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The influence of carrier roughness on adhesion, content uniformity and the in vitro deposition of terbutaline sulphate from dry powder inhalers

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Abstract

The aim of this study was to establish a correlation between carrier characteristics and the dispersibility of drug from the blend. The influence of the roughness of a commonly used carrier material, lactose monohydrate, on the adhesion, dose uniformity, and aerodynamic properties of a model drug, terbutaline sulphate was investigated. Evaluation of adhesion was carried out with a mechanical sieve and an Alpine air-jet sieve. For the characterisation of lactose roughness, we used image analysis software. Aerodynamic evaluation of fine particle dose and emitted dose was obtained using a twin stage impinger. The study with the mechanical sieve demonstrated that at least 60% of drug adheres to lactose. The Alpine air-jet sieve assays showed there was a correlation between drug separation from a carrier by sieving and that obtained from longer in vitro deposition studies. Adhesion, blend homogeneity and stability are related to the surface roughness of the lactose used as carrier. There is a linear relationship between the parameters "fine particle fraction" and "roughness". A compromise between homogeneity and drug liberation must be found: a certain roughness is necessary to allow for drug adhesion and blend homogeneity, but if too high it will prevent drug liberation after inhalation.

Keywords: Terbutaline sulphate; Dry powder inhaler; Roughness; Adhesion; Drug delivery

1. Introduction

Dry powder formulations for inhalation are often composed of fine drug particles and inert coarse carrier particles, typically α-monohydrate lactose. Interactions between particles are mainly dependent on the physicochemical characteristics of the interacting particles, that is to say: particle size, shape, surface morphology, contact area, hygroscopicity (Bell, 1994; Prime et al., 1997). These different properties will influence the drug–carrier blend process and also drug delivery from the carrier and its dispersion.

The fine drug particles are expected to adhere to the carrier surface to form ordered mixtures. The obtention of a homogeneous, stable ordered blend depends on drug percentage, on drug/carrier size ratio, on the shape and surface of the particles. The carrier particles are used to improve the flow of the drug particles, which are usually present in a low concentration, with a drug to carrier ratio of 1:67.5 (w/w) being typical (Kassem, 1990; Timsina et al., 1994; Zeng et al., 2000) for example, in Rotohaler, Diskhaler and Ventoline Rotocaps (Glaxo) and in Cyclohaler (Pharbita) (Timsina et al., 1994). Many authors use a lac-

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tose whose size is between 63 and 90 μm (Bell et al., 1971; Bennett et al., 1999; Timsina et al., 1994; Zeng et al., 2000). More recently, the addition of fine carrier particles to dry powder formulation has been shown to improve the dispersion and deposition of drug particles. The fine particles occupy possible drug binding sites on the lactose particles. Therefore, the interparticle forces between the drug and carrier particles are reduced (Zeng et al., 2000). The concentration and particle size of fine lactose have to be carefully controlled to obtain satisfactory and reproducible pharmaceutical performance from a specific device (Zeng et al., 1998).

Particle interactions are of great importance in dry powder inhaler formulation where the redispersion of drug particles from carrier particles is critical for lung deposition. In such preparations, the inspiratory force of the patient must overcome the adhesion forces between drug and carrier particles to aerosolise particles.

Patient inspiration controls the dose emitted and the fine particle dose generated, especially if device resistance is high because the patient will have to make a greater effort to obtain a given flow rate (Prime et al., 1997).

To improve drug bioavailability in the lungs, it would be interesting to design dry powder inhalers where the quantity of drug released and the fine particle dose are independent of the patients' inhalation flow rate. Using carriers with suitable physicochemical characteristics could contribute to this. The dispersion of drug particles is affected by adhesion forces between the carrier surface and drug particles.

Particle adhesion force is equivalent in magnitude to the force required for particle detachment. Techniques often used to determine interparticle forces within the powder system include vibration, centrifugation and impact separation (Louey et al., 2001; Podczeck and Newton, 1995; Podczeck, 1997, 1999; Shimada et al., 2000).These bulk detachment methods determine adhesion force by measuring the amount or number of drug particles detached from a surface at a given force. More recently, authors have used the atomic force microscope (AFM) consisting of a spherical colloid particle attached to a micro-cantilever, providing an alternative technique where the adhesion force is determined using single particle detachment (Louey et al., 2001). The interactive forces are measured as a function of sample displacement, by recording the deflection of a spring-like probe as the substrate is brought into and out of contact with the colloidal particle. But this AFM technique concerns only one particle and not the overall blend.

Aerodynamic evaluation of fine particles with an impactor can be performed to assess the formulation retained with a given dry powder inhaler (Steckel and Müller, 1997). Besides adhesion, an in vitro test to quantify the respirable amount of drug emitted from an inhaler is a necessary requirement to develop and produce aerosol formulation.

The aim of this study was to investigate the influence of the roughness of a commonly used carrier material (lactose monohydrate) on the adhesion, dose uniformity and aerodynamic properties of a model drug (terbutaline sulphate). Our study focused on roughness because this parameter is supposed to have a strong influence on adhesion (Lucas et al., 1998) and consequently on the bioavailability of the drug. To avoid any interaction between the different parameters, which would limit any assessment to the influence of roughness, other parameters like carrier size, carrier shape and operating conditions were kept constant.

In this study, we wanted to develop a simple method to assess the adhesion of respirable-sized drug-to-carrier particles. The tests used to assess terbutaline sulphate adhesion were based on a mechanical sieve and an Alpine air-jet sieve (Mbanga kendeck, 1979). These tests are simple, and consider the whole blend as it is used in dry powder inhalers. Drug detachment from the carrier is obtained either through mechanical vibrations or by aspiration.

The results of drug separation obtained by sieving were compared to those obtained from in vitro deposition studies with an impinger to evaluate if there was data correlation between the two. It would be ideal to dispose of a simple method to characterise the adhesion and make prediction of the aerodynamic behaviour of the drug possible.

2. Materials and methods

2.1. Materials

- Four α-monohydrate lactoses:
  - Lactochem Inter II noted A and Lactochem regular noted B (Borculo Domo Ingredients, Zwolle, The Netherlands);

- Pharmatose 125 noted C and Pharmatose 325 noted D (DMV International, Vegheln, The Netherlands);

- Micronised terbutaline sulphate, with a volume mean diameter of 2.98 μm for GSD 1.64 (laser scattering, particle suspension in ethanol, Mastersizer S, Malvern, Orsay, France);
- Hard gelatin capsules (size 2);
- Spinhaler (Specia, Montrouge, France). In the Spinhaler, the gelatin capsule is mounted on a rotor upon which are several small fan blades. The capsule is pierced by two small needles when sliding the outer casing of the inhaler parallel to the inner casing. When the patient inhales, the capsule rotates rapidly and empties its content.

2.2. Methods

2.2.1. Preparation of coarse lactose

To limit the influence of lactose particle size, we used the same granulometric fraction for each lactose, that is to say 63–90 μm. It was obtained after passage through an Alpine air-jet sieve (Alpine, Augsburg, Germany). This also made it possible to remove existing fine particles that could be a source of variation in fine particle delivery.

2.2.2. Evaluation of lactose roughness

Two methods were used: one involving image analysis and the other involving atomic force microscopy. The latter was used to confirm the classification of lactoses.

The method we developed makes it possible to compare different lactoses in the same conditions and to classify them according to their roughness, using Optimas image analysis software (Optimas version 6.5, Imasys, Surrennes, France) set up on an IBM computer connected to an optical microscope (Nikon Eclipse E400) via a Sony video camera. With this equipment, the magnification of lactoses is 200. The images are light-transmitted, the particles being between the image sensor and the light source of the microscope. The software then analyses the images with a resolution of 1 pixel/μm. A background correction is made to remove any intensity contribution from variance in the light source, ambient light and electronic noise. Correction is made by subtracting the darkfield from the specimen image and dividing by the brightfield.

Then each particle is individually selected and luminance variation on the surface, that is to say grey-level variations are analysed (R_0). R_0 expresses irregularities on the particle surface and makes it possible to assess if the surface is more or less granular.

For each lactose, R_0 is determined on 80 particles. This is a real value which can be extracted from object surfaces and gives the grey-value variance of pixels within the area boundary (surface of the lactose particle). Data is auto-extracted by the software after selecting the particle. For each surface, 7000 pixels are recorded. The resolution of the grey scale images is 256 × 256 pixels grey levels; the number of bits is 24 bits/pixel. The values obtained are related to roughness and allow lactoses to be classified.

The topography of the lactoses was also assessed by the AFM technique. AFM measurements were performed using a commercial atomic force microscope (Nanoscope IIIa, Digital instruments). Images were acquired in air using the tapping mode, with a size range of 25 μm × 25 μm. The sample mounted on a piezoscanner tube enables three-dimensional movement (x, y and z) relative to the stationary probe. Interactive forces between the probe and sample surface cause vertical (z) displacement of the cantilever, which is monitored by the reflection angle of the laser from the upper side of the cantilever using a split photodiode detector. Lactose particles were immobilised on an AFM stub using double-side adhesive tape. To quantify roughness, the average height deviations of surface asperities were computed.

As a comparative measure, a silicium thin plate with a smooth surface was used and was analysed in the same conditions as lactoses. Its roughness measured by AFM was 0.4 nm. With image analysis, measurements of the surface variance in units of luminance was 37, which is low compared to the values obtained for the lactoses (about 2500–4000 luminance units).

To assess lactose shape, we determined the elongation ratio L/w with L being the length and w the width of particles, measured at right angles.

2.2.3. Blending lactose with terbutaline sulphate

Terbutaline sulphate and lactose were mixed at a ratio of 1:67.5 (w/w), in a Turbula mixer (Bachofen Maschinenfabrik, Basel, Switzerland) for 30 min at 54 rpm. Each blend was prepared in 100 g quantities.

2.2.4. Measurement of average content and content uniformity

The quality of the blends was examined by analysing the quantity of terbutaline sulphate in aliquots (34.25 mg) of sampled powder which is the amount of powder in each capsule. Each aliquot of blend was placed in a 25 ml volumetric flask and made up to the volume with water. Ten aliquots were taken randomly from each blend and each solution was assayed using a UV spectrophotometer with a wavelength of 276 nm. A calibration curve was established from the concentration 60 μg/25 ml to 3750 μg/25 ml. From the 10 results of terbutaline sulphate content in the samples, we calculated the average terbutaline sulphate content. The variation coefficient was used to assess the content uniformity of the blends.

2.2.5. Evaluation of adhesion characteristics

Adhesion characteristics are evaluated by submitting the blend to sieving. Two different kinds of sieving are used: the first is mechanical with the Retsch sieve type 3D (Retsch, Haan, Germany), the second is by air depression with the Alpine air-jet sieve.

In the first case, because of vibrations, particles are submitted to shakes and shocks leading to the passage of particles with a diameter lower than that of the screen aperture.

In the second case, the blend is put on a sieve in a sealed enclosure. Particles are submitted on the one hand to an airflow released by a blow nozzle rotating under the sieve and, on the other hand, to aspiration through the sieve. The particles suspended in air are carried through the sieve thanks to aspiration.

Thirty grams of blend was placed on the 63 μm sieve section of the Retsch apparatus. Three samples of 34.25 mg each corresponding to 500 μg terbutaline sulphate were removed from the powder bed after sieving at different lengths of time: 5, 15, 30 s, 2 min 30 s, 5 min and 10 min. For each sample, we compared the percentage of drug remaining to the initial dose. The same assay was performed with the 63 μm sieve set on the Alpine air-jet appliance.

These assays enabled us to assess blend stability and the ease with which the drug can be separated from lactose. The results are the mean of three replicate measurements.

2.2.6. Preparation of the capsules

The lactose–terbutaline sulphate blends were filled into hard gelatin capsules (size 2) manually so that each capsule contained 500 μg of terbutaline sulphate, that is to say 34.25 mg of blend.

2.2.7. Aerodynamic evaluation of fine particle dose and emitted dose

In vitro deposition of terbutaline sulphate from dry powder formulations was determined using a twin stage impinger (TSI, Apparatus A, European Pharmacopoeia, 2002). The TSI was assembled and loaded with 7 ml of distilled water in stage 1 and 30 ml in stage 2. Each deposition experiment involved the aerosolisation at 60 l/min via a Spinhaler of five capsules, each containing 34.25 mg of blend equivalent to a nominal dose of 500 μg terbutaline sulphate.

The different parts of the TSI were rinsed with water and the amount of terbutaline sulphate deposited in the upper and lower stages was determined using a spectrophometric dosage at a wavelength of 276 nm.

For each blend, the assays were perfomed in triplicate and the following parameters were used to characterise the deposition profiles of the drug:

- the emitted dose (ED), which is the sum of drug collected at upper and lower stages divided by 5,
- the fine particle dose (FPD) defined as the amount of drug deposited in the lower stages of the impinger, because the aerodynamic diameter was less than the cut-off diameter of the TSI (6.4 μm at an air-flow rate of 60 l/min),
- the percentage emission calculated as the ratio of ED to the nominal dose,
- the fine particle fraction calculated as the ratio of FPD to the nominal dose.

The statistical analysis of this data was obtained through a non-parametric test, e.g. the Kruskal–Wallis one-way analysis of variance used for small populations.

3. Results and discussion

The elongation ratios are determined for the four lactoses. They are: 1.725 (±0.375), 1.512 (±0.333), 1.516 (±0.358) and 1.379 (±0.285) respectively, for

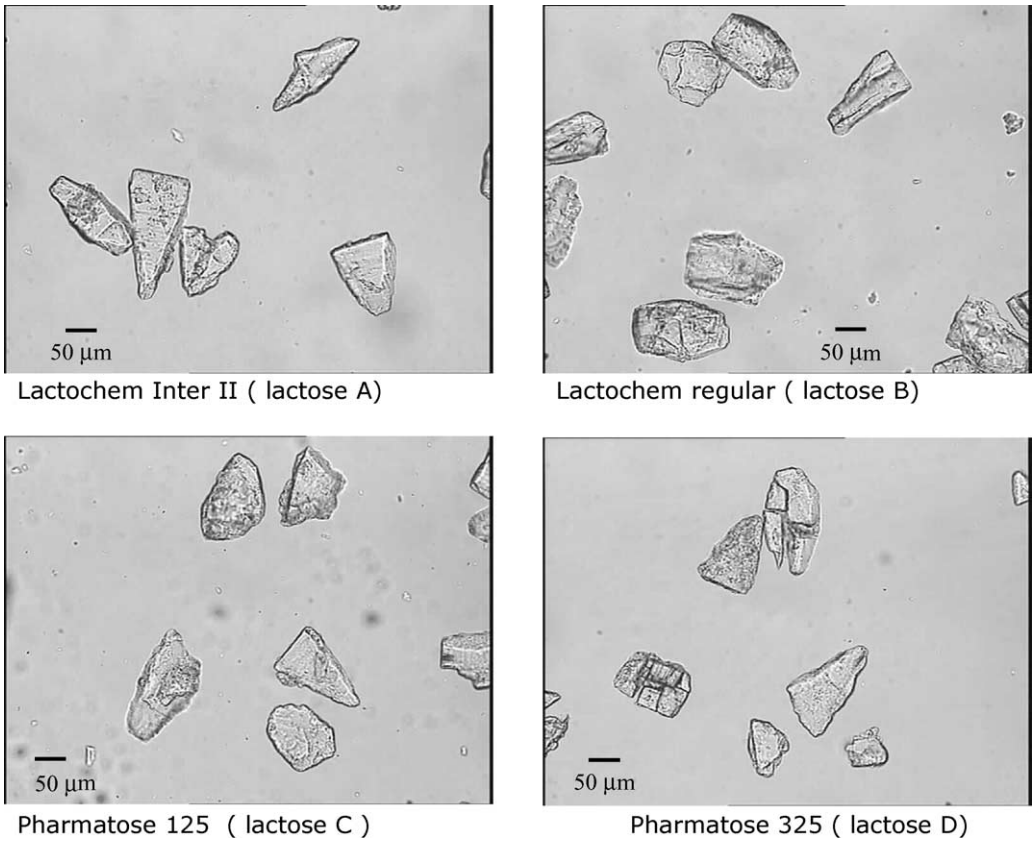

Fig. 1. Photos of the different lactoses studied.

lactoses A–D. They confirm as can be seen in Fig. 1 that the shapes are no different for the four lactoses.

The roughness characteristics of the lactoses studied differ significantly (ANOVA, $P < 0.001$) (Table 1). Lactoses A and D possess a rougher surface (R_0 of 3605 (±657) and 3958 (±735) units of luminance).

The roughness values obtained by AFM for lactoses A–D are 322, 226, 244 and 380 nm, respectively. Classification is the same as that obtained by image analysis.

Table 1
Roughness characteristics of the lactoses studied

Lactose	Roughness R_0 (luminance units) (mean ± S.D.)
A (63–90 μm)	3605 ± 657
B (63–90 μm)	2691 ± 462
C (63–90 μm)	3135 ± 742
D (63–90 μm)	3958 ± 735

Measurement of roughness with AFM is difficult to obtain. Indeed, the AFM analysis makes it possible to measure only local roughness on a small surface of the particle. It is not possible to obtain the global roughness of all the surface of the lactose particle. Indeed, level variations on the particle surface are too great for the deflection amplitude of the cantilever. This is not the case when the particle is less rough.

After blending the lactoses with terbutaline sulphate, we measured the average content and the uniformity of drug content (Table 2). The average terbutaline sulphate contents obtained with the four lactoses are all included in the interval of the nominal content ±5%. The results show that the blend obtained with lactose B presents greater variations in drug content. This lactose is the one for which R_0 is the lowest, reflecting a smoother surface than could be responsible for weaker adhesion. Drug distribution in the blend with lactose A is more homogeneous, prob-

Table 2
Average content and uniformity of drug content for lactose–terbutaline sulphate blends

Lactose	Terbutaline sulphate content (μg)
A (63–90 μm)	491.25 (cv = 4.5%)
B (63–90 μm)	492.5 (cv = 14.33%)
C (63–90 μm)	500.5 (cv = 7.35%)
D (63–90 μm)	483 (cv = 8.6%)

cv, coefficient of variation.

ably because its higher level of roughness strengthens blend homogeneity and drug adhesion. In all cases, blend uniformity is such that "uniformity of dosage units" is obtained.

Tables 3 and 4 present the results of the evaluation of adhesion characteristics by analysing drug present on sieve 63 μm after sieving in different conditions.

When blends are submitted to mechanical vibrations, it is noted that after 10 min, at least 80% of terbutaline sulphate is still fixed on the lactose, except for lactose B where only 60.8% remains. At least 60% of drug adheres to the four lactoses. As drug quantities are higher for lactoses A, C, D than for lactose B and the size of drug particles is identical and narrow, the results indicate that physical interactions between drug particles and lactose B are weaker than for the other lactoses: a lower quantity of drug adheres to the lactose and/or the adhesion force is lower.

When blends are submitted to the Alpine air-jet sieve, terbutaline sulphate is rapidly carried away by the airflow. The quantity of drug present after 5 s is an indicator of the quantity of drug that adheres to the lactose. For lactoses A–C, after 5 s, 50–55% of terbutaline sulphate remains fixed on the lactose. Indeed, if the terbutaline sulphate particles were individualised, they would be carried away through the sieve by aspiration. The exception is lactose D for which about 76% of drug remains, showing a high level of drug adhesion for this lactose.

The evolution with aspiration time shows drug detachment. If the aspiration time increases, the totality of the drug does not separate from the lactose, with important variations according to the lactose under consideration. It is for lactose B that drug concentration on the 63 μm sieve decreases the most rapidly and for which the remaining adhered quantity is the lowest. After 10 min only 15% of terbutaline sulphate remains on lactose B unlike 34.36% for lactose D. As adhesion strength seems to be different according to the lactose considered, the detachment forces required to remove respirable particles are also different and probably related to the physical properties of the lactose particles.

Table 3
Percentage of terbutaline sulphate in the samples taken from the 63 μm sieve of the mechanical sieve at different functioning times

Functioning time of the sieve	A (63–0 μm) (%)	B (63–90 μm) (%)	C (63–90 μm) (%)	D (63–90 μm) (%)
5 s	93.70 (cv = 0.5%)	94 (cv = 1.25%)	96.9 (cv = 2.26%)	98.34 (cv = 2.15%)
15 s	87.50 (cv = 1.32%)	92 (cv = 2.34%)	95.68 (cv = 2.57%)	98.30 (cv = 2.15%)
30 s	86 (cv = 2.33%)	89.2 (cv = 2.5%)	93.07 (cv = 1.32%)	91.44 (cv = 3.5%)
2 min 30	85.23 (cv = 2.7%)	73.2 (cv = 1.6%)	89.07 (cv = 0.55%)	89.72 (cv = 1.36%)
5 min	84.66 (cv = 2.4%)	68.2 (cv = 4.1%)	86.98 (cv = 2.82%)	86.26 (cv = 1.41%)
10 min	83.66 (cv = 3.13%)	60.8 (cv = 3.5%)	84.37 (cv = 1.45%)	84.54 (cv = 1.44%)

cv, coefficient of variation.

Table 4
Percentage of terbutaline sulphate in the samples taken from the 63 μm sieve of the air-jet sieve at different functioning times

Functioning time of the sieve	A (63–90 μm) (%)	B (63–90 μm) (%)	C (63–90 μm) (%)	D (63–90 μm) (%)
5 s	55.71 (cv = 4.1%)	50.8 (cv = 4.5%)	56.54 (cv = 2.17%)	75.91 (cv = 3.21%)
15 s	52.5 (cv = 2.2%)	28.2 (cv = 4.5%)	38.1 (cv = 1.93%)	64.7 (cv = 3.26%)
30 s	39.75 (cv = 1.4%)	23.2 (cv = 5%)	33.92 (cv = 1.1%)	50.38 (cv = 4.8%)
2 min 30	36.9 (cv = 1.1%)	21.5 (cv = 3.3%)	33.05 (cv = 3.6%)	40.2 (cv = 4.9%)
5 min	30.34 (cv = 3.8%)	16.6 (cv = 4.1%)	26.09 (cv = 1.1%)	35.88 (cv = 4.35%)
10 min	29.52 (cv = 1.1%)	15 (cv = 1.1%)	19.13 (cv = 3.9%)	34.36 (cv = 5%)

cv, coefficient of variation.

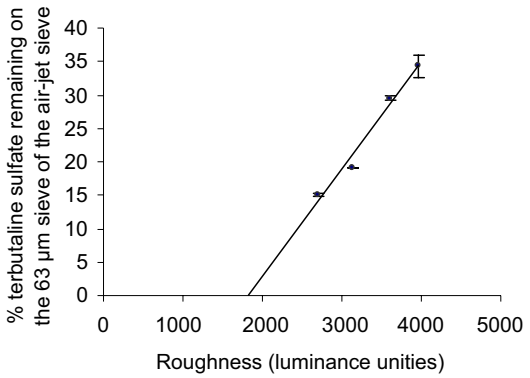

Fig. 2. Percentage of terbutaline sulphate remaining on the 63 μm sieve of the air-jet sieve after10 min in relation to lactose roughness.

The results obtained can be related to roughness. As the coarse lactoses have been subjected to similar preparation conditions, the differences observed may be due to the roughness of lactose particles. Indeed, if we classify the lactoses by decreasing roughness, we have: R_0D > R_0A > R_0C > R_0B. In the same way, if we classify lactoses according to drug adhesion when blends are submitted to aspiration, we obtain: adhesion on D > adhesion on A > adhesion on C > adhesion on B. Aspiration data follows a similar profile to surface roughness measurements. This relation is shown on Fig. 2 with the percentage of terbutaline sulphate on the 63 μm sieve of the air-jet sieve after 10 min in relation to lactose roughness. There is a linear relationship between them with an R^2-correlation coefficient of 0.9764 which indicates a good correlation between the two parameters.

The rougher the lactose surface, the greater terbutaline sulphate adhesion. In fact, an increase in roughness multiplies the contact points between the drug and the carrier and an increase in contact surface favours binding and consequently drug adhesion to the carrier. This stabilises the blend but on the other hand separation of the drug from lactose becomes more difficult when the blend is carried by an airflow.

Sieving by mechanical vibrations is generally well-suited to non-cohesive powders. In the case of cohesive powders, it is preferable to envisage sieving by air depression (Alpine air-jet sieve). Indeed, the energies involved are different. In the first case, particles are submitted to a vibratory movement; in the second case, particles are submitted to an airflow released by a rotating blow nozzle and are suspended. Trials on blends show that a large number of drug particles fixed on a carrier are not detached during sieving by vibrations (Mbanga kendeck, 1979). On the other hand, when sieving by air depression, the energies involved induce particle detachment. These considerations have been checked in this study. The sieving assays by mechanical vibrations make it possible to confirm that the blend is ordered, that it is stable enough to resist the vibrations. On the other hand, the sieving assays by aspiration make it possible to determine how easily the drug separates from lactose. The behaviour of the lactose–drug blend during the assay can give an estimation of the drug capacity to separate from the carrier during inhalation. Strong adhesion of the drug to lactose during the assay presupposes difficult separation of the drug after patient inhalation or the need for greater inhalation airflow.

The aerodynamic behaviour of lactose–drug blends was estimated with TSI making it possible to study the in vitro deposition profile of terbutaline sulphate (Table 5). The emitted dose is high for blends obtained with lactoses A–C; representing 95.35 to 98% of the nominal dose. The emitted dose with lactose B is high and displays few variations whereas the CV of the blend mean content is high (14.33%). Emitted doses were determined after collecting the content of five capsules by aspiration through the twin impinger. The low variations in the emitted dose are related to the number of capsules used that smoothes variations of the blend mean content. The emitted dose is lower (Kruskal–Wallis, $P < 0.1$) for the blend with lactose D. The emitted dose decreases as lactose roughness increases. This could be due to a strengthening of blend adhesion in the device or on the capsule walls because of this roughness.

In all cases, the variation coefficients for the emitted dose are low and satisfy the emitted dose assay of the European Pharmacopoeia.

Fine particle doses differ according to the lactose used (Kruskal–Wallis, $P < 0.02$).With lactose D, the fine particle dose is weak; the fine particle fraction is only 11.20%. This low fraction indicates that terbutaline sulphate does not separate well from the carrier. Indeed, the small size of terbutaline sulphate should allow terbutaline sulphate to reach the lower stage of TSI after aerosolisation unless it remains fixed on the lactose. It is with lactose B that the fine particle dose

Table 5
Terbutaline sulphate deposition in the TSI after aerosolisation of the different blends with the Spinhaler at 60 l/min

Lactose	ED (μg)	FDP (μg)	Percentage emission compared to the nominal dose	Fine particle fraction
A (63–90 μm)	488.33 (cv = 5.05%)	153.33 (cv = 3.76%)	97.66% (cv = 5.05%)	30.66% (cv = 3.76%)
B (63–90 μm)	490 (cv = 2.04%)	233.33 (cv = 4.95%)	98% (cv = 2.04%)	46.66% (cv = 4.95%)
C (63–90 μm)	476.66 (cv = 4.24%)	173.33 (cv = 6.66%)	95.35% (cv = 4.24%)	34.66% (cv = 6.66%)
D (63–90 μm)	415 (cv = 4.53%)	56 (cv = 6.01%)	83.02% (cv = 4.53%)	11.20% (cv = 6.01%)

cv, coefficient of variation.

is the greatest; the fine particle fraction is 46.66%. With lactoses C and A, results are intermediate between those of the two previous lactoses, with a fine particle fraction slightly higher for C compared to A. In all cases, variations in the respirable fraction are low whatever the lactose considered.

We related roughness and fine particle fraction (Fig. 3) and noted the linear relationship between them. The correlation coefficient R^2 of the straight line "fine particle fraction = f (roughness)" is 0.9066 and displays a good correlation between these two parameters. The comparison between roughness and fine particle fraction is possible because we have a binary lactose–terbutaline sulphate mixture. The fine particles of lactose have been removed during the air-jet sieving of the coarse lactose particles and will not influence terbutaline sulphate adhesion to lactose. The fine particle fraction increases as particle roughness decreases. A smoother surface lactose makes it possible to detach a higher drug percentage when the blend is carried by an airflow. Using such a lactose will be better because it will require a lower inspiratory effort from the patient to detach the drug from the lactose and to obtain a good fine particle fraction.

We compared the results of drug separation from the carrier by sieving with that obtained from longer in vitro deposition studies. Fig. 4 presents the relation between fine particle fraction and the percentage of terbutaline sulphate remaining on the 63 μm sieve of the air-jet sieve after 5 s. We noted a linear relationship between them with a correlation coefficient R^2 of 0.9249 which indicates a good correlation between these two parameters. These results concern the first 5 s of aspiration that could be compared to the inhalation time of a patient when he uses a dry powder inhaler.

The method we propose using mechanical and Alpine air-jet sieves is simple, easy to perform, making it possible to characterise adhesion, to forecast blend stability and drug detachment from lactose and to predict the aerodynamic behaviour of the drug.

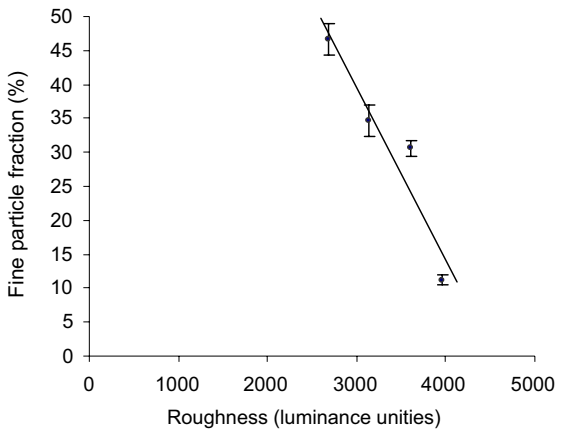

Fig. 3. Fine particle fraction of terbutaline sulphate in relation to lactose roughness.

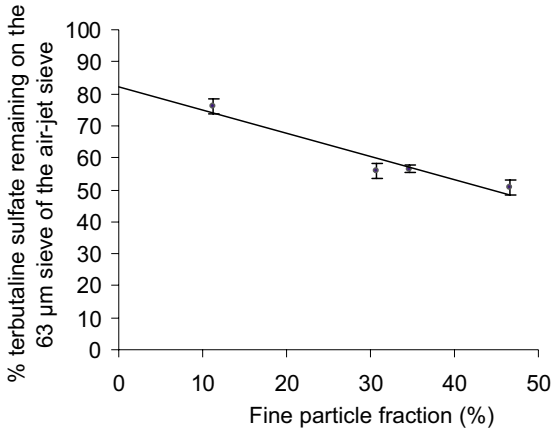

Fig. 4. Relation between fine particle fraction and percentage of terbutaline sulphate remaining on the 63 μm sieve of the air-jet after 5 s.

Image analysis to assess roughness is a good approach although it does not give an absolute value of roughness. Thanks to the differences in light reflection by particles, it however, makes it possible to compare the different lactoses and determine how rough their surface is.

4. Conclusion

The roughness of the lactose used as carrier influences dose uniformity and the dispersion of terbutaline sulphate from powders for inhalation.

Carrier surface roughness is an important parameter to take into account to forecast blend homogeneity, stability and ease of drug detachment. There is a linear relationship between lactose roughness and fine particle fraction. A high degree of roughness favours the homogeneity and stability of the blend and decreases the fine particle fraction. In this case, the patient will have to make a greater respiratory effort to detach the drug from the lactose so that a high percentage of drug reaches deep into the lungs.

The adhesion test using sieving assays makes it possible to forecast drug separation from the lactose carrier more simply that from assays with an impactor.

The different lactoses tested are not interchangeable even if the granulometric fractions are the same. To formulate a powder for inhalation, it is necessary to determine and to control the roughness properties of lactose required to obtain satisfactory drug bioavailability.

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