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Optimisation of dry powder inhalation

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Chapter 9

Air classifier technology (ACT) in dry powder inhalation Part 3: Design and development of an air classifier family for the Novolizer[®] multi-dose dry powder inhaler

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Abstract

In this chapter, the design of a multifarious classifier family for different applications is described. The main development steps are presented as well as some special techniques that have been applied to achieve preset objectives. It is shown that by increasing the number of air supply channels to the classifier chamber (from 2 to 8), the fine particle losses from adhesion onto the classifier walls can be reduced from 75% to less than 5% of the real dose for soft (spherical) agglomerates. By applying a bypass flow that is arranged as a co-axial sheath of clean air around the aerosol cloud from the classifier, the air flow resistance of the classifier can be controlled over a relatively wide range of values ($0.023\text{--}0.041\text{ kPa}^{0.5}\cdot\text{min}\cdot\text{l}^{-1}$). This can be done without affecting the fine particle dose or increasing the fine particle losses in the inhaler. Moreover, the sheath flow can be modelled to reduce the depositions in the induction port to the cascade impactor or in the patient's mouth, which are the result of back flows in these regions. The principle of powder induced pressure drop reduction across a classifier enables assessment of the amount of powder in the classifier at any moment during inhalation, from which classifier loading rates (from the dose system) and discharge patterns can be derived. This principle has been applied to study the residence time of a dose in the classifier as function of the carrier size fraction and the flow rate. It has been found that this residence time can be controlled in order to obtain an optimal balance between the generated fine particle fraction and the inhalation manoeuvre of the patient. A residence time between 0.5 and 2 s at 60 l/min is considered favourable, as this yields a high fine particle dose (depending on the type of formulation used) and leaves sufficient inhaled volume for particle transport into the deep lung.

Keywords: Adhesive mixtures, Air classifier technology, Carrier lactose, Dry powder inhalation, Novolizer, Spherical pellets

1. Introduction

Developments in dry powder inhalation include the introduction of highly potent new drugs like formoterol fumarate (Pohunek et al., 2004), inhaled antibiotics such as tobramycin (Newhouse et al., 2003), gentamicin (Crowther Labiris et al., 1999) and colistin (Le Brun et al., 2002), vaccines (LiCalsi et al., 1999) and systemically acting inhalation drugs. A multitude of examples for systemically acting inhalation drugs has been proposed (e.g. Corkery, 2000), but to date only a few promising developments have been reported (e.g. Skyler et al., 2001). There are many different reasons for a wavering progress in this respect. Many of the macromolecules that are currently under consideration for systemic administration via the pulmonary route are peptides and proteins with molecular weights ranging from 5 to 30 kDa. Such large molecules have to be deposited in the alveolar region, where the absorption area and permeability are both high, to achieve an effective passage to the circulation (Patton, 1996). This requires an aerosol in the aerodynamic particle size range smaller than 2 μm (Corkery, 2000) unless the inspiratory flow rate can be kept extremely low (Brand et al., 2000). Most currently marketed dry powder inhalers (dpi's) can not meet these requirements. Often the therapeutic window for systemically acting drugs is quite narrow, as for insulin (Duddu et al., 2002), and many inhalation studies with this drug have shown low bioavailabilities with a high variation so far (Patton et al., 2004). Furthermore, the receptor interaction of most macromolecular drugs relies on their ternary or quaternary structure. To maintain a good activity in the dry state, they have to be incorporated in sugar glasses (e.g. van Drooge et al., 2004). Sugar glass formulations prepared with spray drying or spray-freeze drying techniques are cohesive and hygroscopic. Moreover, the drug concentrations in these formulations are generally low (maximally 20 to 30%) whereas the powders are highly porous. This increases the volume of powder to be dispersed during inhalation. Inhaled antibiotics are also administered in high doses, although it has recently been shown that when using a highly efficient dpi, the dose of colistin can be reduced by a factor 6 to 7 to obtain the same plasma level as from nebulisation (Le Brun et al., 2002).

The higher demands on the performance of dpi's for new inhalation drugs have challenged researchers to develop new formulations and devices. Many examples of specially engineered drug particles can be given (e.g. Edwards et al., 1998; Venthoye et al., 2001; Schiavone et al., 2004). All these particles have reduced interparticulate forces in common, which improves their dispersibility during inhalation. However, particle engineering techniques are often complex and expensive. A cheaper alternative is to improve the powder de-agglomeration principle of the inhaler device. Different types of powder de-agglomeration forces can be used (e.g. Amass, 1996; Voss and Finlay, 2002) of which inertial forces are the most effective (de Boer et al., 2003). Such forces are for instance applied in new multi dose dpi's as the Airmax[®] (Zeng et al., 2002) and the Twisthaler[®] (Yang et al., 2001), which yield fine particle fractions between 35-40% (Twisthaler[®]) and 50% (Airmax[®]) of the label claim at 60 l/min for formulations without specially engineered drug particles or additives. The effectiveness of inertial forces may depend on how these forces are generated however, as well as on the conditions under which these forces are applied. It has been reported that impaction on a simple mesh screen does not yield high fine particle fractions (Voss and Finlay, 2002), whereas the de-agglomeration efficiency of a jet impinger appears to be highly dependent on the amount of powder to be dispersed (Wang et al., 2004).

Previously, air classifier technology has been introduced as a successful method to apply inertial de-agglomeration forces (de Boer et al., 2003). Results presented from several formulation studies so far have all been obtained with the same basic concept of a classifier (e.g. de Boer et al., 2004a, b; Dickhoff et al., 2003, 2004). This concept has been developed for basic powder interaction studies and does not meet the specifications of an ideal inhaler. The aim of this study is to tackle certain drawbacks and limitations of the basic concept. This,

to make air classifier technology applicable for all types of powder formulations for inhalation, and to comply with preferences and requirements of patients and physicians regarding air flow resistance, consistency of delivered dose, fine particle dose, etc. Only the most relevant design improvements and methods used to achieve these improvements are presented in this manuscript. A family of different classifier concepts has been obtained (designed for the Viatris Novolizer[®] multi-dose dry powder inhaler) for different applications (formulations), which enables to achieve either a high fine particle fraction (fpf) from new drug formulations, or to adjust fpf to the performance of the originator product for generic formulations.

2. Materials and methods

2.1. Materials

Alpha lactose monohydrate carrier fractions of various size ranges were obtained by 20 min vibratory sieving (Analysette 3, Fritsch, Idar-Oberstein, Germany), followed by 20 min air jet sieving (A200, Alpine, Augsburg, Germany), using different Pharmatose products as starting material (DMV International, Veghel, The Netherlands). Micronised lactose fractions 1-8 and 8-16 μm were also obtained from DMV International. Micronised budesonide with an X_{50} of 1.04 μm ($X_{10} = 0.54$; $X_{90} = 2.15 \mu\text{m}$) and disodium cromoglycate (dscg) with an X_{50} of 1.73 μm ($X_{10} = 0.53$; $X_{90} = 4.28 \mu\text{m}$) were supplied by Sofotec (Frankfurt, Germany). An adhesive mixture of Capsulac 60 with 2% budesonide used for the experiments in the Figs. 8 and 10 was also prepared by Sofotec.

2.2. Methods

The size distributions of drugs (with 100 mm lens) and lactose carrier fractions (with 200 and 500 mm lenses) were measured with laser diffraction technique (HELOS Compact model KA, Sympatec, Clausthal-Zellerfeld, Germany). A RODOS dry powder disperser was used at 0.5; 3 or 5 bar (depending on the product). All calculations were made with the Fraunhofer theory.

Soft spherical agglomerates of dscg were prepared by densifying and agglomerating the micronised drug in a small stainless steel mixing container, using a tumbling mixer (Turbula T2C, WA Bachofen AG, Switzerland) at 90 rpm for 10 min. A small amount of large lactose crystals (180-300 μm) was added as pelletising aid. Next, lactose crystals and dscg pellets were separated over a 350 micron 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 350-800 μm was used for experiments.

Cascade impactor analyses were performed with a four stage glass constructed impactor with theoretical cutpoints for the 2nd stage of 12.35 μm at 30 l/min, and 8.74 μm at 60 l/min respectively (for spherical particles with a density of 1.5 g/cm³). Each analysis included five inhalations at a preset flow rate of 30 or 60 l/min. The dose was 3 mg for dscg pellets and 11 mg for adhesive mixtures with budesonide. All data presented are the mean of two analyses. The drug depositions on the different impactor stages were dissolved in 20 ml of liquid, being ethanol (analytical grade) for budesonide and demineralised water for dscg. Also losses in the induction port, classifier and inhaler mouthpiece were analysed. Drug solutions from carrier containing formulations were separated from non-dissolved lactose carrier particles in a centrifuge (Rotana 3500, Hettich, Tuttlingen, Germany) during 5 min at 3000 rpm. Drug concentrations in the solutions were measured with a spectrophotometer (PU 8720 UV-VIS, Philips, Eindhoven, The Netherlands) at wavelengths of 242.8 (budesonide) and 327.2 nm (dscg).

For the pressure drop measurements, differential pressure gauges of the type PD1 in combination with Measuring Converter MC2A (Hottinger Baldwin Messtechnik, Darmstadt, Germany) were used. The natural frequency of the diaphragms used for these gauges (1.6 kHz) is sufficient to monitor the relatively low frequency changes in the pressure drop during inhalation of a dose. For pressure drop reduction (equals residence time) experiments, the pressure drop values corresponding with a preset flow rate across an empty and loaded classifier were recorded subsequently as function of the inhalation time, using a Gould UV-recorder, type EasyGraf TA 240 (Gould Electronics, Ohio, USA) or TestPoint data acquisition software (Keithley, Taunton, USA). (Partial) flow rates were measured with a Brooks thermal mass flow meter, type 5863S in combination with a Brooks readout panel type 0154 (Brooks Instruments, Veenendaal, The Netherlands).

3. Results and discussion

3.1. Reduction of the classifier accumulation

The basic classifier used for various formulation studies and its working principle have been described quite in detail before (de Boer et al., 2003). As shown in Fig. 9.1, the classifier consists of a cylindrical chamber with two tangential air supply channels and an aerosol discharge channel having the same longitudinal axis as the cylindrical chamber.

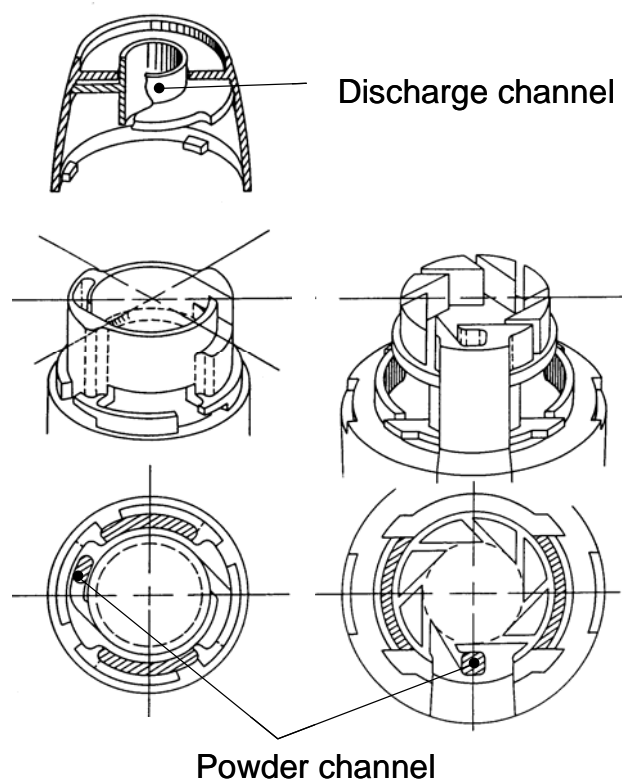


Figure 9.1. Basic classifier concept with two air channels of which one channel is the powder channel towards the classifier (left), and modified classifier with eight air channels (including the powder channel) creating an air barrier that prevents adhesion of fine particles to the cylindrical classifier wall (right).

The discharge channel protrudes from one cylindrical end of the chamber (depicted as a separate plate in Fig. 9.1 in two directions. The projection into the chamber is to improve carrier retention (which enables carrier residue analysis in drug detachment studies). The projection in opposite direction completes the discharge channel in the mouthpiece cylinder. One of the air supply channels serves as a passageway for the powder dose (powder channel). Drawbacks and limitations of this basic concept in Fig. 9.1 include a high air flow resistance and substantial powder deposition in the classifier and the relatively long discharge channel. In addition to that, carrier retention in a patient inhaler is not wanted, because the classifier has to be emptied after each inhalation.

Drug accumulation onto the classifier walls is particularly noticeable when soft agglomerates (spherical pellet formulations) of small particles are dispersed. As shown in Fig. 9.2, particles larger than the cut-off diameter of the classifier (e.g. carrier size fractions 63-106 and 106-150 μm) are retained with 90% efficiency (or higher) over long inhalation times (up to 30 s). But particles 1-8 μm , which are smaller than the cut-off diameter, are not discharged properly (only approx. 40% after 30 s), which is the result of adhesion onto the classifier walls, unless some larger sweeper crystals are added to the formulation (de Boer et al., 2002).

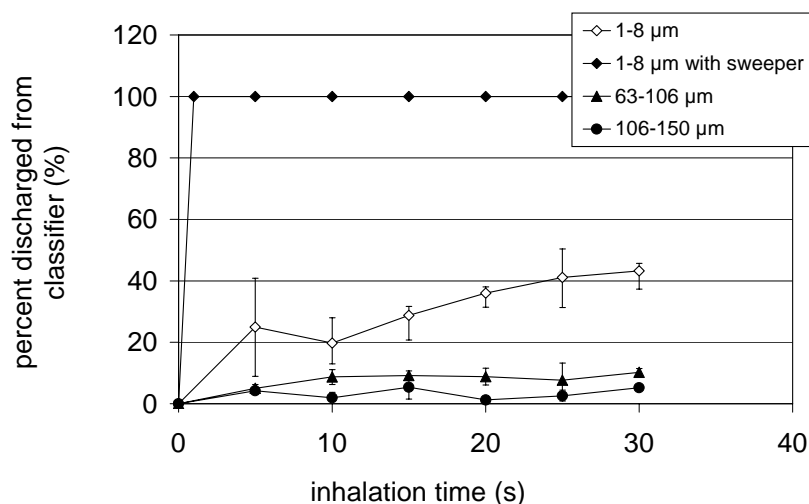


Figure 9.2. Percent discharge from a basic classifier (Fig. 9.1) as function of the circulation time for different lactose size fractions at 30 l/min. Dose is 25 mg. Each data point is the mean of four experiments; spread bars indicate the maximum and minimum values obtained. For each circulation time, a new dose has been added to the classifier.

The use of sweeper crystals is a very effective solution for single dose dpi's which are disposed after use (together with the retained sweeper particles in the classifier). It has been shown that approx. 15% (w/w) of coarse sweeper particles (in the approximate size range between 72 and 250 μm) in the powder is sufficient to reduce cyclone accumulation to less than 5% of the total dose. However, for multi-dose inhalers, the addition of sweeper crystals is not acceptable, as this would require that retained coarse particles are removed after each inhalation. Therefore, a different solution to reduce classifier accumulation has been found. Interruptions of the cylindrical wall have been made as shown in Fig. 9.1 (right). Each of the interruptions in the classifier wall constitutes an air supply channel towards the classifier chamber, and the assembly of channels creates a so-called air barrier that keep particles with low inertia away from the remaining wall sections between these channels. Only larger particles (e.g. carrier crystals) have sufficient inertia to pass across the air barrier and to

collide with the cylindrical wall sections. The different angles of orientation of the air supply channels create regions of turbulent shear. Table 9.1 shows that the air barrier is very effective in reducing the classifier accumulation; losses due to adhesion (for dscg) are diminished from 75 to only 3% when the number of air channels is increased from 2 to 8.

Table 9.1. Air flow resistance of the classifier, and total losses of fine (disodium cromoglycate) particles by adhesion onto classifier walls (as percent of the real dose) for classifier chambers of the same dimensions, but with a different number of air supply chambers (including the powder channel). Individual values are between brackets (n=4 for the classifier with 2 channels; n=2 for both other classifiers).

Number of air supply channels	Flow rate (l/min)	Inhalation time (s)	Classifier resistance to air flow ($\text{kPa}^{0.5} \cdot \text{min} \cdot \text{l}^{-1}$)	Percent losses due to adhesion (%)
2	30	5	0.051	75.1 (59.2-91.0)
4	30	3	0.044	18.4 (17.3-19.4)
8	30	3	0.041	3.2 (2.5-3.8)
	60	3	0.041	4.9 (4.6-5.1)

This increase in the number of air channels reduces the air flow resistance (R) of the classifier (Table 9.1). The interruptions in the cylindrical wall also change the circulation pattern of coarse carrier crystals. The irregular (mostly tomahawk) shape of these particles gives rise to bounce in different directions after collision with the remainders of the cylindrical wall. Instead of circulating only tangentially, rebounding carrier crystals may pass the centre of the classifier chamber and enter the region directly underneath (or even inside) the classifier discharge channel. As a result, carrier retention is strongly reduced. In fact, it takes approximately 1 to 3 s before all large carrier particles of a single dose are discharged completely from the modified classifier concept shown in Fig. 1. This makes this classifier suitable for soft agglomerates as well as for adhesive mixtures without having to empty the classifier after inhalation. The residence time for the carrier crystals strongly improves the drug redispersion from these adhesive mixtures compared to de-agglomeration principles with instantaneous discharge.

3.2. Control of the inhaler resistance and fine tuning of partial flow rates

As indicated in Table 9.1, further reduction of the air flow resistance of the classifier may not be expected from further increasing the number of bypass channels. Besides, eight channels is about the maximal number that can be arranged around a classifier chamber of only 13 mm in diameter, without disturbing the flow pattern inside this chamber or without substantially increasing the resistance of the channels themselves. Therefore, the principle of sheath flow has been applied. This principle is shown in Fig. 9.3. Small sheath flow orifices in the classifier top plate at a radius larger than the cylindrical wall of the classifier chamber (outer diameter) create a bypass for a part of the inspiratory flow. The bypass orifices reduce the total air flow resistance of the classifier and constitute a co-axial sheath of clean air around the aerosol cloud from the classifier. Table 9.2 shows the reduction in air flow resistance for the eight-channel classifier in Fig. 9.1 with different numbers of sheath flow orifices, each of the orifices having a cross section for air flow of 1.75 mm^2 . For comparison, the resistances of two marketed dpi's are shown too. It has frequently been suggested that a low resistance is preferable (e.g. Ashurst et al., 2000), because a high resistance requires a higher effort to generate sufficient flow for powder dispersion (Broeders et al., 2001). This suggests that patients with reduced pulmonary function might be unable to operate high resistance devices successfully.

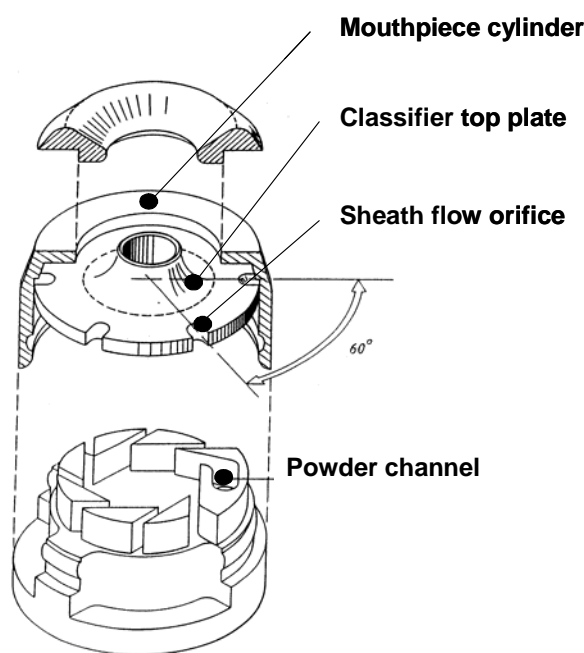


Figure 9.3. Technical drawing showing an eight-channel classifier with bypass orifices for sheath flow, which provide a co-axial sheath of clean air around the aerosol cloud from the classifier.

This is an oversimplification of the situation however. Successful operation includes delivering a high portion of the drug to the lung with minimal drug deposition in the oropharynx (Zeng et al., 2002). If a high fpf is obtained from a high resistance device at a relatively low flow rate, there is a much better deposition in the target area than for the same fpf from a low resistance device at a much higher flow rate. So, a choice has to be made on the fpf-flow rate profile, which is different for currently marketed devices (Steckel and Müller, 1997).

Table 9.2. Air flow resistance (R) of the classifier with 8 air supply channels and a different number of sheath flow orifices (see text), in comparison with R of some marketed dpi's as well as their pressure drops corresponding with 60 (30) l/min.

Number of sheath flow orifices	Air flow resistance (kPa ^{0.5} .min.l ⁻¹)	Flow rate (l/min)	Corresponding pressure drop (kPa)
0	0.041	60	6.05
3	0.035	60	4.41
		30	1.10
6	0.029	60	3.03
		30	0.76
9	0.026	60	2.44
14	0.023	60	1.90
Pharmachemie Cyclohaler	0.019	60	1.30
AstraZeneca Turbuhaler	0.043	60	6.66

Another aspect to consider is the patients' preference for the resistance, which varies between studies (e.g. Clark and Hollingworth, 1993; Andersen et al., 1993; de Boer et al., 1996). Table 9.2 shows that the resistance of a classifier can be controlled within a wide range of values simply by adding different amounts of sheath flow.

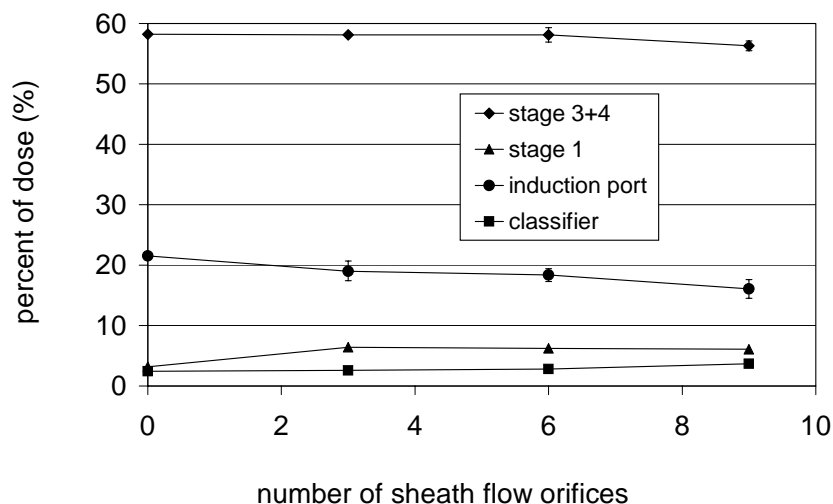


Figure 9.4. Performance of the classifier concept with 8 air channels (Fig. 9.1) as function of the number of sheath flow orifices at 60 l/min (total flow rate) with soft agglomerates of disodium cromoglycate. Each data point is the mean of 2 series of five inhalations (3 mg dose). Stage 3+4 deposition corresponds with a fine particle dose < 8.74 μm (theoretically) for the impactor used. 'Classifier' refers to fine particle losses in the classifier.

Fig. 9.4 shows that the performance of the eight-channel classifier (Fig. 9.1) on soft agglomerates (dscg) at 60 l/min is hardly influenced by the addition of sheath flow. The maximum of nine sheath flow orifices in Fig. 9.4 corresponds with an increase in the cross section for bypass flow of 15.75 mm^2 . The only noteworthy effect is a decrease in the fine particle losses in the induction port to the cascade impactor (from 21.5% without sheath flow to 16% with nine bypass orifices). The decrease is highly reproducible and can be well explained. There is momentum transfer from the aerosol from the inhaler's mouthpiece to the surrounding fluid in the induction port to the cascade impactor or in the patient's mouth (Perry and Chilton, 1973). This causes entrainment of air from the mouthpiece region, which leads to a minor underpressure in this region. As a result, back flows are started from the periphery of the aerosol cloud to balance the pressure in the mouthpiece region with the pressure further downstream of the induction port (or mouth), as shown in Fig. 9.5A. These back flows increase the fine particle contact with the inner walls of the induction port (or the mouth), which is one of the reasons for high fine particle losses in this region. By creating a sheath of clean air around the aerosol cloud, the particle concentration in the zone from where the backflows are withdrawn is reduced (Fig. 9.5B).

The Figs. 9.3 to 9.5 give a rough outline of the classifier improvement with respect to air flow resistance and sheath flow. It may be clear that further optimisation of the dimensions of various classifier parts within the final inhaler concept is necessary. The theoretical model used for further optimisation of the partial flow rates (Φ_{1-3}) and partial air flow resistances (R_{1-4}) is shown in Fig. 9.6. Different modular inhaler concepts with exchangeable parts were used which enabled measurement of the pressure drop across each of the inhaler parts.

Fine tuning was particularly focussed on:

- ✓ obtaining a high and reproducible fine particle dose,
- ✓ minimising the inhaler (classifier) accumulation at flow rates of 30 l/min and higher,
- ✓ maintaining sufficient air velocity through the powder channel for good dose entrainment, and
- ✓ establishing a moderate air flow resistance.

This fine tuning has resulted in the currently applied classifier for generic formulations in the Viatrix Novolizer[®], which has an air flow resistance of $0.028 \text{ kPa}^{0.5} \cdot \text{min} \cdot \text{l}^{-1}$.

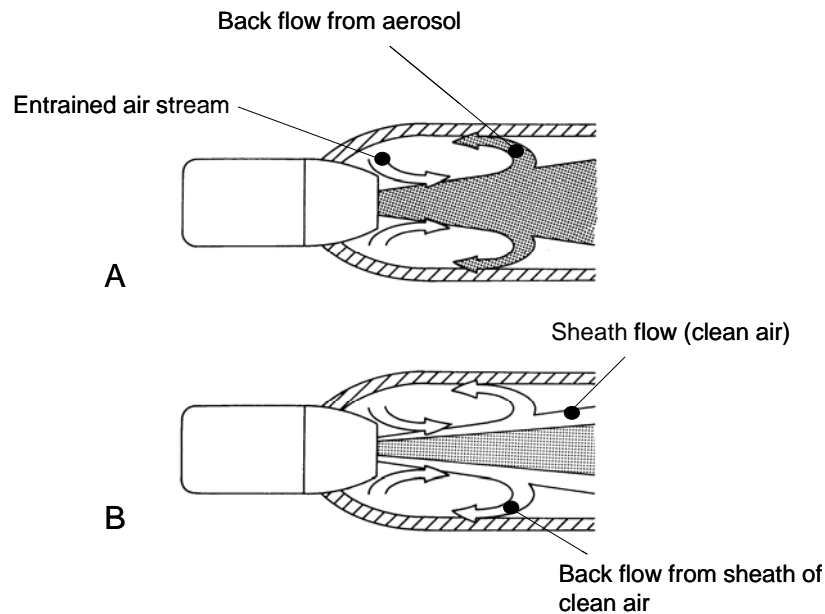


Figure 9.5. Schematic drawing showing back flows from the aerosol cloud (A), respectively from the sheath of clean air around the aerosol cloud (B) in the induction port to the cascade impactor (or the patient's mouth).

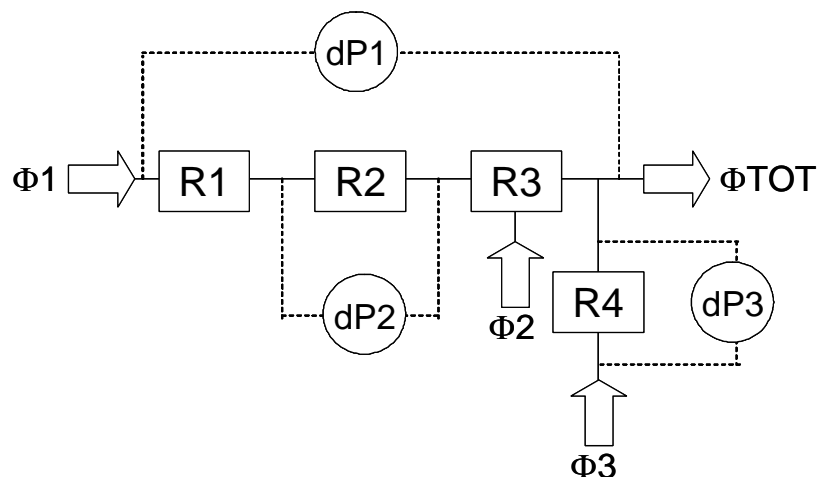


Figure 9.6. Flow scheme of a test inhaler used for classifier optimisation in terms of partial resistances (R) and partial flow rates (Φ). R_1 is the air inlet orifice; R_2 is the dose compartment with powder channel; R_3 is the classifier and R_4 stands for the sheath flow controlling orifices. Φ_1 is the flow through the dose compartment and the powder channel; Φ_2 is the flow through the additional air supply channels of the classifier and Φ_3 is the sheath flow.

3.3. Control of the powder circulation time in the classifier

In the previous paragraphs it has been explained that the classifier in Fig. 9.3 was developed particularly for soft agglomerates. However, the concept in Fig. 9.3 can also be used for the de-agglomeration of adhesive mixtures, although the circulation time for the carrier particles can not be controlled otherwise than by selection of the appropriate carrier size fraction. In a previous study, a high rate of drug particle detachment from carrier crystals has been observed within the first 0.5 s of circulation in a classifier (de Boer et al., 2004a). To obtain a high fine particle dose, the residence time for adhesive mixtures in the classifier should therefore be at least 0.5 s. It could be shown that detachment in the first 0.5 s is primarily for the largest primary drug particles and small drug agglomerates (de Boer et al., 2004b), but most of the agglomerates are broken up before they are discharged as primary entities (at flow rates of 30 l/min and higher). Elongation of the circulation time to a time period between 0.5 and 2 s is beneficial for two different reasons. The fraction of drug detached within the time period between 0.5 and 1.5 s from the start of the inhalation (by weakening of the adhesive forces in the mixture) may be between 50 and 100% of the fraction dislodged in the first 0.5 s. In addition to that, the size of detached particles decreases with increasing circulation time. Therefore, the delivered fpf after 2 s may be twice as high as that after 0.5 s, which endorses the desire to have a good control over the residence time in the classifier. An inhalation time of 2 s at 60 l/min equals an inhaled volume of 2 l, which leaves sufficient volume for particle transport into the deep lung. Much longer circulation times are not desired. So, controlled powder circulation during minimally 0.5 and maximally 2 s is the aim.

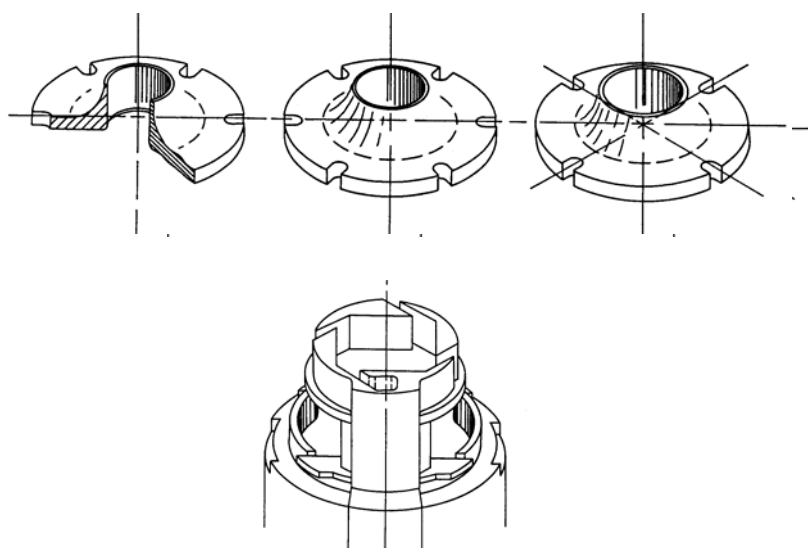


Figure 9.7. Classifier for adhesive mixtures with 4 air channels (including the powder channel) having an octagonal shape with four long particle acceleration sides and four shorter impaction walls. Discharge channels with different diameters control the circulation (residence) time of the powder in the classifier chamber.

Fig. 9.7 shows a basic concept of a classifier with controlled residence time. The classifier chamber is an octagon with sides of different lengths. Four longer sides are to accelerate carrier particles and four shorter sides are for impaction with the carrier particles. Different ratios for the length of the acceleration side to that of the adjacent impaction side have been tested as well as different angles between both sides and different numbers of air

channels. The magnitude of the inertial separation forces depends on the (average) particle velocity in the classifier and the angle of collision. An angle of 90 degrees causes highest impact (highest removal forces), but leaves practically zero residual velocity in the direction of the next impaction plate after collision. Because the dimensions of the classifier are too small to accelerate coarser carrier particles from zero to a stationary velocity between two collisions, the optimum has to be balanced between carrier particle diameter, angle of impact and residual particle velocity after collision. Fig. 9.7 also shows the classifier top plates with different diameters for the discharge channel. The diameter of the discharge channel controls the residence time of the dose in the classifier. By increasing the region in the classifier chamber from which the carrier particles can enter this channel, the rate of discharge can be increased.

3.4. Measurement of the powder circulation time in the classifier

Different techniques have been developed to measure the residence time of the carrier particles (from a single dose) in the classifier. A high accuracy can be obtained from pressure drop measurements across the classifier. Because of the highly turbulent flow through the classifier, the pressure drop across this part of the inhaler determines largely the total pressure drop across the inhaler. When particles with much higher inertia than air are added to the classifier, the degree of turbulence is reduced. This also reduces the pressure drop, whereas the flow rate through the classifier is maintained at the preset value (this, because the resistance of the test inhaler is very low compared to the resistance of the total flow scheme, including a flow controller, an impactor and a filter system). This principle of pressure drop reduction is shown in Fig. 9.8A for the same classifier (shown in Fig. 9.7) with two different discharge channels (7 and 8 mm diameter respectively). For this example, an adhesive mixture with Capsulac 60 as carrier and 2% budesonide has been used (flow rate: 60 l/min). For a better comparison, the pressure drops at the stationary flow rates through the empty classifier (open symbols) have been put to 100% (the actual values in kPa are different between the two classifier configurations). Fig. 9.8A clearly shows that the period over which a reduction in pressure drop exists for the classifier with 7 mm discharge channel is longer than that for the classifier with 8 mm channel (closed symbols). For carrier fractions of the same size distribution, there appears to be a good linear relationship between the amount of particles in the classifier and the magnitude of the obtained reduction in pressure drop for classifier payloads of 3 mg and higher (Fig. 9.8B). The relationships shown in Fig. 9.8B are also for Capsulac 60 with 2% budesonide. The linear relationships can be used to assess the amount of carrier particles in the classifier at any moment during inhalation. Such an assessment is made on the basis of the actual value of the pressure drop reduction as function of the inhalation time (Fig. 9.8C, also for Capsulac 60 with 2% budesonide in different classifier concepts at 60 l/min). Curves as presented in Fig. 9.8C show the differences in loading rate (from the dose system) and discharge pattern from the classifier, which depend not only on the flow rate through the classifier, the dose weight (total classifier payload) and classifier design, but also on the size distribution of the carrier fraction used. The curves may exhibit different shapes (different discharge patterns) for different combinations, but they are highly reproducible for the same combination. This is shown in Fig. 9.8A in which the spread bars are of the same size as the symbols used, except for a few data points. The residence time in this manuscript is simply defined as the time necessary to achieve zero pressure drop reduction; for cyclone optimisation, also the discharge pattern has been taken into consideration however.

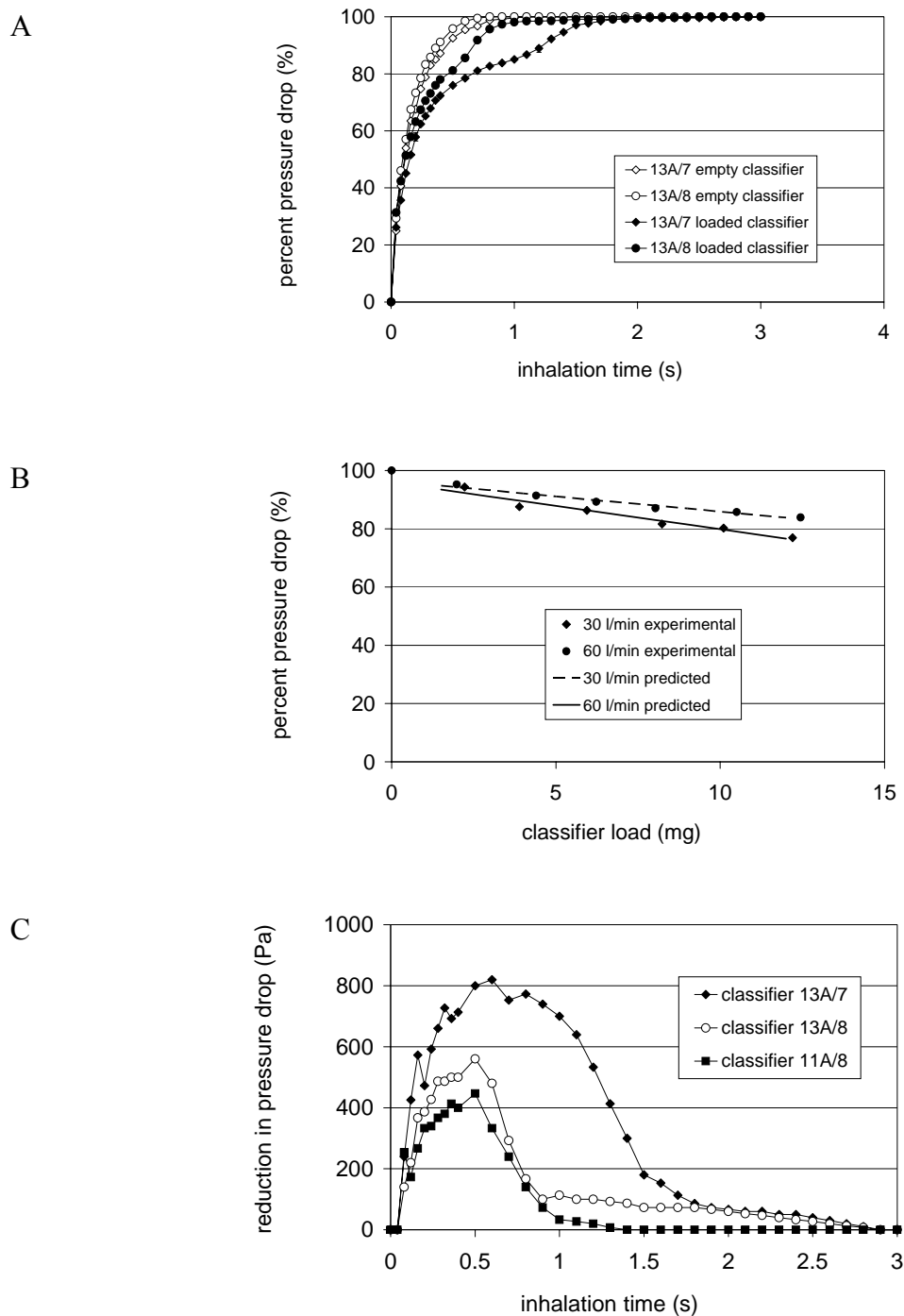


Figure 9.8. Presentation of the pressure drop reduction method for measurement of the residence time of a dose in the classifier (for a budesonide mixture with Capsulac 60 carrier). A shows the pressure drop across the same classifier with and without a carrier dose of 11 mg for two different discharge channels (7 and 8 mm). The pressure drop (Pa) in the stationary (empty) situation has been put to 100%. B shows the percent pressure drop reduction of the 2-channel classifier shown in Fig. 9.1 (with 100% retention) as function of the classifier load. C shows the pressure drop reduction (Pa; compared with an empty classifier) as function of the inhalation time, from which the classifier discharge pattern can be derived.

Fig. 9.9 presents the residence time as function of the mean fraction diameter for different carrier size fractions (from Pharmatose 100M) at three different flow rates. For these experiments, a classifier with 8 mm discharge channel (Fig. 9.7) has been used. The effect of flow rate increases with decreasing mean fraction diameter: for carrier particles above 75 μm , the residence time becomes largely independent of carrier size and flow rate. This makes this type of classifier rather robust in this respect. Moreover, total discharge for larger particles is achieved within the desired range of inhalation times (0.5 - 2 s), which is also a well achievable inhalation time for the patient at these flow rates (30 - 90 l/min). The effect of flow rate on the residence time of fine particle fractions (< 75 μm) is primarily the result of tribocharge. Tribocharge becomes more severe at higher flow rates and results in Coulombic attraction by the classifier walls. Therefore, the smaller the particles are, the less effective the drag force is in keeping the particles in circulation. However, the residence times for these finer fractions can be strongly reduced by mixing them with a few percent of particles of a much large size (> 150 μm). With increasing flow rate, also the cut-off diameter of the classifier decreases, which increases the difference between the cutpoint the mean particle size.

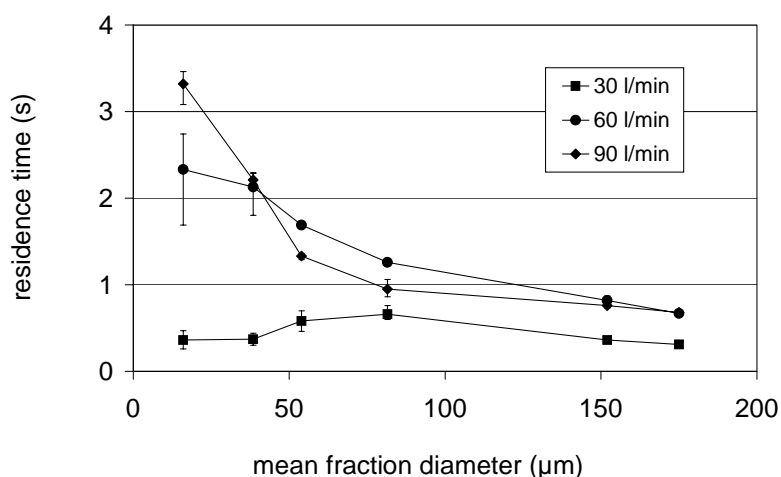


Figure 9.9. Residence time for different carrier size fractions at three different flow rates, as function of the mean fraction diameter, using the classifier in Fig. 9.7 with 8 mm discharge channel and 6 sheath flow orifices. Each data point is the mean of three experiments; spread bars indicate the maximal and minimal values obtained.

The residence time is not the only decisive parameter for the classifier choice however. The obtained fine particle fraction at the established residence time is even more important. This fpf (< 8.74 μm) is shown in Fig. 9.10 as function of the residence time for the same formulation (Capsulac 60 with 2% budesonide) from different classifier concepts (of the type shown in Fig. 9.7), in combination with discharge channels of 6, 7 and 8 mm. (at 60 l/min). The good correlation shows that optimisation between both parameters is very well possible. For this type of formulation, and the type of classifiers used, an fpf of 40% (of the real dose) can be achieved after 1.5 s circulation time in the classifier. The coarse carrier in this formulation has an X_{10} of 126.1 μm ; X_{50} of 233.5 μm and X_{90} = 367.8 μm respectively (mean of six different batches dispersed at 0.5 bar). Because the classifiers used to prepare this figure were all of the same type, a wide range of fpf-values at the same circulation time has not been obtained. However, the figure clearly shows that a wide range of residence times can be obtained for the same formulation at the same flow rate. And by changing the classifier

design (i.e. the de-agglomeration efficacy), the discharge pattern (Fig. 9.8C) or the formulation (e.g. carrier type), the fpf at the same residence time (and the same flow rate) can be controlled over a wide range too.

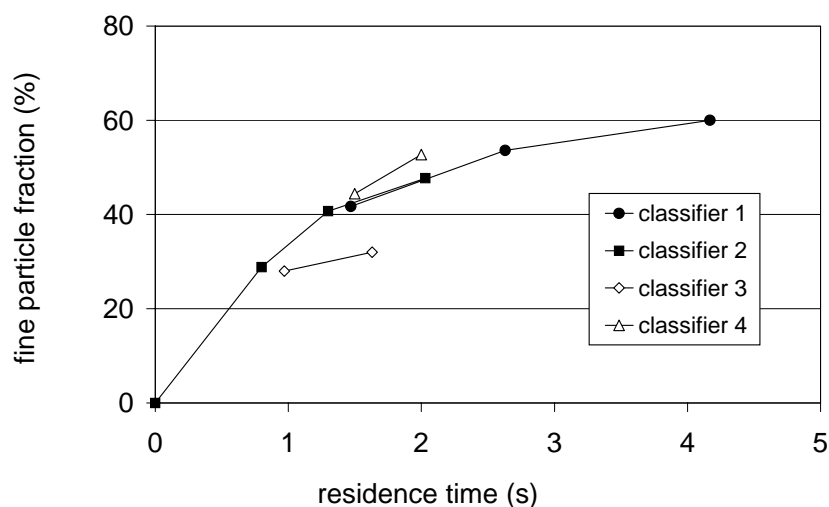


Figure 9.10. Fine particle fraction (fraction $< 8.74 \mu\text{m}$ as percent of the real dose) as function of the carrier residence time in the classifier for a mixture of Capsulac 60 with 2% budesonide at 60 l/min. Different classifiers of the type presented in Fig. 9.7 have been used with different discharge channels. Each data point is the mean of two series of 10 inhalations.

3.5. Incorporation of the classifier into an inhaler

The currently applied classifier for generic formulations in the Viatrix Novolizer[®] is shown in Fig. 9.11A. Basically, the design is the same as shown in Fig. 9.3, only various dimensions have been modified compared to the concept of which the results are presented in Fig. 9.4. The powder channel has become an integral part of the classifier chamber. When attached to the inhaler (as shown in Fig. 9.11B), a depression at the rear end of this channel is facing the dose measuring slide underneath the powder bulk container. The depression is to prevent that powder slides towards the classifier when the inhaler is held oblique. Keeping the dose at the end of a relatively long powder channel maximises the velocity of the particles at which they enter the classifier. Classifiers with controlled residence time (to be used for adhesive mixture formulations with new drugs) are integrated in the inhaler design in exactly the same way as the classifier depicted in Fig. 9.11A. The classifier is positioned directly behind the front of the mouthpiece and its central axis is the same as that of the aerosol jet from the inhaler's mouthpiece. As a result of this arrangement, large (e.g. carrier) particles leaving the classifier with a high tangential velocity, are separated from the drug aerosol by centrifugal action as soon as they exit the discharge channel. Their inertia is too high to be stopped by the sheath flow. This causes these particles to deposit in the front of the mouth (instead of in the back of the throat) from where they can easily be removed by mouth rinsing. This eliminates the occurrence of adverse local side effects, whereas the signalling function (confirming to the patient that a dose has been inhaled) is maintained.

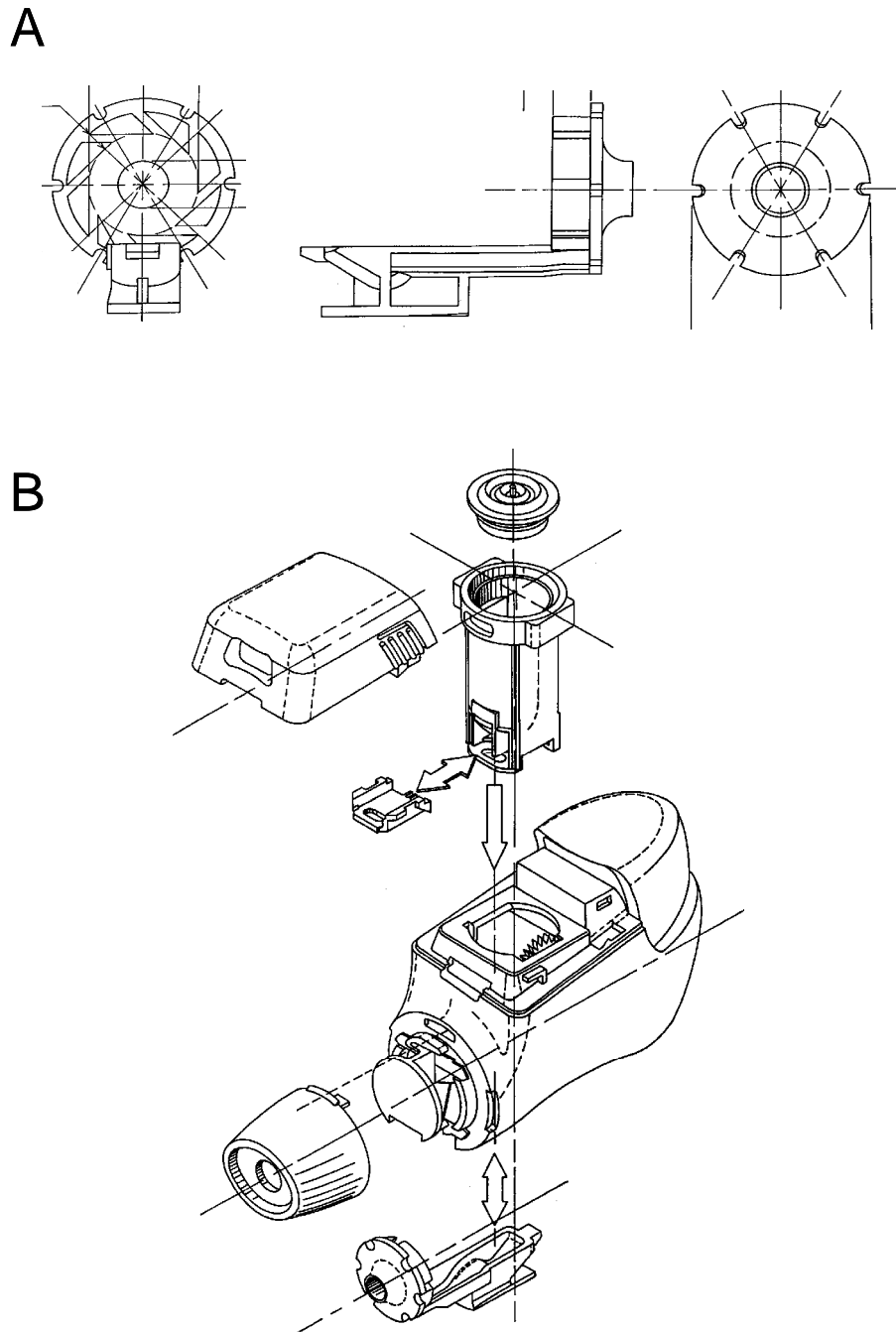


Figure 9.11. Classifier concept with integrated powder channel in the Viatris Novolizer[®] for generic formulations (A) and the position of the classifier in this multi-dose dpi (B).

4. Conclusions

Modifications in the geometry of the air classifier chamber and the application of certain design variations, such as the application of extra air supply channels and sheath flow, allow optimisation of the inhaler performance with respect to the generated fine particle fraction, inhaler losses and inhaler resistance. By optimising the residence time of the carrier particles (or coarse fragments of soft agglomerates) in the classifier, maximal use can be made

of the available energy (within the inhaled air stream) for drug dispersion. Different classifier designs can be applied, which enables achievement of maximal fine particle fractions from different formulation types (adhesive mixtures, nucleus agglomerates and soft agglomerates). For all types of formulations, the drug losses in the inhaler can be less than 5%, even when high *fpf*'s of 50% (or more) are generated. For adhesive mixtures, a wide range of carrier size fractions can be selected (median diameter varying from less than 50 μm to more than 250 μm). Coarse carriers may be beneficial to dose measuring and dose emission accuracy. By adding different amounts of sheath flow, the inhaler resistance to air flow can be controlled within a wide range of values, without affecting the inhaler performance dramatically. The sheath flow may also reduce the fine drug particle deposition in the mouth.

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