International Journal of Pharmaceutics 422 (2012) 75–82

Contents lists available at SciVerse ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Influence of the lactose grade within dry powder formulations of fluticasone propionate and terbutaline sulphate

V.N.P. Le[a], H. Bierend[b], E. Robins[c], H. Steckel[b], M.P. Flament[a,*]

[a] INSERM 1008, College of Pharmacy, Univ. Lille Nord de France, 3 Rue du Prof. Laguesse, 59006 Lille, France
[b] Christian Albrecht University Kiel, Pharmaceutical Institute 9a, 24118 Kiel, Germany
[c] APTAR Pharma., Route des Falaises, BP 37, 27100 Le Vaudreuil, France

ARTICLE INFO

Article history:
Received 27 June 2011
Received in revised form
19 September 2011
Accepted 17 October 2011
Available online 20 October 2011

Key words:
Dry powder inhalation
Lactose
Physicochemical properties
Adhesion
Aerodynamic behaviour
Inverse gas chromatography

ABSTRACT

Dry powder formulations are often composed of fine drug particles and coarser carrier particles, typically alpha-lactose monohydrate. However, the performance of a powder formulation may be highly dependent on the lactose quality and source. This study investigated the characteristics of lactose that influence the drug-to-carrier interaction and the performance of lactose-based dry powder inhaler formulations. The selected lactoses differed in the preparation processes and the content of fine lactose particles. Efficiency testing was done using fluticasone propionate and terbutaline sulphate as model drugs. Inverse gas chromatography was used to determine the surface heterogeneity distribution of different energy sites of the lactose and to understand the mechanism by which the fine carrier particles can improve the performance of dry powder inhalers. To assess the adhesion of respirable-sized drug to carrier particles, a simple method was developed based on aspiration and considering the whole blend as it is used in dry powder inhalers. When the percentage of fine lactose is high, a lower quantity of drug adheres to the lactose and/or the adhesion force is also lower. This was confirmed by the aerosolization assays done in the TSI (twin stage impinger). A correlation was observed between adhesion characteristics and inertial impaction. For both drugs, the fine particle fractions were highest in blends that present a greater proportion of lactose fine particles. A fairly good correlation between the fine particle fractions of both drugs and the peak max value and the AUC (area under curve) were found by inverse gas chromatography. With higher fine particle fraction values, which correspond to higher content of fines, the peak maxima determined by inverse gas chromatography were shifted to higher adsorption potentials, which supports the agglomeration hypothesis.

1. Introduction

Dry powder formulations are often composed of fine drug particles and coarser carrier particles, typically α-lactose monohydrate because it is an inert, cheap, broadly available and non-toxic excipient (te Wierik et al., 2002; Pilcer and Amighi, 2010). This results in the improvement of handling and processing properties, a more accurate dosing of the drug by dilution of the active substance to suitable mass ratio and an increase in device performance (Young et al., 2005). The fine drug particles are expected to adhere to the carrier surface to form interactive mixtures (Hersey, 1975). 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 and hygroscopicity (Guenette et al., 2009; Hassan and Lau, 2009; Bell, 1994; Sumby et al., 1997). 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 efficacy of the inhalation product.

However, the efficiency of a powder formulation may be highly dependent on the lactose quality and source (Steckel, 2002). The lactose needs to be carefully selected for the efficient delivery of a drug from the inhaler. The quality of lactose, that is to say sieved or milled quality, used for the formulation of an inhalation powder may affect the aerodynamic behaviour of drug/lactose blends (Steckel et al., 2004). Furthermore, every drug has its own characteristics regarding its tendency to agglomerate and the ability to form an adhesive mixture with lactose (te Wierik et al., 2002). So, for each drug, specific lactose qualities have to be selected.

More recently, the adhesion of fine carrier particles to dry powder formulation has shown to improve the dispersion and deposition of drug particles (Zeng et al., 1998; Guchardi et al., 2008). In the literature, two different mechanisms have been proposed to explain the improvement of formulation performance by addition of fine particles of carrier. The first hypothesis supposes the

* Corresponding author. Tel.: +33 3 20964974; fax: +33 3 20959009.
E-mail address: marie-pierre.flament@univ-lille2.fr (M.P. Flament).

0378-5173/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2011.10.030

occupation of areas of high adhesion by fine excipient particles. It was proposed that fine excipient particles preferentially bind to the areas on the surface of the coarse carrier with the strongest binding characteristics, thus forcing drug particles to bind to areas with weaker binding characteristics (Jones and Price, 2006). The second hypothesis supposes the formation of agglomerates of drug and fine excipient particles. So, during aerosolization, drug particles are more easily liberated from fine particle multiplets than from the surface of coarse particles, as fine lactose was thought to have a smoother surface than coarse lactose, giving a reduced force of adhesion between drug and fines (Jones and Price, 2006; Lucas et al., 1998a,b). The presence of fine lactose particles in the mixture may be related to an increase in the tensile strength of the powder bulk when it interacts with the airflow. Thus, the aerodynamic drag forces exerted on the powder bulk are increased when increasing the fine lactose particle quantity in the mixture (Shur et al., 2008). Actually, the mechanism of action of the fine particles remains unclear and more work is required to fully elucidate their role.

The concentration and particle size of fine lactose have to be carefully controlled to obtain satisfactory and reproducible pharmaceutical performance from a specific formulation associated with a specific device (Zeng et al., 1998).

The aim of this work was to identify the characteristics of lactose that influence the drug-to-carrier interaction and the performance of dry powder formulation using fluticasone propionate and terbutaline sulphate as model drugs. For this purpose, marketed lactose qualities obtained by milling or by sieving were compared. From the same raw materials, two fractions of lactose were also prepared and tested to help understanding the role of smaller carrier particles on the performance of dry powder formulations.

Inverse gas chromatography (iGC) was used to determine the surface heterogeneity distribution of different energy sites of the lactose and to understand the mechanism by which the fine carrier particles can improve the performance of dry powder inhalers. IGC is a very sensitive technique to reveal differences in surface adsorption energies. By starting a measurement at infinite dilution, initially only the highest energy sites will interact. By increasing the partial pressure more and more in order to reach finite dilution, less active sites will be involved in the interaction and an adsorption potential distribution caused by different energy sites can be generated. The objective is to find a general applicable method to describe the lactose qualities in advance and hence to predict the formulation performance.

2. Materials and methods

2.1. Materials

The two drugs tested were micronized terbutaline sulphate (TBS) and micronized fluticasone propionate (FP) supplied by APTAR Pharma (Le Vaudreuil, France). These drugs present different polarities estimated by their octanol–water partition (Log *P*). TBS is rather hydrophilic (Log *P* 0.67) whereas FP is more lipophilic (Log *P* 3.7). Two lactose grades with comparable mean diameter were used as carrier: lactose A and lactose B. Lactose A is the Lactohale LH 200 (Friesland Foods Domo, Zwolle, The Netherlands), a lactose quality obtained by milling whereas lactose B is the Inhalac 230 (Meggle, Hamburg, Deutschland), a sieved lactose quality. Furthermore, 2 fractions of lactose without particles below 32 μm were prepared from A and B by air-jet sieving through a 32 μm sieve for 30 min with an airflow that produces a pressure drop of 4 kPa.

The drug/carrier blends were aerosolized with the Inhalator Ingelheim (Boehringer Ingelheim, Ingelheim am Rhein, Germany) after filling in hard gelatine capsules (size 3) (Capsugel, Colmar, France).

2.2. Characterisation of the lactose qualities

2.2.1. Particle size distribution

The particle size distribution was determined with a laser particle size analyser Mastersizer S (Malvern, Orsay, France) by the wet way on liquid dispersions using the 300RF lens and the small sample dispersion unit. A small quantity of lactose was dispersed in ethanol with 0.5% polysorbate 80.

For each measurement, the mean diameter, the median diameter, the diameters under which 10% particles (*D* 10%) and 90% particles (*D* 90%) are to be found, respectively, are determined. Each result is the mean of three measurements.

2.2.2. Water content

The water content was determined by Karl-Fisher titration as described in USP XXX method. 1 g of lactose was dissolved in methanol/formamide (50:50) previously titrated out the residual water. Hydranal® Composite 5 was used as Karl-Fischer reagent. Hydranal® Composite 5 has a titer of 5 mg water/mL. It contains iodine, sulphur dioxide in diethylene glycol monoether. The titer of reagent was re-determined before any analysis.

2.2.3. Scanning electron microscopy

Scanning electron microscopy (SEM) was performed using an ITACHI S4700 FEG (secondary electron). The samples were mounted on aluminium stubs and coated with carbon. The images were taken at an accelerated voltage between 3 and 6 kV.

2.2.4. Inverse gas chromatography

The surface heterogeneity distribution of different energy sites of the lactose qualities was determined by means of inverse gas chromatography (SMS-iGC 2000 system, Surface Measurement Systems, London, UK)) at an elutant oven temperature of 35 °C, a column oven temperature of 30 °C, 0% relative humidity and a helium carrier flow rate of 10 ml/min. Helium 5.0 was supplied by Air Liquide (Nanterre, France). 1 g of lactose was packed into a silanized glass column with an inner diameter of 3 mm and a length of 30 cm and mounted with silane treated glass wool. The columns were tapped for 10 min in an iGC column packer (Surface Measurement Systems, London, UK) at medium intensity (corresponds to level 6). The measurement delay for equilibrating at 0% relative humidity was always set to 120 min to remove physisorbed water and impurities adsorbed on the surface. The pulsed injections were carried out by a 0.25 mL gas loop. Ethyl acetate (HPLC grade, Sigma–Aldrich, St Louis, USA) was used as elutant to predict the interaction potential of lactose with non-polar and polar drugs, respectively. The injection concentrations of the solvent vapours were 0.1 p/p° for the reference gas methane (4.5 quality, Messer, Germany) for dead time correction and 0.03, 0.05, 0.1, 0.33, 0.55, 0.77, 1.0, 1.1, 1.2 p/p° for ethyl acetate. All runs were performed in duplicate and detected with a Flame Ionization Detector: for combustion hydrogen 5.0 (Air Liquide, Nanterre, France) and air (filtered and dried by Clearpoint® and Drypoint®, respectively, Beko, Germany) were applied. The iGC raw data were analyzed by means of the iGC Analysis Macros, Version 1.3.3 Standard and Version 1.25 Advanced (Surface Measurement Systems, London, UK). The areas under the curves of the heterogeneity plots were calculated using the software OriginPro 8.5 (OriginLab, Elk Grove Village, USA).

2.3. Blending lactose with drugs

Micronized terbutaline sulphate and lactose were mixed to a ratio of 1:67.5 (w/w) (1.46% w/w), in a Turbula blender for 2 h at

90 rpm under controlled relative humidity. Each blend was prepared in 100 g quantity. Fluticasone propionate and lactose were mixed at concentration of 2.5% (w/w) under the same conditions. The concentration of 2.5% was chosen because this is the standard concentration used by APTAR Pharma for the fluticasone propionate as a model formulation. For the terbutaline sulphate, it was not possible to obtain a homogeneous blend at 2.5% (w/w) so the ratio 1/67.5 often described in the literature was retained.

For each blend, the homogeneity was checked by dosing the drug content on 15 samples and evaluating the content uniformity (see Section 2.5).

2.4. Preparation of the capsules

The lactose/drug blends were filled into hard gelatine capsules (size 3) manually so that each capsule contained 500 μg of drug that is to say 20 mg of blend for fluticasone propionate and 34.25 mg of blend for terbutaline sulphate.

2.5. Measurement of drug content and content uniformity

The quality of the blends was examined by analysing the quantity of drug in aliquots of sampled powder which is the amount of powder in each capsule: 20 mg or 34.25 mg for fluticasone propionate and terbutaline sulphate respectively. Samples were then dissolved in 25 mL of adequate solvant, methanol/water (80:20) for fluticasone propionate and water for terbutaline sulphate.

The quantity of fluticasone propionate was accessed by using HPLC method (ProStar 230, Varian, Paris, France) with a Germini C18 column (150 mm × 4.6 mm, 5 μm) according to an internal validated method of APTAR Pharma. The drug was detected UV spectrophotometrically at a wavelength of 236 nm. The limit of detection and quantification are respectively 0.01 μg/mL and 0.05 μg/ml. Linearity was determined and found to be acceptable for solution ranging from 0.01 to 23 μg/mL with R^2 was found to be 0.9957.

In the case of terbutaline sulphate, the drug concentration was determined by measuring UV absorbance at 276 nm (UV-1650PC, Shimadzu, Kyoto, Japan). The linearity of this method was found in the working range from 1 to 100 μg/mL with R^2 was found to be 0.9999.

From the 15 results of drug content in the samples, we calculated the average content in drug and the mean recovery related to the nominal dose. The variation coefficient was used to assess the content uniformity of the blends.

2.6. Evaluation of adhesion characteristics

To assess the adhesion of respirable sized drug to carrier particles, a simple method was developed based on aspiration and considering the whole blend as it is used in dry powder inhalers. Adhesion characteristics were evaluated by submitting the mixtures to a sieving action by air depression with an Alpine air-jet sieve (Hosokawa Alpine GmbH, Augsburg, Germany) used with an airflow that produced a pressure drop of 4 kPa. 30 g of blend was placed on the 32 μm sieve section of the Alpine air-jet apparatus. Three samples of 20 mg for fluticasone propionate or 34.25 mg for terbutaline sulphate were removed from the powder bed after sieving for different lengths of time: 5, 30, 60,150 and 300 s. For each sample the percentage of remaining drug was compared to the initial dose, which is an indicator of the quantity of drug that adheres to the carrier. Temperature and relative humidity were controlled at 20 °C and 40–45% for all experiments.

2.7. Aerodynamic evaluation of fine particle dose and emitted dose

In vitro deposition of drug from dry powder formulations was determined using a twin stage impinger (TSI, Apparatus A, European Pharmacopoeia, 2009). The TSI was assembled and loaded with 7 ml and 30 ml of solvent in the upper and lower stage respectively. Each deposition experiment involved the aerosolization at 60 l/min via an Inhalator Ingelheim of 5 capsules containing 500 μg of drug. The different parts of the TSI were rinsed and the amount of drug deposited in the upper and lower stage was determined.

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

Temperature and relative humidity were controlled at 20 °C and 40–45% for all experiments.

A statistical ANOVA F test was applied to the results obtained with TSI.

3. Results and discussion

3.1. Characteristics of the carriers

Table 1 presents the particle size of lactose qualities A and B. Both present comparable mean and median diameters but the percentage of particles below 32 μm is different. Lactose A, which is obtained by milling contains a higher percentage of these particles. The milling process produces fine materials that adhere to the surface of the larger particles. This is confirmed by the SEM observations (Fig. 1a and c).

The SEM photographs in Fig. 1 show the morphology of lactose qualities A and B, with and with no particles below 32 μm. They exhibit tomahawk shape, which is typical of α-lactose monohydrate and is the shape of lactose crystal allowed to grow to maturity (Larhrib et al., 1999). The fine particles attached to the large carrier particles are clearly visible in the case of lactose A (Fig. 1a and c). When the lactose is subjected to the Alpine air-jet sieve to remove particles below 32 μm, the decrease in the level of fines is visually observed (Fig. 1b–e). This is accompanied by a decrease in apparent surface roughness.

For all the lactose qualities, the water content measured by the Karl-Fisher titration (data not shown) was about 5%, which is typical of α-lactose monohydrate and is in agreement with the specifications of the European Pharmacopoeia: water content between 4.5% and 5.5%.

The calculated iGC heterogeneity plots with ethyl acetate of the four lactose grades investigated are depicted in Fig. 2. The iGC peak max value in J/mol indicates that the most energy sites of the lactose surface have this stated adsorption potential. With increasing peak max, the area under the curve (AUC) is also augmented. In Table 2, an overview of the single mean values is given.

Table 1
Particle size distribution of the carriers.

Lactose	Mean diameter (μm)	Median diameter (μm)	*D* 10% (μm)	*D* 90% (μm)	% Fines (<32 μm) removed by the air-jet sieve
A	74.76	70.59	7.69	145.73	19.3
B	71.41	69.66	19.42	123.89	9.9

3.2. Content uniformity

Table 3 shows the average drug contents of the carrier/drug blends and coefficients of variation (CV). All formulations present a drug recovery over 97% and a satisfactory uniformity with CV less than 3% (terbutaline sulphate) or 4% (fluticasone propionate). Blend homogeneities seem to be slightly higher in the case of terbutaline sulphate. All individual recovery was comfortably within 85–115% of label claim, suggesting that homogeneous blends were obtained for all drug/lactose blends.

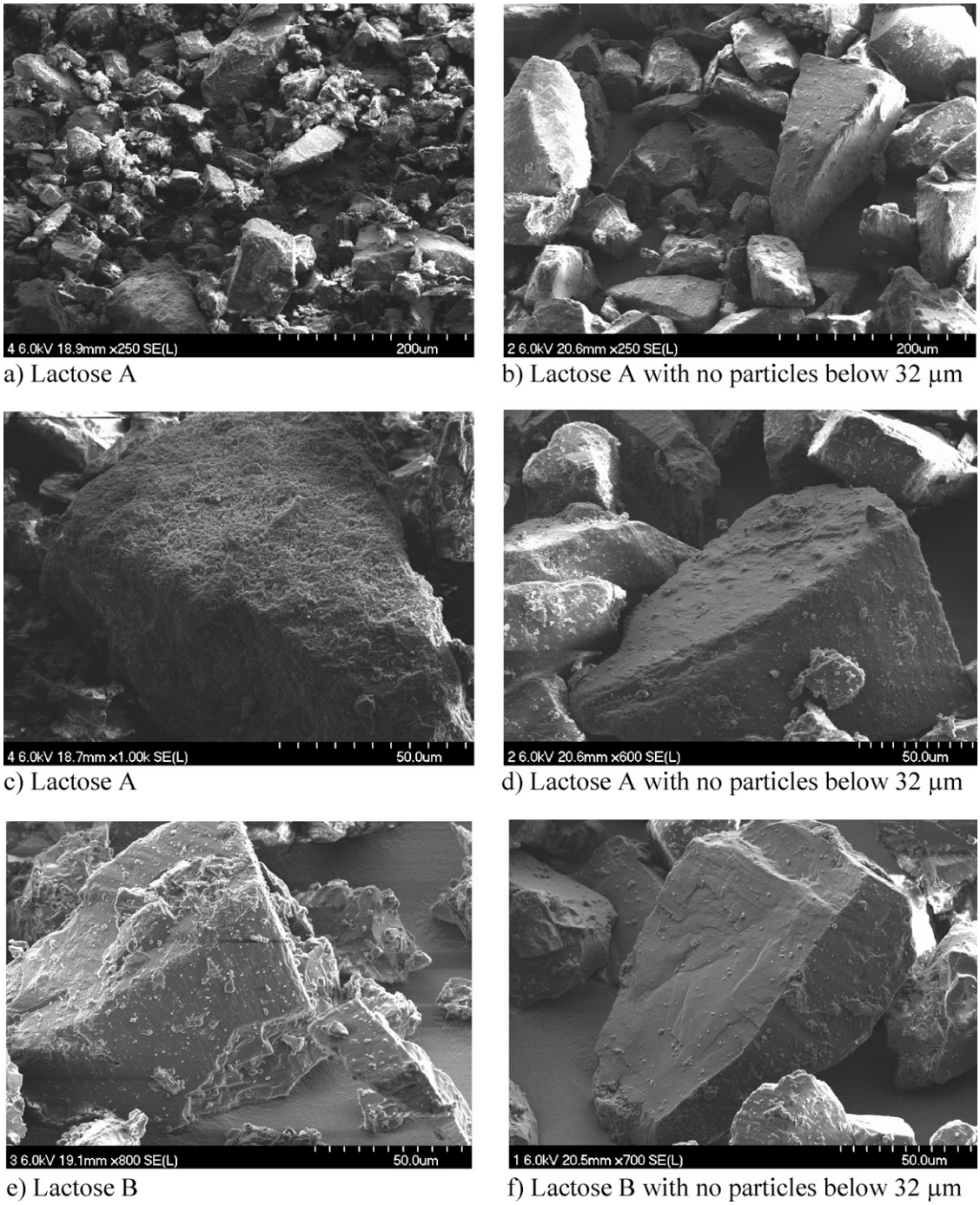

Fig. 1. Scanning electron micrograph of lactose A (a and c), lactose B (e), lactose A with no particles below 32 μm (b and d) and lactose B with no particles below 32 μm (f).

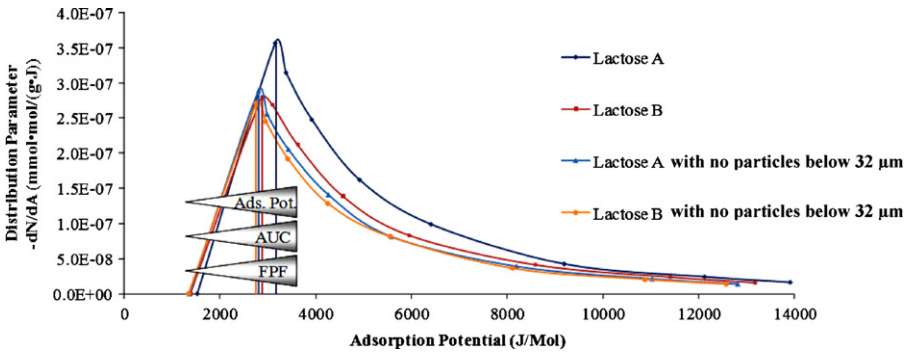

Fig. 2. Surface energetic heterogeneity plots of lactose A and B with and without fines obtained with ethyl acetate (determination of peak max values is indicated by vertical lines: cones symbolize increasing tendencies of adsorption potential maxima and areas under the curves resulting in higher fine particle fractions).

Table 2
Peak max values and areas under the curves (AUC) of the iGC heterogeneity plots measured with ethyl acetate for the lactose grades (mean ± span, $n = 2$).

Lactose grades	iGC heterogeneity plots obtained with ethyl acetate	
	Peak max (J/mol)	AUC × 100,000
Lactose A	3165 (±3)	126.9 (±2.3)
Lactose B	2888 (±8)	103.3 (±2.8)
Lactose A with no particles below 32 µm	2802 (±11)	94.5 (±2.1)
Lactose B with no particles below 32 µm	2761 (±3)	88.3 (±1.1)

3.3. Adhesion characteristics

The adhesion characteristics of the each drug with the four lactose qualities, raw lactoses A, B, and lactoses A and B without particles below 32 µm, by analysing the drug present on the 32 µm sieve after sieving the blends with the Alpine air-jet sieve, were compared.

Fig. 3 presents the percentage of fluticasone propionate (Fig. 3a) or terbutaline sulphate (Fig. 3b) remaining on the carrier in relation to the duration of the sieving step. A similar drug loss over time was observed for all investigated blends. The quantity of drug remaining after 5 s is an indicator of the quantity of drug that strongly adheres to the lactose. Indeed, as drug particle size is much lower than 32 µm, if the drug particles were individualized in the blend and not adhered on the carrier, they would be carried away through the 32 µm sieve by aspiration. After 5 s, about 74% fluticasone propionate remains fixed on lactose A, 79% on lactose B, 87% on lactose A with no particles below 32 µm and 88% on lactose B with no particles below 32 µm. In the case of terbutaline sulphate, after 5 s about 55% remains fixed on lactose A, 70% on lactose B, 76% on lactose A with no particles below 32 µm and 83% on lactose B with no particles below 32 µm. In all case, more fluticasone propionate than terbutaline sulphate remains fixed, particularly in the case of lactose A. With this lactose quality, a lower quantity of drug adheres to the lactose and/or the adhesion force is lower.

The evolution with increasing aspiration times shows drug detachment, particularly during the first 30 s. But, after 5 min, a plateau is obtained, a considerable quantity of drug is not released from the carrier with variations according to the lactose and the drug under consideration. For example, 20% TBS remains fixed on the lactose for the blend lactose A/TBS and 70% FP for the blend lactose B/FP.

For fluticasone propionate (Fig. 3a), adhesion on lactose A is lower, more drug is released. This could be due to the high percentage of fine particles within this lactose A. In the first 60 s, the curves obtained with lactose A with no particles below 32 µm and B with no particles below 32 µm are comparable which tends to confirm the influence of the fine particles of lactose on drug detachment. The curves obtained with lactose B and B with no particles below 32 µm are similar probably because lactose B contains less fine particles than lactose A. When the fine particles of lactose A are removed, the behaviour of the lactose A with no particles below 32 µm is close to the one of lactose B and B with no particles below 32 µm.

In the case of terbutaline sulphate, the same trend is observed but the drug quantities adhering to the lactose is different.

Removal of fine lactose from the coarse lactose carrier reduces the dispersibility of propionate fluticasone propionate and terbutaline sulphate. The mechanism by which lactose fine particles modulate performance remains ambiguous. Two main theories are proposed: the hot-spot theory and the fine particle multiplets theory (Steckel et al., 2004; Zeng et al., 1998; Lucas et al., 1998b; Larhrib et al., 1999; Louey and Stewart, 2002; Adi et al., 2006). The first one supposes the occupation of the high-energy sites on the carrier by the lactose fine particles leaving low energy sites available for the drug, thus enabling greater drug detachment. In the second theory also called redistribution theory, aggregates of drug and lactose fine particles termed multiplets are formed enabling greater drug detachment. In our case, the fine particle multiplets theory seems to be predominant. Indeed, when mixing a fixed amount of fine lactose to the lactose A with no particles below 32 µm for

Table 3
Average drug content of the carrier/drug blends.

Blends	Average drug content (% w/w)	CV (%)	%Recovery
Lactose A + TBS	1.44%	3.05%	98.63%
Lactose B + TBS	1.46%	0.86%	99.99%
Lactose A with no particles below 32 µm + TBS	1.43%	0.62%	97.94%
Lactose B with no particles below 32 µm + TBS	1.46%	0.58%	99.99%
Lactose A + FP	2.47%	2.17%	98.80%
Lactose B + FP	2.43%	3.87%	97.20%
Lactose A with no particles below 32 µm + FP	2.42%	2.06%	96.80%
Lactose B with no particles below 32 µm + FP	2.45%	3.39%	98.00%

CV: coefficient of variation.

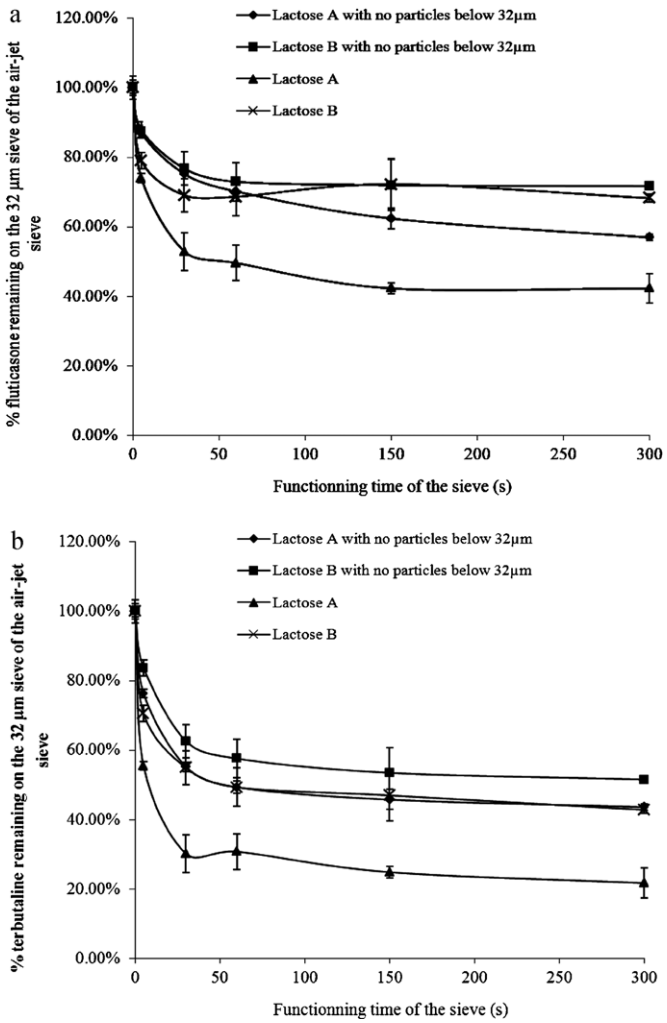

Fig. 3. Percentage of fluticasone propionate (a) or terbutaline sulphate (b) remaining fixed to the lactose in relation to the functioning time of the air-jet sieve.

2 h before or after blending with the fluticasone propionate, the adhesion characteristics were not different (data not shown). The fluticasone propionate dispersion was not influenced by the order of mixing.

Adhesion strength seems to be different depending on the drug. The detachment forces required to remove respirable particles are different and probably related to the surface characteristics of the drug. 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.

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 fluticasone propionate and terbutaline sulphate respectively (Table 4). Twin stage impinger is a simplest method to evaluate the aerodynamic performance of powder formulation, especially for comparing different formulation in development stage (Xu et al., 2010; Behara et al., 2011).

The emitted doses obtained are between 78.4% and 89.0% for terbutaline sulphate, and between 59.4% and 76.9% for fluticasone propionate. For a given drug, the emitted dose varies according to the carrier considered. For a given carrier, the emitted dose is significantly higher for terbutaline sulphate ($p < 0.05$).

Table 4
Emitted doses and fine particle fractions of the blends.

Blends	Emitted dose (% ± rsd)	Fine particle fraction (% ± rsd)
Lactose A + TBS	78.4 (±2.2)	46.0 (±2.7)
Lactose B + TBS	85.5 (±13.2)	30.4 (±2.2)
Lactose A with no particles below 32 µm + TBS	78.5 (±3.7)	26.6 (±1.3)
Lactose B with no particles below 32 µm + TBS	89.0 (±2.2)	23.4 (±0.9)
Lactose A + FP	69.0 (±8.8)	25.2 (±3.7)
Lactose B + FP	76.9 (±0.5)	11.0 (±1.0)
Lactose A with no particles below 32 µm + FP	59.4 (±11.9)	9.4 (±2.8)
Lactose B with no particles below 32 µm + FP	72.3 (±6.9)	7.3 (±0.2)

The fine particle fractions obtained were between 23.4% and 46.0% for terbutaline sulphate and between 7.3% and 25.2% for fluticasone propionate. Here again, for a given drug, the fine particle fractions vary between the different lactose qualities ($p < 0.005$).

Again, for a given lactose, the fine particle fraction strongly depends on the type of drug used ($p < 0.005$) with higher values obtained in the case of terbutaline sulphate. For both drugs, the fine particle fractions are highest in blends with lactose A (raw material, milled quality) that presents a greater proportion of lactose fine particles. The excess of fine lactose may agglomerate with the drug with adhesion forces lower than those obtain between the fine particles and the coarse carrier leading to higher fine particle fractions. It is also possible that a part of the aerosolized particles contains drug/lactose agglomerates with aerodynamic diameter lower than 6.4 µm.

These results are in agreement with the adhesion test that shows lower adhesion on lactose A, with less drug adhered in the case of terbutaline sulphate.

3.5. Correlation between adhesion characteristics and inertial impaction

Results of drug separation from the carrier by jet-sieving were compared to those obtained by TSI. Fig. 4 presents the relationship between fine particle fraction and the percentage of drug remaining on the 32 µm sieve of the air-jet sieve after 30 s. For both drugs, we note a linear relation with a regression coefficient R^2 of 0.9766 and 0.9785 for fluticasone propionate (Fig. 4a) and terbutaline sulphate (Fig. 4b) respectively, which indicates a good correlation between these two parameters.

The method proposed using Alpine air-jet sieve makes it possible to characterize adhesion, to forecast drug detachment and to predict aerodynamic behaviour of the drug. Another advantage of this test is that it considers the whole blend as it is used in dry powder inhalers.

3.6. Correlation between lactose qualities and inertial impaction

The used lactose qualities differed in terms of the fines' content, which is due to the different preparation processes. Lactose A obtained by milling process contains more fine particles. The latter adhere to the surfaces of the larger crystals in edges and clefts, so the drug becomes adhered to the smoother surface of the crystal where it can be removed more easily (Steckel et al., 2006). This was confirmed during the aerosolization tests: for both drugs, higher fine particle fractions are obtained with lactose A that possesses the highest fine particle content. These results confirm the founding of other researches on the effect of polydispersity of particle

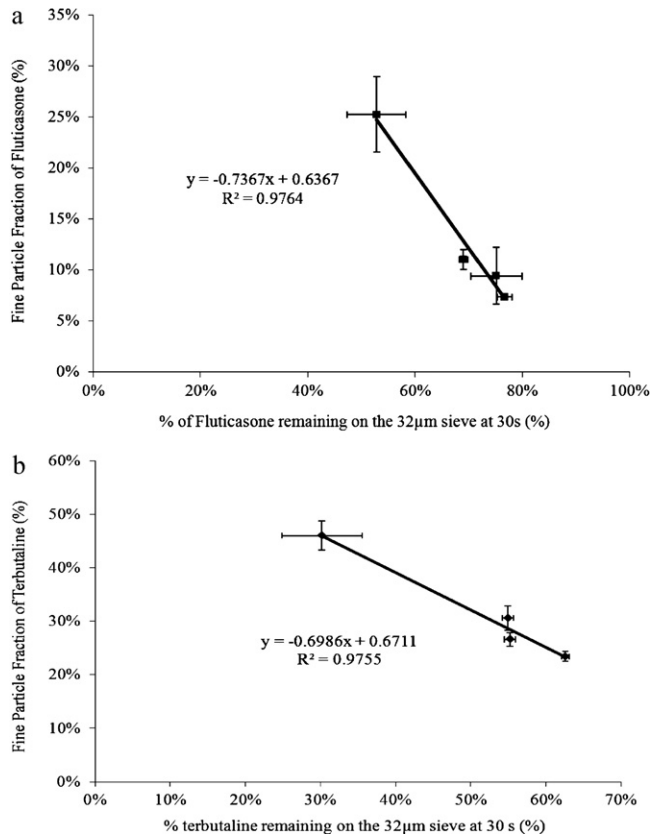

Fig. 4. Relation between fine particle fraction and percentage of fluticasone propionate(a) or terbutaline sulphate (b) remaining on the air-jet sieve after 30 s.

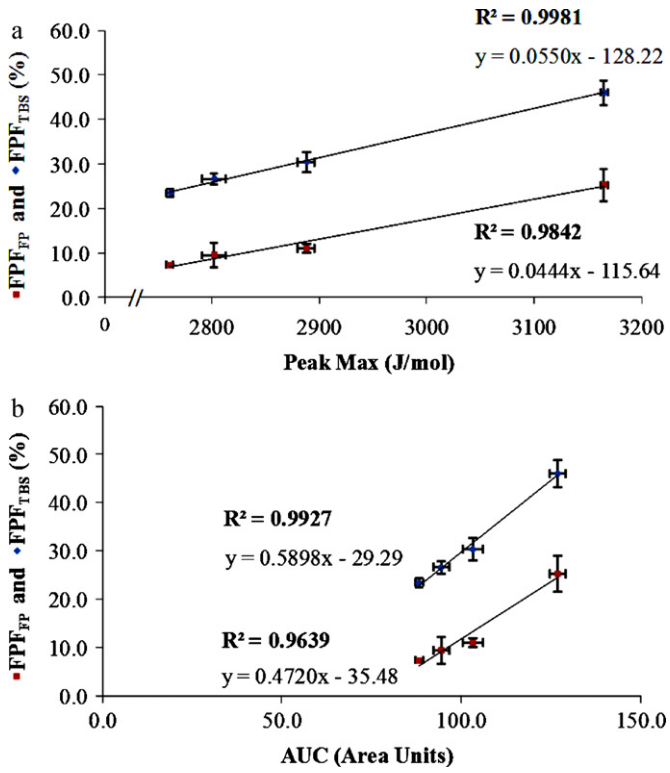

Fig. 5. (a) Fine particle fractions of fluticasone propionate and terbutaline sulphate (mean ± SD, $n = 3$) vs. peak max values of the iGC heterogeneity plots with ethyl acetate for the lactose grades (mean ± span, $n = 2$). (b) Fine particle fractions of fluticasone propionate and terbutaline sulphate (mean ± SD, $n = 3$) vs. areas under the curves (AUC) of the iGC heterogeneity plots with ethyl acetate for the lactose grades (mean ± span, $n = 2$).

size on the aerodynamic dispersion of DPI formulations (Guenette et al., 2009; Steckel et al., 2006).

Investigation of surface energy by iGC provided more information on the surface characteristics of powder, especially after different production steps such as milling (Louey et al., 2003; York et al., 1998), crystallization (Feeley et al., 1998), mechanofusion (Newell et al., 2001). Based on the Hansen solubility parameter theory, the estimation of interaction between different particulate systems is possible. The strength of interaction between lactose monohydrate and different polymorphic forms of salmeterol xinafoate is then calculated. In these studies, the infinite dilution method was used to determine the surface free energy of powder (Kumon et al., 2006). In reality, the surface energy is not evenly distributed on the surface of different particle population. Finite dilution inverse gas chromatography provides more information about the surface energy distribution of the material (Tong et al., 2006; Jefferson et al., 2011).

In this study, finite concentration of probe was used. A fairly good correlation between the fine particle fraction both of fluticasone propionate and terbutaline sulphate and the peak max value and the AUC, respectively ($R^2 = 0.9842$, $R^2 = 0.9981$, $R^2 = 0.9639$, $R^2 = 0.9927$) were found by means of the applied iGC method (Fig. 5a and b). In every case a positive slope of the straight line is obtained, for terbutaline sulphate slightly higher than for fluticasone propionate. With higher fine particle fraction, which corresponds to higher fines content, the peak maxima are shifted to higher adsorption potentials. These results are in accordance with the measurement and modelling of surface energy distribution in lactose powders containing different fine particle quantity (Tong et al., 2006). It means that the fine particles of lactose, having higher surface energy, may give more adhesive interaction with drug particle during dynamic mixing process. This supports the agglomeration hypothesis.

To scan the lactose surface with ethyl acetate turned out to be a suitable method to describe the energetic surface heterogeneity of the lactose grades investigated and to reveal the potential of the lactose qualities regarding their performance for inhalation formulations.

4. Conclusion

Lactose qualities A and B present a different behaviour when they are blended with 2 types of drugs presenting different polarities. Among the parameters tested, the differences are the preparation processes and the content of fine lactose particles. Lactose A obtained by milling process shows a higher adsorption potential measured by iGC and it contains more fine particles which could form agglomerates with the drug. Because of their increased detachment mass, drug particles may be more easily liberated from the coarse lactose in the airflow. With higher FPF values, which correspond to higher fines content, the peak maxima determined by iGC are shifted to higher adsorption potentials, which supports the agglomeration hypothesis. If the peak max value and the AUC from the surface heterogeneity plot are determined by iGC, the different lactose grades can be ranked in an order regarding their suitability for inhalation as carrier material in interactive mixtures, which follow the described agglomeration scheme.

References

Adi, H., et al., 2006. Agglomerate strength and dispersion of salmeterol xinafoate from powder mixtures for inhalation. Pharm. Res. 23, 2556–2565.

Behara, S.R.B., et al., 2011. Structural influence of cohesive mixtures of salbutamol sulphate and lactose on aerosolisation and de-agglomeration behaviour under dynamic conditions. Eur. J. Pharm. Sci. 42, 210–219.
Bell, J., 1994. Dry powder inhalation technology. Pharm. Manufact. Int., 179–182.
Feeley, J.C., York, P., Sumby, B.S., Dicks, H., 1998. Determination of surface properties and flow characteristics of salbutamol sulphate, before and after micronisation. Int. J. Pharm. 172, 89–96.
Guchardi, R., Frei, M., John, E., Kaerger, J.S., 2008. Influence of fine lactose and magnesium stearate on low dose dry powder inhaler formulations. Int. J. Pharm. 348, 10–17.
Guenette, E., et al., 2009. Understanding the effect of lactose particle size on the properties of DPI formulations using experimental design. Int. J. Pharm. 380, 80–88.
Hassan, M.S., Lau, R.W.M., 2009. Effect of particle shape on dry particle inhalation: study of flowability, aerosolization, and deposition properties. AAPS PharmSciTech 10, 1252–1262.
Hersey, J.A., 1975. Ordered mixing: a new concept in powder mixing practice. Powder Technol. 11, 41–44.
Jefferson, A.E., Williams, D.R., Heng, J.Y.Y., 2011. Computing the surface energy distributions of heterogeneous crystalline powders. J. Adhes. Sci. Technol. 25, 339–355.
Jones, M.D., Price, R., 2006. The influence of fine excipient particles on the performance of carrier-based dry powder inhalation formulations. Pharm. Res. 23, 1665–1674.
Kumon, M., Suzuki, M., Kusai, A., Yonemochi, E., Terada, K., 2006. Novel approach to DPI carrier lactose with mechanofusion process with additives and evaluation by IGC. Chem. Pharm. Bull. 54, 1508–1514.
Larhrib, H., Zeng, X.M., Martin, G.P., Marriott, C., Pritchard, J., 1999. The use of different grades of lactose as a carrier for aerosolised salbutamol sulphate. Int. J. Pharm. 191, 1–14.
Louey, M.D., Stewart, P.J., 2002. Particle interactions involved in aerosol dispersion of ternary interactive mixtures. Pharm. Res. 19, 1524–1531.
Louey, M.D., Razia, S., Stewart, P.J., 2003. Influence of physico-chemical carrier properties on the in vitro aerosol deposition from interactive mixtures. Int. J. Pharm. 252, 87–98.
Lucas, P., Clarke, M.J., Anderson, K., Tobyn, M.J., Staniforth, J.N., 1998a. The role of fine particle excipients in pharmaceutical dry powder aerosols. Proc. Respir. Drug Deliv. VI, 243–250.
Lucas, P., Anderson, K., Staniforth, J.N., 1998b. Protein deposition from dry powder inhalers: fine particle multiplets as performance modifiers. Pharm. Res. 15, 562–569.
Newell, H.E., Buckton, G., Butler, D.A., Thielmann, F., Williams, D.R., 2001. The use of inverse phase gas chromatography to study the change of surface energy of amorphous lactose as a function of relative humidity and the processes of collapse and crystallisation. Int. J. Pharm. 217, 45–56.
Pilcer, G., Amighi, K., 2010. Formulation strategy and use of excipients in pulmonary drug delivery. Int. J. Pharm. 392, 1–19.
Shur, J., Harris, H., Jones, M.D., Kaerger, J.S., Price, R., 2008. The role of fines in the modification of the fluidization and dispersion mechanism within dry powder inhaler formulations. Pharm. Res. 25, 1631–1640.
Steckel, H., 2002. Inhalation powders—a simple dosage form for pulmonary delivery? Swiss Pharma 9, 15–28.
Steckel, H., Markefka, P., teWierik, H., Kammelar, R., 2004. Functionality testing of inhalation grade lactose. Eur. J. Pharm. Biopharm. 57, 495–505.
Steckel, H., Markefka, P., teWierik, H., Kammelar, R., 2006. Effect of milling and sieving on functionality of dry powder inhalation products. Int. J. Pharm. 309, 51–59.
Sumby, B., Slater, A., Atkins, P.J., Prime, D., 1997. Review of dry powder inhalers. Adv. Drug Deliv. Rev. 26, 51–58.
te Wierik, H., Diepenmaat, P., Damhuis, R., 2002. Formulation of lactose for inhaled delivery systems. Pharm. Technol. Eur. 11, 1–5.
Tong, H.H.Y., Shekunov, B.Y., York, P., Chow, A.H.L., 2006. Predicting the aerosol performance of dry powder inhalation formulations by interparticulate interaction analysis using inverse gas chromatography. J. Pharm. Sci. 95, 228–233.
Xu, Z., et al., 2010. Dry powder aerosols generated by standardized entrainment tubes from drug blends with lactose monohydrate: 2. Ipratropium bromide monohydrate and fluticasone propionate. Eur. J. Pharm. Sci. 99, 3415–3429.
York, P., Ticehurst, M.D., Osborn, J.C., Roberts, R.J., Rowe, R.C., 1998. Characterisation of the surface energetics of milled dl-propranolol hydrochloride using inverse gas chromatography and molecular modelling. Int. J. Pharm. 174, 179–186.
Young, P.M., et al., 2005. The influence of dose on the performance of dry powder inhalation systems. Int. J. Pharm. 296, 26–33.
Zeng, X.M., Martin, G.P., Tee, S.-K., Marriott, C., 1998. The role of fine particle lactose on the dispersion and deaggregation of salbutamol sulphate in an air stream in vitro. Int. J. Pharm. 176, 99–110.