ELSEVIER

International Journal of Pharmaceutics 160 (1998) 119–130

international journal of pharmaceutics

The relationship between physical properties of lactose monohydrate and the aerodynamic behaviour of adhered drug particles

Fridrun Podczeck

Department of Pharmaceutics, The School of Pharmacy, University of London, 29/39 Brunswick Square, London WC1N 1AX, UK

Received 4 July 1997; accepted 16 September 1997

Abstract

The influence of particle size, shape, particle surface roughness and water loss on drying of lactose monohydrate carrier particles on the aerodynamic properties of dry powder inhalations based on interactive mixtures with a micronized drug has been investigated. Two sets of mixtures were prepared to relate the physical properties of the lactose monohydrate particles to the aerodynamic properties of the formulations: (A) constant mixing time and speed (25 min, 42 rev./min), and (B) optimal mixing time (speed 42 rev./min) to obtain a given adhesion force between drug and carrier particles. All ten lactose monohydrate batches provided different aerodynamic properties under test conditions (A) and (B). The relationship between the physical properties of the lactose monohydrate carrier particles and the aerodynamic properties of the drug is complex, and a simple interchange of the carrier material in terms of brand or grade appears impossible. Particle size, shape, water loss on drying, and to a lesser extent surface roughness influence the loss of drug for example in the device, preseparator and loss due to adhesion. The relationships can be quantified mathematically, if mixing has been undertaken under similar conditions, i.e. identical mixing time and speed (test condition (A)). However, for interactive mixtures, which have been manufactured under test condition (B), the connection between the physical properties of the carrier materials and the aerodynamic behaviour are less quantifiable. A similar adhesion force does not guarantee a similar aerodynamic behaviour of the drug in the cascade impactor. The findings indicate that it is mainly the site of adhesion, i.e. adhesion to fine or larger carrier particles which determines the drug lost in the device and preseparator, and is responsible for deviations in the *MMAD*.

Abbreviations: AR = aspect ratio; B = adjusted multiple determinant; C = circularity; d_g = geometric mean diameter; d_{vs} = Edmundson's weight mean of the surface distribution; F = mean Feret diameter; LDA = loss due to adhesion; $MMAD$ = mass median aerodynamic diameter; NS = new shape factor; P = probability; R^2 = multiple squared correlation coefficient; R_a = rugosity; R_q = root mean square deviation of the roughness profile from the mean line; R_{tm} = maximum peak-to-valley-ratio; RMS = root mean square deviation (residual analysis); s_g = geometric standard deviation (particle size analysis); $Skew$ = skewness; Wa = loss on drying; WL = loss of detached drug on the impactor walls; Y = experimentally observed value; $\hat{Y}$ = predicted value; β = autocorrelation distance; σ_g = geometric standard deviation (aerodynamic particle size distribution).

0378-5173/98/$19.00
PII S0378-5173(97)00313-X

Keywords: Particle size; Particle shape; Particle surface roughness; Water loss on drying; Lactose monohydrate carrier particles; Aerodynamics of dry powder inhalations; Micronized drug

1. Introduction

Dry powder inhalations often consist of mixtures of coarse carrier particles (size 50–200 μm), which are physiologically inert, with drug particles, which are micronized and often dosed only in the microgram range. The physical characterization of the carrier particles in terms of particle size, shape and surface roughness appears to be important with respect to an interchangeability of grades or batches in a formulation. The above properties influence the mixing process, i.e. to achieve a formulation with defined properties mixing time and speed might have to be adjusted depending on the physical measurements of the carrier material. The formulation properties can for example be characterized using adhesion force measurements or by determination of the aerodynamic particle size using a cascade impactor. It had been shown that these two properties are related (Podczeck, 1997a).

Keeping the particulate properties of the drug constant, resuspension of the drug particles from the carrier particles will depend on the particle size of the carrier material and the adhesion and friction properties between drug and carrier particles (Zimon, 1982). Resuspension is easier for smaller carrier particles, because Zimon's resuspension model assumes that the detachment of the drug particle occurs laterally to the carrier surface, i.e. the drug particle slides along the surface until it reaches the edge and falls off. The longer the travelling distance, the greater is the drag force which is needed to overcome adhesion and friction between drug particle and carrier particle surface. Thus the influence of particle size of the carrier material is obvious, and particle surface roughness will be one main factor to consider in terms of adhesion and friction (Corn, 1961; Fuller and Tabor, 1975; Tabor, 1977; Johnson, 1985; Kendall, 1994; Soltani et al., 1995; Maugis, 1996). In the resuspension process, the particle shape is only important for the adhered drug particles, but particle shape of the carrier particles might influence the mixing force due to increased friction (Rumpf, 1990) and thus indirectly the resuspension stage due to increased or decreased adhesion forces.

The aim of this work was to investigate the influence of particle size, shape and particle surface roughness of a commonly used carrier material (lactose monohydrate) on the aerodynamic properties of a model drug (Salmeterol Xinafoate) using interactive powder mixtures of drug and carrier as dry powder inhalations.

2. Materials and methods

Ten batches of medium grade lactose monohydrate from three different manufacturers were used: Pharmatose 125M, 150M, 200M, 325M (batches 027526, 023516, 024521, 043445, respectively; DMV, Veghal, The Netherlands), Lactose *grade a*, *grade b*, *grade c* (batches WN3505, WN1775, WN1733, respectively; specific quality; Borculo Whey Products, Saltney, UK), Granulac 70, 140, Pulmolac 400 (batches 544, 527, 846, respectively; Meggle, Wasserburg, Germany). A laboratory batch of micronized Salmeterol Xinafoate (Glaxo, 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 60 000 m^2 s^{-1} and surface tension 21.5 mN m^{-1}. Salmeterol hydroxynaphthoate (Glaxo, Ware, UK) was used as calibration standard (purity 99.7%). Calcium chloride ($\times$ 6 H_2O, BDH, Poole, UK) was used for humidity control in desiccators.

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). A standard mixing speed of 42 rev./min was used, and the mixing time was varied between 5 and 30 min. The powder blends were filled into preformed blisters (target weight 25 mg) and sealed with aluminium foil using a domestic iron at 210°C. The blisters were cut into round disks similar to those used in Serevent Diskhalers®. The blisters were stored in desiccators, which contained a saturated solution of calcium chloride providing a relative humidity of the storage air of 35% at ambient room temperature. The time span elapsed between mixing and blistering was 24 h to allow for electrostatic charge decay, and the time span between blistering and experiment was at least 3 days to allow the development of stable humidity conditions inside the blisters.

The mass median aerodynamic diameter of the drug particles was determined using a cascade impactor (Mark II, Graseby Andersen, Atlanta, USA) attached to a vacuum pump with an adjustable nominal flow rate between 6 and 100 l min^{-1} (Copley, Nottingham, UK). A standard flow rate of 60 l min^{-1} was used. 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 dissolved in hexane (2% w/w). An accurately defined volume of the solution 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 for at least 1 h. A high-efficiency preseparator (Graseby Andersen, Atlanta, USA) was also used. The glass throat used has been described by the European Community Pharmacopoeia Commission (1993), and is the standard throat required by the European Pharmacopoeia. Because of the coating and the increased flow rate, the preseparator and impaction plates 0 to 4 of the cascade impactor were recalibrated. To match the high elasticity of the drug particles, starch microspheres (grade 45/25, Pharmacia, Uppsala, Sweden) and lycopodium spores were used. The calibration procedure described by Warnke et al. (1994) was adopted. Due to the coating, all cut-off diameters are shifted to larger values.

Prior to each experiment, the accuracy of the flow rate 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. The selected number of 2 disks was cleaned with acetone to remove all ink from the aluminium foil. A disk containing four blisters was inserted into the inhaler device, and a blister was opened by 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 and 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. In this way, the desired number of eight blisters was used. 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, 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 wavelength was 225 nm, and the emis-

sion wavelength 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 a 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 (*MMAD*) and its geometric standard deviation (GSD) were calculated using Probit-analysis, based on the amount of drug impacted on stages 0 to 7 as oversize distribution. The use of oversize distributions instead of the conventionally used undersize distribution is justified by the fact that the majority of drug particles impinges on plates 0 to 2. A correct statistical analysis requires an even distribution of the particles above and below the *MMAD*. To satisfy this requirement, undersize distributions are inadequate, because the percentage impacted on plate 0 is lost for the analysis. (Note that the amount of drug in the preseparator must be excluded from the calculations, because it is not possible to predict the amount of drug that has been detached from the carrier particles.) Oversize distributions, however, provide at least 2–3 points of the distribution above the *MMAD*, thus always one point more than the related undersize distribution. It is important to note, that theoretically, i.e. for ideal statistical fit of the data to the probit function, the *MMAD* is equal for over- and undersize distributions. However, while for undersize distributions the GSD is >1, it becomes <1 for oversize distributions.

The particle size of the different lactose monohydrate batches 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. Particle size and shape were assessed parallel 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, Toyohashi, Japan). Per slide, 512 particles can be measured (maximum hardware storage capacity). The following four 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° steps around each particle; aspect ratio, which is here defined as the ratio between longest Feret diameter and its perpendicular dimension; circularity as defined by Hausner (1966); shape factor *NS* as defined by Podczeck (1997b). For each population, values of Edmundson's weight mean of the surface distribution (Edmundson, 1967) were calculated, as was the geometric mean and standard deviation of the number distribution. The skewness of the number distributions was also determined.

The surface roughness of single lactose monohydrate particles was assessed using a laser profilometer (UBM Microfocus Measuring System, UBM Meßtechnik, Ettlingen, Germany). The light spot diameter is 1 μm, and the sensor aperture angle is 53°. Measurements were performed in a 3D-mode at a frequency of 100 points/s and a measuring depth of $\pm$ 50 μm. Particles larger than 100 μm were used. They were sprinkled onto dark plastic surfaces of known surface roughness. Initially, a 3×3 mm trace was run with a resolution of 100 points/mm to identify the position of the particles on the support disk. The X–Y-coordinates of 10 particles were programmed, and the surface roughness of the particulate surfaces was measured with a resolution of 1000 points/mm. The measured area was 20×20 μm only, because the slope of the roughness profile must not exceed $\pm 7°$ to ensure a determination with high precision. The roughness descriptors R_a (rugosity, i.e. the arithmetic mean of the departures of the roughness profile from the mean line), R_q (root mean square deviation of the asperity hight distribution) and R_{tm} (average peak-to-valley ratio) have been assessed according to BS 1134 (1972).

Table 1
Particle size of lactose monohydrate from different batches (data from Podczeck, 1997c)

Brand name	F (μm)	d_{vs} (μm)	d_g (μm)	s_g (μm)	*Skew*
Lactose *grade a*	36.1 ± 27.9	76.3	23.4	2.1	0.87
Lactose *grade b*	29.8 ± 26.0	78.5	19.2	2.3	0.84
Lactose *grade c*	24.3 ± 19.3	69.3	15.3	2.3	0.59
Pharmatose 125M	24.0 ± 23.9	71.3	11.4	2.7	1.13
Pharmatose 150M	25.2 ± 24.4	72.2	15.5	2.4	1.13
Pharmatose 200M	21.9 ± 21.6	71.5	13.6	2.4	0.96
Pharmatose 325M	29.4 ± 30.9	81.0	16.2	2.8	1.40
Granulac 70	33.4 ± 30.2	86.5	21.4	2.2	0.88
Granulac 140	24.6 ± 24.1	74.0	15.2	2.4	1.07
Pulmolac 400	14.1 ± 7.8	21.2	9.8	1.9	0.23

F, mean Feret's diameter; d_{vs}, Edmundson's weight mean of the surface distribution; d_g, geometric mean diameter; s_g, geometric standard deviation; *Skew*, skewness.

Furthermore, autocorrelation analysis (Whitehouse and Archard, 1970) was undertaken, and the correlation distance (β) and the ratio R_q/β (a measure of the asperity slope) were determined. The results are the arithmetic mean and standard deviation of 10 replicates of the above procedure.

The loss on drying of the lactose monohydrate batches was taken from the manufacturers' quality certificates and was 0.20% for all Pharmatose batches, 0.06% for *lactose grade a* and *lactose grade b*, 0.02% for *lactose grade c*, 0.29% for *Granulac 70*, 0.13% for *Granulac 140*, and 0.15% for *Pulmolac 400*.

3. Results and discussion

The results of the particle size, shape and surface roughness measurements are listed in Tables 1–3. Comparing all size characteristics together it can be concluded that there are no two equivalent lactose monohydrate products in this test series. The Borculo Whey Products batches appear narrower in their size distributions (compare smaller standard deviations for Feret's diameter, Table 1), and the skewness (Table 1) is clearly below those of the other products. DMV and Meggle products are similar in relative width of the size distributions, but the Meggle products provide less skewed size distributions. Despite the differences in particle size, the surface area which is available for contact with the micronized drug particles appears to be less variable for all lactose monohydrate batches. This can be seen by comparing Edmundson's weight mean of the surface distributions, which is indirectly proportional to the surface area of the particles. A relative ranking on the basis of Edmundson's weight mean of the surface distribution would suggest that *Pharmatose 125M*, *150M*, *200M*, and *lactose grade c* provide the largest surface area, whereas *Pharmatose 325M* and *Granulac 70* have the smallest

Table 2
Particle shape of lactose monohydrate particles from different batches (data taken from Podczeck, 1997c)

Brand name	*AR*	*C*	*NS*
Lactose *grade a*	1.53 ± 0.34	0.82 ± 0.24	7.22 ± 0.45
Lactose *grade b*	1.50 ± 0.36	0.90 ± 0.21	7.26 ± 0.44
Lactose *grade c*	1.48 ± 0.91	0.91 ± 0.18	7.26 ± 0.40
Pharmatose 125M	1.47 ± 0.29	0.97 ± 0.26	7.15 ± 0.55
Pharmatose 150M	1.48 ± 0.30	0.93 ± 0.25	7.20 ± 0.51
Pharmatose 200M	1.49 ± 0.30	0.96 ± 0.23	7.19 ± 0.48
Pharmatose 325M	1.47 ± 0.27	0.98 ± 0.26	7.16 ± 0.55
Granulac 70	1.44 ± 0.25	0.92 ± 0.19	7.29 ± 0.47
Granulac 140	1.50 ± 0.32	0.96 ± 0.26	7.12 ± 0.54
Pulmolac 400	1.43 ± 0.26	0.89 ± 0.18	8.35 ± 0.42

AR, aspect ratio; *C*, circularity; *NS*, new shape factor.

Table 3
Surface roughness of coarse lactose monohydrate particles (data taken from Podczeck, 1997c)

Brand name	R_a (μm)	R_q (μm)	R_{tm} (μm)	β	R_q/β
Lactose *grade a*	1.57 ± 0.81	1.97 ± 0.97	3.90 ± 1.51	49.1 ± 18.1	0.040
Lactose *grade b*	1.30 ± 0.50	1.67 ± 0.64	3.39 ± 1.14	55.4 ± 15.7	0.030
Lactose *grade c*	0.60 ± 0.25	0.76 ± 0.30	2.02 ± 0.59	57.0 ± 15.7	0.013
Pharmatose 125M	1.12 ± 0.74	1.23 ± 0.74	1.34 ± 0.93	40.0 ± 11.5	0.031
Pharmatose 150M	0.96 ± 0.78	1.18 ± 0.88	2.47 ± 0.90	44.0 ± 14.3	0.027
Pharmatose 200M	0.75 ± 0.28	0.93 ± 0.30	2.28 ± 0.49	55.0 ± 16.5	0.017
Pharmatose 325M	1.14 ± 0.39	1.45 ± 0.52	3.25 ± 1.00	53.0 ± 19.5	0.027
Granulac 70	1.22 ± 0.45	1.54 ± 0.57	3.43 ± 1.16	47.0 ± 18.9	0.033
Granulac 140	1.45 ± 0.85	1.79 ± 1.03	3.83 ± 1.58	44.0 ± 14.3	0.041

R_a, rugosity; R_q, root mean square value; R_{tm}, maximum peak-to-valley ratio; β, autocorrelation distance.

surface area of the batches studied. In terms of their geometric shape (parallelogram-like shape) all batches except *Pulmolac 400* are similar (compare shape factor *NS*, Table 2). The latter consists of more irregular particles, probably because it is milled down to a very small particle size (compare Table 1). Also, the elongation of the particles appears similar (*AR*, Table 2), with the DMV products being slightly less elongated. The surface roughness appears both different from manufacturer to manufacturer, and to be related to the particle size. The lactose monohydrate particles produced by Borculo Whey Products appear rougher than those from the other manufacturers. Both for DMV and Borculo Whey Products lactose monohydrate, the roughness decreases with a decrease in particle size, whereas for Meggle products the surface roughness increases with a decrease in particle size (Table 3).

Interactive powder mixtures of drug and lactose monohydrate were prepared to test the influence of the physical properties of the carrier material on the aerodynamic behaviour of the drug. In addition to the particulate properties listed in Tables 1–3, the water loss on drying of the powder (see Section 2) was considered, because moisture can influence agglomerate strength and thus the detachment of the drug from the carrier in the air stream. Two blocks of experiments have been tested: (A) the powder mixtures were prepared under standard mixing conditions (42 rev./min and 25 min mixing time), and (B) the mixtures were prepared under optimized conditions, i.e. mixtures which matched a given adhesion force between 6.71×10^{-12} and 7.91×10^{-12} N (adhesion results not shown, but previously published (Podczeck, 1997c)). The principles of the adhesion force measurements have been reported previously (Podczeck, 1997a). Both blocks of results will be discussed separately.

3.1. (A) Powder mixtures prepared under standard mixing conditions

The results obtained from the cascade impactor are summarized in Table 4 and Table 5. The drug loss reported for the device, throat, preseparator and the total loss have been calculated on the basis of the actual dose of drug per blister, whereas the amounts of drug lost due to adhesion and on the impactor walls are based on the amount of drug delivered from the inhaler device. The drug loss due to adhesion is defined as the amount of drug, which cannot be detached from the carrier particles in the air stream and thus cannot enter stages of the impactor below the preseparator.

An increased loss of drug in the device was found for all batches of lactose monohydrate with comparatively large amount of fines, i.e. for *Pharmatose 150M* and *200M*, and for *Pulmolac 400*. These batches therefore appear unsuitable for any dry powder inhalation.

The loss of drug in the preseparator decreases with a decrease in particle size of the lactose monohydrate carrier particles. This suggests that

Table 4
Drug distribution in the cascade impactor (different grades of lactose monohydrate, mixed at 42 rev./min for 25 min)—lost drug

Grade	Device (%)	Throat (%)	Preseparator (%)	*LDA* (%)	Total (%)
Lactose *grade a*	13.18	21.86	32.36	62.45	67.40
Lactose *grade b*	10.67	25.22	29.39	61.13	65.28
Lactose *grade c*	19.05	32.90	25.11	71.65	77.05
Pharmatose 125M	14.08	34.97	33.34	79.50	82.39
Pharmatose 150M	32.83	29.90	23.12	78.93	85.85
Pharmatose 200M	31.18	21.69	20.17	60.82	73.04
Pharmatose 325M	12.63	30.01	44.76	85.58	87.40
Granulac 70	9.92	30.24	50.41	89.53	90.57
Granulac 140	9.69	33.30	40.87	82.13	83.86
Pulmolac 400	29.70	33.08	9.62	60.73	72.39

LDA, loss due to adhesion (undetached drug, corrected for loss in device); total, sum of loss in device, throat and preseparator.

the loss in the preseparator is mainly due to drug still adhering to the carrier particles, both to the coarse and fine fraction. While agglomerates with fine lactose monohydrate particles can reach impaction plates, those with coarse carrier particles are withheld in the preseparator. The more coarse carrier particles exist, the higher is the proportion of drug adhering to them and the greater the amount of drug which will thus be lost in the preseparator.

Table 5
Drug distribution in the cascade impactor (different grades of lactose monohydrate, mixed at 42 rev./min for 25 min)—available drug

Grade	*WL* (%)	*MMAD* (μm)	σ_g^a
Lactose *grade a*	17.55	6.06	0.44
Lactose *grade b*	22.80	6.39	0.53
Lactose *grade c*	24.08	6.08	0.49
Pharmatose 125M	5.00	5.96	0.68
Pharmatose 150M	8.27	8.05	0.63
Pharmatose 200M	7.05	6.12	0.61
Pharmatose 325M	7.49	6.36	0.69
Granulac 70	7.12	8.68	0.64
Granulac 140	4.88	6.27	0.69
Pulmolac 400	22.61	7.86	0.48

WL, loss of detached drug on the impactor walls; *MMAD*, Mass Median Aerodynamic Diameter; σ_g, geometric standard deviation.
[a] Note comments on its evaluation made in Section 2 (Materials and methods).

The loss of drug due to adhesion appears again higher for lactose monohydrate batches with predominantly coarse particles such as *Pharmatose 325M* and *Granulac 70*. Agglomerates with fine lactose monohydrate particles can travel through the preseparator and thus are not evaluated as 'lost'.

With the exception of *Pharmatose 150M*, *Granulac 70* and *Pulmolac 400*, the respiratory properties, which are reflected in the *MMAD*, are similar for the lactose monohydrate batches tested. Thus, while the amount of drug available to penetrate into the lower airways changes according to the adhesion properties (compare LDA, Table 4), the detached drug has similar aerodynamic properties suggesting a similar particle size distribution. The higher *MMAD* values for mixtures with *Pharmatose 150M* and *Granulac 70* appear to be related to the different surface roughness of the carrier particles. Both lactose monohydrate batches were characterized by a large maximum peak-to-valley ratio (R_{tm}) in combination with a small rugosity R_a, whereas the other lactose monohydrate particles have either a large R_{tm} value and a large R_a value, or both values are small. The finding suggests that these two lactose monohydrate batches have an asperity distance in which the finer drug particles are trapped and hence the respirable drug particle size distribution is distorted to larger values.

Mathematical analysis was applied to quantify the influence of the different physical properties of

Table 6
Statistical parameters to validate the quality of multiple regression equations describing the relationship between aerodynamic properties of Salmeterol Xinafoate and the physical properties of lactose monohydrate carrier particles

Parameter	Device	Throat	Total loss	*LDA*	*WL*	*MMAD*
R^2	0.978	1.000	1.000	1.000	0.999	0.760
B	0.940	1.000	1.000	0.998	0.995	0.616
F-value	26.26	>1000	>1000	539.78	423.60	5.27
P-value	0.011	<0.001	0.001	0.002	<0.001	0.050
RMS (%)	7.68	0.07	0.15	0.40	5.04	6.93
Probability for						
F	0.005		0.009	0.011		
d_g	0.005		0.002	0.033	0.012	
d_{vs}	0.022		0.001	0.003		
Skew	0.016		0.001	0.004	0.003	
AR		<0.001	<0.001	0.001		
NS		0.001			<0.001	0.039
C			0.006			
R_q		0.011				
R_{tm}		0.005				
β		0.001				0.264
Wa	0.066	<0.001		0.022	<0.001	0.076

R^2, multiple squared correlation coefficient; *B*, adjusted multiple determinant; *F*, significance of the slope; *P*, probability; *RMS*, root mean square deviation (residual analysis); *F*, Feret's diameter; d_g, geometric mean diameter; d_{vs}, Edmundson's weight mean of the volume distribution; *Skew*, skewness; *AR*, aspect ratio; *NS*, shape factor; *C*, circularity; R_q, root mean square deviation of the roughness profile from the mean line; R_{tm}, maximum peak-to-valley ratio; β, autocorrelation distance; *Wa*, loss on drying; *LDA*, loss due to adhesion; *MMAD*, mass median aerodynamic diameter.

the lactose monohydrate powders on the aerodynamic properties of the powder mixtures. A 'stepwise forward algorithm' in a multiple regression method was used to quantify possible relationships. Table 6 lists the statistical parameters describing the fit of the data and the significance of the equations derived in terms of slope. The results for the residual analyses are presented in Table 7.

The following regression equations have been derived:

$$device = -4.69 \times F + 6.26 \times d_g + 26.46 \times Skew - 1.36 \times d_{vs} + 41.08 \times Wa + 113.94$$

$$throat = -285.22 \times AR - 42.43 \times NS - 69.08 \times Wa - 0.56 \times \beta + 1.74 \times R_{tm} - 2.79 \times R_q + 794.82$$

$$total = -520.07 \times AR + 22.19 \times Skew + 187.37 \times C - 3.04 \times d_{vs} + 4.32 \times d_g + 1.11 \times F + 780.56$$

$$LDA = -676.18 \times AR + 1.56 \times F + 1.48 \times d_g - 1.92 \times d_{vs} + 31.76 \times Skew - 30.92 \times Wa + 1126.59$$

$$WL = -80.62 \times Wa + 110.04 \times NS + 10.91 \times Skew - 0.29 \times d_g - 774.96$$

$$MMAD = 6.20 \times Wa + 12.04 \times NS - 0.06 \times \beta - 78.20$$

Apparently, the loss on drying i.e. the content of free, movable water appears to play a major role in the aerodynamic behaviour found. Hence, the aerodynamic properties cannot only be attributed to particle size, surface roughness and particle shape of the carrier particles. The loss in the device increases with the loss on drying indicating that more moisture prevents the complete emptying of the blisters due to stronger adhesion to the blister material or decreased disaggregation. However, the loss of drug in the throat, on

Table 7
Results of the residual analyses for the regression equations statistically described in Table 6

Lactose batch	Device		Throat		Total loss		*LDA*		*WL*		*MMAD*	
	Y	$\hat{Y}$	Y	$\hat{Y}$	Y	$\hat{Y}$	Y	$\hat{Y}$	Y	$\hat{Y}$	Y	$\hat{Y}$
Lactose *grade a*	13.18	13.17	21.86	21.89	67.40	67.31	62.45	62.34	17.55	17.33	6.06	6.29
Lactose *grade b*	10.67	12.62	25.22	25.19	65.28	65.44	61.13	61.35	22.80	22.63	6.39	6.41
Lactose *grade c*	19.05	18.21	32.90	32.91	77.05	77.15	71.65	71.47	24.08	24.27	6.08	6.07
Pharmatose 125M	14.08	14.17	34.97	34.98	82.39	82.34	79.50	79.71	4.68	4.68	5.96	6.84
Pharmatose 150M	32.83	32.99	29.90	29.88	85.85	85.94	78.93	79.18	8.98	8.98	8.05	7.21
Pharmatose 200M	31.18	33.01	21.69	21.69	73.04	72.84	60.82	60.38	6.58	6.58	6.12	6.46
Pharmatose 325M	12.63	12.89	30.01	30.02	87.40	87.47	85.58	85.21	7.32	7.32	6.36	6.21
Granulac 70	9.92	9.17	30.24	30.25	90.57	90.49	89.53	89.60	7.19	7.19	8.68	8.68
Granulac 140	29.70	27.02	33.08	33.07	72.39	72.40	60.73	61.07	5.26	5.26	6.27	5.81

Y, experimentally observed value; $\hat{Y}$, predicted value.

the impactor walls or due to adhesion to the carrier particles decreases with increased water content. This indicates the role of water as a lubricant, because the amount of loosely bound water and the working conditions (relative humidity of the storage air 35%) do not provide the possibility for capillary forces to occur (Podczeck et al., 1997).

The drug loss in the device appears to decrease with particle size of the carrier, although this is inconsistent with respect to the geometric mean particle size. It can be concluded that the method of particle size analysis has to be taken into account when discussing particle size effects. The amount of fine particles is also important for the estimation of the loss of drug in the inhaler device. From the skewness effect in the related equation it can be concluded that an increase in fine carrier particle fraction increases the loss of drug in the device.

The loss of drug in the throat depends mainly on the particle shape. Elongated particles provide less contact area when impacting on the throat wall, because the particle will move in the air stream with its longest dimension parallel to the air flow. It appears reasonable therefore, that with an increase in aspect ratio the loss of drug in the throat decreases. The influence of the carrier surface roughness is more difficult to interpret because of the nature of surface roughness data. However, it appears that the less rough carrier particle surfaces provide higher losses in the throat. The adhesion to surfaces of low surface roughness is increased (Tabor, 1977; Johnson, 1985; Kendall, 1994; Levins and Vanderlick, 1995; Podczeck et al., 1996) and therefore more drug particles will be carried into the throat as agglomerates with the lactose monohydrate particles. During impact with the throat wall, drug particles can be pushed against the throat wall and thus will adhere to the wall instead of entering the cascade impactor.

The total loss of drug, which includes the loss in the device, throat and preseparator, is only a function of particle size and shape. An increase in particle size of carrier particles appears to increase the total drug loss, probably because of drug-carrier agglomerates depositing in the preseparator. However, an increased amount of fine carrier particles also increases the total loss of drug. This is mainly due to the increased loss in the device.

The loss due to adhesion decreases with an increase in carrier particle aspect ratio, but increases with an increase in carrier particle size and amount of fine carrier particle fraction. The amount of fine carrier particles and the more regular particle shape are advantageous in terms of the mixing process, i.e. for identical mixing conditions (time, speed), adhesion forces will increase due to increased friction and increased contact area. The effect of the particle size, however, is again related to the deposition in the

Table 8
Drug distribution in the cascade impactor (different grades of lactose monohydrate, at optimum speed and time)—lost drug

Grade	Device (%)	Throat (%)	Preseparator (%)	*LDA* (%)	Total (%)
Lactose *grade a*	13.18	21.86	32.36	62.45	67.40
Lactose *grade b*	13.85	25.76	34.35	69.78	73.96
Lactose *grade c*	13.02	34.42	40.84	86.53	88.29
Pharmatose 125M	11.69	28.39	43.44	81.34	83.52
Pharmatose 150M	20.21	28.77	25.35	67.83	74.33
Pharmatose 200M	34.38	24.55	25.45	76.20	84.38
Pharmatose 325M	8.72	33.66	46.39	87.70	88.77
Granulac 70	12.06	30.69	50.39	92.20	93.14
Granulac 140	43.61	32.98	8.61	73.75	85.20
Pulmolac 400	32.70	31.78	13.38	67.11	77.86

LDA, loss due to adhesion (undetached drug, corrected for loss in device); total, sum of loss in device, throat and preseparator.

preseparator, which is accounted for as loss due to adhesion.

The loss of drug on the impactor walls increases for more irregular carrier particles. Presumably, again agglomerates between fine carrier particles and drug are responsible for this finding. The more irregular carrier particles have a more irregular flow pattern promoting the deposition on the impactor walls, and because they carry some drug particles the loss of drug on the walls increases. This opinion is supported by the decrease of wall loss with an increase in carrier particle size, which reduces the amount of drug-carrier agglomerates entering into the impactor in the first place.

The *MMAD* cannot really be predicted from the physical data of the carrier particles. There are too many unknown factors involved, e.g. the entrapment of drug particles in the surface roughnesses, the change in drug particle size distribution and the amount of drug agglomerated to fine carrier particles.

3.2. (B) Powder mixtures with optimized adhesion properties

Table 8 and Table 9 summarize the findings for this set of powder mixtures. In the first instance it should be assumed that a powder mixture with similar adhesion properties to the commercial product Serevent Diskhaler® — median adhesion force between 6.71×10^{-12} N and 7.91×10^{-12} N (95% confidence interval), and interquartile range of the adhesion force distribution between 15.92×10^{-12} N and 18.52×10^{-12} N — should also have similar aerodynamic properties, thus a *MMAD* between 6.47 and 7.78 μm, a loss in the device between about 10 and 20%, and a loss due to adhesion between about 60 and 70% (Podczeck, 1997a). However, the aerodynamic properties vary considerably. Only *Pharmatose 150M*

Table 9
Drug distribution in the cascade impactor (different grades of lactose monohydrate, at optimum speed and time)—available drug

Grade	*WL* (%)	*MMAD* (μm)	σ_g^a
Lactose *grade a*	17.55	6.06	0.44
Lactose *grade b*	22.23	6.19	0.48
Lactose *grade c*	14.73	8.52	0.56
Pharmatose 125M	7.72	5.99	0.69
Pharmatose 150M	4.84	6.48	0.68
Pharmatose 200M	5.78	9.24	0.60
Pharmatose 325M	14.86	8.94	0.61
Granulac 70	9.54	9.20	0.58
Granulac 140	9.12	6.45	0.63
Pulmolac 400	7.62	8.88	0.47

WL, loss of detached drug on the impactor walls; *MMAD*, Mass Median Aerodynamic Diameter; σ_g, geometric standard deviation.

[a] Note comments on its evaluation made in Section 2 (Materials and methods).

fulfils all three criteria listed. If a *MMAD* lower than the lower 95% confidence level of 6.47 μm is accepted as a favourable dosage form property, *Lactose grade a*, and *Lactose grade b* are also acceptable carrier materials.

For many lactose monohydrate batches the *MMAD* values increased, although the optimal adhesion force was found using a shorter mixing time. This could be the result of the physical mechanisms involved in a mixing process. Initially, autoadhesion between drug particles on one side and carrier particles on the other side dominates in the powder bed. Particle movement and particle friction will gradually lead to the adhesion force between drug and carrier particles being the dominant factor. First agglomerates between fine drug and fine carrier particles will be formed, and later such agglomerates might be destroyed due to a stronger adhesion force between larger carrier particles and the drug. For lactose monohydrate batches such as *Pharmatose 200M* and *Pulmolac 400*, which have large amounts of fine carrier particles and for which the mixing time was very small (5.5 and 5.0 min, respectively), drug will mainly stick to the fine carrier particles. Hence, the large *MMAD* is a result of the aerodynamic distribution of these agglomerates in the impactor. The high loss of drug in the device supports this theory.

Surface roughness could explain the high values of *MMAD* found for *Pharmatose 325M* and *Granulac 70*. The loss in the device is reasonably small and the loss in the preseparator is enormous, suggesting that the drug had been adhered to larger carrier particles. Separation in the air stream did not occur, because due to larger surface roughness (very large R_{tm} values), the friction between carrier particle surface and drug particle surface is increased, reducing the possibility of a detachment of the drug from the carrier material.

The large value of *MMAD* for *Lactose grade c* suggests that again the majority of drug strongly adhered to the finer carrier particles. However, the drug adhered to the larger carrier particles obviously cannot be detached and deposits with the carrier particles in the preseparator, whereas the rest of the drug is distributed in the impactor according to the aerodynamic properties of the drug-carrier agglomerates. *Pharmatose 125M* has a lower amount of fines and with this as a carrier, the drug deposits in the impactor as single particles accounted for by the small value of *MMAD*. The majority of drug, however, which adhered to the large carrier particle fraction cannot be detached, due to large surface roughness and thus is lost in the preseparator.

4. Conclusions

The relationship between the physical properties of the lactose monohydrate carrier particles and the aerodynamic properties of Salmeterol Xinafoate is complex, and a simple interchange of the carrier material in terms of brand or grade appears impossible. Particle size, shape, water loss on drying, and to a lesser extent surface roughness influence the loss of drug for example in the device, preseparator and loss due to adhesion. The relationships can be quantified mathematically, if mixing has been undertaken under similar conditions, i.e. an identical mixing time and speed. For interactive mixtures, however, which have been manufactured with the aim to produce an adhesion force similar to the commercial product (Serevent Diskhaler®), the connection between the physical properties of the carrier materials and the aerodynamic behaviour is less quantifiable. A similar adhesion force does not guarantee a similar aerodynamic behaviour of the drug in the cascade impactor. Mainly the site of adhesion — adhesion to fine or larger carrier particles — determines the drug lost in the device and preseparator, and is responsible for deviations in the *MMAD* if compared with the commercial product.

Acknowledgements

This work was financed by Glaxo-Wellcome Research and Development Ltd., Ware, UK. The author is very grateful to Mr Cameron Edwards (Glaxo-Wellcome) for the organization and supply of the Borculo Whey Products lactose batches, to DMV for the generous supply of the Phar-

matose grades, and to Meggle GmbH for providing samples of Granulac and Pulmolac lactose monohydrate. The UBM-laser profilometer was purchased with a grant from the EPSRC.

References

BS 1134, 1972. Method for the Assessment of Surface Texture. British Standards Institution, London.

Corn, M., 1961. The adhesion of solid particles to surfaces. J. Air Pollut. Control Assoc. 11, 523–528.

Edmundson, I.C., 1967. Particle size analysis. In: Bean, H.S., Beckett, A.H., Carless, J.E. (Eds.), Advances in Pharmaceutical Sciences, Vol. 2. Academic Press, London, pp. 95-179.

European Community Pharmacopoeia Commission, 1993. Inhalanda — Monograph for the European Pharmacopoeia. Pharmeuropa 5, 316–327.

Fuller, K.N.G., Tabor, D., 1975. The effect of surface roughness on the adhesion of elastic solids. Proc. R. Soc. Lond. A 345, 327–342.

Hausner, H.H., 1966. Characterization of the powder particle shape. Planseeber. Pulvermet. 14, 75–84.

Johnson, K.L., 1985. Contact Mechanics. Cambridge University Press, Cambridge, pp. 125–129.

Kendall, K., 1994. Adhesion: molecules and mechanics. Science 263, 1720–1725.

Levins, J.M., Vanderlick, T.K., 1995. Impact of roughness on the deformation and adhesion of a rough metal and a smooth mica in contact. J. Phys. Chem. 99, 5067–5076.

Maugis, D., 1996. On the contact and adhesion of rough surfaces. J. Adhesion Sci. Technol. 10, 161–175.

Podczeck, F., 1997a. Optimization of the operation conditions of an Andersen-Cascade impactor and the relationship to centrifugal adhesion measurements to aid the development of dry powder inhalations. Int. J. Pharm. 149, 51–61.

Podczeck, F., 1997b. A shape factor to assess the shape of particles using image analysis. Powder Technol. 93, 47–53.

Podczeck, F., 1997c. The relationship between particulate properties of carrier materials and the adhesion force of drug particles in interactive powder mixtures. J. Adhesion Sci. Technol. 11, 1089–1104.

Podczeck, F., Newton, J.M., James, M.B., 1996. The adhesion force of micronized salmeterol xinafoate particles to pharmaceutically relevant surface materials. J. Phys. D: Appl. Phys. 29, 1878–1884.

Podczeck, F., Newton, J.M., James, M.B., 1997. The influence of relative humidity of the storage air on the adhesion and autoadhesion of micronized particles to particulate and compacted powder surfaces. J. Colloid Interface Sci. 187, 484–491.

Rumpf, H., 1990. Particle Technology. Chapman and Hall, London, pp. 162–163.

Soltani, M., Ahmadi, G., Bayer, R.G., Gaynes, M.A., 1995. Particle detachment mechanisms from rough surfaces under substrate acceleration. J. Adhesion Sci. Technol. 9, 453–473.

Tabor, D., 1977. Surface forces and surface interactions. J. Colloid Interface Sci. 58, 2–13.

Warnke, G., König, D., Bauer, K.-H., Brandl, M., 1994. Aerosol-fractionation performance of a multistage liquid impinger: Evaluation by means of light microscopy and a light extinction particle counter. Pharm. Pharmacol. Lett. 4, 5–7.

Whitehouse, D.J., Archard, J.F., 1970. The properties of random surfaces of significance in their contact. Proc. R. Soc. Lond. A 316, 97–121.

Zimon, A.D., 1982. Adhesion of Dust and Powder, 2nd edn. Consultants Bureau, New York, pp. 307–319.

.