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Influence of carrier on the performance of dry powder inhalers

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Abstract

The aim of this work is to study carriers which can become alternatives to monohydrate lactose in dry powder inhalers and to consider particle parameters that influence adhesion between drug and carrier in dry powder inhalers.

Different forms of mannitol, lactose and maltitol were mixed with either terbutaline sulphate or formoterol fumarate. The blends were submitted to different adhesion tests where drug detachment from the carrier was obtained either through mechanical vibration or by aspiration. Parameters like particle shape, roughness, amorphous content and cristalline form may affect interactions between drug and carrier. In our case, crystallized forms of the carrier offered lower adhesion but better release of the active ingredient than spray-dried forms. The crystallized mannitol produced maximal fine particle dose. The blends of the mannitols and the two active ingredients gave different results.

The two techniques used to assess the adhesion of drugs to carrier particles provide complementary information about drug/carrier interactions and detachment. The mechanical sieving allows to assess blend stability and the air-jet sieving makes it possible to determine how easily the drug separates from carrier. For the drugs tested, the results of fine particle doses are in agreement with the Alpine air-jet sieve results.

The tests used are helpful for the choice of a new carrier in the field of the development of new carriers for dry powder inhalers.

Keywords: Carrier; Drug; Dry powder inhalers; Adhesion; Aerodynamic behaviour

1. Introduction

Dry powder formulations for inhalation are often composed of fine drug particles and inert coarse carrier particles. The fine drug particles are expected to adhere to the carrier surface to form ordered mixtures (Hersey, 1975). 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). 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; Bérard et al., 2002; Ferron, 1994; Prime et al., 1997).

Two contradictory requirements must be fulfilled for this type of dry powder formulation. On the one hand, adhesion between carrier and drug must be sufficient for the blend drug/carrier to be stable. On the other hand adhesion drug/carrier have to be weak enough to enable the release of drug from carrier during patient inhalation (Aiache, 1990). Then, the drug will be able to reach the lungs. During the development of dry powder inhalers, this adhesion must be taken into account. 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, impact separation and more recently atomic force microscope (AFM) (Louey et al., 2001; Podczeck and Newton, 1995; Podczeck, 1997, 1999; Shimada et al., 2000). But, the AFM technique concerns only one particle and not the overall blend.

In a previous work, we developed a simple method to assess the adhesion of respirable-sized drug to carrier particles (Flament et al., 2004). Drug detachment from the carrier was obtained either through mechanical vibration or by aspiration. The tests used are simple and consider the whole blend as it is used in dry powder inhalers.

For the moment, glucose and above all lactose are the only carriers used in dry powder inhalers. The advantages of

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monohydrate lactose are its well-investigated toxicity profile, its broad availability and its relatively low price. However, lactose has drawbacks. The biggest is its reducing sugar function which prevents its use with more and more important drugs: peptidic drugs. Several studies on technological properties of dry powder inhalers proposed alternatives to lactose such as mannitol (Steckel and Bolzen, 2004; Tee et al., 2000). Mannitol does not have a reducing sugar function and is less hygroscopic. Maltitol can be interesting thanks to its high sweetening power compared to other polyols. It allows a good observance by the patient.

The aim of this work is to study carriers which can become alternatives to lactose in dry powder inhalers and to determine particle parameters that influence adhesion between drug and carrier in dry powder inhalers.

2. Materials and methods

2.1. Materials

- *Four carriers*. Crystallized mannitol (Pearlitol 110 C), spray-dried mannitol (Pearlitol 100 SD), crystallized maltitol (Maltisorb P90) provided by Roquette frères (Lestrem, France) and spray-dried lactose (Lactopress SD 250) supplied by Borculo Domo (Zwolle, The Netherlands).
- *Two model drugs*. 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), and micronised formoterol fumarate with a volume mean diameter of 7.98 μm for GSD 2.1 (laser scattering, particle suspension in acetonitrile, Mastersizer S, Malvern, Orsay, France).
- *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 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.
- Hard gelatin capsules (size 2).

2.2. Methods

2.2.1. Preparation of carriers

To limit the influence of particle size, the same granulometric fraction was used for each carrier, that is to say 63–90 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 90 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 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 (Zeng et al., 2000).

2.2.2. Photos of carrier

They were obtained by scanning electron microscopy thanks to a microscope Quanta 200 F (FES Company).

2.2.3. Carrier/drug blending

The drug and the carrier 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. Average content

The quality of the blends was examined by analysing the quantity of drug 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 100 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 an UV spectrophotometer with a wavelength of 276 nm for terbutaline sulphate and of 214 nm for formoterol fumarate. From the results obtained for every capsule, we have determined average content for terbutaline sulphate and for fumarate formoterol. A calibration curve was realised for each drug. For terbutaline sulphate, calibration curve was linear from 0 to 200 μg/ml ($A = 0.0641c$, $r^2 = 0.9997$). For formoterol fumarate, calibration curve was linear from 0 to 5.40 μg/ml ($A = 0.8431c$, $r^2 = 0.9991$). The reproducibility of the UV methods was checked by repeating a measurement 10 times; the coefficient of variation was below 3%. The carriers did not modify the UV measurements.

2.2.5. Evaluation of adhesion

For the whole experiences realised, temperature and relative humidity were controlled that is to say 20 °C and 20%. Adhesion characteristics are evaluated by submitting the blend to sieving. Two different kinds of sieving are 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 are 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 is to assess the stability of the blend.

In the second case, the blend is put on a sieve in a sealed enclosure. Particles are submitted on the first 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. The objective of this test is to assess the ease with

which the drug can be separated from the carrier when the blend is carried by an airflow.

For the two types of tests, 30 g of blends were 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. For each sample, we compared the percentage of drug remaining to the initial dose.

The results are the mean of three replicate measurements.

2.2.6. Preparation of the capsules

The drug/carrier blends were filled into hard gelatin capsules (size 2) manually so that each capsule contained 500 μg of drug, 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 drugs 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 aerosolisation at 60 l/min via a Spinhaler of 10 capsules, each containing 34.25 mg of blend equivalent to a nominal dose of 500 μg drug. At the end of the test, the different parts of the TSI were rinsed with water and the amount of drug deposited in the upper and lower stages was determined using a spectrophotometric dosage at the wavelength of 276 nm for terbutaline sulphate and at the wavelength of 214 nm for formoterol fumarate.

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

Table 1
Average content of the carrier/drug blends

Blend carrier/drug	Average content of drug (μg)
Pearlitol 100 SD/terbutaline sulphate	483.45 (CV = 2.25%)
Pearlitol 110 C/terbutaline sulphate	478.00 (CV = 4.79%)
Lactose 250 SD/terbutaline sulphate	504.57 (CV = 0.76%)
Maltisorb P90/terbutaline sulphate	490.64 (CV = 1.47%)
Pearlitol 100 SD/formoterol fumarate	494.80 (CV = 6.75%)
Pearlitol 110 C/formoterol fumarate	501.28 (CV = 2.65%)

CV, coefficient of variation.

- Emitted dose (ED) is the sum of drug collected at the upper and lower stages divided by 10, the number of capsules used.
- Fine particle dose (FPD) defined as the amount of drug deposited in the lower stage of the TSI, because the aerodynamic diameter was less than the cut-off diameter of the impinger (6.4 μm at an air-flow rate of 60 l/min), divided by 10.
- Emission percentage corresponding to the ratio of ED to the nominal dose.
- Fine particle fraction corresponding to the ratio of FPD to the nominal dose.

Analysis of variance (ANOVA) was realised for the results obtained with TSI. This test was realised with SPSS software.

3. Results

After blending the drugs with the carriers, the average content was measured (Table 1). The average contents in drug are all included in the interval of the nominal content (500 μg) ±5%.

As regards the evaluation of adhesion characteristics, we first of all consider blends containing terbutaline sulphate. Terbutaline sulphate is fixed on different carriers that are cristallized or spray-dried.

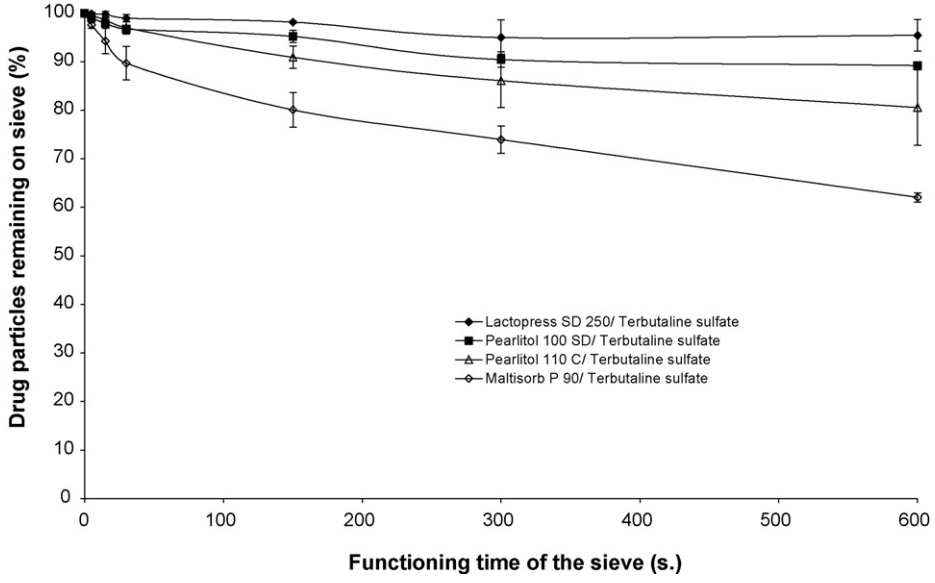

Fig. 1. Percentage of terbutaline sulphate remaining fixed to the carrier in relation to the functioning time of the mechanical sieve.

Fig. 1 presents the percentage of terbutaline sulphate remaining fixed on the carrier in relation to the functioning time of the mechanical sieve.

Whatever the carrier considered, the shape of the curve is the same one.

After 10 min of mechanical vibrations, it is noted that at least 95% of terbutaline sulphate is still fixed on the Lactopress SD 250, 90% on the Pearlitol 100 SD, 80% on the Pearlitol 110 C and 60% on the Maltisorb P90. This is for the two spray-dried carriers that adhesion of terbutaline sulphate is the higher, with a maximum in the case of the Lactopress SD 250. Comparison of the two mannitols shows that adhesion is lower in the case of the crystallized form of mannitol. The results indicate that physical interactions between drug particles and the crystallized maltitol (Maltisorb P90) are weaker than for other carriers.

Adhesion of terbutaline sulphate is lower on the crystallized forms of carriers compared to the spray-dried forms.

Fig. 2 presents the results obtained when the blends are submitted to the Alpine air-jet sieve. Here again, whatever the carrier considered, the shape of the curve is the same one.

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 carrier. Indeed, as drug particle size is very lower than 63 μm, if the drug particles were individualised 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 30% terbutaline sulphate remains fixed on the Pearlitol 110 C, 40% on the Maltisorb P90, 62% on the Pearlitol 100 SD and 72% on the Lactopress SD 250.

The evolution with aspiration time shows drug detachment. But, after 10 min, a considerable quantity of active ingredient is not released from the carrier, with important variations according to the carrier under consideration. As adhesion strength seems to be different according to the carrier considered, the detachment forces required to remove respirable particles are also different and probably related to the physical properties of the carrier particles. This is with Pearlitol 110 C that the release of terbutaline sulphate is the higher, and it is the lower with Lactopress SD 250.

The nature of the carrier (crystallized or spay dried) influences significantly the release of terbutaline sulphate. It seems that the crystallized forms allow a larger release of drug than the spray-dried forms studied.

By way of comparison, we tested crystallized and spray-dried mannitol in blend with another drug: formoterol fumarate which is less hydrophilic than terbutaline sulphate.

Fig. 3 shows the results of blends submitted to mechanical sieve.

After 10 min, at least 70% and 80% of formoterol fumarate, respectively, adheres to the Pearlitol 110 C and to the Pearlitol 100 SD. Adhesion of formoterol fumarate is higher on the spray-dried form of mannitol than on the crystallized form. This result joins that obtained for terbutaline sulphate. But, wathever the mannitol considered, adhesion of formoterol fumarate is lower than that of terbutaline sulphate.

When the blends are submitted to the air-jet sieve (Fig. 4), there is no difference between the release of formoterol fumarate from cristallized mannitol and from the spray-dried mannitol. After 5 s, 40–45% of formoterol fumarate remains fixed on the two mannitols. Contrary to terbutaline sulphate, the influence of the cristalline form of the carrier (spray-dried or crystallized) does not appear. It may be concealed by different properties of the drugs.

The aerodynamic behaviour of drug carrier/blends was estimated with twin-stage impinger making it possible to study the in vitro deposition profile of terbutaline sulphate (Table 2) and formoterol fumarate (Table 3) when drugs are fixed to different carriers.

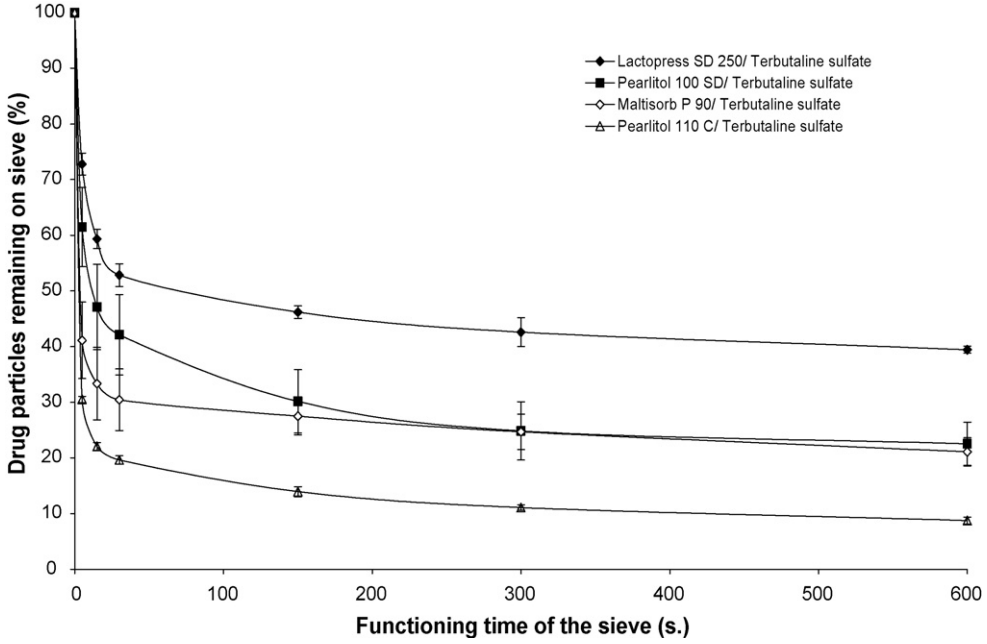

Fig. 2. Percentage of terbutaline sulphate remaining fixed to the carrier in relation to the functioning time of the air-jet sieve.

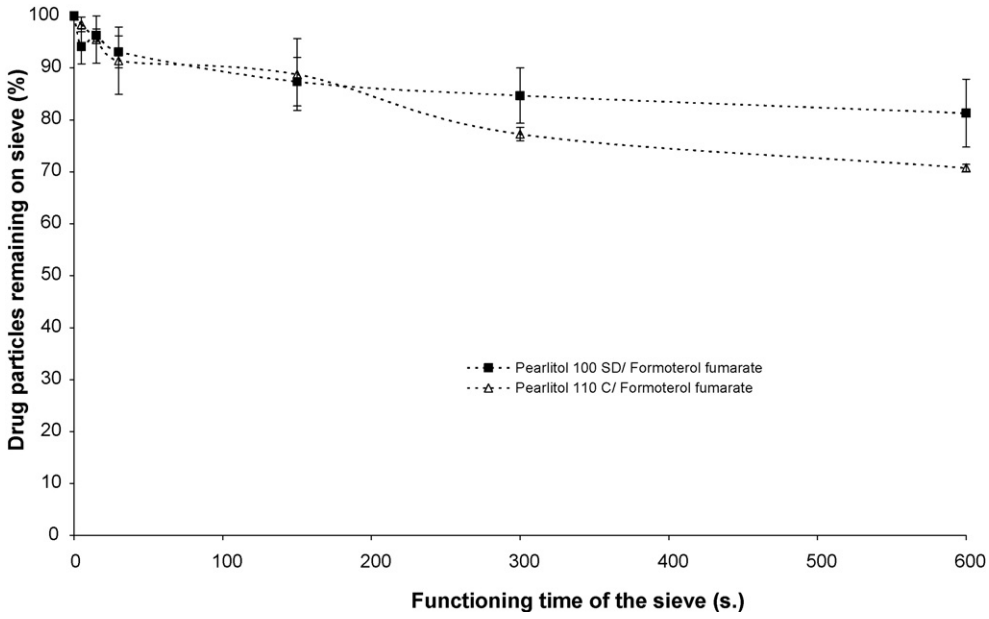

Fig. 3. Percentage of formoterol fumarate remaining fixed to the carrier in relation to the functioning time of the mechanical sieve.

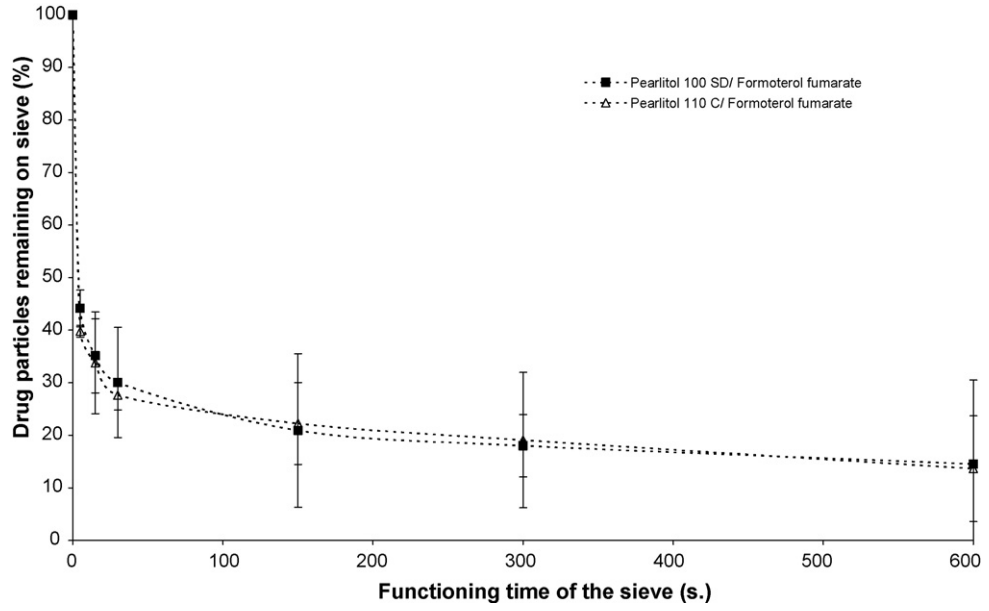

Fig. 4. Percentage of formoterol fumarate remaining fixed to the carrier in relation to the functioning time of the air-jet sieve.

In the case of terbutaline sulphate, emitted doses vary from 78.62% to 98.06% of the nominal dose which satisfies the specifications of the European Pharmacopoeia for the uniformity of delivered dose. Higher emitted dose is obtained with Lactopress SD 250, then Pearlitol 100 SD, Pearlitol 110 C and finally Maltisorb P90. Emitted doses obtained with Pearlitol 100 SD and Pearlitol 110 C differ significantly (ANOVA, p-value = 0.6%) as well as those obtained with Pearlitol 100

Table 2
Terbutaline sulphate deposition in the TSI after aerosolisation of the different blends with the Spinhaler at 60 l/min

	Pearlitol 110 C	Pearlitol 100 SD	Maltisorb P90	Lactopress SD 250
Emitted dose (μg)	413.35 (CV = 2.16%)	459.65 (CV = 4.65%)	393.11 (CV = 1.81%)	490.3 (CV = 2.49%)
Emission percentage (%)	82.67 (CV = 2.16%)	91.93 (CV = 4.65%)	78.62 (CV = 1.81%)	98.06 (CV = 2.49%)
Fine particle dose (μg)	90.72 (CV = 2.07%)	65.48 (CV = 3.36%)	57.72 (CV = 7.95%)	65.00 (CV = 6.93%)
Fine particle fraction (%)	18.14 (CV = 2.07%)	13.09 (CV = 3.36%)	11.54 (CV = 7.95%)	13.00 (CV = 6.93%)

CV, coefficient of variation.

Table 3
Fumarate formoterol deposition in the TSI after aerosolisation of the different blends with the Spinhaler at 60 l/min

	Pearlitol 110 C	Pearlitol 100 SD
Emitted dose (μg)	260.69 (CV = 2.99%)	284.38 (CV = 2.43%)
Emission percentage (%)	52.14 (CV = 2.99%)	56.87 (CV = 2.43%)
Fine particle dose (μg)	17.74 (CV = 6.43%)	18.11 (CV = 4.48%)
Fine particle fraction (%)	3.55 (CV = 6.43%)	3.62 (CV = 4.48%)

CV, coefficient of variation.

SD and Lactopress SD 250 (ANOVA, p-value = 4%). Emitted doses obtained with Pearlitol 110 C and Maltisorb P90 are not significantly different (ANOVA, p-value = 14.5%). The results indicate that emitted doses are higher with the spray-dried forms of carrier than those with the crystallized forms tested.

As regards fine particle doses, the results with the two spray-dried carriers, Pearlitol 100 SD and Lactopress SD 250, are close (ANOVA, p-value = 91%). In the same way, the Maltisorb P90 is not significantly different from the Lactopress SD 250 (p-value = 12%) and from the Pearlitol 100 SD (p-value = 10%). On the other hand, there is a significant difference between the two cristalline forms of mannitol (ANOVA, p-value = 0.03%). Fine particle dose obtained with the crystallized mannitol Pearlitol 110 C is much higher than the others. This last result is in agreement with the results obtained with the Alpine air-jet sieve.

In the case of the formoterol fumarate, the emitted doses are about 50% of the nominal dose and are much lower than those obtained with terbutaline sulphate. The emitted dose is higher with the spray-dried form of mannitol, as for terbutaline sulphate. Fine particle doses are close for the two carriers tested and confirm the results obtained with the Alpine air-jet sieve. They are much lower than those obtained for terbutaline sulphate. This difference can be explained by the difference of size between the drugs, the mean diameter of formoterol fumarate being higher than the one of terbutaline sulphate (see Section 2.1).

4. Discussion

The experimental results enable us to consider the parameters influencing drug/carrier adhesion. Sieving of carriers makes it possible to minimize the influence of size and granulometric distribution of the carrier particles. On the other hand, the shape of particles is not the same one. The spray-dried carriers are roughly spherical in shape and porous as it can be see in Fig. 5. The crystalline carriers present a tomahawk shape as it can be see in Fig. 6. Particle shape may significantly affect the extent of particle surface contact, and therefore the magnitude of shorts arranges van der Waal' S forces (Bell, 1994). The less spherical the particles are, the more significant the adhesion drug/carrier is (Bell, 1994). However adhesion of terbutaline sulphate on Pearlitol 100 SD is stronger than the one on Pearlitol 110 C, less spherical. Moreover, Pearlitol 110 C releases more terbutaline sulphate than Pearlitol 100 SD when the blends are carried away by an airflow. Parameters other than shape play a significant role in the adhesion phenomena.

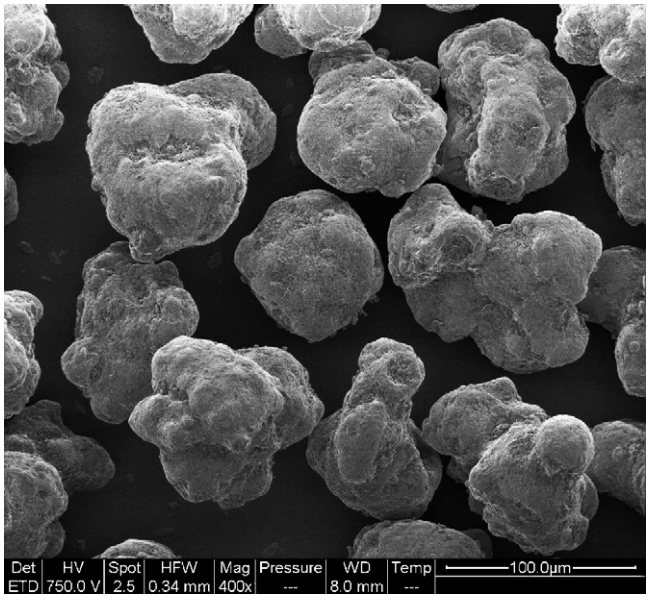

Fig. 5. Scanning electron microscopy of Pearlitol 100 SD blended with terbutaline sulphate.

For carriers having a less rough surface, interaction forces between drug and carrier are weaker then allowing a better release of the drug from the carrier after patient inhalation (Zeng et al., 2001). Pearlitol 100 SD is rough in its surface and porous (Fig. 5). Pearlitol 110 C (Fig. 6), less rough presents a more significant fine particle fine dose than Pearlitol 100 SD. The reduction of particle roughness increases the percentage of respirable particles in dry powder inhalers (Ganderton, 1992). In view of the results obtained, the roughness criterion seems more important than shape criterion.

Lactopress SD 250 released few terbutaline sulphate compared to other carriers when tested on the Alpine air-jet sieve and

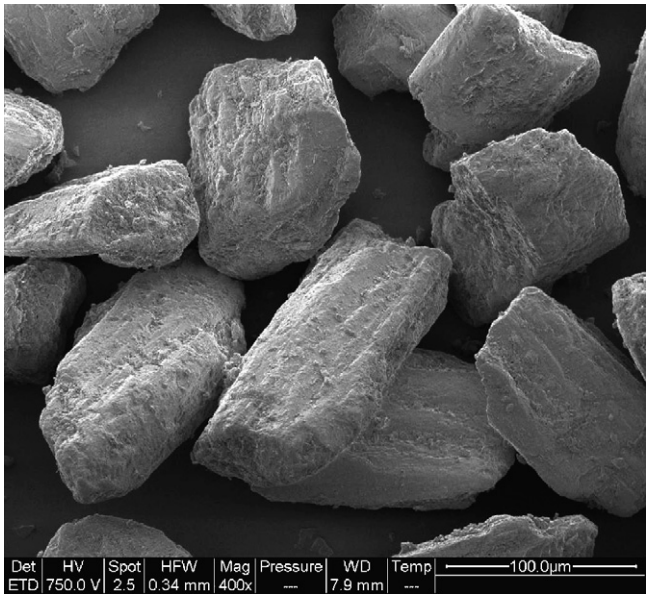

Fig. 6. Scanning electron microscopy of Pearlitol 110 C blended with terbutaline sulphate.

more particularly when compared to another spray-dried carrier, the Pearlitol 100 SD. The fact that Lactopress SD 250 may contain up to 15% of amorphous lactose could explain this result. Amorphous state has a great internal energy and a great energy of surface which improves adhesion and thus limits drug release.

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. No blend releases more than 40% of drug after 10 min mechanical vibrations. Blends with the spray-dried forms of carriers are more stable than those with the crystallized forms.

The results obtained for the two drugs submitted to the Alpine air-jet sieve are not the same. Electrostatic properties of the drugs seem to have an influence. During the assay, the electrostatic charges of particles increase because of blend frictions to the air-jet sieve's lid made of methyl polymethylmethacrylate (PMMA). The blends with formoterol fumarate adhere more to the lid surface than those with terbutaline sulphate which indicates the presence of electrostatic charges. In the case of formoterol fumarate, electrostatic properties seem decisive for the release of drug.

The analysis of the results obtained with the twin-stage impinger shows that the emitted is higher for the spray-dried forms than for crystallized forms whatever the drug considered. The fine particle dose is the highest for Pearlitol 110 C. This is the carrier for which drug release was the higher during the assay with the Alpine air-jet sieve. Emitted doses are lower in the case of formoterol fumarate which reinforces the hypothesis of the influence of its electrostatic properties.

For one drug the influence of carriers is very important. If we changed the drug, the influence of carriers also changed. The study of different carriers has to be in relation to one drug. The drug/carrier couple must be taken into account. Generalization of the performances of one carrier of dry powder formulation to different drugs is not possible.

5. Conclusion

The experimental results confirm that interactions drug/carrier are depending on the drug and on the carrier whose role is paramount in the adhesion phenomena. Parameters like particle shape, roughness, amorphous content and cristalline form may affect interactions between drug and carrier. The drug/carrier couple must be taken into account.

In our case, adhesion of the drugs is higher on the spray-dried form of the carriers. The maximum fine particle dose of terbutaline sulfate is obtained with the crystallized form of mannitol.

The two techniques used to assess the adhesion of drugs to carrier particles provide complementary informations about drug/carrier interactions and detachment. These tests are simple, and consider the whole blend as it is used in dry powder inhalers. The mechanical sieving allows to assess blend stability. The air-jet sieving makes it possible to determine how easily the drug separates from carrier. The behaviour of the drug/carrier blend during the assay can give an estimation of the drug capacity to separate from the carrier during inhalation. For the drugs tested, the results of fine particle doses are in agreement with the Alpine air-jet sieve results.

These tests are helpful for the development of new carriers for dry powder inhalers and notably to obtain a carrier which provides a stable blend and a maximal fine particle dose.

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