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Research paper

Flowability characterisation of drug–excipient blends using a novel powder avalanching method

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ABSTRACT

The scope of the work is twofold, first to introduce a new avalanche testing instrument and secondly to characterise flowability of pharmaceutical blends comprising of coarse and fine particles. The results were compared with established powder characterisation instruments like the angular shear cell and a flow through orifice tester. These different methods were applied to a broad concentration range of binary mixtures comprising coarse, well-flowing lactose and micronised, poorly flowing albendazole. Some of the mixtures were further analysed with scanning electron microscopy. The results showed clear changes in the flow behaviour of the mixtures that were considered as critical flow concentrations (CFCs). At least three drug concentrations were observed for which the flow behaviour essentially changed. Accordingly, different flow regions were identified, which were explained on the basis of changed particle packing configurations. A theoretical model successfully provided a first estimation of the initial two CFCs. In conclusion, the novel avalanche testing instrument provided complementary information to conventional flowability methodologies, and a thorough assessment of pharmaceutical blends is needed to avoid CFCs in view of a robust formulation development and hence with respect to building quality into the design of the solid dosage forms.

1. Introduction

Powder flowability has been a subject of extensive research in the pharmaceutical industry for quite some time, especially with respect to preformulation and development of solid dosage forms. A considerable effort has been spent in obtaining free-flowing powders and granules for tablet and capsule manufacturing [1]. The affects of poor flow were observed in the weight variation of tablets [2] and in the filling performance of capsules [3], which both are critical regarding a poor content uniformity. Powders and their blends have been traditionally characterised using a flow through an orifice tester or using an angular shear cell. The angle of repose, Carr's compressibility index and the Hausner ratio are further commonly used as markers of powder flowability. A pioneering work of Rastogi and Klinzing [4] already used a rotating drum for powder characterisation. This rotating drum assembly was lacking an image analysis, so that only limited parameters could be measured (time between avalanches, strange attractor plots). Later, several authors studied the avalanching behaviour of powders in a modified version of the rotating drum, which still lacked the image analysis, in an attempt to understand, compare and rank them with respect to their flow characteristics [5–8].

The usefulness of the powder avalanching studies to determine the effect of an added ingredient on the rheology of the mixture was already investigated by Kaye et al. [5] more than a decade ago. Pharmaceutical powder mixtures with poor flow were also tested regarding flowability using various methods [9], and most recently new indices for characterising the powder flow based on avalanching behaviour were reported [10]. Quintanilla et al. [11] looked into the critical behaviour in avalanches of slightly cohesive powders, whereas Alexander et al. [12] recently reported the flow dynamics of substantially cohesive powders in rotating cylinders. Thus, the investigations of avalanching behaviour of a sample in a rotating drum started with simple, free-flowing powders and extended with time to more cohesive materials. This information has significantly helped the scientific community to better understand powder behaviour in a rotating drum.

The current study has two objectives. The first aim is to introduce a novel avalanching instrument, which constitutes of a rotating drum allowing a complete powder avalanche analysis and to

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use the same for the flowability characterisation of pharmaceutical powder blends. Unlike the powder avalanching instruments used in the past, this advanced instrument is coupled with an image analysis system enabling the determination of diverse parameters characterising the avalanches. This would enable better understanding of the powder avalanching behaviour.

A second and equally important aim of this study is to investigate the flowability of binary powder blends consisting of coarse and fine materials. This is of special interest because flowability of blends is essentially complex, since flow properties are not only influenced by the physicochemical material factors, but also to a great extent by the particle packing. The particles in multicomponent mixtures can assume various packing organisations. The simplest pharmaceutically relevant mixture is binary blends of a drug with an excipient. Such blends provide packings of multisized particles for which empirical equations were derived to calculate the packing density [13–15]. The prediction of the packing properties is even more complex, if interaction between the particles is assumed. Several investigations were made to understand the affects of interparticulate interactions on mixing homogeneity in binary powder blends consisting of fine and coarse particles [16–21]. Barra et al. [22] questioned whether the organisation of a binary powder mix can be predicted based on surface energy, cohesion parameter and particle size of its components. The authors were successfully predicting a possible adherence of small particles to a coarse excipient, which is also known from inhalation technology [23], but the attempts were not able to reliably predict any packing configuration of binary blends. This was partially due to additional effects in pharmaceutical blends such as the particle shape [24] increasing the heterogeneity in powder mixtures. Attempts were made to model these effects of heterogeneity in binary mixtures by means of percolation theory [25], which mainly focussed on the geometry of the particle packing. Thus, the physics of binary particle mixtures is still not well understood [26], but the packing organisation defines the material flow properties. These technical blend properties can greatly change, if the packing organisation is altered at different mixture ratios. Such changes of flowability with different mixing ratios are important to understand. It is a required knowledge to adequately formulate pharmaceutical powder blends that requires designing quality into the product [27–29].

The significance of the first objective is to better study powder avalanching behaviour with the aid of image analysis. Testing of flowability of pharmaceutical blends and granules is important in view of filling performance of tablets and capsules. Additionally, this new methodology bears the potential of an at-line process analytical technology (PAT) as the measurements can be performed quite quickly. In line with this consideration, the second aim of the study is directed towards a better understanding of powder blends regarding their flow performance. A rational choice of mixing ratios should be enabled, so that both objectives of this study would contribute towards a quality by design (QbD) concept.

2. Materials and methods

2.1. Materials

A commonly used pharmaceutical excipient, PrismaLac® 40 (MEGGLE, Wasserburg, Germany), which is coarse grade lactose, was chosen for the study due to its good flow performance. Albendazole (Satwik Drugs Limited, Hyderabad, India) was chosen as the model drug because of its poor flow and cohesiveness. The materials used were from single lots for all the work reported and were used as received. The physical characteristics of the materials are compiled in Table 1.

2.2. Methods

2.2.1. Primary characterisation of powders

The true densities of the powders were determined with Multi-Pycnometer® (Quantachrome GmbH, Odelzhausen, Germany) using helium as the displacement gas. The bulk and tapped densities were measured in a graduated cylinder using a type SVM 102 bulk density instrument (Erweka® GmbH, Heusenstamm, Germany) and was operated according to USP Method II. The particle size distribution (PSD) of the powders was determined using a Sympatec Helos/Rodos® laser diffraction particle size analyser (Sympatec GmbH, Clausthal-Zellerfeld, Germany) using a dry powder disperser operated at 3 bar for albendazole. PrismaLac® 40 was dispersed in ethanol, and 50 ml cuvette was used for analysis.

2.2.2. Preparation of binary mixtures

A broad range of concentrations of binary mixtures were prepared for studying the flowability. The concentrations were 0%, 1%, 2.5%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 60%, 70%, 80% and 100% w/w of albendazole in the blend. In order to break down agglomerates, albendazole was initially sifted through a 250-μm sieve and PrismaLac® 40 through a 850-μm sieve. These materials were then weighted and added into 500 ml amber plastic bottles and mixed for 10 min in a TURBULA® T2A shaker-mixer (Willy A. Bachofen AG, Muttenz, Switzerland) at 52 rpm. We selected a common mixing time of 10 min and further checked the range of 5–15 min with respect to altered flow properties using different mixing ratios.

2.2.3. Avalanche testing of binary mixtures

The flowability of the binary mixtures was tested in a rotating sample drum using a commercial powder avalanching tester (REVOLUTION®, Mercury Scientific Inc., SC, USA). The instrument was provided with a bigger sample drum assembly, which consisted of an anodized aluminium ring (110 mm diameter, 35 mm wide) and two borosilicate glass plates on either side. A powder sample measuring device having a volume of 118.3 ml was provided with the instrument and was used to standardise the sample volume of the different measurements. The drum assembly was mounted centrally on two silicone rollers fixed to a horizontal drive shaft, which was run by a motor that rotated the drum. A digital video camera interfaced to a computer and controlled with image processing software captured images of the sample. For every image taken, the software calculated multiple parameters associated with powder avalanching. The images were captured at the rate of 10 frames per second. After loading the powder into the sample drum, a preparation time of 30 s was allowed before the analysis was started following which the sample drum was rotated at a speed of one rotation per minute. This rotation speed was chosen after evaluating a broad range of drum speeds (0.5, 0.7, 1.0, 1.5 and 2.0 rpm) and subsequently looking at the corresponding flow regimes exhibited by the mixtures. At higher speeds (>2 rpm), no pronounced differences were seen between the samples studied. The time for data collection for this instrument can be chosen based on number of avalanches or number of data points. In this study, the data collection was limited to 2048 data points (run time: 234 s), and this duration was selected to ensure a sufficient number of data points for analysis. The avalanche was the discharge of the particles inside the rotating drum. Such collective sudden particle movement was identified by the software using the cross-section image and a certain threshold has to be defined. This avalanche threshold was maintained at a minimum in order to collect all of the avalanches. All tests were performed in triplicate, and mean and standard deviation are reported. All the experiments were done at ambient conditions with an average relative humidity of roughly 45%. Avalanche time was measured as the time taken

Table 1
Physical characteristics of materials.

Material	Description	Particle size distribution	Bulk density (g/cc; $n = 3$)	Tapped density (g/cc; $n = 3$)	True density (g/cc; $n = 3$)
Albendazole	USP grade	D_5: 3.5 μm D_{50}: 4.5 μm D_{95}: 5.8 μm	0.238 ± 0.005	0.341 ± 0.004	1.345 ± 0.001
PrismaLac® 40	Coarse sieved crystalline alpha-lactose monohydrate	D_{10}: 260 μm D_{50}: 478 μm D_{90}: 705 μm	0.535 ± 0.012	0.596 ± 0.003	1.528 ± 0.001

for the event. Mean avalanche time was computed by dividing the observation time by the total number of avalanches in a test. For the avalanche power, the software calculated the changes in the potential energy before and after an avalanche, and the dimensions were cm^3 mm (volume of the bulk times the height) as defined by the manufacturer. The avalanche angle (degrees) was computed by collecting the angle of the powder at the maximum position prior to the start of the avalanche occurrence, and the result was reported as the average value for all the avalanche angles. The rest angle was the angle at the rest position of the powder at the end of an avalanche occurrence also reported as the average value of all the rest angles.

2.2.4. Shear cell testing of binary mixtures

The ShearScan TS12® (Sci-Tec Inc., CT, USA) is an automated shear cell, and for this entire study, a rotational split cell was used for determining the powder flow behaviour of the mixtures. The rotational split cell consisted of a base ring with attached inner and outer sides, upper floating inner and outer rings, and a twisting lid. Samples were compressed between the rings by force on the lid and were sheared by rotational motion between the upper floating rings and lower fixed rings. The shear force was transmitted through the lid and measured as torque in the base. The samples were prepared by carefully pouring the powder mixtures into the gap between the rings followed by scraping the excess powder using the rotating scraper provided with the cell and the sample weight noted. The cell was then placed on the mounting device, and the twist-top carefully positioned on the sample surface, taking care not to exert any stress on the sample bed. The failure stress was measured at a normal consolidation stress of 8 kPa. The measurements of a yield locus were repeated in triplicate using fresh samples, and the angle of internal friction as well as the cohesion was calculated automatically by the instrument software.

2.2.5. Powder flow through an orifice

A commercially available powder flow testing instrument (COPLEY Scientific, Nottingham, UK) was used for monitoring the flow rate of material through an orifice. A truncated cone with a circular orifice diameter of 15 mm was used. The flow rate was measured in discrete samples by observing the time it took for a constant volume of the sample to pass through the orifice to the nearest hundredth of a second. Volume flow rate was used in order to avoid the bias of the results in favour of high-density materials. No vibrator was attached to the instrument.

2.2.6. Scanning electron microscopy of binary mixtures

Scanning electron microscopy (SEM) (TM 1000® Tabletop Microscope, Hitachi, Japan) was used to access the surface morphology and texture of pure materials and binary mixtures. The instrument consisted of a pre-centred cartridge filament for the electron gun and operated at an accelerating voltage of 15 kV. High-sensitive solidstate backscattered electron (BSE) served as the detector. Two vacuum pumps (turbo molecular pump and diaphragm pump) operated to evacuate the chamber prior to sample observation. Samples were sprinkled on a double-sided sticky tape (on metal holders) mounted on the SEM stage and observed under the microscope.

2.2.7. Statistical analysis

STATGRAPHICS Centurion XV, version 15.2.06 was used for analysis of the data including the calculation of the Pearson product moment correlations.

3. Results and discussion

3.1. Investigation of the blend flowability using micronised albendazole and a coarse grained lactose (PrismaLac® 40)

3.1.1. Flow behaviour and trend analysis in the rotating drum

Different flow regimes were differentiated in a rotating drum. Fig. 1 depicts the various flow regimes observed during the analysis of the samples. The cascading behaviour was observed for most of the samples, but mixtures containing higher albendazole amounts showed a tendency towards cataracting, and this flow behaviour was clearly observed for the pure drug, due to its high cohesiveness. Finally, a slumping behaviour of the samples was also occasionally seen.

Apart from the flow regime, it was interesting to analyse trends in a series of avalanches for a given sample. The Hurst exponent (H) [30], in this study the "avalanche Hurst exponent", was estimated for an avalanche power set by the instrument software, and it provided a measure, whether there were memory effects inspecting a series of sequentially following avalanches. All H values of the different blends were in a close range of about 0.1–0.2 being clearly below 0.5. Such flow behaviour can be called as being "anti-persistent" [31]. Thus, an avalanche with a smaller avalanche power will most likely follow the avalanche with a larger avalanche power.

3.1.2. Interpretation of the avalanche test parameters together with the results of SEM

Lower avalanche times and narrower avalanche time distributions are an indication of easy and consistent flow. Pure PrismaLac® 40 flowed evenly and with a smooth surface, while the cohesive pure albendazole flowed inconsistently with an irregular surface. Powders exhibiting sharp and narrow avalanche time distribution spectrums are more preferable to work with than those displaying

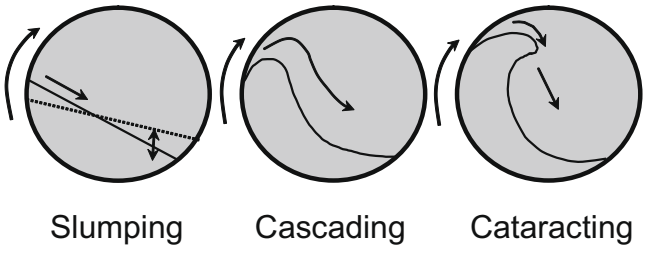

Fig. 1. Types of powder flow regimes observed in this study (adapted from Hancock et al. [8]).

a plateau and broader distributions. We observed as the albendazole concentration in the blend increased, the avalanche time spectrum exhibited a flat peak and broader distributions. Fig. 2 shows the change in flow behaviour of the blends by means of the mean avalanche time. Different ranges were clearly observed, and the transition was not sharp so as to precisely determine the true infliction points. A first critical flow concentration (CFC) was assigned to a very small amount of drug concentration, which for the first time showed altered flow behaviour of the blend when compared with the pure excipient (the theoretical concepts of CFCs are explained in Section 3.2). This first concentration (X_{C1}) must occur below 1% w/w, since here already an altered flow was observed compared with the pure PrismaLac® 40. From a technological viewpoint, the second critical concentration (X_{C2}) appears to be of a higher interest, and it was revealed close to 15–20% w/w of drug regarding the mean avalanche time (Fig. 2). This result was in good agreement with the findings of the avalanche power (Fig. 3) as well as with the results of the avalanche angle (Fig. 4). Considering the results of the mean avalanche time and avalanche power, it was possible to assign a third critical concentration (X_{C3}) between 35% and 45% w/w. However, this transition was rather smooth with respect to avalanche power and when comparing with the results of the avalanche time. Such transition could hardly be observed with the data of avalanche angle, and it appears that this parameter could be less discriminating the flow behaviour. Beyond the critical concentration X_{C3}, the different flow parameters all displayed higher variability. In this range, the drug increasingly dominated leading to erratic flow performance. Further, abrupt changes of flow behaviour can also exist in this range of drug dominance, but their analysis was problematic due to the high experimental variability, and this range appears to be also of a lesser technological importance.

Different packing configurations were also seen by scanning electron microscopy (Fig. 6). Comparing the blend of 20% w/w (Fig. 6c) with the pure components (Fig. 6a and b) indicate that smaller drug amounts mainly fill the voids of the excipient particle packing, while some of the albendazole particles were also adhered to excipient surfaces. This initial drug adhesion was not too pronounced, so that the excipient particles still displayed their original shape. Certainly, the filling of particle voids cannot be entirely reflected by SEM pictures like Fig. 6c, since the sample preparation under vacuum partially removed some of the drug in the voids.

The drug adhesion to the lactose was prevailing in a further range from ~20% to about 40% w/w giving rise to the formation

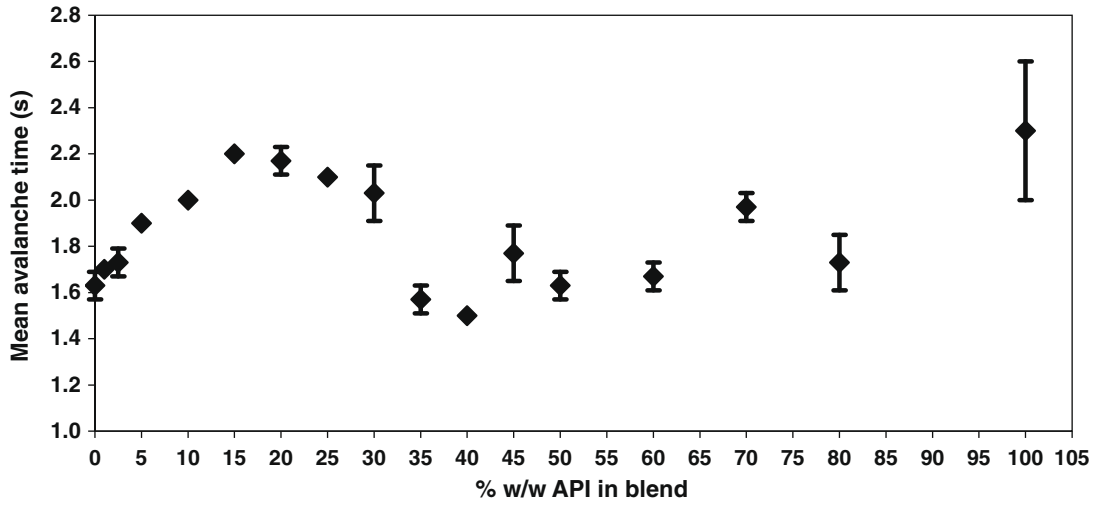

Fig. 2. Mean avalanche times of various concentrations of albendazole in PrismaLac® 40.

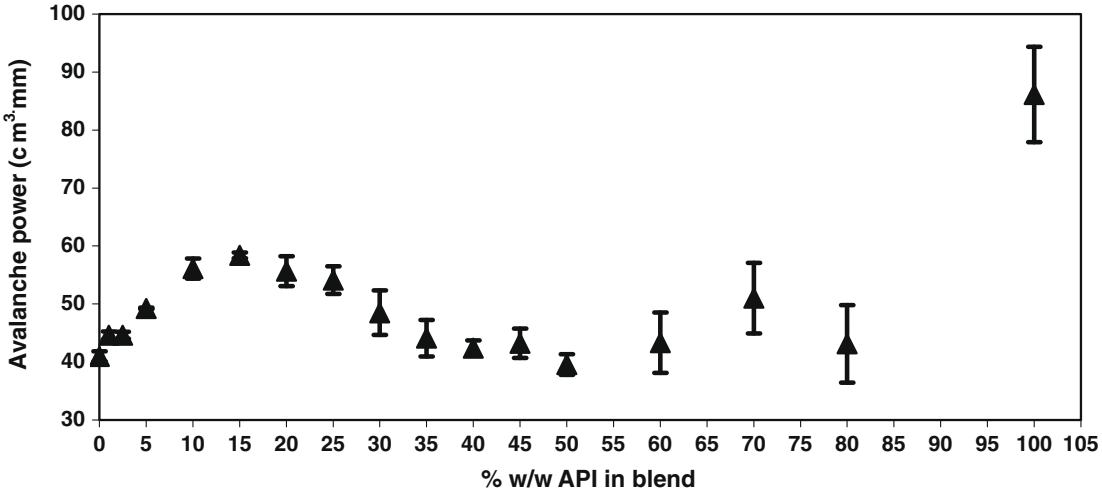

Fig. 3. Avalanche powers of various concentrations of albendazole in PrismaLac® 40.

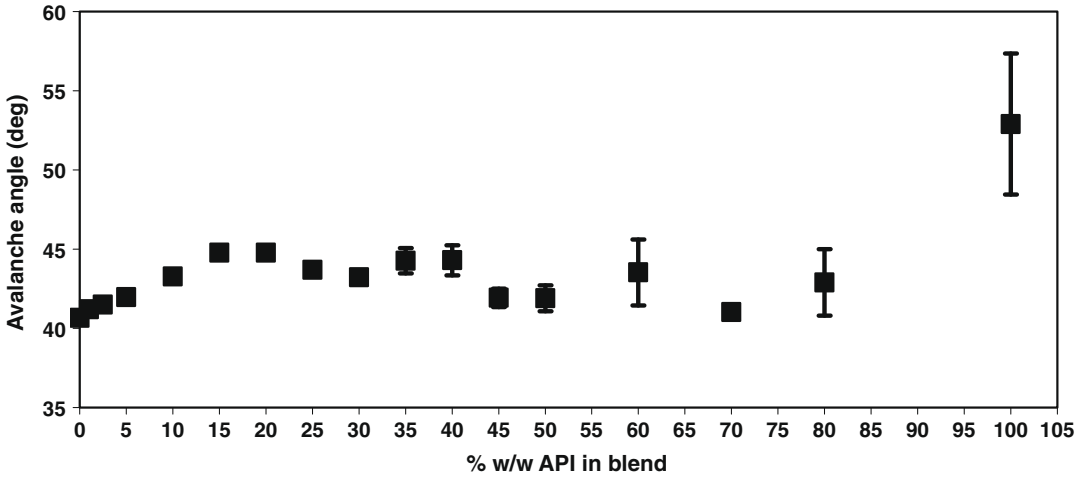

Fig. 4. Avalanche angles of various concentrations of albendazole in PrismaLac® 40.

of large and round apparent particles. As an effect of this layering, as seen in the change from Fig. 6c and d, the observed flow behaviour in the drum was dominated by the coated particles. The size and nearly spherical shape facilitated the overall flowability, so that the flow performance in this range was improved to a level that was comparable with the pure excipient. Beyond 40% w/w (Fig. 6e and f), the coating of the lactose particles also continued resulting in the formation of even larger apparent particles. At 80% w/w concentration, a few perfectly round particles were observed some of which had a diameter of as large as ~2000 μm as seen in Fig. 6f.

A fraction of the drug particles was not part of the excipient coating process and was expected to influence the overall flow behaviour. This dominance of drug particles is the likely reason why beyond 40% w/w, the observed flow in the drum was increasingly impaired.

These results of the avalanching analysis together with images of SEM can be summarised in the following way. A small amount of drug <1% w/w was already sufficient enough to alter the flow performance of the pure excipient. The more drug was added, the poorer the flowability became since the small drug particles filled the voids of the excipient particles, while the excipient particles still retained their shape. This could have affected the overall flow performance. However, at a second critical concentration, there was a trend towards lower mean avalanche time and avalanche power that was paralleled by an increasing process of drug particles layering the excipient particles. This process led to more ordered structures with round excipient particles of a bigger apparent size. These changes of apparent size and shape were most likely the cause of the decreasing mean avalanching time and power, which was indicative for improved flowability. This improved flowability ended at a concentration of about 40% w/w albendazole and higher drug amounts gradually worsened the flow. We observed further increase in the avalanching parameters beyond a concentration of about 80% w/w; however, such higher concentration is of lesser technological importance for powder blends. At very high drug amounts, a powder blend formulation would be strongly discouraged, as it would be predominantly defined by the drug particle performance, and a granulation step would be required.

3.1.3. Comparison with results from flow through an orifice

The flow of powders through a flow through an orifice instrument is under the influence of gravity and most telling of the flow behaviour. Fig. 5 shows the flow behaviour through a 15-mm orifice. On a first glance, the flow rate appeared to be corresponding

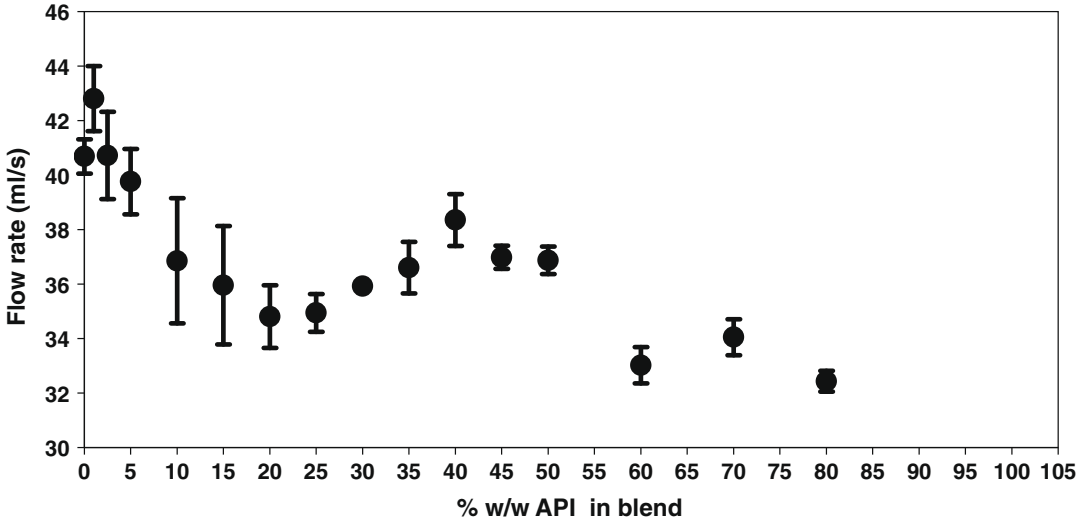

Fig. 5. Flow rate of the binary blends through a 15-mm orifice.

to that observed with the mean avalanche time of the powder avalanching tester. The flow rate was highest at the 1% w/w concentration followed by a continuous and gradual decrease until ~20% w/w. Further, the flow rate started to increase up until ~40% w/w but did not increase beyond the pure excipient flow rate. Beyond ~40% w/w, the flow rate appeared to become erratic. Pure albendazole did not flow through the orifice as it was very cohesive. This behaviour was in good agreement with the data observed with mean avalanche time (Fig. 2).

3.1.4. Comparison with shear cell data

It should be recalled that the powder blends inside the rotating drum were under the influence of small shear forces, whereas in a shear cell, the same were under the influence of an externally ap-

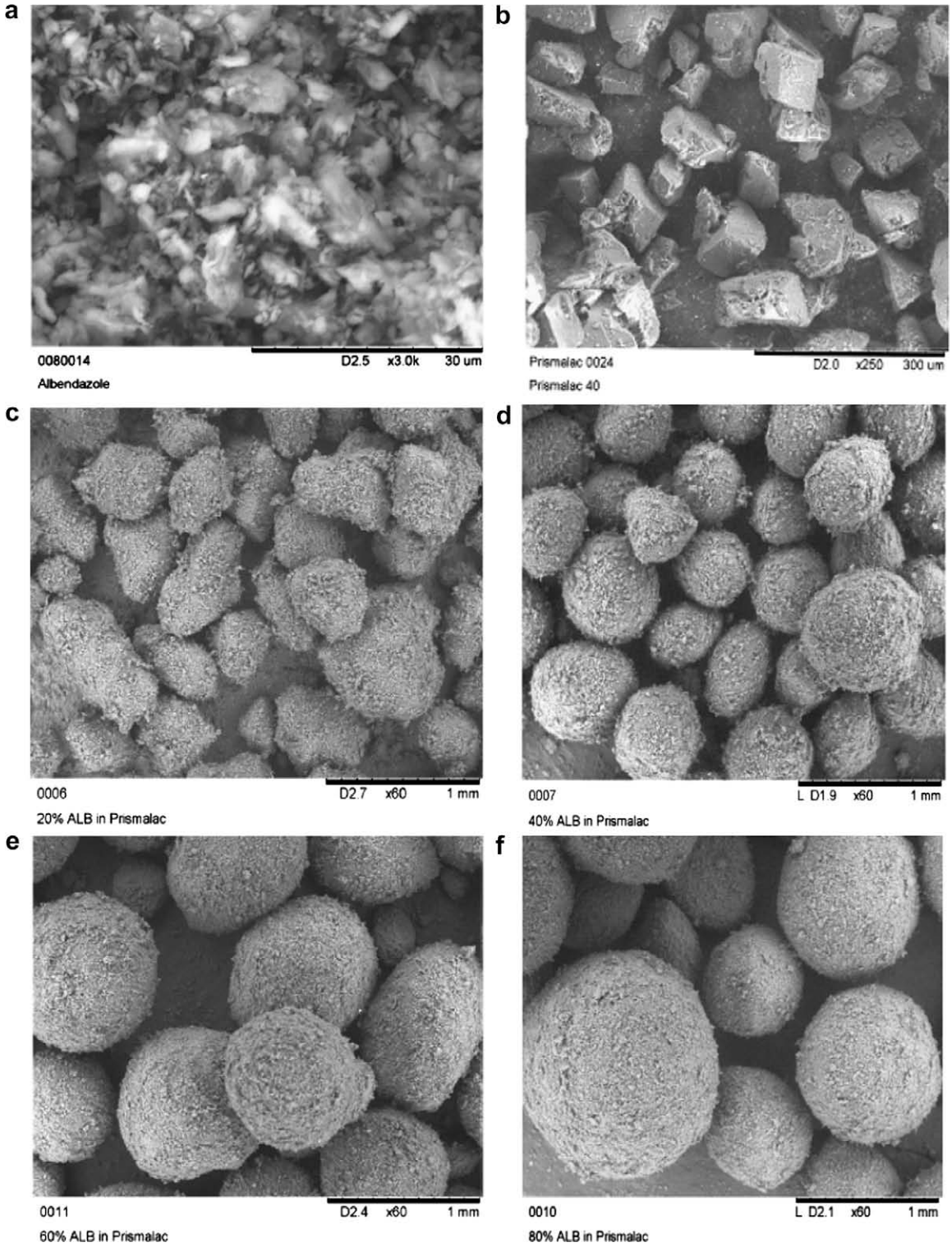

Fig. 6. Scanning electron micrographs of (a) albendazole, (b) PrismaLac® 40, (c) 20% w/w albendazole in PrismaLac® 40 blend, (d) 40% w/w albendazole in PrismaLac® 40 blend, (e) 60% w/w albendazole in PrismaLac® 40 blend and (f) 80% w/w albendazole in PrismaLac® 40 blend.

plied large normal stress. The results are discussed in light of cohesion and angle of internal friction. We observed with increasing drug concentration in the blend the cohesivity increased with pure albendazole displaying highest cohesivity of 3 kPa. On the other hand, the angle of internal friction exhibited a constant decrease from 25% to 70% w/w implying this mixture region flowed better than the other regions observed. However, a direct comparison between the parameters studied in powder avalanching tester and that of shear cell would be simply misleading the information since these are two extreme cases of consolidation. While in the powder avalanching tester, the blends flow under practically unconsolidated conditions, the shear cell measures at a largely consolidated state. The binary mixtures, after analysis with shear cell, were observed under SEM, and we found that the round structure of the particles was destroyed, because of the large normal stress applied during measurements. An example of such a phenomenon is shown in Fig. 7, in which the destruction of the round particles after consolidation is obvious.

The results indicated that an applied normal stress may profoundly alter the structure in a powder system. A comparison of material flow properties under such differing conditions is, therefore, *a priori* of only limited value. This should be kept in mind, if the flow in a process is considered. A measured flowability parameter can only be expected to be predictive for a process, in which the underlying structure is not substantially changed.

3.2. Theoretical aspects of critical mixing ratios

Molerus [32,33] described the theoretical aspects of the influence of finer particle content on the flow behaviour of a coarse bulk material. Based on similar theoretical concepts, we have extended his theoretical considerations to powder mixtures. In a binary blend, the mass of the drug, m_D can be expressed by visualising n_D spherical particles of radius r_D, having a particle density that shall equal to the true density, ρ_{TD}:

$$m_D = \frac{4}{3}\pi \cdot r_D^3 \cdot n_D \cdot \rho_{TD} \tag{1}$$

A similar expression can be proposed for n_E excipient particles with a mass m_E and radius r_E having the corresponding true density of ρ_{TE}. Thus, Eq. (2) is directly obtained for a mixing fraction X of the blend:

$$X = \frac{m_D}{m_D + m_E} = \frac{1}{1 + \left(\frac{r_E}{r_D}\right)^3 \cdot \frac{n_E}{n_D} \cdot \frac{\rho_{TE}}{\rho_{TD}}} \tag{2}$$

For very low values of X, it is expected that the flow behaviour of the excipient is not perturbated by the few drug particles. It is interesting to ask that how many drug particles can be accommodated by a coarse excipient to show practically unaltered excipient flow performance. Molerus studied a similar problem of particle packings having coarse and fine fractions [32]. It was rationalised that in a cubic packing, a unit cell can be imagined having the dimension of the coarse particles. The fine particles may then theoretically cover three edges of this unit cell without affecting the cubic packing. For a micronised drug and a coarse excipient, the Molerus assumption leads to the following ratio of particle numbers:

$$\frac{n_E}{n_D} = \frac{1}{3\left(\frac{r_E}{r_D}\right)} \tag{3}$$

Using this Eq. (3) in combination with Eq. (2) leads to a critical mixing ratio X_{c1}, with an analogous expression as previously found by Molerus for the blends of coarse and fine particle fractions of a single material.

$$X_{C1} = \frac{1}{1 + \frac{1}{3}\left(\frac{r_E}{r_D}\right)^2 \cdot \frac{\rho_{TE}}{\rho_{TD}}} \tag{4}$$

For increasing amounts of drug $X > X_{c1}$, it is expected that the packing of the excipient is increasingly perturbated by the amount of drug, but still the excipient dominates overall flow behaviour. A second critical concentration can be defined assuming that the voids of the excipient packing are entirely filled by the drug particles. Molerus estimated also this critical concentration from packings of coarse and fine particles in a single powder sample; however, his estimation was based on a cubic packing of the coarse particles [33]. In the following modified approach, we did not assume any specific packing configuration of the excipient particles, and Eq. (5) is proposed for the excipient void volume that is entirely filled with the drug:

$$V_{EVoids} = \frac{4}{3}\pi \cdot r_D^3 \cdot n_D \cdot \rho_{RDVoids}^{-1} = V_{tot} \cdot (1 - \rho_{RE}) \tag{5}$$

The relative density $\rho_{RDVoids}$ denotes the volume fraction of the drug particles relative to the entire void volume in the excipient packing.

On the other hand, the relative density of excipient particles, ρ_{RE} is given by Eq. (6)

$$\rho_{RE} = \frac{4/3 \cdot \pi \cdot r_E^3 \cdot n_E}{V_{tot}} \tag{6}$$

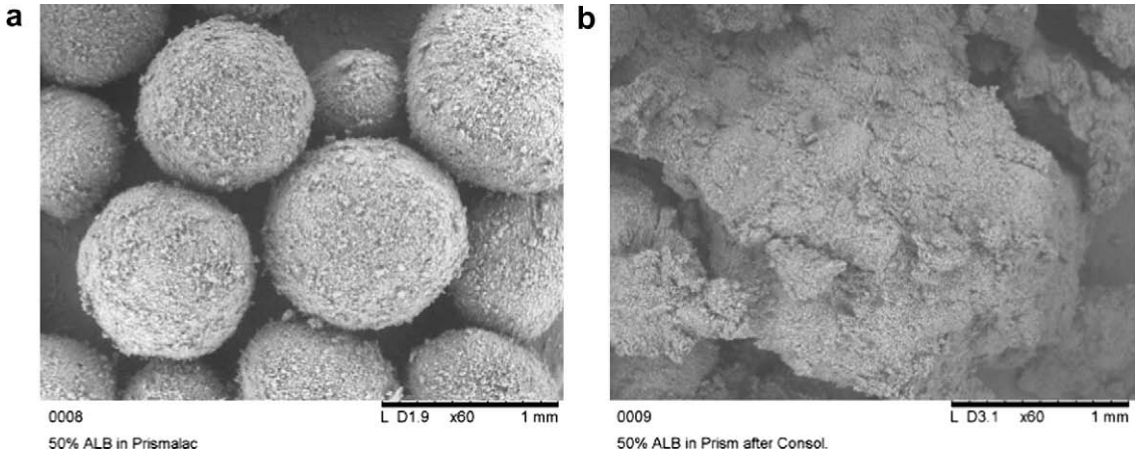

Fig. 7. Scanning electron micrographs of 50% w/w albendazole in PrismaLac® 40 blend (a) before consolidation under shear cell and (b) after consolidation at 8 kPa.

Combination of Eqs. (5), (6), and (2) leads to:

$$X_{C2} = \frac{1}{1 + \rho_{RDVoids}^{-1} \cdot \frac{\rho_{RE}}{1-\rho_{RE}} \cdot \frac{\rho_{TE}}{\rho_{TD}}} \quad (7)$$

The relative density of the drug in the voids ($\rho_{RDVoids}$) can be approximated by its relative bulk density, ρ_{RDBulk} and the relative bulk density of the excipient, ρ_{REBulk} may hold for the value of the relative excipient density (ρ_{RE}) at the critical mixing ratio:

$$X_{C2} \cong \frac{1}{1 + \rho_{RDBulk}^{-1} \cdot \frac{\rho_{REBulk}}{1-\rho_{REBulk}} \cdot \frac{\rho_{TE}}{\rho_{TD}}} \quad (8)$$

Eq. (8) can alternatively be written by using the ratio of the excipient bulk density to that of the drug, r_{Bulk}:

$$X_{C2} \cong \frac{1}{1 + \frac{r_{Bulk}}{1-\rho_{REBulk}}} \quad (9)$$

Table 1 lists the physical characteristics of the materials and using Eq. (4) results in $X_{C1} = 0.02\%$, whereas Eq. (9) yields $X_{C2} = 22.4\%$. The first calculated critical concentration was too low to be precisely visualised from Figs. 2–5. However, it is in agreement with the observation that addition of 1% w/w drug generally displayed a difference in the measured flow parameters of the pure excipient.

The theoretical model is certainly simple in the way that it does only consider the drug filling into the excipient voids, while parallel adhesion of drug particles is ignored. Given the simplicity of the theoretical arguments, the calculated second critical concentration was in close agreement with the findings of the different avalanche flow parameters for which a change at around 15–20% w/w drug was observed. A slightly higher theoretical value of 22.4% was in good agreement with the flow through orifice experiments in which a change at ~20% w/w was observed (Fig. 5).

There must exist further critical concentrations for which the particle packing undergoes fundamental change. However, basic theoretical assumptions were at least shown to roughly predict the initial two critical concentrations of the model blends.

3.3. Correlation of parameters obtained from avalanching powder analyser and flow through orifice

Pearson product moment correlations were computed to get an insight of the various significant correlating parameters. Focussing on some of the statistically significant parameters, a correlation of 0.87 ($p = 0.000$) was observed between avalanche angle and avalanche power. The avalanche angle and rest angle had a correlation of even 0.94 ($p = 0.000$). This high correlation suggests the use of either of the parameters for interpreting the angle during avalanching. Additionally, a correlation of 0.83 ($p = 0.000$) between avalanche power and avalanche time was also seen. Significant correlations of flow parameters were also found with respect to the variance of some avalanche parameters. Negative correlations were seen between flow rate through the orifice and with both the mean of avalanche power variance [−0.72 ($p = 0.002$)], as well as the mean of avalanche time variance [−0.57 ($p = 0.021$)].

4. Conclusions

A novel method for characterising powder flow was applied to pharmaceutical blends consisting of micronised drug and a coarse excipient. This novel method was helpful in characterising the model blends, and the different avalanche parameters were consistent and to some extent also comparable to the results of the flow through orifice. No meaningful comparison could be made with the shear cell, since the applied normal stress significantly altered the structure of the powder system. With respect to the second aim of the study, which is the characterisation of the binary blends, we observed critical changes in the flow behaviour. A simple theoretical approach was provided to calculate the two initial critical flow concentrations (CFCs), which successfully provided a good agreement with the experimental findings.

High avalanche values in combination with a drastic change close to a critical flow concentration should be avoided for the design of a robust formulation thus enabling researchers to build quality into the design of the dosage form. Mixing ratios during formulation development could be chosen on a rational basis, also in production, avalanche parameters could be monitored making revolutionary powder analyser a viable at-line PAT tool. This new approach could help in avoiding issues of flow performance during upstream manufacturing, namely, tabletting and capsule filling. Further investigations are planned to study the critical concentrations and the validity of the theoretical model in mixtures made from a series of excipients and other poorly flowing, cohesive drugs.

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