details). After each inhalation, the Novopulmon cartridge was weighed on an analytical balance (Mettler AT261, Greifensee, Switzerland) to assess corresponding metered mass. Only for values in Table 4, the mouthpiece of the Jethaler (containing the drug-lactose tablet) was weighed similarly to obtain the mean weight of ten successive doses.

3.5. Microscopy

A Nikon SMZ-U Zoom (1 : 10) light microscope (Nikon, Japan) was applied to inspect the front surface of the drug-lactose compact after removal of the mouthpiece cylinder from the Jethaler. The micrographs in Figs. 3A, 6 and 7 were also prepared with this microscope in combination with a Nikon Digital Net Camera DN100. For the scanning electron micrographs of the front surface of the Jethaler tablet (Fig. 3B), a JSM 6301-F microscope (Jeol, Japan) was used. For the SEM micrograph, the tablet was carefully removed from the discharge channel and glued in upright position on an aluminium specimen holder with two component epoxy resin, having a conductive top layer of black carbon. The tablet was coated with 150 nm of gold/palladium in a 120 B sputtering device (Balzers UNION, Liechtenstein) before the micrographs were taken at an acceleration voltage of 1.5 kV.

3.6. Laser diffraction analysis

A Sympatec HELOS BF/Magic laser diffraction apparatus, in combination with an INHALER 2000 special adapter (both Sympatec, Goslar, Germany), was applied to measure the size distribution of drug and lactose particles in the aerosol cloud from the Jethaler at 1 to 4 kPa. All experiments were performed with an R5-lens (focal length 500 mm for size range 4.5 to 875 μm) to measure specifically the larger particles in the shavings from the ring tablet. At each pressure drop across the inhaler, ten successive inhalations were performed with sufficient interval time to prevent stressing of the tablet (see paragraph 2.4).

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