FLOWING PROPERTIES OF SPRAY-DRIED POWDERS BEFORE AND AFTER GRANULATION

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ABSTRACT

We study the flowing properties, the density and the packing dynamics of spray-dried powders produced with different nozzels and different airflow rates. At the exception of one powder, the obtained grains are small and have a low flowability due to cohesiveness. Therefore, an extra-streaming process is necessary before tableting. The spray-dried grains have been granulated with both High shear granulation (HSG) process and Fluid bed top spray granulation (FBG) process. The obtained granules have a lower cohesiveness than the spray-dried powder. We show how the association of three recently developed flow measurement techniques (improved angle of repose measurement with GranuHeap instrument, cohesiveness measurement with GranuDrum instrument and improved tapped density measurement with GranuPack instrument) can be used to draw conclusion about the process-ability in a tableting process. Finally, we show how these results are correlated with grain sizes/shape distributions.

KEYWORDS

Granulation, Spray-drying, Flowing properties, GranuHeap, GranuDrum, GranuPack

1. INTRODUCTION

Granular materials, fine powders and nanostructured powders are widely used in pharmaceutical industrial applications [1-4]. Roughly 80% of the pharmaceutical products in US are tablets and capsules involving powders and granular materials [1]. A robust manufacturing process involving powder requires reliable powder flow properties. Unfortunately, pharmaceutical powders are usually cohesive and a deep understanding of the forces acting between the grains is necessary. Moreover, post-processing methods are commonly used to reduce the cohesiveness [5,6].

Powder behaviour is influenced by (i) steric repulsions, (ii) friction forces (iii) cohesive forces and (iv) interaction with the surrounding gas [7,8]. The steric repulsion is related to the grain geometry. Friction forces are influenced by both surface state (rough or smooth surface) and chemical nature of the grains. Cohesive forces may be induced by the presence of liquid bridges [9,10], by electrostatic charges [11-14], by van der Waals interactions [15] or more rarely by magnetic dipole-dipole interactions[16]. The predominance of one of these forces depends on both the environmental conditions and the physico-chemical properties of the grains.

In the present paper, we show how spray-dried powders can be characterized before and after granulation with recently developed measurement devices to predict the process-ability (for example tableting). According to the spray-drying method, in particular according to the nozzle characteristics, the obtained powder is processable or not. Afterward, we discuss how the granulation step modifies powder flowing behaviour. In particular, we focus on two granulation methods: High shear granulation (HSG) process and Fluid bed top spray granulation (FBG) process.

2. EXPERIMENTAL METHOD

Spray-drying

Amorphous solid dispersion (ASD) was obtained by spray-drying a 10% (w/w) Ethanol solution containing 20% indomethacin (modeldrug) and 80% PVP-K30. Spray-drying was performed by the ProCepT spray-drier, using two different nozzles: bi-fluid and ultrasonic nozzle in order to obtain different particle sizes.

Granulation

Wet granulation was performed with fluid bed top spray granulation (FBG) and with high shear granulation (HSG, MiPro) both from ProCept. In order to obtain a good granulation process 50% MCC was added to the spray-dried powder. As granulation liquid 5% (w/w) PVP-K30 in EtOH was used. In the fluid bed the temperature was kept low (Product temperature 30 °C) to avoid an additional negative effect on the ASD. HSG was more efficient compared to FBG as only 0.5% of PVP-K30 was needed to obtain a strong granule where by FBG 3.8% PVPK30 was needed to obtain a granule with similar characteristics. In order to obtain a product with a similar EtOH content, the granules obtained by FBG were additionally dried for 1 hour in the fluid bed.

As the amount of granulation liquid needed is lower during HSG, HSG should be the preferred wet granulation technology to granulate ASDs. However, in all cases the ASD was maintained with a Tg of 110 °C. So the addition of the EtOH (and increased temperature) had no influence on the ASD.

GranuHeap

GranuHeap instrument is an automated repose angle measurement technique based on image processing [6]. A powder heap is created on a cylindrical support to be analyzed by image processing. 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 in the case of the present study), the initialization tube moves up at a constant speed of 5 mm/s. Thereby, the powder is flowing from the tube to form a heap on the cylindrical support, which is then evaluated by image analysis. A controlled rotation of the support allows obtaining different heap projections. In the present study, 16 images separated by a rotation of 11.25° were recorded. A custom image recognition algorithm determines the position of the powder/air interface. The repose angle refers to the angle of the isosceles triangle with the same projected surface as the powder heap. The isosceles triangle corresponds to the ideal heap shape. The lower the repose angle is, the better the powder flowability is. The deviation between the real heap shape and the triangular heap gives the static cohesive index (not considered in the present paper).

GranuDrum

GranuDrum instrument is an automated powder flowability measurement technique based on the rotating drum principle [6,7]. A horizontal cylinder with vertical glass sidewalls called drum is half filled with the sample of powder. For the present study, the drum rotates around its axis at an angular velocity from 2 RPM to 10 RPM. A CCD camera takes snapshots (50 images separated by 0.5s) at each angular velocity. The air/powder interface is detected on each snapshot with an edge detection algorithm. Afterward, the average interface position and the fluctuations around this average position are computed. Then, for each rotating speed, the flow angle is computed from the average interface position and the dynamic cohesive index is measured from the interface fluctuations. Indeed, interface fluctuations are induced by the cohesive forces between the grains. Typically, a low value of the flow angle corresponds to a good flowability. The dynamic cohesive index is close to zero for non-cohesive powders and increases when the cohesive forces intensify. In addition, this method gives the opportunity to study complex rheological properties of powders (shear thinning, shear thickening and thixotropic behavior) by varying the rotating speed.

GranuPack

GranuPack instrument is an automated and improved tapped density measurement technique [6]. The behavior of the powder submitted to successive taps is analyzed with an automated device. The Hausner ratio Hr (or the Carr index), the initial density ρ_0 and the final density ρ_{500} are measured precisely. Moreover, dynamical information and an extrapolation of the maximum density ρ_∞ can be extracted from compaction curves (not shown in the present study). The compaction curve is a plot of the bulk density as a function of the tap number. At the beginning of the measurement, the powder is placed in a metallic tube with a rigorous initialization process. Afterwards, a light hollow cylinder is placed on the top of the pile to keep it flat during compaction. A single tap consists in moving up the tube containing the powder sample to a height of ΔZ = 1mm and then performing a free fall. The free fall height ΔZ can be adjusted. The height h of the powder bed is measured automatically after each tap. From the height h, the volume V of the bed is computed. As the powder mass m is known, the bulk density ρ is evaluated automatically and plotted after each tap. The bulk density is the ratio between the mass m and the volume V of the powder. The measurements have been performed with 35ml of powder subjected to 500 taps.

Size distribution

The particle size distribution of the spray-dried powders was obtained by dry powder laser diffraction. Powders were dispersed with compressed air at 1.5 bar through a RODOS dry disperser before sizing with a HELOS laser diffraction sensor (measurement range R1: 0.18 – 35 µm and R3: 0.5 – 175 µm) (all from Sympatec, Etten-Leur, The Netherlands). The particle size distribution of the granules was evaluated by dynamic image analysis with QicPic granulo-morphometer from Sympatec. The granules were gravimetric dosed via the GRADIS disperser.

3. MATERIALS

Four powders with different granulometries were created by spray-drying. The powders and the associated production process are listed in Table 1. For all powders, a complete amorphous system was created. The powder P1 was spray-dried with a small cyclone, 0.2mm nozzle and an air flow rate of 5.5 L/min at 2.75 bar. The powder P2 was spray-dried with a large cyclone, 0.6 mm nozzle and an air flow rate of 8 L/min at 0.41 bar. The powder P3 was spray-dried with large cyclone, 0.6 mm nozzle and an air flow rate of 4.1 L/min at 0.41 bar. Finally, the powder P4 was spray-dried with an ultrasonic nozzel at a frequency of 25 kHz at 35%.

Table 1. Listing of powders and granules considered in the present study with the corresponding production process.

Name	Short name	Process	Information
Powder1	P1	Spray-drying	Bi-Fluid nozzle
Powder2	P2	Spray-drying	Bi-Fluid nozzle
Powder3	P3	Spray-drying	Bi-Fluid nozzle
Powder4	P4	Spray-drying	Ultrasonic nozzle (25KHz)
Granules1	G1	High shear granulation (HSG)	with Powder2
Granules2	G2	High shear granulation (HSG)	with Powder4
Granules3	G3	Fluid bed top spray granulation (FBG)	with Powder4

The granules were created starting from powders P2 and P4. The reasons of this selection will be discussed hereafter. Granules G1 were produced with HSG starting from powder P2. Granules G2 and G3 were produced starting from powder P4 with respectively HSG and FBG.

A tableting study has shown that the powder P4 can be used as it for tableting. This point will be discussed hereafter.

4. RESULTS AND DISCUSSION

Particle sizes

The main parameters extracted from grain size distributions are summarized in Table 2. Both powders and granules are covering a wide range of grain sizes. Compared to the spray-dried powder the particle size increased for all granules combined with a decrease of the Span, indicating a more narrow particle size distribution. The powder P4 which is directly processable for tabletting has the highest grain size among the spray-dried powders. The granules obtained by HSG (G2) or FBG (G3) of powder P4 resulted in a similar particle size distribution.

Table 2. Listing of powders and granules considered in the present study with the corresponding production process.

	D10 (um)	D50 (um)	D90 (um)	Span
P1	0,63	3,33	8,11	2,25
P2	1,87	9,25	24,73	2,47
P3	3,81	18,48	46,08	2,29
P4	16,09	48,05	116,20	2,08
G1	41,73	97,99	209,32	1,71
G2	87,12	252,79	475,29	1,54
G3	154,63	291,39	516,46	1,24

Repose angle

Figure 1 shows typical pictures obtained with GranuHeap. One can see that the different powders have qualitatively very different behaviours and that the flowability of granules is better. The quantitative results obtained with GranuHeap are shown in Figure 2. Globally, the repose angle decreases when the grain diameter increases. The powder P1 is found to be an exception to this general rule because this fine powder has the tendency to form agglomerates. The repose angle decreases significantly after granulations, showing the better flowability of granules. Among the spray dried powders, powder P4, which is directly processable in tabbletting, has the lower repose angle.

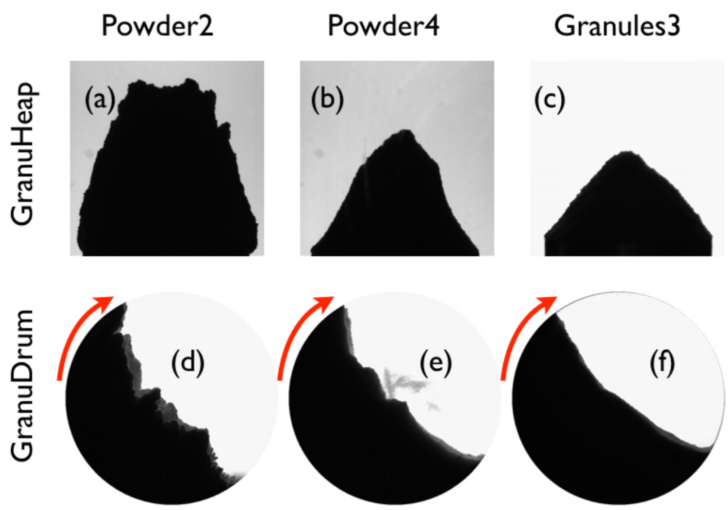

Figure 1. Typical pictures of heaps and of the flow inside the rotating drum with two powders (P2 and P4) and with granules G3.

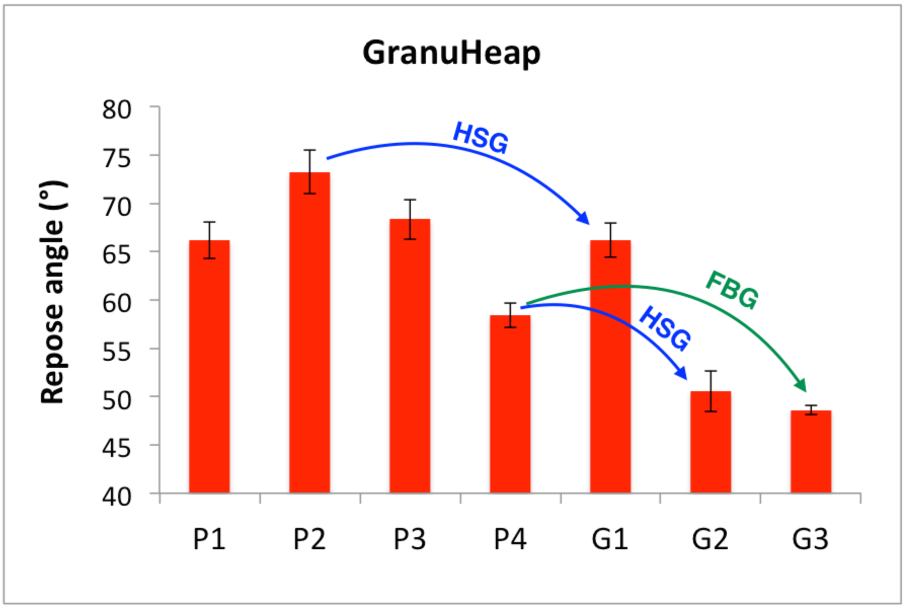

Figure 2. Repose angle measured with GranuHeap. The measurement has been repeated three times to perform an average and the error bars correspond to the standard deviation.

One should note that the error bars corresponding to the standard deviation over three repose angle measurements are relativelly small compared to the differences between the samples. This good reproducibility is obtained thanks to both the measurement automatization and the use of a camera in GranuHeap instrument.

Based on the repose angle results obtained with the powders, the choice was made to granulate two of them having respectivelly bad and good flowing behavior. That's the reason why we choose to granulate powder P2 and powder P4 by both high shear granulation (HSG) and fluid bed granulation (FBG). However P2 seemed to be too fine to be granulated in the fluid bed.

Dynamic cohesive index

The angle of repose gives a static and straightforward picture of the powder flowing properties. If rheological information is needed, flow measurements at different shear rate or different speeds are needed. The cohesiveness has been measured with GranuDrum at different speeds for the powders (see Figure 3) and for the granules (see Figure 4). Globally, Powder P2 has the higher cohesiveness and powder P4 has the lowest cohesiveness. However, the cohesiveness of powder P2 decreases with the rotating speed, showing a shear thinning behaviour generally due to aeration. This kind of behaviour could be interesting for some processes and could also cause complications (dosage fluctuation for example) due to unexpected variations of the flowing properties. Typically, a low and constant cohesiveness is recommended. The granules G1 obtained from granulation of powder P2 show a constant cohesiveness slightly lower than the cohesiveness of the powder. The decrease of cohesiveness is more important for granules G2 and G3 obtained by granulation of powder P4.

The dynamic cohesive index measurements also show that powder P4 has the lowest cohesiveness compared to the other spray-dried powders.

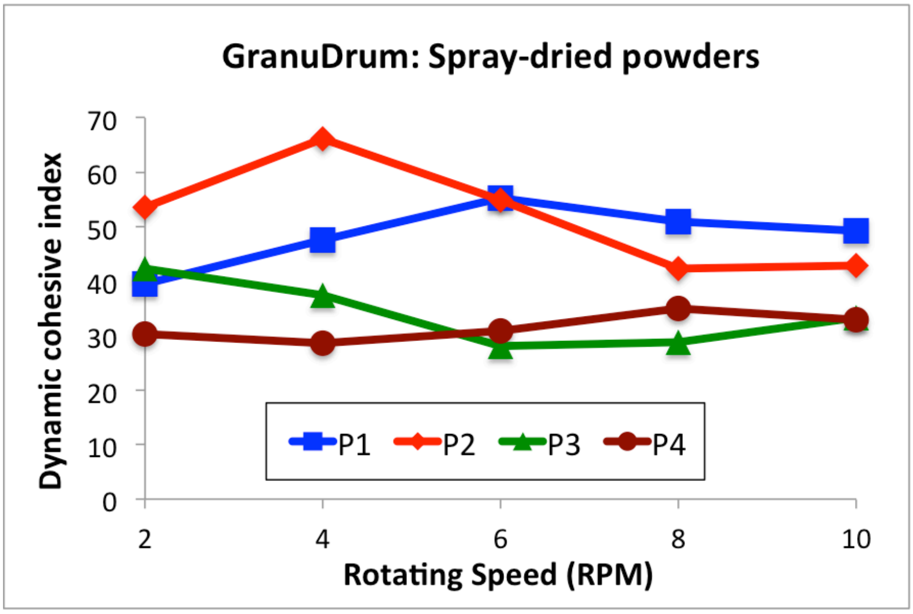

Figure 3. Dynamic cohesive index of the powders measured from the fluctuations of the flow in GranuDrum.

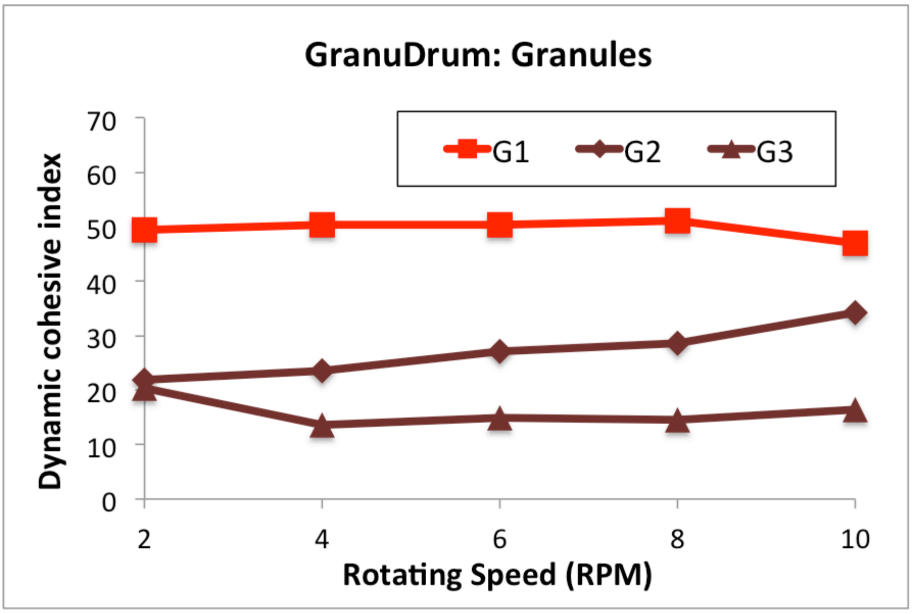

Figure 4. Dynamic cohesive index of the granules measured from the fluctuations of the flow in GranuDrum.

Density

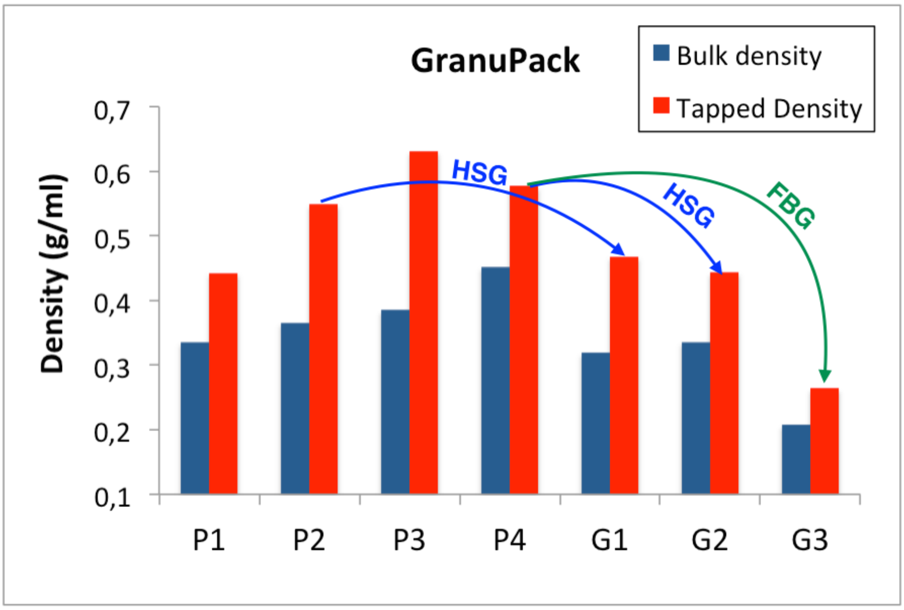

Figure 6. Bulk and tapped densities obtained with the automatic measurement instrument GranuPack.

The bulk and tapped densities of the granules are lower than the density of the powders (see Figure 6). Typically, the density decreases with the cohesiveness. In the present case, the decrease of the density after granulation is attributed to the modification of the size distribution width (Span). It is well known that a granular material having a larger Span (as the spray-dried powder) has a higher density because the small grains fill the gaps between the big grains. The GranuPack results are the result of the competition between cohesive forces and geometric (grain size/shape) effect.

5. CONCLUSION

Depending on the spray-drying process (nozzels and airflow rates), different grain sizes are produced leading to different flowing and packing behaviours. The powder P4 obtained with the ultrasonic nozzle shows good flowing indexes (low angle of repose, low cohesiveness and relatively high density) and can be used directly in tableting processes. The other powders have a lower average grain sizes and consequently worst flowing properties. Therefore, an extra-streaming process is necessary before tableting.

A selection of two spray-dried powders (best and worst flowing properties) have been granulated with both High shear granulation (HSG) process and Fluid bed top spray granulation (FBG) process. Globally, the granulation improves the powder flow properties. The effect is particularly well evidenced by the angle of repose measured with the automatized GranuHeap instrument. Moreover, the rotating drum measurements (GranuDrum) shows that the flow properties of the granules are more stable while the powders have more complex rheological behaviour. Finally, the GranuPack instrument shows significant differences of bulk and tapped densities before and after granulation. These differences are the result of interplay between the effect of the cohesive forces and of the grain size distribution width.

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