The Development of a Cascade Impactor Simulator Based on Adhesion Force Measurements to Aid the Development of Dry Powder Inhalations

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Adhesion and friction forces are the main physical factors determining the re-suspension of a micronized drug from carrier particles during inhalation. Hence, it appears useful to link adhesion and friction force measurements to the *in vitro* testing of dry powder inhalations, namely the assessment of the mass median aerodynamic diameter (*MMAD*) using an eight-stage Andersen cascade impactor. Interactive mixtures of micronized Salmeterol Xinafoate adhered to irrespirable lactose monohydrate carrier particles were used as model dosage forms. The adhesion force between the drug and carrier particles was assessed using a centrifuge technique, and the *MMAD* was determined under standardized working conditions using the Andersen-Cascade impactor (Mark II). A cascade impactor simulator (CIS), which is a computer programm containing a re-suspension model to assess the amount of drug detached from the carrier particles during inhalation, was developed and validated using the experimental data. It could be shown, that the CIS provided a good estimate of the loss of drug due to adhesion to the carrier particles and the loss of drug on the cascade impactor walls. Small deviations between the theoretical and experimental mass median aerodynamic particle diameters however were found. These deviations were shown to be mainly due to the experimental error introduced by the cascade impactor, and that the error due to the experimental adhesion measurements is negligibly small. Hence, the CIS developed could be a useful tool in early development stages of dry powder inhalations to predict the *in vitro* aerodynamic performance of drug particles.

Key words adhesion; cascade impactor simulator; dry powder inhalation; re-suspension model

A thorough *in vitro* test to quantify the respirable amount of drug emitted from an inhaler is a necessary requirement for the development and production of aerosol formulations. The size distribution of aerosol particles will strongly influence the therapeutic effect due to its proportional deposition in the respiratory tract. A particle size between 25 and 0.3 μm is regarded to be possibly inhaled and kept in the airways,[1] but favourably the upper particle size should not exceed 8—9μm.

Using impaction methods, the aerodynamic particle size distribution of the respirable fraction of a drug can be found from pure determination of weight,[2] which has its advantage. However, when compared to direct particle size measurements, the values obtained by impaction will contain considerable errors,[3-5] which require detailed mathematical analysis. The performance of different impactors in terms of their inclusion into the European Pharmacopoeia as a standard method was studied by Aiache *et al.*[6] The use of the multi-stage Anderson cascade impactor (Mark II) was found to produce results with a larger variability due to the more complex assessment procedure involved. However, this method is more often used in the development stage to gain more detailed information about the aerodynamic properties of the formulation, whereas simpler techniques are more often used for in-process and quality control.

In the development of dry powder inhalations, a general problem appears to be, that a reasonably sized powder batch has to be prepared for testing. In those cases, where a drug is diluted with a carrier material such as lactose to form an interactive mixture, at least 100 g powder should be mixed to provide practically relevant mixing conditions. Assuming that several batches are necessary to find an optimal inhalation formulation, a considerable amount of drug and carrier material is effectively lost. Hence, it would be desirable to device a physical method, which characterizes the inter-particulate contact, and also allows prediction of the aerodynamic behaviour of the drug when delivered into a cascade impactor. In this way, material, time and money could be saved.

Adhesion forces are the main physical factors determining the re-suspension of the micronized drug from the carrier during inhalation.[7] Friction forces are however also largely involved. Adhesion and friction can be measured between single particles for example using a centrifuge[8,9] requiring only a minimum amount of material, *i.e.* a few milligram. However, to date no numerical model has been reported in the literature, that links the adhesion and friction forces obtained in such measurements directly to the *in vitro* aerodynamic behaviour of the drug particles for example in a cascade impactor. The aim of the present work was to establish such a link and to provide a cascade impactor simulator (CIS), which can theoretically assess the *in vitro* aerodynamic performance of drug particles adhered to a carrier material. The CIS will be validated using drug–carrier mixtures, of which the adhesion and aerodynamic properties are evaluated experimentally.

Theory

The CIS developed provides the link between adhesion and friction force measurements performed on drug particles adhering to carrier particles and the common *in vitro* test of dry powder inhaler formulations using an eight-stage Andersen cascade impactor (Mark II).

To devise a CIS, the first problem to overcome was to find an appropriate re-suspension model, which allows the estimation of the drug particle size distribution that will be detached from the carrier particles in an air stream. Re-suspension models have mainly been developed for turbulent air flow, and the variety available has several

shortcomings.[10] To date, three general models are widely accepted in adhesion science for re-suspension of aerosols: 1. the Reeks-Reed-Hall model[11] for turbulent air flow, 2. the Braaten model[12] for turbulent air flow, and 3. Zimon's model for laminar air flow.[13] Thus investigations into the nature of the air stream acting on the drug particles during detachment were carried out. It is to note, that with respect to the adhesion theory this considers the character of the air stream when closely passing the carrier particle surface, not the general air flow in the cascade impactor. The relevant Reynold's number is in this case defined as[13]:

$$Re=\frac{d\cdot v_{det}}{\eta_{kin}} \tag{1}$$

where d=diameter of the drug particles, v_{det}=air flow rate ($m^3\,s^{-1}$), and η_{kin}=kinematic viscosity of the air. The constant η_{kin} is related to the dynamic viscosity of the air, η_{dyn}, *via* the true density of the air, ρ_o:

$$\eta_{kin}=\frac{\eta_{dyn}}{\rho_o} \tag{2}$$

The value of ρ_o for air at a temperature of 20 °C ($\approx$293.14 K) and a pressure of 760 mmHg ($\approx$101.325 kPa) is 1.18 $kg\,m^{-3}$. Sutherland's empirical equation[14] can be used to calculate η_{dyn}:

$$\eta_{dyn}=C_1\frac{T^{3/2}}{T+C_2} \tag{3}$$

where T=temperature (K), and C_1 and C_2 are constants (1.4644×10^{-6} and 110.6, respectively; see Franzen *et al.*[15]) Using Eqs. 2 and 3, η_{dyn} is $1.82\times10^{-5}\,kg\,m^{-1}\,s^{-1}$, and η_{kin} is $1.54\times10^{-5}\,m^2\,s^{-1}$. Reynold's number increases with increased air flow rate. Therefore, it was calculated for an air flow rate of 60 $l\,min^{-1}$. For a minimum respirable particle size of the drug of 0.3 μm *Re* becomes 0.019 and, assuming a maximum difference of about 10 μm in size, for a maximum particle size of 8.3 μm Re is 0.539. The critical *Re*-threshold levels to change from a laminar into a laminar-turbulent air flow, and to change from a laminar-turbulent into a turbulent air flow are 5 and 70, respectively.[16] Hence, during detachment of the drug particles from the carrier particles in the air stream under the above defined experimental conditions, laminar air flow conditions exist near the particulate interface, and therefore only model 3 is applicable.

Zimon[13] has shown that the important quantity to detach the particles from a surface in an air stream is the drag force F_{drag}, which is defined by

$$F_{drag}=\mu_s\cdot F_{ad} \tag{4}$$

where μ_s=static coefficient of friction, and F_{ad}=adhesion force. He also showed, that in the calculations of the drag force from adhesion forces the structure of the boundary layer has to be taken into account. Under the conditions of a laminar boundary layer, F_{drag} can be calculated from

$$F_{drag}=0.94\cdot\rho_o d_p^2 v_\infty\left(\frac{\eta_{kin}}{x}\right)^{1/2} \tag{5}$$

where ρ_o=true density of the air, d_p=size of the adhered particle, v_∞=free flow velocity of the air, and x=distance of the adhered particle from the leading edge of the carrier surface. The quantity of x can be approximated from the particle size d_c of the carrier material by $x=0.5\times d_c$.

The reverse problem, *i.e.* the calculation of the air flow rate necessary to detach a particle, can be solved combining Eqs. 4 and 5:

$$v_\infty=\frac{\mu_s\cdot F_{ad}}{0.94\rho_o d_p^2\left(\frac{\eta_{kin}}{0.5d_c}\right)^{1/2}} \tag{6}$$

The drug particles in a powder aerosol are not monosized, and hence adhesion force measurements will result in an adhesion force distribution rather than in a single adhesion value. The force necessary to detach particles varies proportionally with their particle size, and typically S-shaped detachment force distribution functions arise. In some cases, these functions may follow a normal distribution,[17] but for particles, which have a log-normally distributed polydispersity of size, a log-normal adhesion force distribution was found.[18] However, under certain circumstances, for example for irregular particles or extremely rough surfaces in contact, detachment force distributions of polydispersely size-distributed particles can deviate completely from normal or log-normal shape.[19] The CIS has therefore to provide 3 different approaches to link the adhesion force distributions obtained to the original particle size distribution of the adhered drug.

In the first situation, the density function of a normal distribution is

$$y=p(x)=\frac{1}{\sigma\sqrt{2\pi}}e^{-(x-\mu)^2/2\sigma^2} \tag{7}$$

where μ=mean value of the population, and σ=standard deviation of the population. In the second case, the density function of the log-normal distribution can be approximated from

$$y=p(\ln x)=\frac{p(x)\cdot\ln x}{0.4343} \tag{8}$$

This has the advantage that in both cases μ can be estimated using the median adhesion force, because both in a normal distribution and in a transformed log-normal distribution μ and the median are identical. (Note, that transformed means that the original bell shape has been found by drawing $p(x)$ as a function of the numerical values of $\ln(x)$ on an arithmetic scale.) The true value of σ can be estimated iteratively for the best fit of the experimental adhesion force distribution to the theoretical one.

In the third situation, the frequencies can be extrapolated stepwise between each measuring value of the adhesion force distribution. The latter should be used, if estimates of the normal or log-normal distribution show a considerable lack of fit, especially at higher adhesion force values.

In all cases, the finally chosen approximation of the total adhesion force distribution is related to the particle size distribution in equal terms. During an iteration cycle, for a given adhesion force between 99.999% and 0.001%

probability of the adhesion force distribution the accurate probability density is calculated. The equivalent cumulative probability density of the particle size distribution is determined, and consequently the equivalent particle size is known. The air flow rate to detach such particles is calculated using Eq. 6 and compared with the flow rate chosen for the cascade impactor. The iteration mechanism stops if the calculated flow rate is smaller than the flow rate used in the cascade impactor, and the minimum particle size that can be detached is hence known. The sum of the frequencies of the drug particle sizes which cannot be detached is defined as "drug loss due to adhesion."

To use the remaining particle size distribution in a cascade impactor simulator, two normalization steps have to be performed. First, the microscopically evaluated particle sizes (equivalent circle diameters) need to be transformed into aerodynamic particle diameters[15]:

$$d_{ae}=d_p\left(\frac{\rho_p\cdot C(d_p)}{\rho_o\cdot C(d_{ae})}\right)^{1/2} \tag{9}$$

where d_{ae} = aerodynamic particle diameter, d_p = original equivalent circle particle diameter, ρ_p = density of the particle, ρ_o, unified density ($\approx 1000\,kg\,m^{-3}$), and C = Cunningham slip correction factor. The latter can be calculated from

$$C=1+\frac{2\lambda}{d_p}(1.23+0.41e^{-0.44(d_p/\lambda)}) \tag{10}$$

where λ is the mean free wave length of the gas molecules. The value of λ can be obtained from

$$\lambda=2\frac{\eta_{dyn}}{p}\left(\frac{\pi R_m T}{8M}\right)^{1/2} \tag{11}$$

where p = air pressure, R_m = molar gas constant, and M = molar mass of the air ($M=\rho_o V_o$; V_o = molar volume assuming ideal gas behaviour).

Secondly, the remaining particles are those, which will enter the cascade impactor, and which will be distributed according to their aerodynamic behaviour. It appears reasonable to quantify the total amount of particles entering the cascade impactor with 100%. Thus the frequency of the polydisperse particles needs to be recalculated based on this assumption.

Numerical cascade impactor simulators have been described earlier.[20-23] The model used here is equivalent to that described by Ludwig[20]:

$$G_m=\int_0^\infty E_m(d_{ae})F_m(d_{ae})dd_{ae} \tag{12}$$

where G_m = amount of material collected at stage m, $E_m(d_{ae})$ = collection efficiency of the m^{th} stage as a function of the aerodynamic particle diameter, $F_m(d_{ae})$ = particle size distribution of the material entering the m^{th} stage. The particle size distribution of the material to be collected must be provided as a single frequency distribution, whereas the collection efficiency must be provided as a cumulative frequency distribution. The relative amount of particles retained from each collection stage is the quotient between the area under the integral given in Eq. 12 and the area under the single frequency distribution of the drug.

The loss on the cascade impactor walls (WL) due to Brownian motion, gravitational settling, bounce and blow-off effects can be roughly estimated using a polynomial expression derived by Franzen and Fißan[24]:

$$WL=-0.0253-0.0216\ln d_p+0.0744\ln^2 d_p+0.0188\ln^3 d_p-0.00677\ln^4 d_p \tag{13}$$

A problem arises, if a preseparator has been used. In the case of a dry powder inhalation, where the drug is adhered to a carrier particle, carrier particles will reach the stage of the preseparator. Thus in the preseparator the amount of drug experimentally determined is the sum of drug still adhered to those carrier particles which passed the throat and entered the preseparator, and those drug particles which were detached in the throat but retained by the preseparator. Furthermore, wall loss of the drug may also occur. Hence, the CIS must treat the preseparator stage separately. First the amount of drug retained will be calculated according to Eq. 12. Secondly, the amount of drug lost on the wall is calculated using Eq. 13. Repeating the calculation of the wall loss after entering stage 0, the difference between the two wall loss values calculated approximates the wall loss in the preseparator. The sum of the drug lost due to adhesion (see above) and the amount of drug withheld in the preseparator due to impaction and wall loss is here defined as the "apparent drug loss due to adhesion," because in the experiments it is not possible to separate the different entities in the preseparator stage.

The CIS developed has been computed, and the following input parameters are required: median adhesion force and interquartile range; percentage drug remained adhered for different spin-off forces (see Materials and Methods); static coefficient of friction between drug and carrier particles; air flow rate; geometric mean diameter (number distribution) of the carrier particles; cumulative particle size distribution (equivalent circle diameter) of the drug in 0.1 μm steps (data as ASCII file); cumulative collection efficiency distributions for preseparator and stages 0 to 7 in 0.1 μm steps (data as ASCII file); minimum and maximum particle size for drug and collection efficiency distributions; density of the drug.

The simulation process can be monitored. The final output of the program provides information about: minimum particle size that can be detached from the carrier particles; percentage powder collected at each stage; loss of drug due to adhesion; loss of drug in the preseparator; loss of drug on the impactor walls (excluding preseparator); apparent loss due to adhesion as defined above.

Experimental

Materials Medium grade lactose monohydrate (Borculo Whey Products Ltd., Saltney, UK) was used as carrier material. A laboratory batch of micronized Salmeterol Xinafoate (GlaxoWellcome Research & Development, Ware, UK) was used as model drug.

For the chemical evaluation of the drug by means of an HPLC method, the following materials were used: methanol HPLC grade, analar grades of hexane, sodium dodecyl sulphate, glacial acetic acid, silicon oil (all BDH, Poole, UK). The silicon oil is characterised by the following parameters: density $0.976\,g\,cm^{-3}$, refractive index 1.403, kinematic viscosity $60000\,m^2\,s^{-1}$ and surface tension $21.5\,mN\,m^{-1}$. Salmeterol

hydroxynaphthoate (GlaxoWellcome Research & Development, Ware, UK) was used as calibration standard (purity 99.7%).

Diiodomethane (Aldrich Chemicals Co., Ltd., Fillingham, UK) has been used as suspension liquid for particle size analysis.

Methods The particle size of lactose monohydrate and Salmeterol Xinafoate was determined using image analysis. An appropriate amount of powder was suspended in diiodomethane, and the suspension was spread onto a microscopy slide. A cover slip was added allowing the suspension to settle homogeneously between the two glass surfaces. The particle size was assessed with a seescan image analyzer (Solitaire 512, Seescan, Cambridge, UK), which is attached to a microscope (Olympus BH-2, Tokyo, Japan) *via* a miniature video camera module (CCD-4, Rengo Co., Ltd., Toyohashi, Japan). Per slide, 512 particles can be measured (maximum hardware storage capacity). The following 2 parameters were assessed for each individual particle: Feret's diameter, which is here defined as the average value of 36 single measurements, which are made in 10 degree steps around each particle; and equivalent circle diameter. For lactose monohydrate, the geometric mean and standard deviation of the number distribution was calculated from the distribution of Feret's diameters as described by Martin *et al.*.[25]

Interactive powder mixtures were produced using 200.0 mg Salmeterol xinafoate and 99.8 g lactose monohydrate. The powders were accurately weighed into a 500 ml glass jar, which then was closed and fixed into a Turbula T2C mixer (Willy A. Bachofen AG Maschinenfabrik, Basel, Switzerland). Five different mixing speeds could be used: 20, 30, 42, 62, 90 rpm, and the mixing time was varied between 5 and 25 min. The powders were filled into preformed blisters (target weight 25 mg) and sealed with aluminium foil using an iron at 210 °C. The blisters were cut into round disks similar to those used in Diskhalers®.

The adhesion force between drug and lactose monohydrate carrier particles was determined using the centrifuge technique, which is outlined in detail by Podczeck and Newton.[26] An Ultracentrifuge (Centrikon T-1080, Kontron Instruments, Milan, Italy) with a vertical rotor (TV-850, DuPont Sorvall, Wilmington, U.S.A.) and a set of specially developed adapters (Ventura Scientific, Orpington, UK) was used. The adhesion samples were prepared using aluminium disks as support surfaces, which were covered on one side with a double-sided sticky tape. A paper ring of matching size, which had an inner open area of about 7 mm diameter, was stuck on top of the sticky tape allowing the removal of the disks from the adapters in the experimental stage. Particles of the interactive mixtures were sprinkled on top of the remaining sticky surface, and the disks were gently tapped to allow an orientation of the lactose monohydrate carrier particles to be attached in their most stable position. The number of drug particles initially adhered to the carrier particles was determined using the image analyzer in a manual mode. The surfaces were illuminated using a cold light source (High Light 3002, Olympus Co., Hamburg, Germany), which was attached parallel to the surface, about 1.5 cm from the periphery. The two light beams were placed at an angle of 180° to each other to minimize the formation of shadows. The initial number of drug particles was about 150 per surface, and 6 surfaces were used parallel in each experiment. A spin-off force was applied, and the number of particles remained adhered was determined. An adhesion force distribution was obtained by successively increasing the spin-off force after each counting. The median adhesion force, which is the force value where 50% of the particles are detached, and the interquartile range, which is the difference of the force values necessary to detach 75% and 25% of the particles initially adhered, was calculated from each individual adhesion force distribution. In this way, a quantitative characterization of the average adhesion force and its variability was possible without making any assumption about the nature of the underlying distribution function. All results are the mean and standard deviation of these characteristic values using 6 replicates.

The mass median aerodynamic diameter of the drug particles was determined using a cascade impactor (Mark II, Graseby Andersen, Atlanta, U.S.A.) attached to a vacuum pump with an adjustable nominal flow rate between 6 and 100 l min^{-1} (Copley, Nottingham, UK) under standardized operation conditions.[27] The operation air flow rate was set to 60 l min^{-1}, and preseparator and collection plates 0 to 4 were calibrated employing the procedure described by Warnke *et al.*[1] using starch microspheres and lycopodium spores. To reduce the rebouncing effect due to the high elasticity of the drug particles, the stainless steel collection plates were coated with silicon oil. The silicon oil was suspended in hexane (2%). An accurately defined volume of the suspension was distributed on each collection plate to give a film thickness of 3.75 μm, and the plates were left to dry under ambient room conditions at least for one hour. A high-efficiency preseparator (Graseby Andersen, Atlanta, U.S.A.) was also used. The glass throat used has been described by the European Community Pharmacopoeia commission,[28] and is the standard throat required by the European Pharmacopoeia. Prior to each experiment the accuracy of the flow rate selected was tested and adjustments were made when necessary. Afterwards, the preseparator was filled with 5.0 ml methanol and the mouth piece was attached to the throat. For each experiment, 2 disks (equivalent to 8 single doses) were cleaned with acetone to remove all ink from the aluminium foil. A disk containing 4 blisters was inserted into the inhaler device (Diskhaler®), and a blister was opened lifting the inhaler device lid and thus pushing the piercing pin into the blister. The lid was carefully closed avoiding the loss of any powder adhered to the piercing pin. The device was inserted into the mouth piece assuring its correct horizontal position. The pump was switched on for 3 s. The inhaler device was removed from the mouth piece, and the disk was turned so that a further blister could be opened. Empty disks were stored in a petri dish, and also the inhaler device was stored in a petri dish, until the analytical assessment of the drug content, which remained, took place.

The amount of drug on each collection plate, in the backup filter, in the throat, preseparator, device stage (*i.e.* in the empty disks and the inhaler device) and on the impactor walls (*i.e.* the stainless steel stages without collecting plates) was determined using an HPLC method. The drug was washed into volumetric flasks of the following volume using methanol: device, throat, preseparator into 100.00 ml each, collection plates 0 to 7 and backup filter into 25.00 ml each, impactor walls into 50.00 ml. Thus, 13 different samples were collected for each experiment.

A carefully degassed buffered mobile phase, which contained methanol and aqueous buffer (sodium dodecyl sulphate–acetic acid 0.0025 M) in a ratio of 10 : 1 was used in the HPLC procedure. A short Hypersil column (ODS 5 μm, Shandon HPLC, Runcorn, UK) was placed into a temperature control unit (TC 1900, ICI, Instruments, Dingley, Australia) maintaining a working temperature of 40 °C. The flow rate of the mobile phase was set to 1 ml min^{-1} using a standard pump module (Consta Metric 3000, LDC, Milton Roy, UK). The drug content was detected using a fluorescence detector (abi 980, ABI Instruments, UK). The excitation wave length was 225 nm, and the emission wave length was 345 nm. The light intensity was recorded using a chart recorder (Servoscribe RE 511.20, BBC Goerz, Metrawatt, Vienna, Austria). The area under the peaks was measured using a planimeter (Allbrit, London, UK). Usually, 100 μl were injected *via* an injection port with an 100.0 μl injection loop. Each sample solution was injected at least twice to guarantee the reproducibility of the results. The sensitivity of the detector was adjusted in accordance with the concentration of the drug. A standard solution of 0.7 μg ml^{-1} salmeterol hydroxynaphthoate was used to calibrate the method. The standard was injected at least twice for each level of sensitivity. A short computer program was written to calculate the amount of drug per sample and blister from the analytical data.

The mass median aerodynamic diameter and its geometric standard deviation were derived graphically using probability paper, based on the amount of drug impacted on stages 0 to 7.

Results and Discussion

Interactive powder mixtures of 0.2% Salmeterol xinafoate and lactose monohydrate were produced varying the mixing time and speed according to a composite design. This statistical design was used to explore a wide range of values of the influence factors chosen in a systematic manner with the aim of proving that the CIS has not only a limited applicability to mixtures of the author's choice but also works for a wide range of possible mixture properties. All experiments using these mixtures were performed in random order.

Table 1 summarizes the median adhesion forces and interquartile ranges of the adhesion force distributions obtained under the different mixing conditions and Table 2 lists the observations made using the cascade impactor.

An increase in mixing time increases the median adhesion force in all cases. However, the influence of the mixing speed is not a simple process. Both a very slow mixing speed, and a very high mixing speed result in increased adhesion properties compared to medium mixing speed levels. At a very low mixing speed particles have more contact time with each other, which has been shown to increase adhesion forces.[29] On the other hand, a high speed results in an increased mixing force and thus in more asperity deformation during the contact of the particles. The associated increase in true area of contact is the reason for the increase in adhesion force. Hence, at medium mixing speed levels, lower adhesion forces will result. The mass median aerodynamic diameter (*MMAD*) decreased with a decrease in mixing speed, but increased with an increase in mixing time, except for a mixing speed of 42 rpm. The latter suggests that the *MMAD* could follow an optimum function in the sense of a minimum value at a medium mixing time.

For the simulations using the CIS the following constant input values were used: static coefficient of friction between drug and lactose monohydrate, 0.31[9]; geometric mean diameter of the carrier particles, 23.4 μm; minimum particle size of the drug 0.2 μm; maximum particle size of the drug 7.3 μm. The use of a literature value for the static coefficient of friction is justified by Amonton's law and the fact, that it is a constant independent of contact area[30] and thus particle size.

Table 3 lists the important parameters simulated. The "experimental loss due to adhesion" has been calculated on the basis of the amount of drug which has left the inhaler device. Thus the relative proportion listed here is not equivalent with the sum of the throat and preseparator value listed in Table 2. This correction was necessary, because the loss in the inhaler device cannot be approximated to date. The value of the "apparent loss due to adhesion" has been explained in the theoretical section, as has the "theoretical wall loss." The "experimental wall loss" has been again calculated on the basis of the drug detached from the carrier to match the information provided by the CIS. Thus, the relative proportion listed

Table 1. Median Adhesion Force and Interquartile Range of Micronized Salmeterol Xinafoate Adhered to Lactose Monohydrate Carrier Particles in Interactive Powder Mixtures Prepared in a Turbula Mixer

Mixture	Mixing time (min)	Speed (rpm)	M ($\times 10^{-12}$ N)	IQR ($\times 10^{-12}$ N)
1	15	90	12.25±2.08	26.58± 4.07
2	10	62	10.18±1.70	23.69± 0.86
3	20	62	41.97±6.44	64.48± 4.42
4	5	42	2.99±0.22	5.62± 1.02
5	15	42	6.55±0.13	17.00± 0.35
6	25	42	7.65±1.61	17.39± 1.51
7	10	30	7.28±1.70	18.86± 2.88
8	20	30	28.65±3.16	68.06±10.97
9	15	20	10.09±1.50	18.83± 1.40

Arithmetic mean and standard deviation of 6 replicates. M, median adhesion force; IQR, interquartile range.

Table 2. Mass Median Aerodynamic Diameter and Drug Loss of Interactive Mixtures of 0.2% Salmeterol Xinafoate and Lactose Monohydrate

Mixture	1	2	3	4	5	6	7	8	9
Mixing time (min)	15	10	20	5	15	25	10	20	15
Mixing speed (rpm)	90	62	62	42	42	42	30	30	20
1. Drug on carrier									
Device (%)	11.95	15.07	11.78	12.84	13.43	13.18	28.95	13.55	16.23
Throat (%)	22.15	14.63	22.59	18.90	24.00	21.86	14.26	21.74	19.93
Preseparator (%)	32.25	32.28	35.65	35.86	30.73	32.36	32.69	37.18	31.54
Total (%)	66.34	61.98	70.02	67.60	68.16	67.40	75.89	72.47	67.71
2. Drug apparently detached from the carrier									
Total (%)	33.66	38.02	29.98	32.40	31.84	32.60	24.11	27.53	32.29
of which lost on impactor walls (%)	4.97	5.16	4.67	4.64	5.13	5.72	4.00	4.57	6.54
MMAD (μm)	5.59	5.90	6.35	5.60	5.55	6.20	5.58	6.30	5.37
GSD (μm)	0.46	0.52	0.41	0.48	0.48	0.63	0.50	0.49	0.48

MMAD, mass median aerodynamic diameter; *GSD*, geometric standard deviation.

Table 3. Results Obtained for Powder Mixtures 1 to 9 Using the CIS and Comparable Experimental Values

Mixture	Speed (rpm)	Time (min)	$LDA_{(app.)}$ (%)	$LDA_{(exp.)}$ (%)	$WL_{(theor.)}$ (%)	$WL_{(exp.)}$ (%)	$MMAD_{(theor.)}$ (μm)	$GSD_{(theor.)}$ (μm)
1	90	15	65.67	61.77	15.97	14.76	5.95	0.54
2	62	10	61.21	55.23	15.88	13.57	5.90	0.55
3	62	20	79.37	66.02	16.78	15.58	6.15	0.57
4	42	5	43.09	62.83	15.51	14.32	5.64	0.54
5	42	15	52.48	63.22	15.69	16.11	5.79	0.54
6	42	25	56.08	62.45	15.74	17.55	6.25	0.69
7	30	10	58.62	66.07	16.08	16.59	5.80	0.54
8	30	20	72.46	68.16	16.45	16.60	6.00	0.56
9	10	15	61.21	61.45	15.88	20.25	5.85	0.55

LDA, loss due to adhesion; *WL*, wall loss; *MMAD*, mass median aerodynamic diameter; *GSD*, geometric standard deviation; app., apparent; theor., theoretical; exp., experimental.

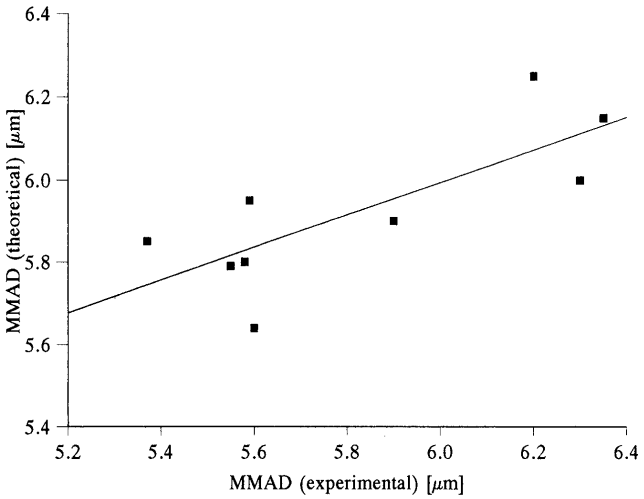

Fig. 1. Relationship between Experimental and Theoretical *MMAD*

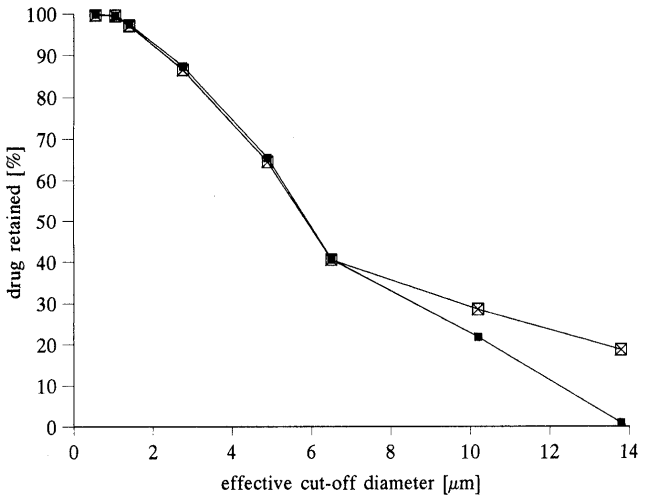

Fig. 2. Comparison of the Experimental (□) and Theoretical (■) Aerodynamic Particle Size Distributions for the Best Fit of the *MMAD* (Experiment 2)

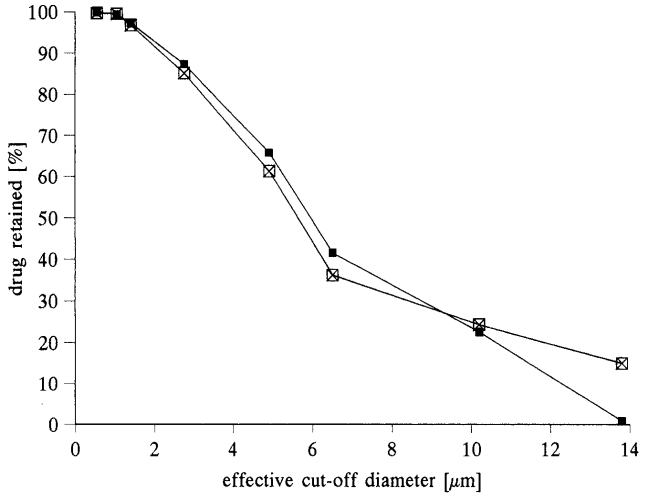

Fig. 3. Comparison of the Experimental (□) and Theoretical (■) Aerodynamic Particle Size Distributions for the Least Fit of the *MMAD* (Experiment 9)

here is different from the value provided in Table 2. The *MMAD* and geometric standard deviation (*GSD*) values have been calculated from the cumulative percentage of drug retained at each simulated collection plate, in a similar manner to the calculation of the experimental values.

The estimates of the amount of drug lost due to adhesion to the carrier particles are both higher (experiments 1—3, 8) or lower than the experimental values. In 2 cases the loss is over- or underestimated by more than 10% (experiments 3 and 4), and in 2 cases the estimate differs by less than 4% (experiments 1 and 9). This appears a reasonable result. During the calculations it was observed that particles of an equivalent circle diameter below 1.2 μm are in no case detachable from the carrier material, even for very low adhesion forces. This suggests that the micronization process could be stopped earlier to give particles of an equivalent circle diameter above about 1 μm only.

The wall loss calculated by the CIS closely matches the experimental values except for mixture 9. The wall loss can therefore be regarded as closely predictable.

The *MMAD* predicted was found both above or below the experimental values, and in 3 cases closely matching the experimentally measured *MMAD* (experiments 2, 4 and 6). Figure 1 illustrates this finding. Employing a linear regression of the second kind to adjust for the uncertainty due to the experimental error of the *MMAD* (here used as X-variable), residual analysis has shown that the average error in predicting the *MMAD* using the CIS is 5% (root mean square deviation 5.2%). Several reasons should be considered to introduce errors into this prediction: First, variability of the experimental results of the adhesion and impaction measurements; secondly, measurement errors during the particle size analysis of the drug distorting the particle size distribution; and thirdly, erroneous collection plate efficiency curves due to a limited possibility for calibration (see experimental section). To find out the proportion of the errors introduced to the experimental values by the adhesion force measurements and in the cascade impactor, the variation of the theoretical *MMAD* due to a variable adhesion was determined. The median adhesion forces are presented as arithmetic mean and standard deviation (see Table 1), and therefore the error of the measurements is known. For the largest variability in median adhesion force (mixture 9), the value of the theoretical *MMAD* changes by ± 0.1 μm when simulated in the CIS, whereas on average the variability of the theoretical *MMAD* value is only ± 0.03 μm. Hence, the deviations of the model values from the experimental results are mainly due to high variability of the cascade impactor experiments.

Figures 2 and 3 compare the theoretical with the experimentally obtained aerodynamic particle size distributions for matching *MMAD* and largest difference in *MMAD*, respectively. Obviously, major deviations always occur at collection plates 0 and 1. Considering the maximum particle size of the drug (7.3 μm), one should not expect larger amounts of drug to be found on collection plate 0, and also find only a limited amount of drug on collection plate 1. To find out, why in practice, however, considerable quantities of drug were found on these 2 plates, a reference experiment was performed: Only 1 single

dose was emitted from the inhaler device, and the collection plates 0 and 1 were inspected microscopically. Especially on plate 0, drug particles were found to be adhered to fine lactose particles. Thus, for the amount of drug found on these plates, lactose–drug agglomerates should be considered instead of single particles. The aerodynamic behaviour of such agglomerates explains the higher amount of drug found experimentally. However, to date there exists no model which could quantify or predict the occurrence of such agglomerates. In terms of assessing the *MMAD*, the deviations at this two collection plates are less important, especially if it is considered that the most desired amount of particles will impinge on plates 2 to 4.

Conclusions

The simulation of the aerodynamic behaviour of drug particles in dry powder inhalations following the drug–carrier principle on the basis of median adhesion force measurements provides reliable estimates of the aerodynamic behaviour of the dry powder inhalation formulation, and the CIS developed could become a useful tool in an early development stage, where only limited amounts of drug are available. In this respect, either one powder mixture can be produced under standard mixing conditions to allow the measurement of the static coefficient of friction and an average median adhesion force, or particle-on-particle experiments as described earlier[8] can be performed for the same reason. In the latter case 1 to 2 mg of drug would be sufficient, but the press-on force to simulate the mixing force applied would have to be adjusted. By variation of input parameters such as the particle size of drug and/or carrier material, or by varying the adhesion force values, a feasibility study could be performed, which allows the theoretical assessment of several influence factors on the inhalation performance. The true development stage could then be started with mixture candidates which are most likely to succeed, and the number of experiments to be performed could be sufficiently reduced.

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