Available online at www.sciencedirect.com
ScienceDirect
European Journal of Pharmaceutics and Biopharmaceutics 70 (2008) 380–388
European Journal of Pharmaceutics and Biopharmaceutics
www.elsevier.com/locate/ejpb

Research paper

Comparison of physical and inhalation properties of spray-dried and micronized terbutaline sulphate

Thanh Huong Hoang Thi [a], Florence Danède [b], Marc Descamps [b], Marie-Pierre Flament [a,*]

[a] *Laboratoire de Pharmacotechnie Industrielle, Faculté des Sciences Pharmaceutiques et Biologiques, Université de Lille, Lille Cedex, France*
[b] *Laboratoire de dynamique et structures des matériaux moléculaires, Université de Lille 1, Villeneuve d'Ascq Cedex, France*

Received 3 December 2007; accepted in revised form 4 April 2008
Available online 11 April 2008

Abstract

Terbutaline sulphate particles, for use in dry powder inhaler formulations, were prepared by spray-drying, using a Büchi 190 mini spray dryer. Spray-drying conditions were chosen to allow the production of spray-dried terbutaline sulphate with a size similar to micronized terbutaline sulphate, that is to say about 2.9 μm of volume mean diameter. The physical properties and in vitro inhalation behaviour of micronized and spray-dried terbutaline sulphate were compared. X-ray diffraction, DSC, SEM and laser size analysis were investigated. Spray-dying produced spherically shaped particles with amorphous structure.

After blending with different lactoses, adhesion and aerodynamic properties were investigated. Evaluation of adhesion was carried out with a mechanical sieve and an Alpine air-jet sieve. The adhesion of terbutaline sulphate on the lactoses tested was lower in the case of the spray-dried drug. Aerodynamic evaluation of fine particle dose and emitted dose was conducted using a twin stage impactor. The emitted doses and the fine particle doses were higher with the spray-dried terbutaline sulphate.

The Alpine air-jet sieve assays showed that there was a correlation between drug separation from a carrier by sieving and that obtained from longer in vitro deposition studies. There was a linear relationship between the adhesion characteristics and the fine particle dose.
© 2008 Elsevier B.V. All rights reserved.

Keywords: Terbutaline sulphate; Spray-drying; Dry powder inhaler; Physicochemical properties; Adhesion; Aerodynamic behaviour

1. Introduction

Dry powder formulations for inhalation are often composed of fine drug particles and inert coarse carrier particles, typically α-monohydrate lactose. The fine drug particles are expected to adhere to the carrier surface to form ordered mixtures [1]. 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 aerosolize particles. 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 [2,3]. These different properties will influence the drug-carrier blend process and also drug delivery from the carrier and its dispersion. So, the knowledge of these physicochemical characteristics is particularly important to obtain reproducible and efficient administration.

Particle size of the drug is a major factor in dry powder inhaler formulations, with an accepted optimum size between 0.5 and 7 μm required to avoid deposition in the oropharynx and maximise deposition in the lower respiratory tract [4]. In current practice, the desired particle size is achieved by milling of large drug crystals by fluid energy mills or pearl ball mills. The disadvantages of such techniques are, besides indirect safety concerns due to the dust

* Corresponding author. Laboratoire de Pharmacotechnie Industrielle, Faculté des Sciences Pharmaceutiques et Biologiques, rue du Professeur Laguesse, BP 83, 59006 Lille Cedex, France. Tel.: +33 3 20 96 40 40; fax: +33 3 20 95 90 09.
E-mail address: marie-pierre.flament@univ-lille2.fr (M.-P. Flament).

0939-6411/$ - see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejpb.2008.04.002

exposure during processing, that these techniques rely on a high energy input which is not effectively used for the size reduction [5]. Moreover, the small size as well as the irregular shape of the milled particles render them extremely difficult to disperse [6].

Spray-drying offers an alternative approach to the generation of particles with respirable size. In spray-drying, a drug solution is atomized to fine droplets which are evaporated in a warm air current to form dry particles [7]. This one-step process can be used to produce dry powders from solutions, with greater control over particle size, morphology and powder density than destructive methods of powder production, such as micronization [8]. However spray-drying may have a strong impact on the physicochemical properties of the drug, and thus on their aerodynamic properties. Different studies were performed using spray-drying to generate dry powders suitable for inhalation [9–15] but as far as the authors know, no reports concerning the production of spray-dried terbutaline sulphate in relation to inhalation properties have yet been published.

The aim of this work was first to determine if terbutaline sulphate particles of sufficiently regular shape and small size suitable for use in inhalation therapy were obtainable using a spray-drying process. Then, physical properties of the spray-dried particles we produced were compared to those of micronized terbutaline sulphate classically used in the dry powder formulations. The adhesion and aerosolization properties were also appraised after blending with different lactoses used as carriers. The objective was to establish a relationship between physical properties and in vitro deposition of terbutaline sulphate.

2. Materials and methods

2.1. Materials

- Four α-monohydrate lactoses: Inhalac 120 and Inhalac 230 (Meggle, Wasserburg, Germany) Lactohale 100 and Lactohale 200 (Borculo Domo, Zwolle, The Netherlands)
- Micronized terbutaline sulphate, used as supplied, with a volume mean diameter of 2.98 μm for GSD 1.96 (laser scattering, Mastersizer S, Malvern, Orsay, France)
- Spray-dried terbutaline sulphate, produced in the laboratory, with a volume mean diameter of 2.81 μm for GSD 1.36 (laser scattering, Mastersizer S, Malvern, Orsay, France)
- Hard gelatine capsules (size 2)
- Inhalator Ingelheim (Boehringer Ingelheim, Ingelheim am Rhein, Germany)

2.2. Methods

2.2.1. Spray-drying methodology

Micronized terbutaline sulphate (TBS) was dissolved in water and the solution was spray-dried using a Büchi 190 mini spray-drier (Büchi Laboratorium-Technik, Flawil, Switzerland).When spray-drying the aqueous solution, an inlet air temperature of 120 °C and an outlet temperature of 80 °C were used, with the aspirator level at its maximum. TBS concentration, airflow rate, pressure and pump setting were modified to determine the operating conditions that allow the production of spray-dried TBS with a size similar to the one of the micronized TBS.

Powders were stored in a desiccator at 20 °C and 12% RH until analysis.

2.2.2. Assessment of physicochemical properties of terbutaline sulphate

Both the micronized and spray-dried TBS were analysed.

Scanning electron microscopy (SEM) was performed using an ITACHI S4700 FEG (secondary scattering electron) at an accelerated voltage between 3 and 6 kV.

The crystallinity of the powders was assessed by X-ray diffraction (XRD) with a PANalytical X'Pert Pro MPD diffractometer, equipped with a Cu X-ray tube (λCuKα: 1540 Å). Samples were placed into Lindemann glass capillaries (diameter 0.7 mm). The measurements were performed in transmission mode with incident beam parabolic mirror and X'celerator detector.

Differential scanning calorimetry (DSC) experiments were performed with the DSC 2920 microcalorimeter of TA Instruments. Samples were placed into non-hermetic aluminium pans and heated from −40 to 120 °C at 5 °C/min under a nitrogen purge. The reference was an empty aluminium pan. Temperature and enthalpy readings were calibrated using pure indium at the same scan rates as were used in the experiments.

The size of TBS particles was determined with a laser size analyser Mastersizer S (Malvern, Orsay, France) using the 300 mm lens and the dry way. The average particle size distribution was measured from three replicates of each sample.

2.2.3. Preparation of carriers

To limit the influence of particle size, the same granulometric fraction was used for each carrier, that is to say 63–125 μm. It was obtained after a first mechanical sieving Retsch type 3D (Retsch, Haan, Germany) and a second through an Alpine air-jet sieve (Alpine, Augsburg, Germany). For the mechanical sieving, carriers were poured into a 125 μm sieve which had been placed upon a 63 μm sieve. The particles were sieved for 15 min with a 2 mm amplitude agitation. Particles retained on the 63 μm sieve were then poured into the 63 μm sieve of the Alpine air-jet sieve and sieved for 15 min with an airflow that produces a pressure drop of 4 kPa. The last sieving made possible to remove fine particles of carriers that can be at the surface of large particles of carrier and that could be a source of variation in fine particle delivery. Indeed, 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 [16].

The lactoses used present tomahawk shaped particles. After sieving, the mean diameters measured by laser scattering (Mastersizer S, particle suspension in ethanol) were 115 μm (GSD of 1.05), 80 μm (GSD of 1.15), 105 μm (GSD of 1.57) and 85 μm (GSD of 1.59) for the Inhalac 120, Inhalac 230, Lactohale 100 and Lactohale 200, respectively.

2.2.4. Blending lactose with terbutaline sulphate

TBS and lactose were mixed to 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.

2.2.5. Measurement of average content

The quality of the blends was examined by analysing the quantity of TBS 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 (UV-1650PC, Shimadzu, Kyoto, Japan) with a wavelength of 276 nm. The calibration curve was linear from 0 to 200 μg/ml ($A = 64.43965\,c + 0.00077$, $r^2 = 0.99998$). From the 10 results of TBS content in the samples, we calculated the average content in TBS and the mean recovery related to the nominal dose.

2.2.6. Evaluation of adhesion characteristics

For all experiments realised, temperature and relative humidity were controlled at 20 °C and 20%. Adhesion characteristics were evaluated by submitting the blend to sieving. Two different kinds of sieving were used with the same aperture (63 μm):

- A mechanical sieving with the Retsch sieve type 3D, shaking with a 2 mm amplitude.
- An air depression sieving with an Alpine air-jet sieve, used with an airflow that produces a pressure drop of 4 kPa.

In the first case, because of vibrations, particles were submitted to shakes and shocks leading to the passage of particles with a diameter lower than that of the screen aperture. The objective of this test was to assess if the blend was sufficiently stable to resist to the vibrations.

In the second case, the blend was put on a sieve in a sealed enclosure. Particles were 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 were carried through the sieve thanks to aspiration. The objective of this test was to assess the ease with which the drug can be separated from the carrier when the blend is carried by an air-flow.

For the two types of tests, 30 g of blends was placed on the 63 μm sieve section of the sieves. Three samples of 34.25 mg corresponding to 500 μg drug were removed from the powder bed after sieving at different lengths of time: 5, 15, 30, 150, 300 and 600 s. The drug content in the samples was determined by UV spectrophotometry (UV-1650PC, Shimadzu, Kyoto, Japan). For each sample, we compared the percentage of drug remaining to the initial dose.

The results are the mean of three replicate measurements.

2.2.7. Preparation of the capsules

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

2.2.8. Aerodynamic evaluation of fine particle dose and emitted dose

In vitro deposition of TBS from dry powder formulations was determined using a twin stage impinger (TSI, Apparatus A, European Pharmacopoeia, 2005). The TSI was assembled and loaded with 7 ml of distilled water in the upper stage and 30 ml in the lower stage. Each deposition experiment involved the aerosolization at 60 l/min via an Inhalator Ingelheim of 10 capsules, each containing 34.25 mg of blend equivalent to a nominal dose of 500 μg TBS.

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

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

- the emitted dose (ED), which was the sum of drug collected at upper and lower stages, divided by 10, the number of capsules tested
- the fine particle dose (FPD) defined as the amount of drug deposited in the lower stages of the TSI, because their aerodynamic diameter was less than the cut-off diameter of the TSI (6.4 μm at an airflow rate of 60 l/min), divided by 10, the number of capsules tested
- the percentage emission calculated as the ratio of ED to the average content
- the fine particle fraction calculated as the ratio of FPD to the emitted dose.

A statistical ANOVA F test was applied to the results obtained with TSI. Double way ANOVA test was used considering the type of drug and the type of lactose.

3. Results and discussion

3.1. Physicochemical properties of the drugs

Table 1 presents the particle size of the spray-dried TBS according to the operating conditions and compares them to the size of the micronized TBS. The influence of TBS concentration, air pressure and pump setting was very low. When increasing the airflow rate from 500 to 800 l/h, the size markedly decreased. The airflow rate was the amount of compressed air needed to disperse the solution. When the airflow rate increased, more energy was available for fluid dispersion and the size of the obtained particles decreased. The (D) conditions of spray-drying made it possible to achieve a size of TBS close to the one of micronized TBS. The median diameters of about 2.5 μm and the mean diameters of about 2.9 μm were suitable to be used in dry powder inhalers and avoid deposition by inertial impaction in the oropharyngeal cavity [8]. These (D) conditions were those used to produce the spray- dried TBS for blending with the different lactoses.

According to the scanning electron micrographs (Fig. 1), the micronized TBS was in the form of typical crystalline particles with needle-like microstructure. Micronization forced larger particles to fragment, forming irregular small particles. On the other hand, the electron micrographs of the spray-dried TBS showed that the particles had a uniform spherical shape.

Fig. 2 shows the XRD scans of spray-dried and micronized TBS. The XRPD diagram of the micronized product (Fig. 2b) presented many sharp Bragg peaks and was typical of a crystalline material. On the contrary the X-ray diagram of the spray-dried particles showed only a typical amorphous hollow with no sign of Bragg peak. The compound was thus X-ray amorphous. It could be either nanocrystalline or truly an amorphous solid, i.e., a glass. In order to check the exact nature of the compound, DSC analysis was performed to detect a possible glass transition. The melting point of terbutaline sulphate is 246–248 °C. The DSC scan of spray-dried TBS (Fig. 3) showed a Cp jump around 79 °C which was the evidence of a glass transition (Tg) at this temperature. This demon-

Table 1
Influence of the spray-drying conditions on the TBS particle size obtained by laser diffraction

Terbutaline sulphate	Operating conditions				Particle size		
	TBS concentration (w/v)	Air pressure (bar)	Airflow rate (l/h)	Pump rate	Median diameter (μm)	Mean diameter (μm)	GSD
Micronized	–	–	–	–	2.53	2.98	1.96
Spray-dried (A)	10 %	4	500	3	5.48	5.84	1.34
Spray-dried (B)	10 %	5	500	2	6.18	6.37	1.00
Spray-dried (C)	5 %	4	500	3	4.88	5.09	1.21
Spray-dried (D)	5 %	4	800	3	2.56	2.81	1.36

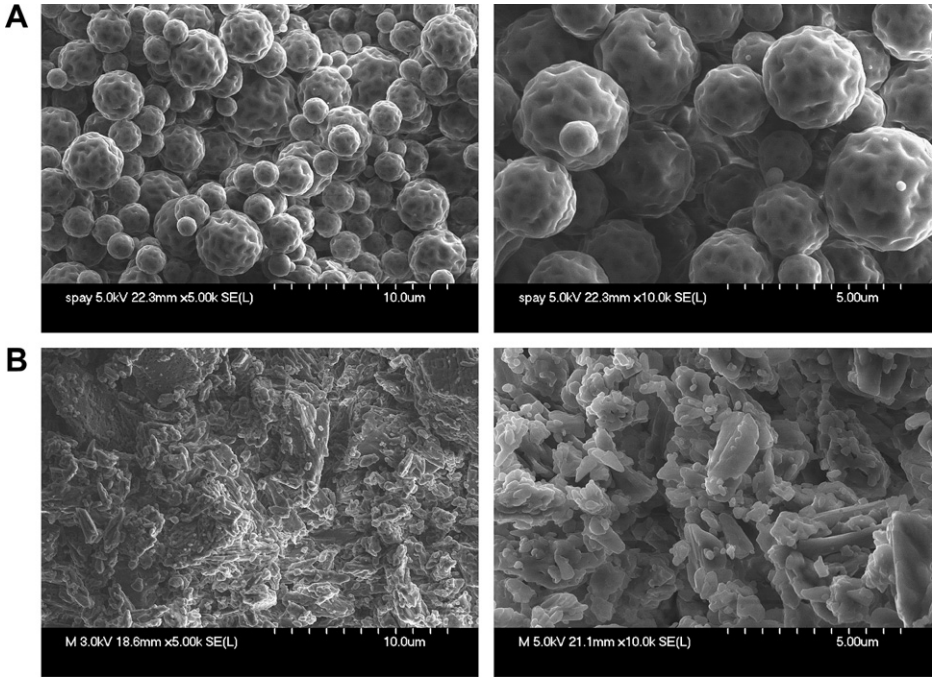

Fig. 1. Scanning electron micrograph of terbutaline sulphate spray-dried (A) and micronized (B).

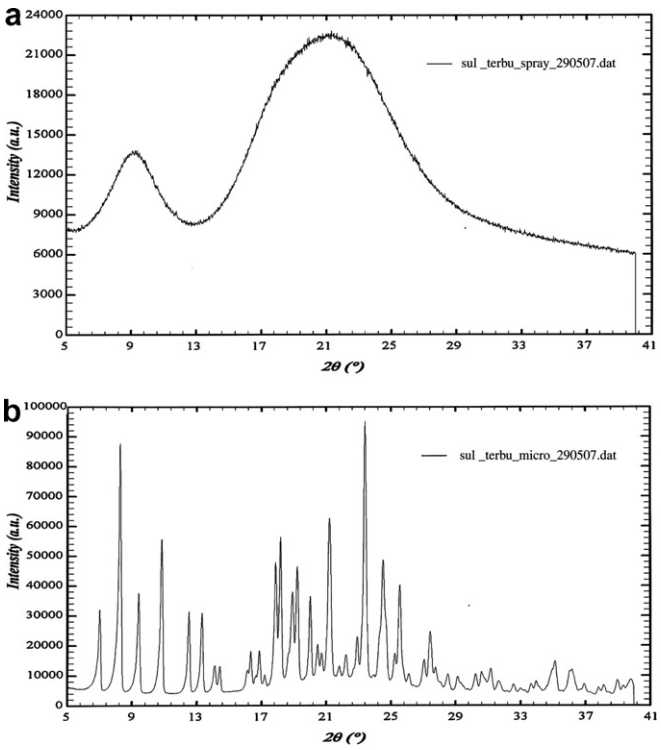

Fig. 2. XRD scans of terbutaline sulphate spray-dried (a) and micronized (b).

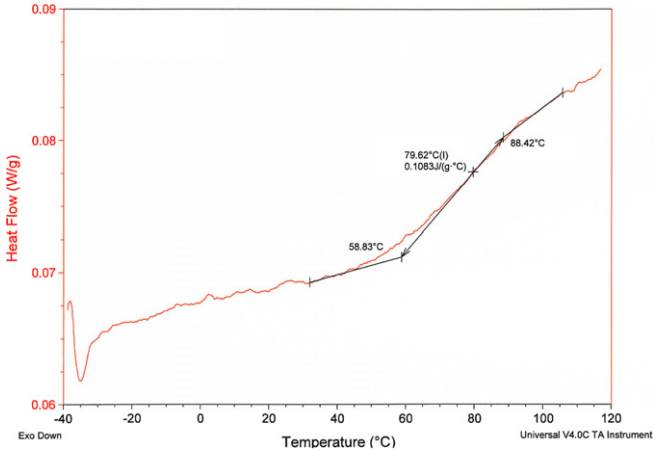

Fig. 3. DSC scan of spray-dried terbutaline sulphate.

strated the truly amorphous structure of the spray-dried TBS. This finding was in agreement with previous works in which spray-drying was shown to "decrease crystallinity" [9,17,18]. This was explained by the rapid solidification during the spray-drying [19]. The molecular structure of spray-dried particles was thus totally disordered. However, since room temperature was about 60 °C below Tg, we can expect amorphous spray-dried particle to be really solid particles.

3.2. Content uniformity

After blending each drug with the different carriers, we measured the average drug content (Table 2). All the blends showed a mean recovery of TBS between 95.5% and 104.5% and a satisfactory mixing uniformity of the drug with coefficients of variation less than 2%. All individual recovery was comfortably within 85–115% of label claim, suggesting that homogeneous blends were obtained whatever the drug and the lactose used [20].

Table 2
Average contents of the carrier/drug blends

Carrier/drug blend	Average content of drug (μg)	Mean recovery related to the nominal dose
Inhalac 120/spray-dried TBS	499.47 (CV = 1.84%)	99.90%
Inhalac 230/spray-dried TBS	488.56 (CV = 0.92%)	97.70%
Lactohale 100/spray-dried TBS	477.49 (CV = 0.77%)	95.50%
Lactohale 200/spray-dried TBS	482.74 (CV = 1.30%)	96.50%
Inhalac 120/micronized TBS	522.51 (CV = 0.72%)	104.50%
Inhalac 230/micronized TBS	513.39 (CV = 1.04%)	102.7 %
Lactohale 100/micronized TBS	506.79 (CV = 0.74%)	101.3 %
Lactohale 200/micronized TBS	516.10 (CV = 1.22%)	103.2 %

CV, coefficient of variation.

3.3. Adhesion characteristics

We compared the adhesion characteristics of the two drugs that is to say the micronized TBS and the spray-dried TBS, by analysing drug present on 63 μm sieve after sieving the different blends drug/lactose in different conditions.

Fig. 4 presents the percentage of drug remaining on the carrier in relation to the functioning time of the mechanical sieve. After 10 min of mechanical vibrations, it was noted that at least 65.83% of spray-dried TBS was still fixed on the Inhalac 230, 60.51% on the Inhalac 120, 41.4% on the Lactohale 100 and 40.9% on the Lactohale 200. In the case of the micronized TBS, the quantities still fixed on the carriers were higher: 89.6% on the Inhalac 230, 86.7% on the Inhalac 120, 88.97% on the Lactohale 100 and 74.85% on the Lactohale 200. As drug quantities adhered were lower for spray-dried TBS than for micronized TBS and as the particle size was identical for the two drugs with narrow size distribution, the results indicated that physical interactions between the drug and the carriers were weaker in the case of spray-dried TBS.

The sieving assays by mechanical vibrations made it possible to confirm that the blends were ordered, that is to say stable enough to resist the vibrations. After 10 min of mechanical vibrations, no blend released more than 25% of micronized TBS and 40% to 60% of spray- dried TBS.

Fig. 5 presents the percentage of drug remaining on the carrier in relation to the functioning time of the Alpine air-jet sieve. This sieving by aspiration made it possible to determine how easily the drug separated from the carrier. The drug was rapidly carried away by the airflow. The quantity of drug present after 5 s was an indicator of the quantity of drug that strongly adhered to the lactose.

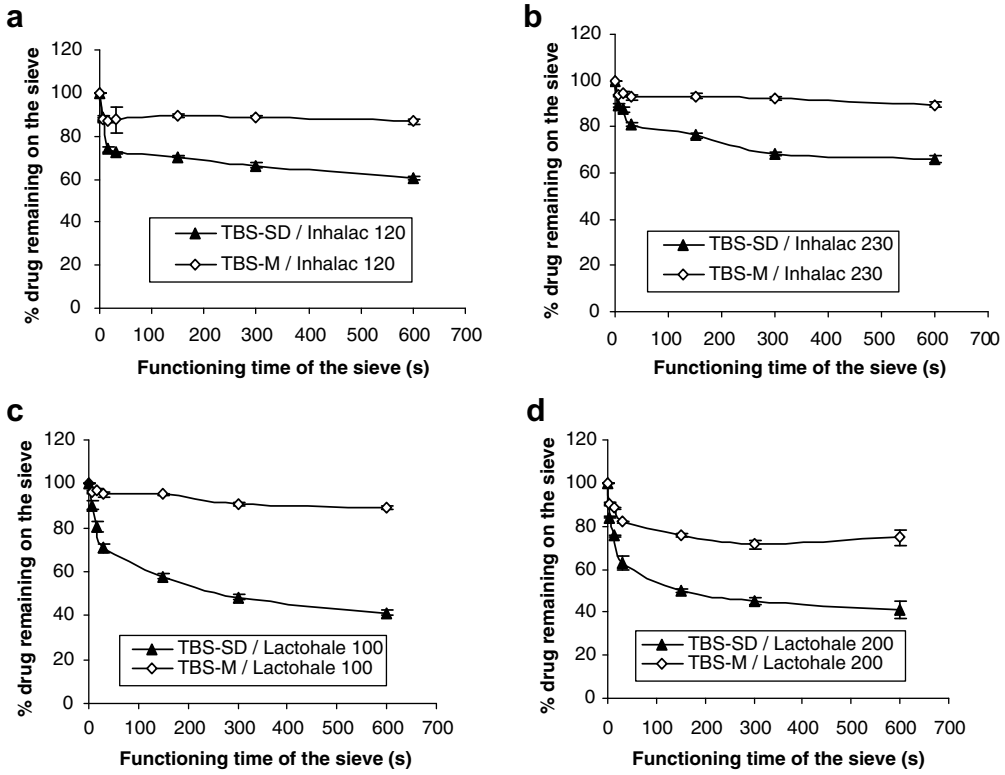

Fig. 4. Percentage of terbutaline sulphate (TBS) spray-dried (SD) or micronized (M) remaining fixed to the carrier ((a), Inhalac 120; (b), Inhalac 230; (c), Lactohale 100; (d), Lactohale 200) in relation to the functioning time of the mechanical sieve.

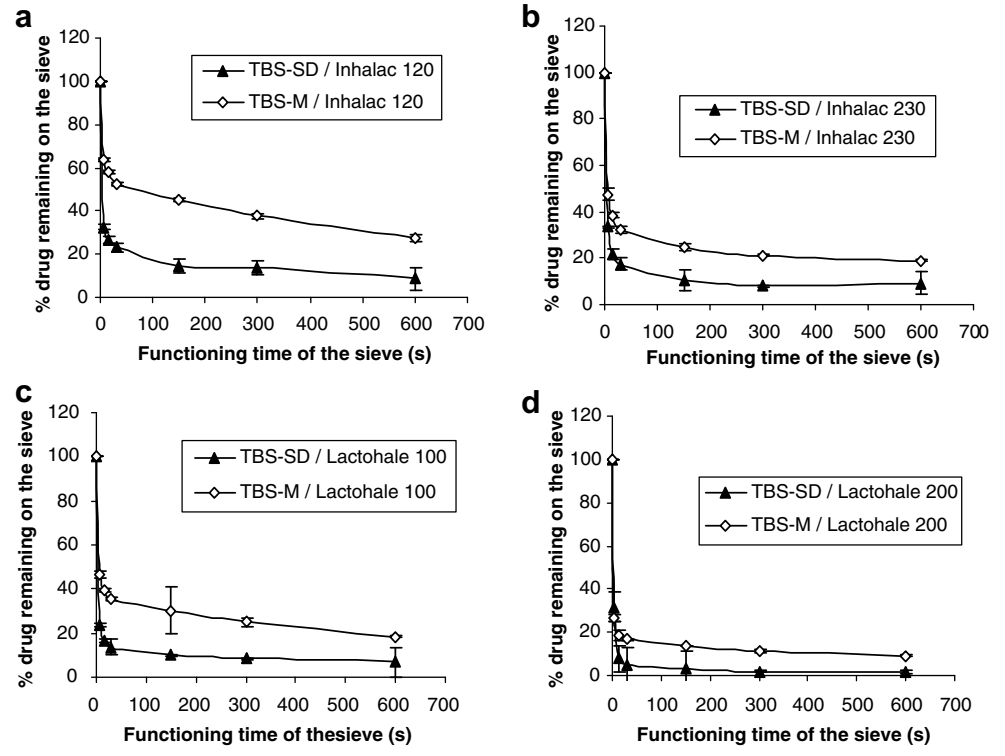

Fig. 5. Percentage of terbutaline sulphate (TBS) spray-dried (SD) or micronized (M) remaining fixed to the carrier ((a), Inhalac 120; (b), Inhalac 230; (c), Lactohale 100; (d), Lactohale 200) in relation to the functioning time of the air-jet sieve.

Indeed, as drug particle size was much lower than 63 μm, if the drug particles were individualized in the blend and not adhered on the carrier, they would be carried away through the 63 μm sieve by aspiration. After 5 s, about 33% of spray-dried TBS remained fixed on the Inhalac 120, Inhalac 230, Lactohale 200 and 24% on the Lactohale 100. For the micronized TBS, about 63% remained fixed on the Inhalac 120, 47% on the Inhalac 230, Lactohale 100 and 27% on the Lactohale 200. In all cases, more micronized TBS than spray-dried TBS remained fixed.

The evolution with aspiration time showed drug detachment, particularly during the first 30 seconds. After 10 min, only 1.8% to 9.2% of spray-dried TBS remained fixed on the lactoses but in the case of micronized TBS, a consequent quantity of about 10% to 30% was not released from the different lactoses. Adhesion strength seemed to be different according to the type of TBS considered. The detachment forces required to remove respirable particles were different and probably related to the physical properties of the drug. Adhesion was lower with the spray-dried TBS. This could be attributed to the sphericity of those particles. Indeed particle shape may significantly affect the extent of particle surface contact, and therefore the efficiency of short-range Van der Waal's forces [2]. Adhesion between drug particle and carrier will be increased by increasing particle roughness and decreasing drug particle sphericity; conversely, decreased adhesion can be promoted by increasing particle smoothness and sphericity [2]. That was what occurred during spray-drying.

The behaviour of the drug/carrier blend during the assay gave an estimation of the drug capacity to separate from the carrier during inhalation. Strong adhesion of the drug during the assay presupposed the difficult separation of the drug after patient inhalation or the need for greater inhalation airflow.

3.4. Aerosolization properties of the dry powders

The aerodynamic behaviour of the drug/lactose blends was estimated with TSI making it possible to study the in vitro deposition profile of spray-dried and micronized terbutaline sulphate (Table 3).

The emitted doses obtained were between 65.66% and 77.20% for the spray-dried TBS, and between 59.31% and 69.20% for the micronized TBS. For a given TBS, the emitted dose varied according to the lactose considered ($p < 0.5$). For a given lactose, the emitted dose varied according to the drug considered ($p < 0.5$). The emitted doses were significantly higher for the spray-dried TBS ($p < 0.5$).

The fine particle fractions obtained were between 29.70% and 42.98% for the spray-dried TBS, and between 24.95% and 34.03% for the micronized TBS. Here again, for a given TBS, the fine particle fractions varied according to the lactose considered ($p < 0.001$). And, for given lactose, the fine particle fractions varied according to the TBS considered ($p < 0.005$). The higher fine particle doses were obtained with the Lactohale 200 whatever the TBS ($p < 0.01$). Whatever the lactose tested, higher particle doses were obtained with the spray-dried drug ($p < 0.005$) which indicated that the spray-dried TBS was better separated from the carrier; its dispersibility was higher. These results were in agreement with the adhesion tests that showed lower adhesion of spray-dried TBS on the different carriers.

3.5. Correlation between adhesion characteristics and inertial impaction

In Fig. 6, the fine particle doses for the different blends obtained with the Twin Stage Impactor were plotted against the quantity of drug remaining on the Alpine air-jet sieve after 30 s for the same blends. We noted a linear relationship between the adhesion characteristics obtained with our method and the fine particle dose obtained by impaction test with a correlation coefficient R^2 of 0.8521 which indicated a good correlation between these two parameters.

The method we proposed using Alpine air-jet sieve made it possible to characterize adhesion, to forecast drug

Table 3
Terbutaline sulphate deposition in the TSI after aerosolization of the different blends with the inhalator Ingelheim at 60 l/min (mean (±cv), $n = 3$)

	Inhalac 120	Inhalac 230	Lactohale 100	Lactohale 200
Emitted dose (μg)				
Spray-dried TBS	340.25 (7.2)	343.86 (10.9)	368.18 (8.6)	316.99 (4.8)
Micronized TBS	313.86 (5.7)	355.25 (10.7)	335.59 (7.4)	306.11 (10.0)
Fine particle dose (μg)				
Spray-dried TBS	106.24 (7.7)	114.52 (6.8)	109.34 (10.2)	136.24 (10.2)
Micronized TBS	79.34 (10.9)	88.65 (10.1)	87.62 (6.1)	104.17 (6.2)
% Emission				
Spray-dried TBS	68.12 (7.2)	70.38 (10.9)	77.20 (8.6)	65.66 (4.8)
Micronized TBS	60.00 (5.7)	69.20 (10.7)	66.22 (7.4)	59.31 (10.0)
Fine particle fraction (%)				
Spray-dried TBS	31.22 (7.7)	33.30 (6.8)	29.70 (10.2)	42.98 (10.2)
Micronized TBS	25.28 (10.9)	24.95 (10.1)	26.11 (6.1)	34.03 (6.2)

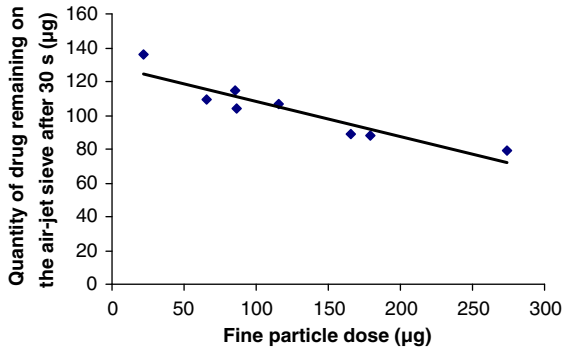

Fig. 6. Relation between fine particle dose and quantity of drug remaining on the air-jet sieve after 30 s.

detachment from lactose and to predict aerodynamic behaviour of the drug. This method of adhesion evaluation considered the whole blend as it is used in dry powder inhalers which was different of techniques like AFM that concerns only one particle and not the overall blend.

4. Conclusion

Spray-drying of a solution of terbutaline sulphate produced a fine powder of spherical shaped particles, with a size adapted for pulmonary delivery. Spray-drying provided a useful mean of controlled particle size production. The spray-dried particles were found to be amorphous with a glass transition temperature situated at Tg ≅ 79 °C. This assured that the particles were rigid. The results confirmed that the drug/carrier interactions were depending on parameters like the shape and the crystalline form. The shape argument prevailed because the room temperature during the adhesion and aerosolization experiments was much lower than the Tg (about 60 °C below the Tg). So, the particle rigidity minimized the contact area with the carrier and so made the separation from the carrier easier. Adhesion on the different lactoses tested was lower for the spray-dried terbutaline sulphate which led to higher fine particle doses during the impaction assays. In this case, the patient will have to make a lower respiratory effort to detach the drug from the lactose so that a high percentage of drug reaches deep into the lungs.

The different lactoses tested were not interchangeable even if the granulometric fractions were the same, probably because of different surface properties like roughness [21].

Some lactoses were more efficient for the aerozolization and the dispersion of the drug whatever the terbutaline sulphate considered; that was the case of Lactohale 200 for example.

The techniques used to assess the adhesion of drugs to carrier particles provided complementary informations about drug/carrier interactions and detachment. The behaviour of the drug/carrier blend during the air-jet sieve assay made it possible to determine how easily the drug separated from carrier. The results of fine particles doses were in agreement with the Alpine air-jet sieve results, with a linear relationship between them. These tests are useful for the development of dry powder inhalers to obtain a stable blend and a maximal fine particle dose.

Acknowledgement

We thank Ahmed Addad from the LSPES (UMR CNRS 8008) for his help in SEM measurements.

References

[1] J.A. Hersey, Ordered mixing: a new concept in powder mixing practice, Powder Technol. 11 (1975) 41–44.
[2] J. Bell, Dry powder inhalation technology, Pharm. Manufact. Int. (1994) 179–182.
[3] D. Prime, P.J. Atkins, A. Slater, B. Sumby, Review of dry powder inhalers, Adv. Drug Deliv. Rev. 26 (1997) 51–58.
[4] P.J. Davies, G.W. Hanlon, A.J. Molyneux, An investigation into the deposition of inhalation aerosol particles as a function of air flow rate in a modified "Kirk Lung", J. Pharm. Pharmacol. 28 (1976) 908–911.
[5] H. Steckel, L. Pichert, B.W. Müller, Influence of process parameters in the ASES process on particle properties of budesonide for pulmonary delivery, Eur. J. Pharm. Biopharm. 57 (2004) 507–512.
[6] C. Bosquillon, P.G. Rouxhet, F. Ahimou, D. Simon, C. Culot, V. Préat, R. Vanbever, Aerosolization properties, surface composition and physical state of spray-dried protein powders, J. Control. Release 99 (2004) 357–367.
[7] M.B. Chougule, B.K. padhi, K.A. Jinturkar, A. Misra, Development of dry powder inhalers, Recent Patents Drug Deliv. Formul. 1 (2007) 11–21.
[8] N.R. Rabbani, P.C. Seville, The influence of formulation components on the aerosolisation properties of spray-dried powders, J. Control. Release 110 (2005) 130–140.
[9] M.T. Vidgrén, P.A. Vidgrén, T.P. Paronen, Comparison of physical and inhalation properties of spray-dried and mechanically micronized disodium cromoglycate, Int. J. Pharm. 35 (1987) 139–144.
[10] A. Chawla, K.M.G. Taylor, J.M. Newton, M.C.R. Johnson, Production of spray dried salbutamol sulphate for use in dry powder aerosol formulation, Int. J. Pharm. 108 (1994) 233–240.
[11] R. Vanbever, J.D. Mintzes, J. Wang, J. Nice, D. Chen, R. Batycky, R. Langer, D.A. Edwards, Formulation and physical characterization of large porous particles for inhalation, Pharm. Res. 16 (1999) 431–437.
[12] C. Bosquillon, C. Lombry, V. Preat, R. Vanbever, Influence of formulation excipients and physical characteristics of inhalation dry powders on their aerosolisation performance, J. Control. Release 70 (2001) 329–339.
[13] A. Najafabadi, K. Gilani, M. Barghi, M. Rafiee-Tehrani, The effect of vehicle on physical properties and aerosolisation behaviour of disodium cromoglycate microparticles spray dried alone or with L-leucine, Int. J. Pharm. 285 (2004) 97–108.
[14] C. Bosquillon, V. Preat, R. Vanbever, Pulmonary delivery of growth hormone using dry powders and visualisation of its local fate in rats, J. Control. Release 96 (2004) 233–244.
[15] D.O. Corrigan, O.I. Corrigan, A.M. Healy, Physicochemical and in vitro deposition properties of salbutamol sulphate/ipratropium bromide and salbutamol sulphate/excipient spray dried mixtures for use in dry powder inhalers, Int. J. Pharm. 322 (2006) 22–30.
[16] X.M. Zeng, G.P. Martin, C. Marriott, J. Pritchard, The influence of carrier morphology on drug delivery by dry powder inhalers, Int. J. Pharm. 176 (2000) 93–106.
[17] O.I. Corrigan, E.M. Holohan, Amorphous spray dried hydroflumethiazide-polyvinyl pyrrolidone systems, J. Pharm. Pharmacol. 36 (1984) 217–221.
[18] O.I. Corrigan, E.M. Holohan, K. Sabra, Amorphous forms of diuretics prepared by spray drying, Int. J. Pharm. 18 (1984) 195–200.

[19] T. Sebhatu, M. Angberg, C. Ahlneck, Assessment of the degree of disorder in crystalline solids by isothermal microcalorimetry, Int. J. Pharm. 104 (1993) 135–144.
[20] US Pharmacopeia, (905) Uniformity of dosage units: content uniformity (2004) 2396–2397.
[21] M.P. Flament, P. Leterme, A. Gayot, The influence of carrier roughness on adhesion content uniformity and the in vitro deposition of terbutaline sulphate from dry powder inhalers, Int. J. Pharm. 275 (2004) 201–209.