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Linking flowability and granulometry of lactose powders

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ABSTRACT

The flowing properties of 10 lactose powders commonly used in pharmaceutical industries have been analyzed with three recently improved measurement methods. The first method is based on the heap shape measurement. This straightforward measurement method provides two physical parameters (angle of repose α_r and static cohesive index σ_r) allowing to make a first screening of the powder properties. The second method allows to estimate the rheological properties of a powder by analyzing the powder flow in a rotating drum. This more advanced method gives a large set of physical parameters (flowing angle α_f, dynamic cohesive index σ_f, angle of first avalanche α_a and powder aeration $\%_{ae}$) leading to deeper interpretations. The third method is an improvement of the classical bulk and tapped density measurements. In addition to the improvement of the measurement precision, the densification dynamics of the powder bulk submitted to taps is analyzed. The link between the macroscopic physical parameters obtained with these methods and the powder granulometry is analyzed. Moreover, the correlations between the different flowability indexes are discussed. Finally, the link between grain shape and flowability is discussed qualitatively.

1. Introduction

Granular materials and fine powders are widely used in pharmaceutical applications (Ashurst et al., 2000; Warnke et al., 1996; Kaialy and Nokhodchi, 2015; Tavares Cardoso et al., 2011) as excipient or active ingredient in formulations. As excipient, lactose powders are involved in many processes: tabletting (Keleb et al., 2004), wet and dry granulation (Braumann et al., 2010; Kumar et al., 2014), blending, caps filling, etc. Therefore, any progress in the understanding of lactose powders flowing behaviors can have huge consequences for pharmaceutical industries. Indeed, a powder with inappropriate flowing properties can cause serious complications in production lines (clogging, agglomeration, segregation, etc.).

To control and to optimize processing methods, these materials have to be precisely characterized. The characterization methods are related either to the properties of the grains and to the behavior of the powder bulk. Unfortunately, the relation between the grain properties and the powder behavior is far to be obvious (de Gennes, 1999; Lumay et al., 2012). Therefore, both measurement types have to be performed. Many advanced methods are available to measure the grain characteristics: laser diffraction to obtain the grain size distribution (Tinke et al., 2009), granulomorphometer to measure the grain shape, X-ray diffractometer to characterize the grain crystallinity, SEM microscopy to visualize the surface and the shape of the grains, ... However, concerning the physical behavior of powder bulk (flowability, packing fraction, etc.), most of the techniques used in R&D or quality control laboratories are based on old measurement techniques (European Pharmacopoeia). During the last decade, interesting techniques have been developed like shear cells (Schulze, 2011; Saw et al., 2014) and powder rheometers inspired by liquid rheometers (Freeman, 2007). However, the evolution of this field is still at its beginning. Indeed, even from a fundamental point of view, the determination of the physical laws that govern the behavior of a granular material is still a matter of intense debates in the physics community.

In previous studies (Lumay et al., 2012; Traina et al., 2013), we have shown how classical powder characterization techniques (angle of repose, tapped density and rotating drum) can be updated to meet the present requirements of R&D laboratory and production department. In particular, we have shown that the automatization of the measurements and the development of rigorous initialization methods is necessary to obtain reproducible and interpretable results. Moreover, the use of image analysis techniques is a

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considerable added value for flowability measurement techniques. Indeed, the quality and the quantity of informations extracted from the measurement are improved. In addition, the inspection of the resulting images by the operator provides additional informations.

In this paper, we show how three recently improved flowability measurement methods can be used practically to characterize the physical behavior of lactose powders. Moreover, the correlations between the flowability indexes obtained with the different methods are discussed. Finally, the results are correlated with the grain size distributions and grain shapes.

2. Materials and methods

2.1. Materials

The lactose powders analyzed in the present study are produced by the company Meggle and are widely used in pharmaceutical industries. The powders are separated in four groups corresponding to different production methods and different areas of application: Tablettose for tabletting processes, Granulac for granulation processes, Inhalac for dry powder inhaler applications and Flowlac for direct compression processes. The information provided by Meggle are summarized in Table 1. All the sample are α-lactose monohydrate powders. The Tablettose powders are obtained from agglomeration. Granulac powders come from milling process. Inhalac powders are sieved and milled lactose powders. Finally, Flowlac powders are obtained from spray-dried lactose suspensions. Flowlac powders are optimized to have a high flowability and compressibility.

2.2. Methods

To evaluate the rheological properties of the powder samples, three recently developed experimental set-ups were used (Lumay et al., 2012): (i) GranuHeap to measure static properties (angle of repose α_r and static cohesive index σ_r), (ii) GranuDrum to measure the flowing properties (flowing angle α_f, dynamic cohesive index σ_f, first avalanche angle α_a and powder aeration ($\%_{ae}$) during a flow) and (iii) GranuPaq to measure quasi-static properties (Hausner ratio Hr, bulk density $\rho(0)$, tapped density $\rho(500)$ and densification characteristic time $n_{1/2}$). Table 2 summarizes the quantities measured with GranuHeap, GranuDrum and GranuPaq instruments.

In order to check the robustness of the measurement methods, the measurements have been repeated three times with three selected samples. These samples have been selected after a first measurement with GranuDrum instrument and correspond to (i) the lactose powder with the higher cohesive index, (ii) the lactose powder with the lower cohesive index and (iii) the powder with an intermediate cohesive index.

Table 1
Technical data provided by the producer Meggle about the powders: bulk density ρ_B, tapped density ρ_{tap}, Hausner ratio Hr and mean grain size $d(0.5)$ expressed in μm.

Powder	Code	ρ_B	ρ_{tap}	Hr	$d(0.5)$
Tablettose 70	T70	0.53	0.64	1.21	NC
Tablettose 80	T80	0.62	0.77	1.24	NC
Tablettose 100	T100	0.58	0.72	1.24	NC
Granulac 70	G70	0.71	0.91	1.28	NC
Granulac 140	G140	0.63	0.89	1.41	NC
Inhalac 70	I70	0.63	0.72	1.14	215
Inhalac 120	I120	0.73	0.83	1.14	132.5
Inhalac 230	I230	0.71	0.85	1.20	90
Flowlac 90	F90	0.56	0.67	1.20	NC
Flowlac 100	F100	0.59	0.71	1.20	NC

Table 2
Definition of the quantities measured with GranuHeap, GranuDrum and GranuPaq instruments.

Quantity	Definition	Instrument
α_r	Repose angle	GranuHeap
σ_r	Static cohesive index	GranuHeap
α_f	Flowing angle	GranuDrum
σ_f	Dynamic cohesive index	GranuDrum
α_a	First avalanche angle	GranuDrum
$\%_{ae}$	Powder aeration during a flow	GranuDrum
$\rho(0)$	Initial density	GranuPaq
$\rho(500)$	Density after 500 taps	GranuPaq
$n_{1/2}$	Characteristic tap number	GranuPaq
Hr	Hausner ratio	GranuPaq
$\rho(\infty)$	Extrapolated optimal density	GranuPaq

During the measurements, the relative humidity in the lab was ranging from 30%RH to 40%RH and the temperature was fixed to 20 °C. Any preconditioning process was applied to the powder samples before the measurements.

2.2.1. Heap shape

When a powder is poured onto a surface, a heap is formed. It is well known that both the repose angle α_r and the heap shape strongly depend on grain properties. In particular, the heap shape depends on the powder cohesiveness (de Ryck et al., 2005, 2010). A cohesive powder forms an irregular heap (see Fig. 1c) while a non-cohesive powder forms a regular conical heap (see Fig. 1a). Therefore, a precise measurement of the heap shape provides useful information about the physical properties of the powder sample. Unfortunately, the final heap shape is highly sensitive to its formation method, in particular with cohesive powders. Therefore, an automated initialization protocol and a precise measurement method have to be defined.

GranuHeap instrument (Lumay et al., 2012) is an automated heap shape measurement method based on image processing and analysis. A powder heap is created on a cylindrical support. In order to obtain reproducible results, an initialization tube with an internal diameter equal to the circular support is installed on the support. After filling the initialization tube by hand with a fixed volume of powder (100 ml for the present study), the tube goes up at the constant speed of 5 mm/s. Thereby, the powder is flowing from the tube to form a heap on the cylindrical support. A controlled rotation of the support allows obtaining different heap projections corresponding to different heap orientations. In the present study,

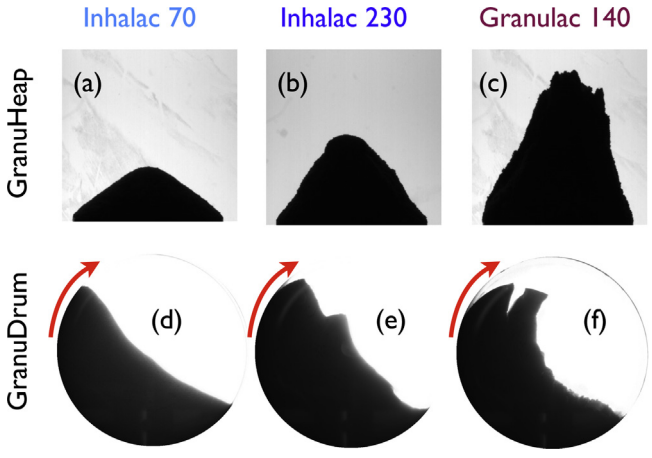

Fig. 1. Pictures of the heaps (a–c) and of flow inside the rotating drum (d–f) obtained with three lactose powders. The Inhalac 70 (a,d) is a non-cohesive powder while the Granulac 140 (c,e) is a cohesive powder. The cohesiveness of the Inhalac 230 (b,e) powder is intermediate.