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Powder Technology 146 (2004) 206–213

POWDER TECHNOLOGY

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Comparison of different flowability tests for powders for inhalation

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Received 9 October 2003; received in revised form 12 July 2004; accepted 10 August 2004

Abstract

A series of placebo powders for inhalation was characterized regarding bulk density and powder flowability using different techniques. The powders were of the ordered mixture type and were prepared by mixing a pharmaceutical carrier grade of lactose with different fractions of intermediate sized and fine (i.e., micronized) lactose. A modified Hausner Ratio was obtained by measurement of the poured and the compressed bulk densities. Other tests investigated were the angle of repose, the avalanching behaviour using the AeroFlow, and the yield strength using the Uniaxial tester. Furthermore, the relation between ordered mixture composition and flowability was examined.

Of the methods investigated, the modified Hausner Ratio discriminates well between the investigated powders and seems to have the widest measuring range. It was also found that the poured and compressed bulk densities provide information about the packing of the particles in the powders. A good correlation was obtained between the modified Hausner Ratio and the angle of repose. The AeroFlow was suitable for powders with a low percentage of fine particles, but could not discriminate between the more cohesive powders. The Uniaxial tester, on the other hand, seems to be better suited for more cohesive powders.

Regarding the powder composition, addition of micronized particles has a strong influence on the flowability of ordered mixtures, while intermediate sized particles have little impact on the powder flow.

Keywords: AeroFlow; Angle of repose; Flowability; Hausner ratio; Ordered mixture; Uniaxial tester

1. Introduction

Knowledge about flow properties of powders is very important when developing powder processes and handling procedures. In the case of pharmaceutical dry powders for inhalation, the active drug substance must be in the size range of 1–5 μm in order to be respirable and thus constitutes an extremely cohesive powder. The ability to adjust and control the flow properties of such powders during processing and formulation work is of key importance for a successful product development. For example, mixing of such cohesive powders is a real challenge [1], and in addition, dry powder formulations need to be filled with high speed and precision into inhalers or into blister cavities. Furthermore, the flowability of the powder formulation may influence the performance of the drug product. It may affect factors such as the emptying of the dose from the inhaler and the aerosolization of the powder into respirable particles upon inhalation [2]. There are today two main ways to induce improved flowability to pharmaceutical formulations for inhalation; one is to form spherical aggregates of the drug substance particles, in some cases with the addition of micronized excipients. The second and more widely used is to mix the active drug with a carrier of larger particle size, normally lactose, to obtain an "ordered mixture", i.e., with the drug particles adhering to the surfaces of the carrier particles. In this work, we will investigate this latter type of powders for inhalation, using different methods to assess powder flow.

During the years, a variety of methods for assessment of powder flow have been developed. An introduction to the area is given by Staniforth [3]. The most important type of method seems to be the shear test, in which the force

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doi:10.1016/j.powtec.2004.08.003

required to shear a powder under well-defined conditions is measured. The area was pioneered by Jenike [4] who also developed the theoretical framework. Other commonly used shear testers include the Ring Shear Testers [5], the Johanson Indicizer [6,7] and the Uniaxial Tester developed by POSTEC, Porsgrunn, Norway [8,9].

The compressibility of a powder is a commonly used indicator of flowability and is often expressed using the Hausner Ratio, which is the ratio between the tapped and the loose-packed bulk densities of the powder [10]. Compressibility is also one of the tests proposed by Carr [11] for the assessment of powder flow properties. Other tests included in the evaluation according to Carr are the angle of repose, the angle of spatula and the cohesion, or alternatively the particle size uniformity coefficient.

Another commonly used flow indicator is the time it takes for a powder to flow out of a funnel with a well-defined orifice [3]. More recently, the AeroFlow apparatus has been developed, which characterizes the avalanching behavior of a powder rotated in a drum [12,13]. A recent comprehensive review by Schwedes [14] has main focus on the shear tests but also mentions alternative ways to assess powder flow properties.

To be useful in pharmaceutical product development, a flowability test should correlate either with key quality measures of the product or with processing performance, such as yield, process times, etc. Additionally, for routine use in production, a flowability test must be robust and simple. Rather than a full characterization of flow properties by different principles and at different conditions, a simple "flowability" test confirming that the powder fulfils the requirements is desired. Ultimately, such a test may be used for process analysis and contribute to improved production control and thereby assure a consistent quality of the pharmaceutical product.

In this study, a series of ordered mixture-type formulations consisting of carrier particles, intermediate-sized particles and micronized particles was prepared and the flowability was evaluated using four different methods. These were (i) a modified Hausner Ratio based on measurements of poured bulk density (PBD) and compressed bulk density (CBD), (ii) the angle of repose, (iii) the average time between avalanches using the AeroFlow instrument and (iv) the yield stress from the POSTEC Uniaxial tester measured at one single pre-consolidation stress. Lactose monohydrate is by far the most widely used excipient for inhalation; therefore, lactose monohydrate was used as carrier particles and also as intermediate sized particles. To simulate the active micronized drug, micronized lactose with a size distribution and shape similar to that of commonly used active substances for inhalation, was used. This is appropriate as powder flow properties are governed more by physical than by chemical properties. However, for active substances with special shape or size characteristics, e.g., needle-shaped particles, or with special surface properties, these placebo-ordered mixtures will not be fully representative.

The compositions of the mixtures were varied in a very broad range to assess the effect of the different components on the flowability. Most of the compositions do not represent true ordered mixtures according to the original definition, as there is an excess of fine particles relative to the available surfaces of the carrier particles. Such mixtures are often referred to as adhesive mixtures or interactive mixtures [15,16] and have recently obtained much interest for use in dry powder inhalers as improved drug deaggregation and fine particle delivery has been observed [17–19]. Also the use of intermediate size particles in powders has been investigated [17]. We will use the term "ordered mixture" to include all these kinds of mixtures. The ordered mixtures investigated in this study thus cover a wide range of compositions relevant for dry powder inhalation.

2. Experimental

2.1. Ordered mixtures

Placebo-ordered mixtures were prepared by mixing carrier with various amounts of medium sized and micronized particles. As carrier, Pharmatose 325M from DMV, Holland, with a mass median diameter (MMD) of approximately 50 μm, was used. This grade has a narrow particle size distribution (100%<100 μm, at least 70%<63 μm, 5–10%<32 μm), which gives good flow properties [20]. The intermediate sized component was Pharmatose 450M also from DMV, Holland, a milled grade with an MMD of about 20 μm. It has a broader particle size distribution with at least 90% smaller than 45 μm [21].

The micronized lactose was manufactured by AstraZeneca, with an MMD close to 2 μm and was fully crystalline. The micronized lactose corresponds to the active micronized drug in pharmaceutical dry powders for inhalation.

Mixing was performed using a 10-l tumbling mixer equipped with baffles (Bohle, Germany) for 4 h at a speed of 30 rpm. The compositions are given in Table 1. A bracket system is used to denote the compositions, where the numbers refer to the percentage amounts of carrier, intermediate sized particles and micronized particles,

Table 1
Composition of ordered mixtures

Denomination	Pharmatose 325M, % w/w	Pharmatose 450M, % w/w	Micronized lactose, % w/w
[100/0/0] (Pure carrier)	100	0	0
[95/5/0]	95	5	0
[95/2.5/2.5]	95	2.5	2.5
[90/7.5/2.5]	90	7.5	2.5
[95/0/5]	95	0	5
[90/5/5]	90	5	5
[90/2.5/7.5]	90	2.5	7.5
[85/7.5/7.5]	85	7.5	7.5
[80/10/10]	80	10	10

respectively. According to previous experience, compositions with an increased amount of fine particles (from top to bottom of Table 1) are expected to display increased cohesion. SEM pictures of the lactose carrier particles and two of the mixtures are shown in Fig. 1a–c.

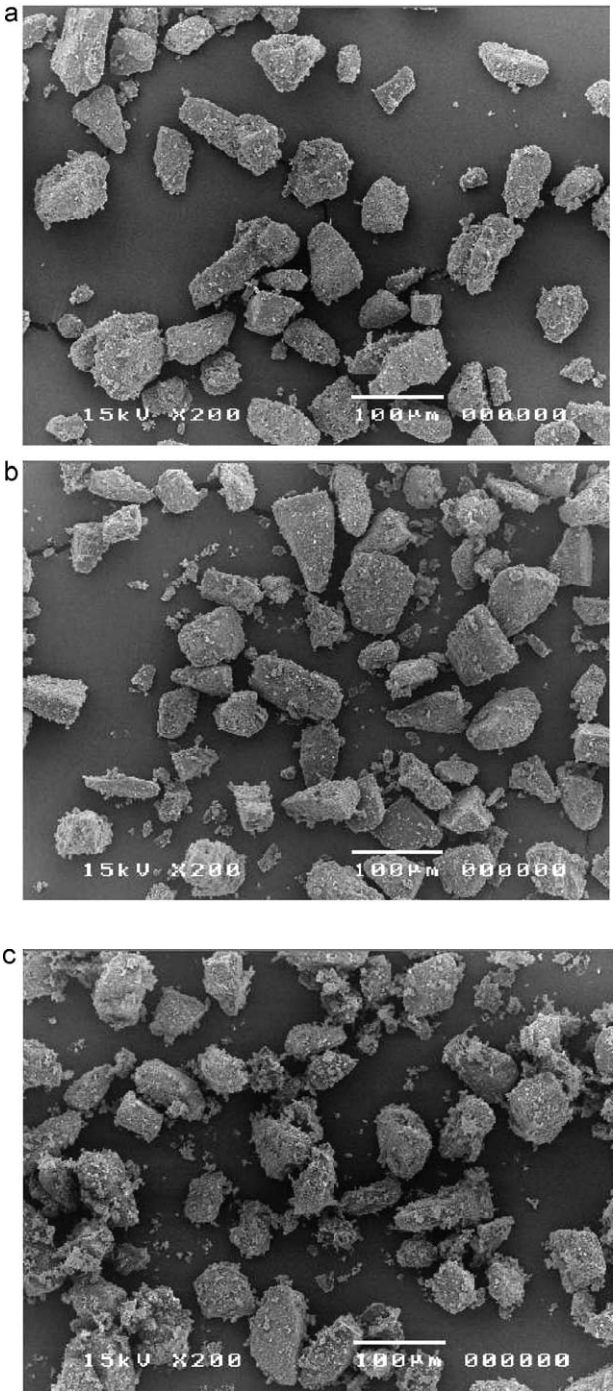

Fig. 1. SEM pictures using JEOL JSM-5200 of (a) carrier lactose Pharmatose 325M, (b) mixture containing 5% intermediate lactose, i.e., [95/5/0], and (c) mixture containing 5% micronized lactose, i.e., [95/0/5]. It can be noted that also for pure carrier, small particles attached to the large particles are present. In (c), aggregates of micronized particles, some free and some attached to the carrier particles, can be observed.

A rough estimate of the surface coverage of the carrier particles by micronized particles can be carried out. If we assume that a spherical carrier particle of size D μm is completely covered by spherical micronized particles of diameter d μm, the volume (weight) ratio of micronized particles in the mixture can be calculated to:

$$\mathrm{VolRatio} = \frac{4\frac{d}{D}}{1+4\frac{d}{D}} \quad (1)$$

This means that if a 50-μm carrier particle is completely covered by 2-μm micronized particles, the volume ratio will be 0.14. Such packing is of course unrealistic, and already at much lower concentrations, the micronized particles will form aggregates, which attach to carrier surfaces [18,19]. This is demonstrated in Fig. 1c, where aggregates are observed at a concentration of 5% of micronized lactose.

2.2. Methods

Poured bulk density was measured using a set of two cylinders. A small cylinder (inner diameter 22 mm, length 90 mm) open in both ends, is placed inside a slightly larger cylinder (inner diameter 25 mm) of known volume, approximately 20 cm^3. The inner cylinder is filled with powder using a spoon, and thereafter slowly raised, letting the powder flow out into the larger cylinder evenly. Finally, the excess powder is scraped off carefully and the weight is measured.

Compressed bulk density was measured using GeoPyc 1360 from Micromeritics, USA. A sample of known weight (about 1.5 g) is introduced into a cylinder, diameter 1.9 cm, which is then mounted horizontally into the instrument. The powder is compressed a number of times with a piston, while the cylinder is rotated. The volume is measured after compression to 10 N and the compressed bulk density is calculated. This method was preferred to the more commonly used tap density method because it requires much less powder, which is important when dealing with pharmaceutical powders. Control measurement comparing the two methods indicated no significant difference for the pure carrier, but for the ordered mixtures somewhat higher values (5–10%) were obtained using the GeoPyc than using the ordinary tap volumeter. This can be expected as the entire powder sample is compressed in the GeoPyc, while a pressure gradient over the height of the cylinder is the case in the tap volumeter, the pressure at each level being provided by the weight of the powder above that level.

A *Hausner Ratio* is calculated as the ratio between CBD and PBD. As the CBD using GeoPyc tends to be somewhat higher than the tap density, this ratio will be somewhat higher than the normal Hausner Ratio. We will therefore call this a modified Hausner Ratio, the notion of a Hausner Ratio still being valid as the GeoPyc and the tap volumeter relies on similar principles, i.e., compression of powder under conditions where the particles are able to rearrange.

Angle of repose was measured using the PharmaTest Flow-time and Cone Angle Tester from PharmaTest Apparatebau, Germany, giving the poured angle of repose [3]. One hundred milliliters of powder was used and the angle of the formed pile on the circular plate under the funnel was measured. It is generally difficult to measure cohesive powders properly, and for very cohesive powders a unique angle of repose cannot be defined [3,22]. Method improvements to handle more cohesive powders have been reported [23], and in the present work, the powder was carefully poured through the funnel to avoid blockage.

2.3. AeroFlow

The avalanching behavior of the powders was investigated using the AeroFlow from TSI, USA. In this instrument, the powder is rotated in a transparent Plexiglas drum and the times between avalanches are detected photoelectrically. Short and reproducible times between avalanches indicate a good flowability while long and/or irregular times indicate poor flowability [12]. A regular periodic avalanching behaviour was first observed when performing measurements for an extended period of time. This was found to be due to spots of powder adhering to the Plexiglas surfaces, which interfered with the photoelectric detection system and were thus wrongly interpreted as avalanches. By treating the surfaces with a dilute solution of sodium laurylsulfate, followed by thorough drying, such adhesion could be avoided. The surface treatment had no detrimental effect on the powder properties itself, as demonstrated by the fact that the avalanche pattern did not change over time during the measurement. Further, it was found that using sandpaper instead of the metal grid supplied from the manufacturer at the peripheral wall of the drum was advantageous in preventing the powder from sliding. The method finally chosen for the measurements was rotation at a speed of 120 s/revolution for 900 s, but to avoid initial effects, only avalanches registered in the interval 100–900 s were used in the calculations.

2.4. Uniaxial tester

The Uniaxial tester, developed by POSTEC in Norway is a shear tester that can be used for quality control of powder flow [8,9]. The powder sample is pre-filled into a cylindrical space of a supporting die (volume approximately 120 cm^3, diameter approximately 36 mm), which is then mounted into the tester. Pressure is applied to the powder by means of a piston and consolidation is carried out until the preset value is attained. Wall friction is minimized by confining the powder in an elastic membrane and applying lubricant between this membrane and the supporting die. After consolidation, the piston is withheld at the end position for a relaxation period of 2 min, whereafter it is carefully lifted up from the sample and the supporting die is removed. Finally, pressure is again applied to the plug-shaped sample, and the strength required for breaking the sample, i.e., the yield strength, is registered. In this work, the yield strength at a consolidation pressure of 400 kPa was used for comparison between the different powders. The relatively high pressure was chosen because some of the powders did not form powder plugs at lower pressures. Measurement of the yield strength at 50, 100, 200 and 400 kPa was performed for one of the mixtures and a linear relation between yield strength and consolidation pressure was obtained (data not shown). This indicates that no fragmentation of the lactose particles occurs at the applied pressures. The piston speed was set to 4.6 mm/min during consolidation and 1.0 mm/min during the yield test.

To assess the robustness of the different methods, all powders were tested in triplicate for all tests. All experiments were performed at AstraZeneca R&D Lund, Sweden.

3. Results and discussion

3.1. Poured bulk density

The measured values for PBD and theoretically calculated values are plotted in Fig. 2. For pure carrier PBD was measured to ρ_{50}=0.66 g/cm^3 and the corresponding values for the intermediate grade and for the micronized lactose were ρ_{20}=0.42 g/cm^3 and ρ_2=0.25 g/cm^3, respectively (see Table 2). These values, transformed into specific volumes, have been used to calculate theoretical bulk densities, ρ_t, for the different powders according to

$$\frac{1}{\rho_t} = \frac{x_2}{\rho_2} + \frac{x_{20}}{\rho_{20}} + \frac{x_{50}}{\rho_{50}} \quad (2)$$

where x_2, x_{20} and x_{50} are the weight fractions of the 2, 20 and 50 μm size particles, respectively. If the measured bulk

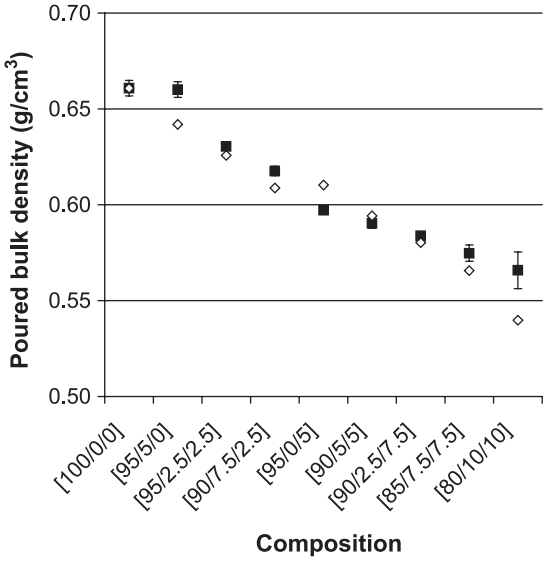

Fig. 2. Poured bulk density. Measured values (filled squares), compared to calculated values (rhombs). Error bars indicate one standard deviation.

Table 2
Poured and compressed bulk densities for the lactose grades used

	MMD (μm)	PBD (g/cm^3)	CBD (g/cm^3)
Pharmatose 325M	50	0.66	0.81
Pharmatose 450M	20	0.42	0.76
Micronized lactose	2	0.25	0.45

density is the same as the calculated value, ρ_t, this indicates that the particles are packed in a similar way in the mixture as in the corresponding raw material.

As expected, the PBD decreases when fine powder is added to the coarser carrier particles. This is also predicted from Eq. (2) as there is a fair overall correlation between measured and calculated data in the figure. But it can be observed that the mixture with 95% carrier and 5% intermediate sized lactose (the second sample) has a PBD which is significantly higher than the calculated value. This can be explained by the broader particle size of the mixture as compared to the lactose grades used, which enables better packing. This effect is well understood and has been modeled [24,25]. The opposite behavior is however seen for the mixture of carrier and micronized lactose ([95/0/5], 5th sample), which has a PBD lower than the calculated value. This is most likely due to the attachment of the micronized particles to the carrier, making the surfaces of the carrier particles rougher, and thereby preventing closer packing. To conclude the observations from the poured density measurements, it seems that by comparing the measured PBD to theoretically calculated values, we may gain some insight into the packing structure of the mixtures.

3.2. Compressed bulk density

Measured and calculated CBD values are given in Fig. 3. In analogy to above, theoretically calculated CBD values for the ordered mixtures have been derived based on the CBD values of the pure components (see Eq. (2), CBD values in Table 2). As is seen from Fig. 3, there is a marked increase in CBD when adding intermediate and/or micronized particles to the carrier, as compared to the pure carrier. This is quite opposite to the results for PBD. The increase cannot be predicted from calculations based on the CBD values of the pure components, as is evident from Fig. 3. Intermediate and micronized particles this time seems to give similar effects, compare for example mixtures 2, 3 and 5 which all have 95% carrier but different contents of intermediate and micronized particles, and mixtures 4, 6 and 7, which all have 90% carrier.

The explanation for the observed increase relative to pure carrier is that both intermediate particles and (aggregates of) micronized particles are able to distribute in-between the carrier particles when subject to the combined pressure and rotation of the GeoPyc instrument, and again the resulting very broad particle size distribution of the mixtures entails a significant increase in CBD. At the highest contents of intermediate and micronized lactose, i.e., the four last compositions in the series, the CBD starts to decrease slightly and a pattern similar to that for the calculated CBD appears, but at a higher level.

3.3. Hausner Ratio

Based on the PBD and CBD data presented above, the modified Hausner Ratio was calculated for each mixture. As seen in Fig. 4, all mixtures display an increase compared to the pure carrier. Clearly, the modified Hausner Ratio demonstrates a significant increase in cohesivity by the introduction of micronized particles. Thus, comparing mixtures 1 and 5, the ratio increases

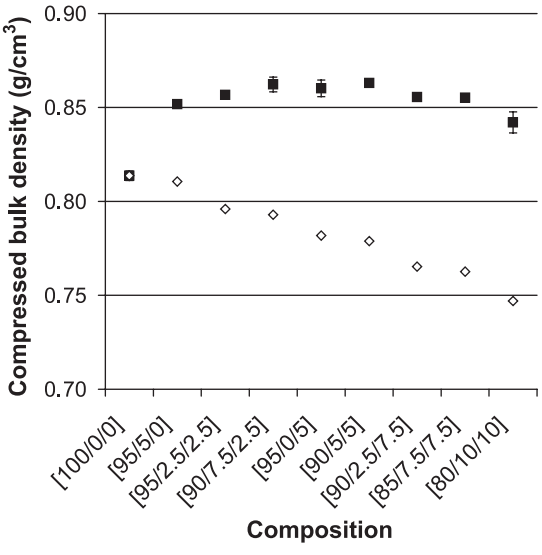

Fig. 3. Compressed bulk density. Measured values (squares) with error bars, compared to calculated values (rhombs). Error bars indicate one standard deviation.

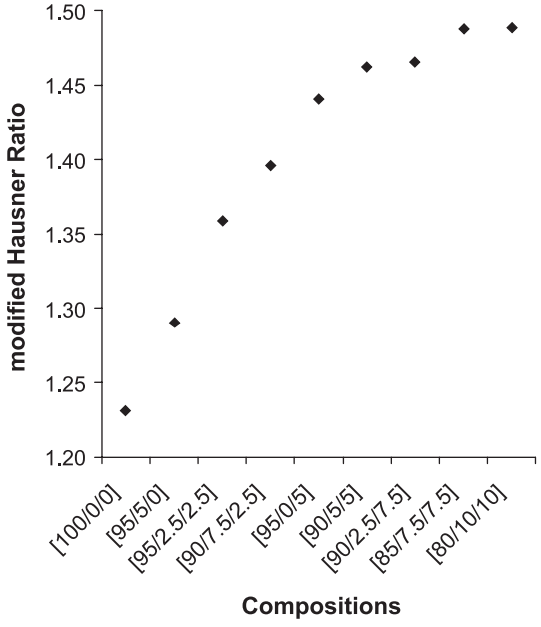

Fig. 4. Hausner Ratio.

from 1.23 to 1.43, i.e., a 15% increase when the amount of micronized particles is increased from 0% to 5%. The introduction of intermediately sized particles still increases the ratio, but to a lesser degree. Comparing mixture 1 with 2, mixture 3 with 4, mixture 5 with 6 and mixture 7 with 8, respectively, an increase of less than 5% in the ratio results when increasing the intermediate particle fraction from 0% to 5% or from 2.5% to 7.5%. It can be concluded that the modified Hausner Ratio discriminates well between the investigated mixtures, but levels out at about 1.5 for the most cohesive powders. It should be pointed out that this is not a limiting value for the modified Hausner Ratio. As an example, the ratio is around 1.8 for the intermediate sized and the micronized lactose, according to data from Table 2.

3.4. Angle of repose

The results for angle of repose are given in Fig. 5. As expected, the more cohesive powders have a higher angle of repose. The first four samples differ significantly, but for the last four mixtures, the angles obtained are similar at a level just above 50°. A reason for this may be the difficulty of measuring angle of repose for cohesive powders [3,22], but on the other hand, the standard deviations obtained are not larger for these mixtures than for the first mixtures of the series and we therefore believe that the data obtained are relevant.

There is a linear correlation between angle of repose and the modified Hausner Ratio, as is shown in Fig. 6. It can thus be concluded that the Hausner Ratio, although it does not measure flowability directly, is a relevant indicator of the flowability for this kind of mixtures. It should be noted that the correlation is not expected to be valid for powders with higher cohesion than the mixtures in this study, due to limitations of the angle of repose measurement.

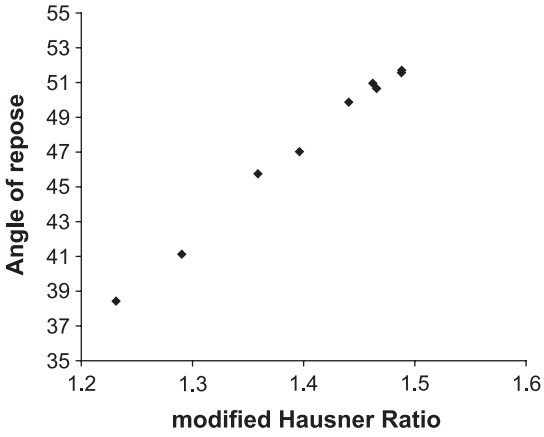

Fig. 6. Correlation between angle of repose and Hausner Ratio.

3.5. AeroFlow

In Fig. 7, the average time between avalanches obtained from the AeroFlow instrument is shown. Mixtures with less than 5% of micronized lactose behave as expected, i.e., the more fine and/or intermediate particles in the mixture, the longer the time between avalanches, indicating a reduced flowability. For mixtures with 5% or more of micronized lactose, however, there is no significant difference in the average time between avalanches, and, furthermore, the standard deviation between measurements tends to increase. For the last mixture in the series, the standard deviation was extremely high. This was found to be due to formation of aggregates in the samples. In this case, the AeroFlow monitors the flow of these aggregates instead of the particulate flow of the powder. This finding

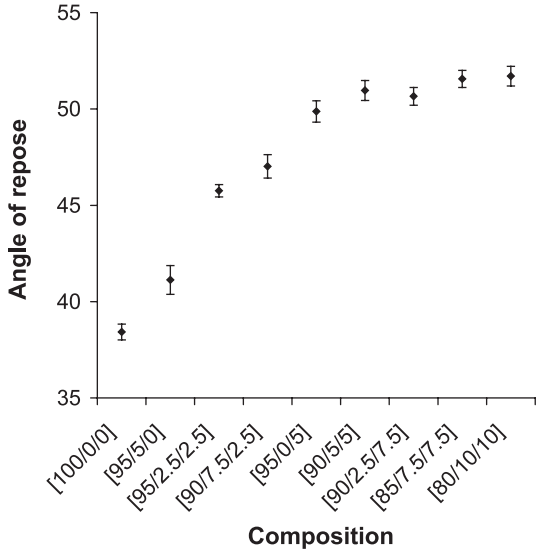

Fig. 5. Angle of repose. Error bars indicate one standard deviation.

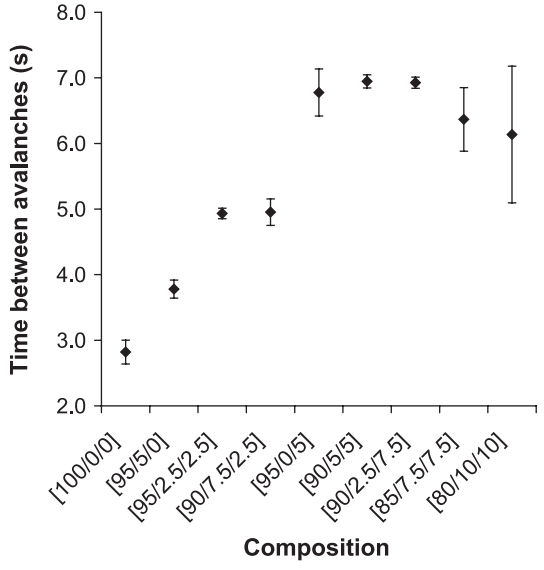

Fig. 7. Average time between avalanches obtained from the AeroFlow. Error bars indicate one standard deviation.

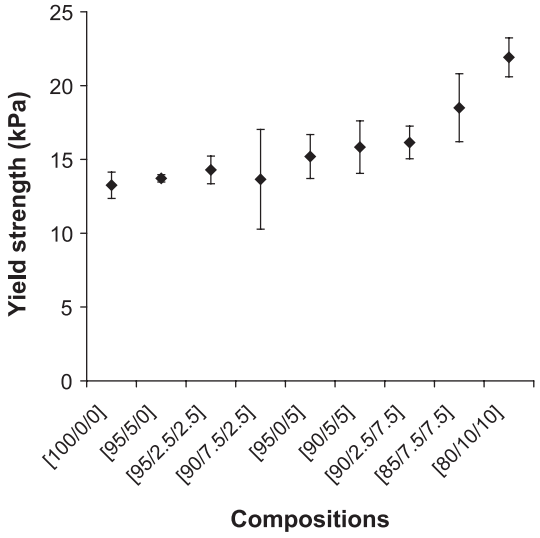

Fig. 8. Yield strength obtained from the Uniaxial tester at a consolidation pressure of 400 kPa. Error bars indicate one standard deviation.

highlights a general problem when using AeroFlow: The results can either be due to particulate flow or to the flow of aggregates formed during rotation of the powder. To find out, it is recommended to continue to rotate the powder after the actual measurement period with the doors of the instrument open, to inspect if changes have occurred to the powder.

To summarize, the results obtained show that the AeroFlow can discriminate between ordered mixtures with a relatively good flow but not between the more cohesive mixtures of this series.

3.6. Uniaxial tester

Yield strength results obtained from the Uniaxial tester are shown in Fig. 8. No significant differences are seen between the first six mixtures with average yield strengths all in the range of 13–16 kPa. This is quite opposite to the results obtained from the other methods. However, the last two mixtures of the series display an increase in yield strength, again in contrast to the results from Hausner Ratio and angle of repose. It can be concluded that the Uniaxial tester cannot discriminate between ordered mixtures with good flowability, but on the other hand, it seems suitable for assessment of more cohesive powders. This is also supported by other studies [26].

4. Conclusions

This study shows that different techniques for assessment of powder flow perform quite differently when applied to ordered mixture type powders for inhalation. Apart from practical differences such as in the amount of powder required and the time to perform a measurement, and to differences in precision, the investigated methods clearly also have different working ranges. The working ranges for the methods with regard to the powders investigated in this work are indicated in Table 3.

The modified Hausner Ratio, assessed by measuring the poured and the compressed bulk density, is a simple method and was shown to be reliable for assessing powder flow of ordered mixtures. The modified Hausner Ratio discriminates well between the ordered mixtures with 5% micronized lactose or less and seems to have the widest working range. It was also demonstrated that poured and compressed bulk density data can be used to gain insight into the packing of the particles in the mixtures.

The angle of repose is a straightforward and well-established method, and the results obtained in this study correlates well with the Hausner Ratio. The method is, however, restricted to powders with low to intermediate cohesivity since more cohesive powders do not have a well-defined angle of repose.

The AeroFlow is suitable for ordered mixtures with 5% micronized lactose or less, but cannot discriminate between the more cohesive powders. A warning should be raised as cohesive powders may display short times between avalanches due to aggregate formation, and thereby wrongly be assessed as having good flow. The instrument is easy to use and operator-independent, but care has to be taken to avoid sliding of powder and powder adhering to the glass walls, as such events will be detected by the photoelectrical detection system and may be mis-interpreted as avalanches.

The Uniaxial tester was not appropriate for the powders investigated in this study but was able to sort out the most cohesive mixtures in the series, in contrast to all the other methods. The Uniaxial tester thus seems to be better suited for more cohesive powders, which may be expected as it is a shear tester.

Regarding the powder composition, it can be concluded based on the combined results from the four different tests that the fraction of micronized lactose has a strong influence on the flowability of the ordered mixtures, particularly at levels up to 5%. The fraction of intermediate sized lactose, on the other hand, has a much lower impact on the flowability of the ordered mixtures in the range studied.

Table 3
Working ranges of the methods investigated with regard to ordered mixtures for inhalation

Powder method	Free flowing	Intermediate	Cohesive
Hausner Ratio	+	+	?
Angle of repose	+	+	–
AeroFlow	+	?	–
Uniaxial tester	–	–	+

(+) means discriminates well, (–) means does not discriminate and (?) means not fully assessed in this study.

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