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International Journal of Pharmaceutics 310 (2006) 81–89
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

Air classifier technology (ACT) in dry powder inhalation Part 4. Performance of air classifier technology in the Novolizer® multi-dose dry powder inhaler

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Received 13 December 2004; received in revised form 2 November 2005; accepted 7 November 2005
Available online 25 January 2006

Abstract

In this study, the in vitro fine particle deposition from a multi dose dry powder inhaler (Novolizer®) with air classifier technology has been investigated. It is shown that different target values for the fine particle fraction (fpf < 5 μm) of the same drug can be achieved in a well-controlled way. This is particularly relevant to the application of generic formulations in the inhaler. The well-controlled and predictable fpf is achieved through dispersion of different types of formulations in exactly the same classifier concept. On the other hand, it is shown that air classifier-based inhalers are less sensitive to the carrier surface and bulk properties than competitive inhalers like the Diskus®. For 10 randomly selected lactose carriers for inhalation from four different suppliers, the budesonide fpf (at 4 kPa) from the Novolizer® varied between 30 and 46% (of the measured dose; R.S.D. = 14.2%), whereas the extremes in fpf from the Diskus® dpi were 7 and 44% (R.S.D. = 56.2%) for the same formulations. The fpf from a classifier-based inhaler appears to be less dependent of the amount of lactose (carrier) fines (<15 μm) in the mixture too. Classifier-based inhalers perform best with coarse carriers that have relatively wide size distributions (e.g. 50–350 μm) and surface discontinuities inside which drug particles can find shelter from press-on forces during mixing. Coarse carrier fractions have good flow properties, which increases the dose measuring accuracy and reproducibility. The fpf from the Novolizer® increases with increasing pressure drop across the device. On theoretical grounds, it can be argued that this yields a more reproducible therapy, because it compensates for a shift in deposition to larger airways when the flow rate is increased. Support for this reasoning based on lung deposition modelling studies has been found in a scintigraphic study with the Novolizer®. Finally, it is shown that this inhaler produces a finer aerosol than competitor devices, within the fpf < 5 μm, subfractions of particles (e.g. <1, 1–2, 2–3, 3–4 and 4–5 μm) are higher.

Keywords: Air classifier technology; Dry powder inhalation; Carrier lactose; Fine particle fraction; Novolizer®; Adhesive mixtures

1. Introduction

A dry powder inhaler consists of a number of functional parts, of which the powder formulation, the dose (measuring) system and the powder de-agglomeration principle are the most basic ones. Through the years it has become clear that none of these functional parts can be optimised without taking account of the performance of the others. The factors that determine the magnitude and consistency of the fine particle fraction (fpf) from powder inhalers are complex and interact with each other (Frijlink and de Boer, 2004). These interactions include for instance the relationship between the carrier size and carrier surface properties, or the effect of carrier size (distribution) on the dose accuracy and the interparticulate forces in the mixture. Many of the requirements for carrier properties are contradictory or dissimilar for different devices. Fine carrier fractions, or the addition of certain fractions of fine lactose particles to coarser carriers, have been shown to increase the fine particle fractions from most marketed inhalers (e.g. Steckel and Müller, 1997; Zeng et al., 1998, 2001; Louey and Stewart, 2002). Also to enhance powder discharge from capsule inhalers finer carrier

DOI of original article:10.1016/j.ijpharm.2005.11.030.
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doi:10.1016/j.ijpharm.2005.11.029

fractions may be preferred (Bell et al., 1971), since powders with a median diameter of more than 100 μm may not be entrained by the air stream effectively (Steckel et al., 2004). In contrast, volumetric dose measuring systems, making use of the force of gravity, like for instance in the Pulvinal® (Meakin et al., 1998) and the Clickhaler® (Thibert et al., 2002), may perform better when large carrier particles or narrower size fractions are used. However, too large diameters have to be avoided as they exhibit high carrier surface rugosities. This reduces the drug particle detachment during inhalation (e.g. Kawashima et al., 1998), unless inertial separation forces are generated by the inhaler during inhalation. For such inhalers, high rugosities may even be beneficial, particularly at moderate to high carrier payload, because they may keep the adhesive forces in the mixture low (Dickhoff et al., 2003). As a result of these complications and conflicting demands, it is very difficult to obtain the best possible performance of a dpi regarding both fpf and dose consistency. It would be helpful to the formulation scientists if the freedom of choice for the carrier properties could be increased, e.g. by making the fine particle dose less dependent on the carrier properties.

In a previous study, the design and development of the Novolizer® air classifier technology as a de-agglomeration principle has been presented (de Boer et al., 2006). The aim of this study was to investigate the performance of these classifiers on different types of powder mixtures for inhalation. It will be explained how the fine particle fraction from the same classifier concept can be controlled to match a wide range of fpf-target values by choice of the type of formulation and/or by controlling the adhesive forces in the powder mixture, without using specially engineered particles or adding special agents to reduce the interparticulate forces in the mixture. Because drug redispersion in a classifier is less dependent on carrier surface properties than that in turbulent shear inhalers, carrier bulk properties can be selected rather freely. This enables the utilization of inertial and frictional press-on forces during the mixing process to actually control the magnitude of the adhesive forces (and by that, the fpf), which is desired for the development of generic formulations in the inhaler. It will be shown that a certain robustness with respect to carrier surface properties makes the fpf from an air classifier less dependent of the type of marketed lactose carrier used for mixture preparation than turbulent shear inhalers. This increases the freedom of choice for the carrier in respect of flow properties and dose consistency. Finally, an aim of this study is to discuss the preferable output from a dpi. It is postulated, supported by lung deposition modelling data and the results from a scintigraphic study, that an increasing fpf with increasing flow rate may yield a more constant therapy than a constant fpf at all flow rates.

2. Materials and methods

2.1. Materials

Alpha lactose monohydrate carrier fractions 90–106 and 250–315 μm were obtained by 20 min vibratory sieving (Analysette 3, Fritsch, Germany) followed by 20 min air jet sieving (A200, Alpine, Germany), using Pharmatose 100M and 80M as starting material, respectively (DMV International, The Netherlands). Micronised lactose 1–8 μm (X_{50} = 3.4 μm) for the preparation of soft spherical agglomerates was also supplied by DMV International. Micronised salbutamol sulfate with an X_{50} of 1.4 μm (X_{10} = 0.7 μm; X_{90} = 3.4 μm) was donated by RIVM (The Netherlands). Micronised budesonide (X_{10} = 0.7 μm; X_{50} = 1.3 μm; X_{90} = 3.0 μm) was supplied by Sofotec (Germany). Mixtures of 2% budesonide with 10 different marketed carrier lactose products (Figs. 3 and 4) were prepared in a tumbling mixer (Turbula 2TC, WA Bachofen, Switzerland) at 90 rpm (10 min) in a 160 ml stainless steel mixing container. Mixtures of 10% budesonide or 10% salbutamol sulfate with three different carrier types (DMV Pharmatose 90M, Meggle Inhalac 70 and Meggle Capsulac 60), used for the experiments in Fig. 2, were manufactured by Sofotec (Germany). Sofotec also prepared the mixtures of budesonide (2%), salbutamol sulfate (1%) and formoterol fumarate (0.1%) with Capsulac 60 (Figs. 5 and 6). Novopulmon® 200 Novolizers® (with budesonide) were purchased from Viatris (Germany), and Pulmicort® 200 Turbuhaler® (AstraZeneca, UK), Flixotide® 250 and Serevent® 50 Diskus® (GSK, UK) and Cyclohaler® with budesonide 200 Cyclocaps® (PCH Pharmachemie, The Netherlands) were obtained from a local pharmacy. For the experiments of which the data are presented in the Figs. 3 and 4, an especially prepared Diskus® was used which enabled us to test different adhesive mixtures in this device (after it was checked that the performance of the proprietary formulation was not influenced by the modifications made to the inhaler).

2.2. Methods

The size distributions of drugs (with a 100 mm lens) and lactose carrier products and special carrier size fractions (with 200 and 500 mm lenses) were measured with laser diffraction technique (HELOS BF MAGIC, Sympatec, Germany) using standard Windox software. A RODOS dry powder disperser was used to disperse the powders into the laser beam at 5 bar, except for DMV Pharmatose GR001 and Meggle Capsulac 60 which were dispersed at 3 bar to prevent attrition. All calculations were made with the Fraunhofer theory.

Soft spherical agglomerates of salbutamol (0.9, 1.8, 3.6 and 7.5%, w/w) with micronised lactose 1–8 μm were prepared by densifying and agglomerating the micronised drug in a stainless steel mixing container (160 ml), using a tumbling mixer (Turbula T2C, WA Bachofen AG, Switzerland) at 90 rpm for 10 min. A small amount of stainless steel beads with a well-defined size distribution was added as pelletising aid. Next, beads and salbutamol pellets were separated over a 315 μm sieve (by mild hand sieving) and the drug agglomerates were spheronised on a 200 μm vibratory sieve (Fritsch Analysette 3, Fritsch GmbH, Germany) for 20 min. Finally, pellets larger than 800 μm were removed (again by mild hand sieving), and the pellet fraction 315–800 μm was used for experiments.

Adhesive mixtures of micronised salbutamol sulfate (0.45, 0.9, 1.8 and 3.6% w/w) with lactose carrier size fractions 90–106 and 250–315 μm were prepared in the same stainless

steel mixing container (without beads), using the same tumbling mixer (10 min at 90 rpm) as applied for the preparation of the soft spherical agglomerates.

The salbutamol contents in the mixtures and soft spherical agglomerates were determined on 20 samples of approximately 25 mg each. The samples were dissolved in demineralised water and the solutions were analysed with a Philips spectrophotometer (PU 8720 UV–VIS, The Netherlands) at a wavelength of 276.5 nm.

Two different cascade impators were used for the different studies presented in this paper. For the experiments in the Figs. 1 and 6, a 4-stage glass constructed impactor was applied as described by Hallworth and Andrews (1976). The experiments for Figs. 2–4, 7 and 8 were conducted with an Erweka multistage liquid impinger. For all figures, the fine particle fractions <5 μm, and the subfractions therein, were calculated from the stages 2 to 4 (plus filter) depositions. Only for the Figs. 3 and 4 (data derived from DMV International) fpf is defined as the sum of the stage 3+ 4+ filter depositions (fpf < 5.9 μm for both devices). Analyses were performed at preset flow rates (Figs. 1 and 2) or at preset pressure drops across the inhaler (Figs. 3, 4, 6 and 8). All data presented are the mean of two series of 10 doses each. Solvents used on the impactor stages were ethanol (analytical grade) for budesonide and formoterol, and demineralised water for salbutamol sulfate. Drug solutions were separated from non-dissolved lactose carrier particles in a centrifuge (Rotana 3500, Hettich, Germany) during 5 min at 3000 rpm. Budesonide and salbutamol concentrations were measured with a spectrophotometer (Philips PU 8720 UV–VIS, The Netherlands) at 242.8 and 276.5 nm, respectively. Formoterol concentrations (Fig. 6) were measured with a HPLC (Waters 510, USA), using a Waters 484 detector at a wavelength of 286 nm.

The procedures for residence time measurement (Figs. 5 and 6) have been described in detail before (de Boer et al., 2006).

3. Results and discussion

3.1. Controlling fpf with air classifier technology

One of the objectives for design and development of air classifier technology was to obtain a versatile powder deagglomeration principle that enables both adjustment of the fine particle output to that of a proprietory dpi in case of generic formulations and maximisation of the fpf in case of formulations for new chemical entities. A great challenge has been found in achieving these goals with the same classifier concept (de Boer et al., 2006). Success depends on understanding of the mechanisms of particle separation and powder circulation in an air classifier, and also on knowledge of the particle interaction forces in the different inhalation powders. When exactly the same classifier design is used, different target values for fpf can only be achieved by controlling the particle interaction forces in the powder and the residence time in the classifier. Fig. 1 shows a typical example for salbutamol formulations. The objective was to develop three different formulations which delivered 13.75, 27.5 and 55% fine particle fraction (as percent of the real dose) at 60 l_N/min, for different dose weights, ranging from 50 to 400 μg of salbutamol (as sulfate). Fig. 1 shows that even when the same multifunctional classifier design (from the Novolizer®) is used, the target values can adequately be achieved.

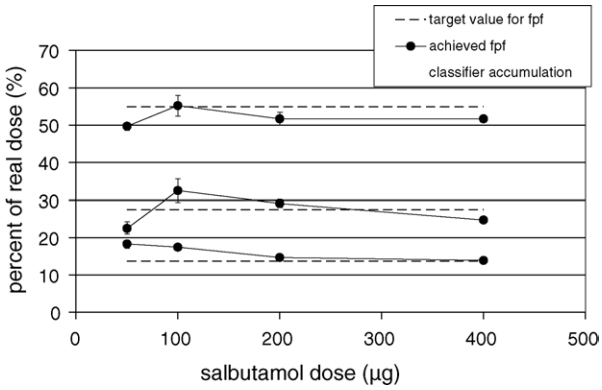

Fig. 1. Figure showing three different target values for fpf < 5 μm at 60 l_N/min (13.75, 27.5 and 55% of the real dose, respectively) and fpf-values actually achieved with different salbutamol formulations using the marketed Novolizer® (closed symbols). All data points are the mean of two series of 10 inhalations; spread bars indicate the maximal and minimal values.

For the highest fpf-values in Fig. 1, soft spherical agglomerates of mixtures of micronised salbutamol and lactose (fraction 1–8 μm) were used. The agglomerates were densified to control the agglomerate strength and to match the control value for fpf. The drug contents in the agglomerates were adjusted to the desired drug dose and the mass metered by the slide connected to the powder reservoir of the Novolizer. They increased from 0.86% for the 50 μg dose to 1.70% (100 μg), 4.05% (200 μg) and 8.10% (400 μg), yielding mean salbutamol doses of 45.4 μg (at a mean metered mass of 6.38 mg), 120.7 μg (7.11 mg), 205.43 μg (6.09 mg) and 415.6 μg (6.16 mg), respectively. The differences in metered mass were the result of different size distributions for the pellets within the sieve fraction 315–800 μm. Only agglomerates with less than 5% variation coefficient in content were used. When the powder was densified to a lesser extent, fine particle fractions up to 80% appeared to be possible with the same classifier (at the same flow rate), not only for salbutamol sulfate but also for a more hygroscopic product like disodium cromoglycate. To achieve the other target values for the fpf, adhesive mixtures were prepared with different carrier size fractions (90–106 μm for the intermediate fpf-value and 250–315 μm for the lowest fpf-value), having different bulk properties and also different degrees of surface rugosity. In this way, the size and effectiveness of the press-on forces during the mixing process, and therefore, the interparticulate forces in the mixture could be controlled (de Boer et al., 2005; Dickhoff et al., 2003, 2004). For all types of formulations and at all drug concentrations, the drug accumulations in the classifier were less than 5%.

3.2. Classifier robustness with respect to carrier type

In the previous chapter it has been explained that different values for the fpf of the same drug from the same classifier (at the same flow rate) can be obtained by using different types of

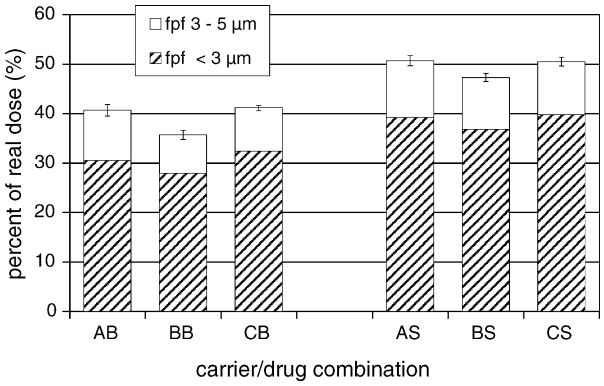

Fig. 2. Fine particle fractions <3 and <5 μm from the marketed Novolizer® for three different coarse carrier types with 10% (w/w) budesonide or salbutamol, at 65 l_N/min (3.33 kPa). Mean of two series of 10 inhalations each; spread bars indicate the difference between both series. In the letter combinations on the ordinate, the first letter A is for Pharmatose 90M; B is for Inhalac 70 and C is for Capsulac 60. The second letter refers to the drug in the mixtures: budesonide (B) or salbutamol sulfate (S).

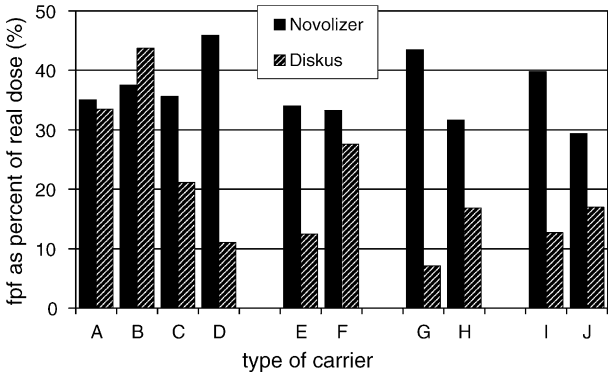

Fig. 3. Fine particle fractions (<5.9 μm, being the stage 3+ 4+ filter depositions in the MSLI) at 4 kPa from the marketed Novolizer® and Diskus® dry powder inhalers for 2% budesonide mixtures with different brands of inhalation lactose: Respitose SV007 (A), Respitose ML001 (B), Respitose ML001A (C), Respitose GR001 (D) all from DMV International; Lactohale 100 (E), Lactohale 200 (F) from Borculo; Inhalac 70 (G), Inhalac 230 (H) from Meggle; MM250 (I) and MM50 (J) from Epikure. Mean of two series of 10 inhalations each.

powder formulations. In this chapter, it will be shown that the performance of the Novolizer® in respect of powder dispersion appears to be relatively insensitive to the type of carrier lactose used in adhesive mixtures when for instance compared to the Diskus® dry powder inhaler. This seems in disagreement with what can be found in literature about the effect of carrier properties on the fine particle dose. It has been described that the addition of fine particles to drug carriers increases the fine particle dose from inhalers (e.g. Arnold et al., 1995). For the explanation, many different proposals have been made (e.g. Zeng et al., 1998; Podczeck, 1999; Louey and Stewart, 2002). It has also been recognised that there is a limit to the amount of fines in carrier fractions because of deteriorating flow properties, which affect the dose reproducibility in a negative way (Zeng et al., 2001). Therefore, optimisation of inhalation powders is finding the right balance between consistency of delivered dose and the fine particle dose.

Fig. 2 shows that when three different brands of coarse carrier lactose are used, the fpf from the Novolizer® for salbutamol and budesonide mixtures varies less than 2.5% of the mean value (39.2% for budesonide and 49.5% for salbutamol). Even when completely different lactose carrier types are used, the fpf-values obtained with the air classifier based inhaler vary only between 30 and 46% of the real dose (mean is 37% in Fig. 3). In contrast, the fpf from the Diskus® for the same formulations (at the same flow rate) varies between 7 and 44% (mean is only 20% in Fig. 3). The lactose types used for the experiments in Fig. 3 vary particularly in the amount of fines (<15 μm), the median particle diameter and the span of the size distribution (Table 1). The carrier types used in Fig. 2 contain practically no fines (<15 μm), and have about the same median diameter and span of the size distribution. They differ particularly in the surface rugosity. From scanning electron microscopic investigation it is known that Pharmatose 90M and Inhalac 70 are coarse crystalline materials with many surface discontinuities, whereas Capsulac 60 (though presented by the manufacturer as a crystalline brand of lactose) has a granular appearance with many deep surface depressions. Such depressions provide shelter to adhering drug particles from press-on forces during mixing, which helps keeping the adhesive forces in the mixture low (Dickhoff et al., 2003).

The difference in behaviour between the Novolizer® and Diskus® inhaler can be explained with the difference in their de-agglomeration principles in relation with the carrier properties. In the Novolizer® air classifier, inertial separation forces are generated during inhalation, as described previously (de Boer et al., 2006). In contrast, the Diskus® utilises turbulent shear for powder dispersion. Although differences in fpf for different formulations from the same inhaler cannot be explained satisfactorily with single parameters, Fig. 4 shows that fpf relates differently to the span of the carrier size distribution (4A), the median carrier diameter (4B) and the percent of fines in the carrier (4C) for both inhalers. This is for the same formulations as used in Fig. 3. The calculated (linear) trend line in Fig. 4A

Table 1
X_{10}, X_{50} and X_{90}-values from cumulative volume distribution curves as function of the diameter for the carriers in the formulations used to prepare Figs. 2–4

Carrier type	X_{10} (μm)	X_{50} (μm)	X_{90} (μm)	Fraction of particles <15 μm
Pharmatose 90 M	59.5	162.3	263.9	0.4
Inhalac 70	100.1	170.5	235.4	0.2
Capsulac 60	74.3	163.6	285.8	0.2
Respitose SV007	4.9	75.3	149.9	18.3
Respitose ML001	3.3	43.0	135.5	26.9
Respitose ML001A	55.2	113.3	220.5	1.0
Respitose GR001[a]	81.6	200.5	319.2	3.1
Lactohale 100	40.1	111.4	191.8	4.4
Lactohale 200	7.3	71.8	139.5	14.1
Inhalac 230	55.7	99.3	144.8	2.5
MM250	118.4	223.3	369.8	1.1
MM50	12.7	52.9	118.6	12.2

Data obtained from laser diffraction analysis; RODOS dispersion at 5 bar, except for the coalescent and granular products (Capsulac 60 and Respitose GR001) that were measured at 3 bar. All values are the mean of three analyses.

[a] Product in development by DMV International, The Netherlands.

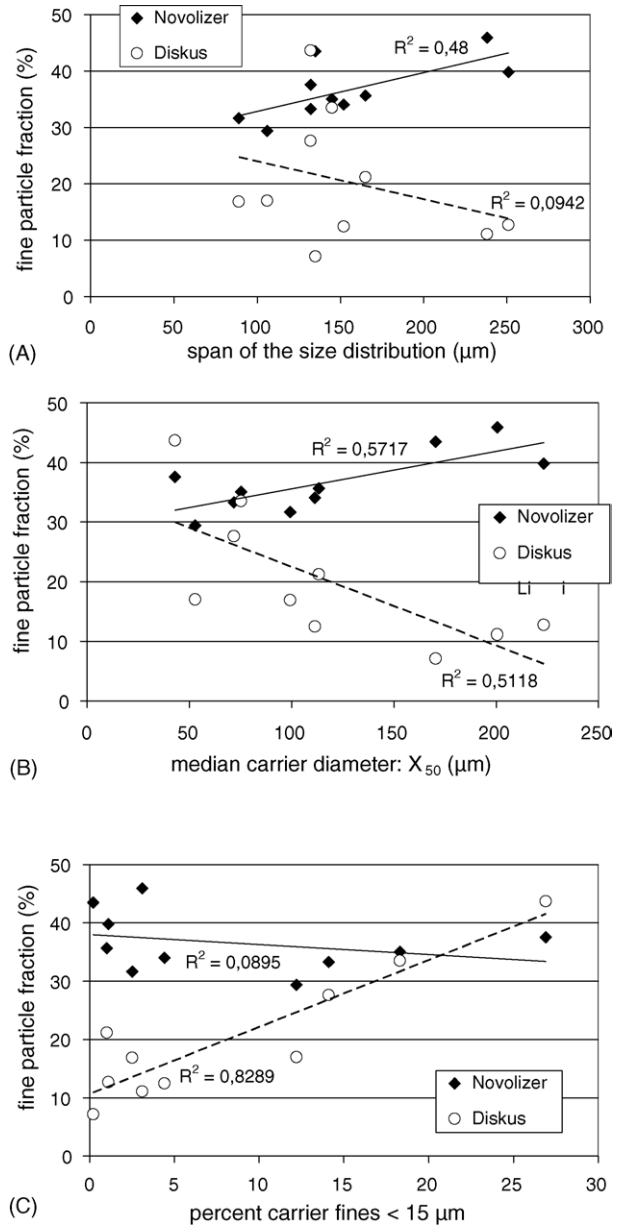

Fig. 4. Fine particle fractions <5.9 μm (stage 3+ 4+ filter depositions in the MSLI at 4 kPa) for 2% budesonide formulations from the Novolizer® and Diskus® as function of: (A) the span of the size distribution of the carriers used in the formulations, (B) the median diameter (from laser diffraction analysis) of the carriers and (C) the volume percent of carrier particles <15 μm. The carriers are the same as in Fig. 3.

suggest that the fpf from the Novolizer® (slightly) increases with increasing span of the carrier size distribution ($r = 0.69$). For the Diskus® the relationship between these two parameters is less clear ($r = -0.31$) but the calculated trend is opposite to that found for the Novolizer®. Using coarse carriers has a negative effect on the fpf from the Diskus® (Fig. 4B; $r = -0.72$), whereas fpf from the Novolizer® slightly increases with increasing median carrier diameter ($r = 0.76$). Finally, Fig. 4C indicates that fpf from the Novolizer® does not seem to depend on the amount of fines <15 μm in the carrier product ($r = -0.30$). This, in contrast with fpf from the Diskus® ($r = 0.91$) which increases strongly when the amount of fines is increased. The difference in performance between both inhalers is consistent in indicating that a high fpf from the Novolizer® does not require a carrier type with a small median diameter or with a certain amount of fines (<15 μm). On the contrary, fine carrier particles may worsen the powder circulation in a classifier during inhalation as a result of tribocharge. Large carrier particles perform much better in the Novolizer® notwithstanding the fact that they exhibit high press-on forces during mixing. However, the effectiveness of these forces in increasing the adhesive forces in the mixture may be low, depending on the total volume of the carrier surface discontinuities (inside which drug particles find shelter from the press-on forces), the carrier payload and the mixing conditions (Dickhoff et al., 2004). Additionally, the magnitude of the press-on forces can be reduced by increasing the span of the size distribution which worsens the flow properties of the powder mixture (e.g. in terms of Hausner ratio: Fig. 4A). For turbulent shear inhalers, like the Diskus®, there is no advantage from a high carrier surface rugosity since drug particles inside the carrier discontinuities also find shelter from the removal (drag and lift) forces during inhalation. And because the size of the discontinuities generally decreases with the median carrier diameter (de Boer et al., 2005), the fpf from turbulent shear inhalers increases with decreasing median carrier diameter, or an increasing fraction of fines in the carrier product (Fig. 4B and C).

The fpf from the Novolizer® is nearly the same for all brands of lactose: on average 38.5, 33.7, 37.6 and 34.6% for DMV International, Borculo, Meggle and Epikure products, respectively. The fpf for the Diskus® varies from 27.4% for DMV lactose (highest value) to only 12.0% for Meggle lactose (lowest value). The large degree of independence of the carrier lactose type in respect of fpf provides a great freedom of choice for the carrier regarding the flow properties (carrier size distribution) with which the dose measuring reproducibility can be controlled. Examples of the dose weighing accuracy and reproducibility by the Novolizer® (which is not related to the air classifier technology) have been given by others (e.g. Reiners et al., 2000).

3.3. Optimising between fpf and residence time

Previously, it has been described how the discharge rate of a powder dose (adhesive mixture type of drug formulation) from a particular classifier concept can be measured and controlled with the diameter of the discharge channel (de Boer et al., 2006). In the same study it was explained how the de-agglomeration efficiency of a classifier can be optimised by varying the classifier shape (and dimensions) or the angles of impaction. The optimal design may be different for different powder formulations (e.g. carrier size fractions), although the classifier in the currently marketed Novolizer® performs adequately with soft spherical agglomerates as well as with adhesive mixtures, even when different carrier products are used (Figs. 1–4). Fig. 5 shows the residence times at 30 and 60 l_N/min for three different drug formulations as function of the diameter of the discharge channel for a classifier that has been optimised for coarse carrier products (X_{50} between 150 and 200 μm). The classifier resistance as

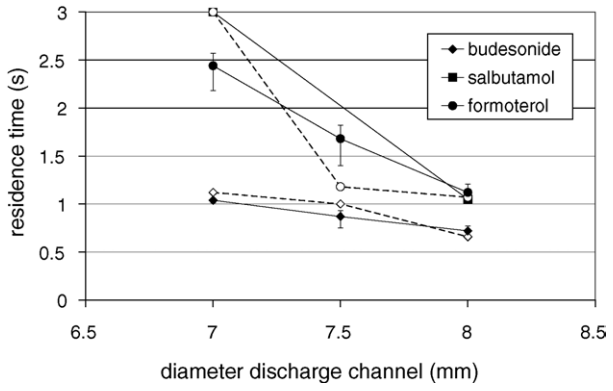

Fig. 5. Time necessary to completely empty the classifier (referred to as residence time) as function of the diameter of the classifier discharge channel for three different drug formulations in the same classifier concept. Closed symbols (continuous lines): 60 l_N/min (corresponding with 4 kPa); open symbols (dotted lines): 30 l_N/min (corresponding with 1 kPa). Each data point is the mean of three measurements; spread bars indicate the maximal and minimal values.

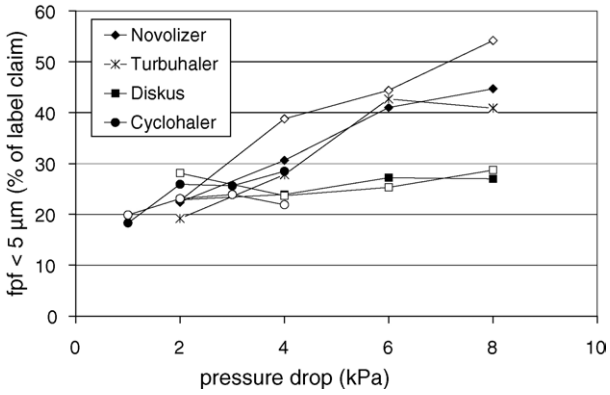

Fig. 6. Fine particle fractions <5 μm as percent of label claim for four different marketed dry powder inhalers at four different pressure drops. Open symbols are for budesonide (Novolizer® and Cyclohaler®) and fluticason (Diskus®); closed symbols are for salbutamol (Novolizer® and Cyclohaler®) and salmeterol (Diskus®). The Turbuhaler® (asterisks) was also tested with budesonide.

Table 2
Some characteristics of the classifier with different discharge channels of which the powder residence time and in vitro deposition results are shown in Figs. 5 and 6, respectively

Diameter discharge channel (mm)	7	7.5	8
Total inhaler resistance ($kPa^{0.5}$ $min\,l^{-1}$)	0.036	0.034	0.033
kPa at 30 l_N/min	1.17	0.98	0.96
kPa at 60 l_N/min	4.67	3.92	3.69
Classifier flow as fraction of total flow	0.60	0.61	0.64

All discharge channels have the same construction and differ only in the diameter.

function of the discharge diameter is given in Table 2. This table also presents the pressure drops across the inhaler corresponding with 30 and 60 l_N/min. According to pharmacopoeial procedures, the entire dose has to be delivered in a time period within which 4 l of air is withdrawn from the inhaler's mouthpiece (USP 27, 2004). However, patients suffering from pulmonary disease may have a reduced pulmonary function and be unable to inhale 4 l of air. Also a fraction of the inhaled volume is necessary for drug transport into the peripheral lung. Therefore, delivery of the entire dose in the first 2 l of inhaled air is to be preferred. For a flow rate of 60 l_N/min, this equals an inhalation time of 2 s. For the carriers used in the drug formulations that are presented in Fig. 5, a discharge channel of 7.5 or 8 mm would therefore be satisfactory. Although the relationships at 30 l_N/min (open symbols) are influenced by the occurrence of some tribocharge, the results confirm previously reported data (de Boer et al., 2006) which show that the residence time for coarse carriers is practically independent of the flow rate through the classifier. The aim to control the residence time within a time period of 1–2 s (at 60 l_N/min and higher) is also in good agreement with the time period in which the (sub-)maximal fpf can be obtained (de Boer et al., 2004a, 2006) and with what patients can achieve. Newman et al. (2000) reported inhaled volumes through the Novolizer® of 3.13 l (at an average flow rate of 99 l/min), 2.96 l (65 l/min) and 2.77 l (54 l/min) without giving the instruction to inhale as long as possible.

3.4. Fine particle fraction as function of the inspiratory effort

For generic drug formulations, the aim is not to be as good as possible, but to be equivalent to the originator product on the market. Fig. 6 shows the fpf < 5 μm for budesonide and salbutamol formulations from the currently marketed Novolizer® in comparison with the fpf's from the a few competitor devices at four different pressure drops (2, 4, 6 and 8 kPa). The Cyclohaler® has been tested at a lower range of pressure drops (1–4 kPa), because this inhaler has a lower air flow resistance. The flow rate through the Cyclohaler® at 2 kPa (82 l_N/min) is about the same as that through the Novolizer at 4 kPa (80 l_N/min). In comparison, 4 kPa equals 89 l_N/min through the Flixotide® (fluticason) Diskus® and 75 l_N/min through the Serevent® (salbutamol) Diskus®. Only the flow rate through the Turbuhaler® is substantially lower at this pressure drop: 52 l_N/min.

The relationships between the fine particle fraction and pressure drop for the Turbuhaler® and Novolizer® differ fundamentally from those obtained with both Diskus® inhalers and the Cyclohaler®. The fpf from the first two inhalers increases with increasing kPa (to values >40–50% of the label claim), whereas that from the Diskus® inhalers and the Cyclohaler® is nearly the same (approximately 25% of the label claim) at all pressure drops. The reason for this difference in performance is a difference in de-agglomeration mechanism; the Novolizer® and Turbuhaler® make use of other types of separation forces than the Diskus® and Cyclohaler®. In the Novolizer® and Turbuhaler®, inertial and frictional forces are primarily responsible for fine particle detachment and break-up of drug agglomerates, respectively. The higher the kinetic energy of the inspiratory flow, the higher these forces will become and the more effective drug redispersion will be. In the Diskus® and in the Cyclohaler®, drug redispersion depends primarily on turbulent shear (drag and lift forces). For this type of inhalers, the magnitude of the separation forces is less relevant than their effectiveness in getting hold of the drug particles that adhere to the carrier surfaces. Drug particles in carrier surface

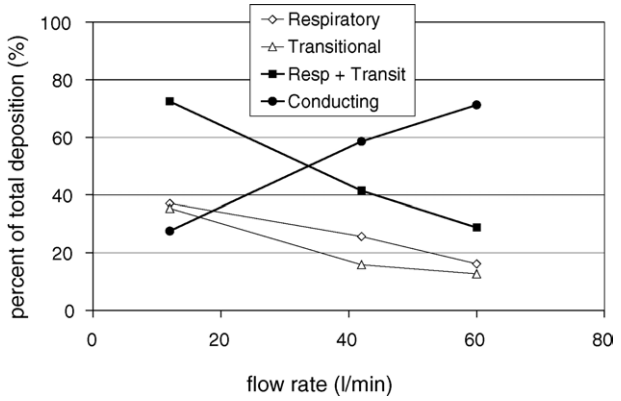

Fig. 7. Example of the shift in deposition from the respiratoy zone (airway generations 23–17) and transitional zone (generations 16–12) to the conducting zone (generations 0–11) for particles with an aerodynamic diameter of 5 μm, when the inspiratory flow rate is increased. The figure is based on calculations of Gerrity (1990). 'Resp + Transit' is the sum of respiratory and transitional deposition fractions. All regional deposition fractions have been expressed as percent of total deposition fraction (on average 0.828 for all flow rates).

discontinuities may not be affected by these forces. Therefore, carrier surface irregularities are much more important when turbulent shear inhalers are used than they are for dpi's making use of inertial separation forces. The Cyclohaler® could be regarded as a hybrid in terms of de-agglomeration however. Next to turbulent shear, there may be a contribution from inertial and frictional forces to drug particle dislodgment, as carrier particles collide with the inner capsule walls during capsule spinning. They may also collide with the inner wall of the capsule circulation chamber upon discharge from the capsule.

It has been mentioned that a constant fine particle fraction at all flow rates yields a more constant therapy. Therefore, it is recommended that the aerodynamic particle size of the aerosolised drug is independent of the inspiratory effort (e.g. Zeng et al., 2002). This may be questioned on the basis of theoretical considerations, however. Lung deposition modelling studies all show the same trend of a shift in deposition towards higher airways for the same particles when the inspiratory flow rate is increased. This is due to a higher momentum of these particles at a higher air velocity, which increases the contribution of inertial impaction to upper lung deposition. A very clear example for particles with an aerodynamic diameter of 5 μm is given by Gerrity (1990). Fig. 7 is based on his calculations and shows how the deposition fraction in the conducting airways (generations 0–11) increases with increasing flow rate at the cost of the deposition fractions in the respiratory (generations 17–23) and transitional (generations 12–16) airways. In Fig. 7, the partial deposition fractions have been expressed as percent of the total deposition fraction. The conclusion that increasing the inspiratory flow rate reduces the fraction of aerosol that is deposited in the respiratory generations is confirmed by others (e.g. Martonen et al., 1992; Brand et al., 2005). To compensate for this shift in deposition to higher airways when the flow rate through an inhaler is increased, a higher fine particle dose will have to be delivered in order to obtain the same amount of drug in the target area (assuming that this is in the respiratory and transitional airways). The increase in fpf with increasing inspiratory effort may have to be rather substantial, considering that a moderate increase in the flow rate (with 40 l/min) already halves the central and deep lung deposition of 5 μm particles (for the range of flow rates in Fig. 7). Good support for this reasoning is obtained from a scintigraphic study of Newman et al. (2000), who measured a rather constant ratio (0.9–1.0) for the peripheral lung deposition to central lung deposition for budesonide inhaled from the Novolizer® at 54, 65 and 99 l/min, respectively. If the fpf would have been the same at all flow rates, a decreasing ratio with increasing flow rate would have been more likely. Peripheral lung deposition itself increased only from 6.5 to 8.5% between lowest and highest flow rate. This is a relatively small increase considering the much greater difference in delivered fine particle fraction (<5 μm) between 54 (approximately 23%) and 99 l/min (approximately 45%) for the same drug from this device (see Fig. 6). In the same study, Newman et al. showed that the oropharengeal deposition (including mouth deposition) is rather constant from the Novolizer® at all flow rates too. This seems to confirm an increase in the deposition of detached fine drug particles in the (oro)pharynx when the flow rate is increased, as the deposition in the oral cavity from drug still attached to carrier becomes less (because of an improved de-agglomeration). The conclusion regarding mouth deposition may be considered somewhat arguable however, considering the extreme variation that may occur in the cross section of the upper airway, as has recently been observed with MRI technique (Ehtezazi et al., 2004). This variation may have a dramatic effect on the particle deposition in this region (Ehtezazi et al., 2005a), although this upper airway deposition seems to vary rather with the inhaler resistance than with the flow rate (Ehtezazi et al., 2005b).

3.5. Size distribution within the fine particle fraction

In spite of delivering the same fine particle fraction (<5 μm) at the same flow rate, the lung deposition of inhalers may be different when the size distribution within the fpf is not the same. This should not necessarily result in different efficacies (Weda et al., 2002), but it could cause considerable differences in side effects (Weda et al., 2004). Fig. 8A shows the subfractions of particles <1, 1–2, 2–3, 3–4 and 4–5 μm within the total fine particle fraction <5 μm for the cortico steroid formulations from the Novolizer®, Turbuhaler®, Diskus® and Cyclohaler® at 4 kPa. For a better comparison, all subfractions have been presented as percent of total fpf (defined as particles <5 μm). The differences are quite noticeable, e.g. the subfraction of particles <2 μm varies from 28.8 (for Diskus®) to 58.7% (for Novolizer®) of total fpf. Also at other pressure drops the aerosol from the Novolizer® is finer. The difference between the inhalers is not necessarily a result of different de-agglomeration efficiencies. There may also be differences in the primary particle size distributions of the drugs. Sometimes, somewhat broader size distributions are intentional, as larger drug particles are detached more easily from the carrier crystals than smaller ones. It could also be the result of a sustained action of the forces that separate the drug and carrier particles during inhalation. Previously, it has been shown that the particle size of detached particles decreases with increasing circulation time in a classifier (de Boer et al., 2004b).

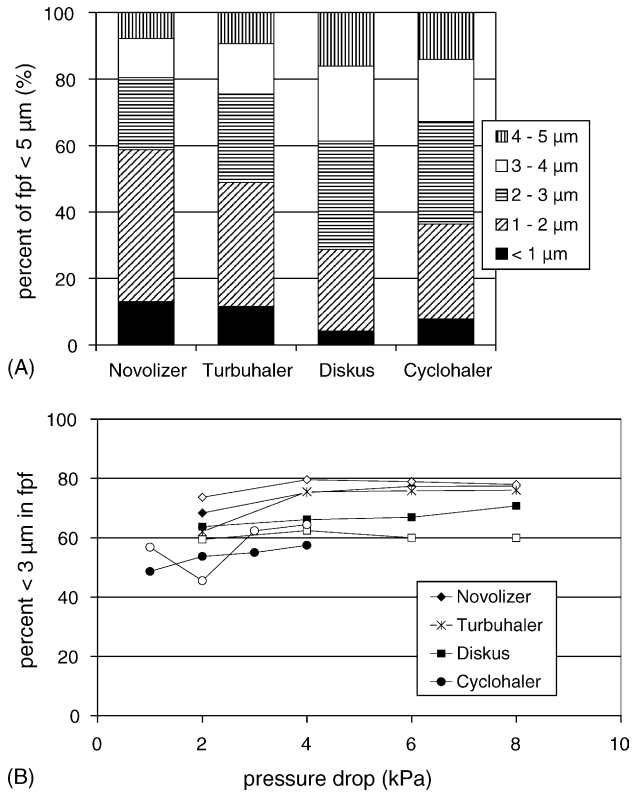

Fig. 8. (A) Distribution of fine particles within the fraction <5 μm at 4 kPa for the four different cortico steroid dry powder inhalers in Fig. 6. (B) The fraction of fine particles <3 μm as percent of the fraction of fine particles <5 μm for the same inhalers and formulations as shown in Fig. 6.

The percent of particles smaller than 3 μm in the fine particle fraction (fpf < 5 μm) at different pressure drops across the inhaler is shown in Fig. 8B. Only the Turbuhaler® approaches the high value of nearly 80% for the Novolizer®. Finer particles may travel deeper into the lung. Evidence for that is obtained from various in vivo deposition studies (e.g. Newman et al., 2000).

4. Conclusions

Target values for the fine particle fraction can be achieved with great precision when air classifier technology is used as de-agglomeration principle. The targets can be attained simply by using different types of powder formulations (soft spherical agglomerates and adhesive mixtures) in the same classifier and by making good use of the knowledge of the parameters that are relevant to the drug-to-carrier interactions in the inhalation powder. Yet, air classifier technology is relatively insensitive to variations in the carrier surface and bulk properties within the same type class of lactose compared to other de-agglomeration principles (as concluded from comparison with the Diskus® multi dose dry powder inhaler). Rather coarse carrier fractions can be used and the presence of a certain fraction of fine carrier particles (e.g. <15 μm) in the mixture is not necessary to obtain a high fpf. By using a wide carrier size distribution (e.g. ranging from 50 to 350 μm), inertial and frictional press-on forces during the mixing process can be kept low, whereas the effects of tribocharge in the classifier are suppressed. As a result, the circulation velocity in the classifier is high. The result of these choices is that the magnitude of the adhesive forces in the mixture is reduced and that of the separation forces during inhalation is increased. Like the Turbuhaler®, the Novolizer® produces an increasing fpf with increasing pressure drop across the inhaler. This increase in fpf is expected to compensate for the shift in deposition to higher airways at higher inspiratory flow rates. Lung deposition data obtained with the Novolizer® (Newman et al., 2000) seem to confirm this expectation. Finally, the Novolizer® produces a much higher fraction of extra fine particles (1–3 μm) within the fine particle fraction (fpf < 5 μm) than competitor devices. In vivo deposition data of Newman et al. (2000) suggest that this extra fine particle fraction contributes to a higher intermediate and peripheral lung deposition.

Acknowledgments

The authors are grateful to Mrs. Beekhuis for carefully screening the manuscript and the members of the research workshop of the Medical Faculty (University of Groningen) for constructing various test inhalers with great precision and dedication. They would also like to thank DMV International for lending relevant results from their own investigations to this study, and particularly Mrs. Gruben who collected these results.

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