

ORIGINAL ARTICLE

Fractal aspects of the flow and shear behaviour of free-flowable particle size fractions of pharmaceutical directly compressible excipient sorbitol

Fraktální aspekty sypného a smykového chování volně sypných velikostních frakcí přímo lisovatelné farmaceutické pomocné látky sorbitolu

Hana Hurychová • Václava Lebedová • Zdenka Šklubalová • Pavlína Džámová • Tomáš Svěrák • Jan Stoniš

Received November 29, 2016 / Accepted December 1, 2016

Summary

Flowability of powder excipients is directly influenced by their size and shape although the granulometric influence of the flow and shear behaviour of particulate matter is not studied frequently. In this work, the influence of particle size on the mass flow rate through the orifice of a conical hopper, and the cohesion and flow function was studied for four free-flowable size fractions of sorbitol for direct compression in the range of 0.080–0.400 mm. The particles were granulometrically characterized using an optical microscopy; a boundary fractal dimension of 1.066 was estimated for regular sorbitol particles. In the particle size range studied, a non-linear relationship between the mean particle size and the mass flow rate Q_{10} (g/s) was detected having a maximum at the 0.245 mm fraction. The best flow properties of this fraction were verified with a Jenike shear tester due to the highest value of flow function and the lowest value of the cohesion. The results of this work show the importance of the right choice of the excipient particle size to achieve the best flow behaviour of particulate material.

Key words: flowability • size fraction • sorbitol for direct compaction • Jenike shear tester • fractal dimension

Souhrn

Sypnost práškových pomocných látek je přímo ovlivněna jejich velikostí a tvarem, ačkoliv granulometrické ovlivnění tokového a smykového chování partikulárních materiálů není studováno příliš často. V práci byl sledován vliv velikosti částic čtyř velikostních frakcí sorbitolu pro přímé lisování v rozmezí 0,080–0,400 mm na rychlost sypání otvorem kónické násypky a na kohezi a tokovou funkci. Částice byly granulometricky charakterizovány pomocí optické mikroskopie; pro pravidelné částice sorbitolu byla určena lineární fraktální dimenze 1,066. Ve studovaném rozmezí velikosti částic byla detekována nelineární závislost mezi střední velikostí částic a hmotnostní rychlostí sypání Q_{10} (g/s) s maximem pro frakci 0,245 mm. Pomocí Jenikeho smykové cely byly výborné tokové vlastnosti této frakce ověřeny díky nejvyšší hodnotě tokové funkce a nejnižší kohezi. Výsledky potvrzují důležitost správného výběru velikosti částic pomocné látky k dosažení nejlepších tokových vlastností materiálu.

Klíčová slova: sypnost • velikostní frakce • sorbitol pro přímé lisování • smykový přístroj Jenike • fraktální dimenze

Introduction

In the production of pharmaceutical solid dosage forms, the ability of particulate matter to flow directly influences the manufacturing processes, such as filling and discharging of hoppers, mixing and homogenization, as well as the die filling of the tablet presses. Flow behaviour of powder is directly related to its properties out of them the size and shape of individual particles, the attractive inter-particulate forces and the adhesive forces to the equipment wall are dominant¹.

In order to test flowability, many methods have been developed. Generally, it is accepted that it is difficult to

H. Hurychová • V. Lebedová • doc. PharmDr. Zdenka Šklubalová, Ph.D. (✉) • P. Džámová • J. Stoniš
Charles University, Faculty of Pharmacy, Department of Pharmaceutical Technology
Akademika Heyrovského 1203/8, 500 05 Hradec Králové, Czech Republic
e-mail: zdenka.skclubalova@faf.cuni.cz

T. Svěrák
University of Technology, Faculty of Chemistry, Institute of Materials Science, Brno, Czech Republic

compare the results directly; it is necessary to collect the conclusions of more methods in order to describe the material properties completely²⁾. The traditional simple methods for routine testing include the measurement of angle of repose, the evaluation of bulk and tapped density, and the calculation of Hausner ratio (*HR*) and/or the compressibility index (Ph. Eur. 9.0, 2.9.36). However, the estimation of the flow rate through an orifice of a hopper, using either the mass flow rate (g/s) or the volume one (ml/s), presents a better illustration of the flow behaviour. The method is recommended for a free-flowable material with a regular flow pattern. The use of a flat-bottomed cylindrical hopper having a changeable orifice is recommended although the automatic testers obviously use the conical one; the most suitable orifice diameter is estimated experimentally^{3, 4)}. Generally, the power law with the exponent of 5/2 fits the relationship between the orifice diameter and the flow rate for monodisperse powders well⁵⁾. The equation seems satisfactory for material with a particle diameter greater than approximately 0.50 mm. This limit recently seems to be overcome as many of new pharmaceutical materials, particularly those for direct compression, remain free-flowable although their particles are much smaller⁶⁾.

However, the use of shear tester measurement represents the most precise estimation of the flowability of free-flowing and/or cohesive powders. The translational Jenike shear tester is standard equipment (ASTM D6128-16) in which the tangential shear strain τ (Pa) needed to move a layer of the consolidated material under the influence of a normal shear stress σ (Pa) is measured. From the σ - τ relationship (*yield locus*, *YL*) under various normal loads, a variety of parameters can be detected such as the angle of internal friction, the cohesion, the flow function, etc. Except for the Jenike shear tester, the annular one⁷⁾ and the powder rheometer⁸⁾ could be also utilized.

As mentioned above, the main factors influencing the flow behaviour of particulate material include their size, a shape and a surface topography. All are dominant for the arrangement of a particle in a powder bed as well as for mutual interactions and cohesive forces between them. Generally, it is difficult to simply describe the particle properties for an irregular 3D shape. Most methods simplify the 3D image of the particle into a 2D diameter (e.g. microscopy) or approximate it to a sphere which is e.g. usual for laser diffraction^{9, 10)}. In addition to these methods, fractal geometry represents a complex research method for the ragged surface objects. A particle geometry can be determined using a fractal dimension, *FD*, which is derived from the slope of the Richardson plot related the logarithms of the step length to the logarithms of the boundary perimeter¹¹⁾. In order to obtain the particle perimeter, highly sophisticated computer systems employ the principle of structured walking, box-counting and others as reviewed by Allen et al.¹²⁾. In a view of the complexity of the object morphology, i.e. ruggedness (roughness, lacunarity) of the outline structure, linear *FD* numerically ranges within 1 to 2 for simple crystals and agglomerates^{13, 14)} while the values of *FD* 2 to 3 are referred to for 3D structures¹⁵⁾. In

pharmaceutical technology, fractals are mostly used to describe the dissolution kinetic¹³⁾ but have also been used successfully in the study of flow and consolidation behaviour of particle materials^{16, 17)}.

In this experimental work, the influence of the mean particle diameter of four particle size fractions of a model free-flowable excipient, sorbitol for direct compaction, in a range of 0.080 – 0.400 mm on the flow and shear behaviour was studied. The particles were characterized using granulometric descriptors including fractal dimension obtained by optical microscopy.

Experimental part

Materials

Sorbitol for direct compaction (Merisorb® 200 Pharma, Tereos Syral SAS Nesle, France) was used as a free-flowable model excipient. The particle size was estimated using a Malvern Mastersizer 2000 (Malvern Instruments Ltd, UK) using the Mie theory of light scattering. The measurements were carried out in dry mode (air dispersion). The median particle diameter $x_{50} = 0.250$ mm was noted for bulk sorbitol.

The particle morphology was investigated using scanning electron microscopy with a FEG electron gun (FIB-SEM TESCAN LYRA3GMU) at an acceleration voltage of 5 kV. The samples were placed on a carbon conductive tape in order to conduct the measurements and an approx. 10 nm thick gold layer was subsequently sputtered onto the sample surface. Figure 1 illustrates the shape of particles.

Size fractions 0.080–0.125, 0.125–0.200, 0.200–0.300 and 0.300–0.400 mm were obtained using a Vibratory Sieve Shaker AS 200 basic (Retsch, Germany) with the use of the following sieves: 0.080; 0.125; 0.200; 0.300, and 0.400 mm. The mean particle size x (mm) was expressed as a geometrical mean of the used screens, i.e. 0.100, 0.158, 0.245, and 0.346 mm.

Methods

The flow and shear measurements were carried out at standard laboratory temperature in the range of 22 ± 1 °C and relative air humidity in the range of $32 \pm 2\%$ (Hygrometer 608-H1, Testo, China).

Optical microscopy

The granulometric characteristics and the linear fractal dimension, *FD*, were obtained using optical microscope BX 51 (Olympus, Japan) with a digital camera, and the automatic detection of particles and reading of results (computer SW analySIS auto 5.1). A small amount of powder sample was uniformly laid on a glass slide without agglomerates. No dispersing medium was used. Samples were observed at a magnification of 10 times (the pixel size 0.2164 μm); the specific digital camera (resolution of 4140×3096 pixel) and video (resolution 1360×1024 pixel) combination were used for the photographs of 100 particles ($n = 100$). In all cases, binary images were obtained from digitalized images using a relative grey-level threshold of 40%, pixel connectivity was 4. Table 1 lists the granulometric characteristics of the sorbitol size fractions.

Bulk and tapped density

The density of sorbitol size fractions was measured using a tapped density tester SVM 102 (Erweka, Germany) in accordance with the Ph. Eur. 9.0 (2. 9. 34). The 50.0 g of powder was carefully poured into the 100.0 ml graduated cylinder. The bulk density d_c (g/ml) was calculated from the known mass of the powder and its volume. After 1250 taps (250 ± 15 taps/min from a height of 3 ± 0.2 mm) the volume of powder was recorded and the tapped density d_t (g/ml) was estimated. In Table 2, the average of ten measurements are presented; data are completed with standard deviation (SD).

The Hausner ratio, *HR*, was calculated using equation [1] where V_0 is the bulk volume (ml) and V_{1250} is the tapped volume (ml) of the sample after 1250 taps.

$$HR = \frac{V_0}{V_{1250}} \quad [1]$$

Flow rate through an orifice

The flow rate of the sorbitol size fractions was measured in discrete samples using an Automated powder and granulate tester GTB (Erweka, Germany) in agreement with the Ph. Eur. 9.0 (2. 9. 36). A stainless steel conical hopper with a capacity of 200.0 ml having an internal angle wall inclination of 40° was used to measure the time it took to empty 100.0 g of material through the circular aperture with a diameter $D_0 = 10.0$ mm. The mass flow rate Q_{10} (g/s) was calculated; the average of ten measurements with the *SD* are presented in Table 2.

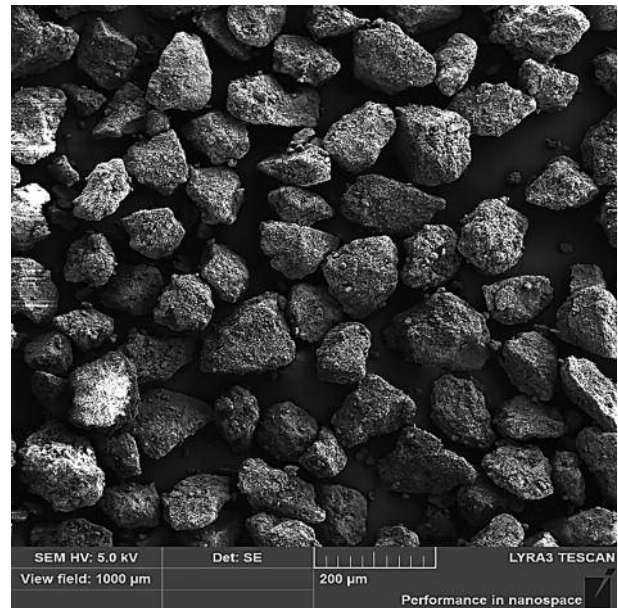


Figure 1. SEM picture of sorbitol particles

Shear testing

The shear properties of the sorbitol size fractions were measured using a translational Jenike shear cell having a diameter of 100.0 mm in accordance with the recommendations of ASTM D6128-16. A constant speed of 4 mm/min was used for the force-measuring pin. The material was uniformly filled into the shear cell with the gentle compression. Consolidation proceeded at

Table 1. The granulometric characteristics of sorbitol size fractions

Size fraction (mm)	x (mm)	ECD (µm)	F _{min} (µm)	F _{max} (µm)	P (µm)	SF	SPH	FD
0.080–0.125	0.100	118.73	105.26	147.27	439.83	0.72	0.56	1.069
0.125–0.200	0.158	173.48	154.44	213.23	646.51	0.71	0.57	1.068
0.200–0.300	0.245	268.86	243.91	324.56	968.36	0.76	0.63	1.061
0.300–0.400	0.346	368.29	335.65	442.18	1350.11	0.75	0.63	1.064

x – geometric mean of the used range of the sieves, ECD – equivalent circle diameter, F_{min} – Feret min, F_{max} – Feret max, P – perimeter, SF – shape factor, SPH – sphericity, FD – fractal dimension

Table 2. The bulk characteristics of sorbitol size fractions

x (mm)	d_c (g/ml)	d_t (g/ml)	HR	Q_{10} (g/s)
0.100	0.561 ± 0.003	0.647 ± 0.003	1.15	8.11 ± 0.154
0.158	0.602 ± 0.004	0.681 ± 0.006	1.13	11.71 ± 0.259
0.245	0.621 ± 0.005	0.707 ± 0.005	1.14	12.68 ± 0.155
0.346	0.642 ± 0.003	0.726 ± 0.005	1.13	12.33 ± 0.147

x – geometric mean of the used range of the sieves, d_c – bulk density, d_t – tapped density, HR – Hausner ratio, Q_{10} – mass flow rate (10 mm orifice)

Table 3. The flow and shear characteristics of sorbitol size fractions

x (mm)	d_{cons} (g/ml)	σ_1 (kPa)	σ_c (kPa)	τ_c (kPa)	ϕ_i (°)	ϕ_e (°)	ff
0.100	0.543	14.27	0.48	0.16	21.31	22.22	30
0.158	0.547	14.50	0.16	0.05	21.51	21.80	91
0.245	0.554	14.83	0.07	0.02	22.13	22.26	212
0.346	0.543	14.06	0.25	0.09	20.13	20.61	56

x – geometric mean of the used range of the sieves, d_{cons} – consolidated density, σ_1 – major principal stress, σ_c – unconfined yield strength, τ_c – cohesion, ϕ_i – angle of internal friction, ϕ_e – effective angle of friction, ff – flow function

a consolidating normal stress of 10.15 kPa and 20 twists. The sample was subjected to the same normal stress to shear (preshear point) and subsequently to the reduced stresses of 7.62 kPa – 5.21 kPa – 2.72 kPa, respectively, to obtain the corresponding shear points. The measurements were repeated three times, each time using a fresh powder sample. Using Mohr's circles analysis of the graphical plot of σ - τ relationship for the reduced normal load (GeoGebra SW), the shear characteristics were estimated. The average of three measurements (the values were similar) for each powder sample is summarized in Table 3. The consolidated density d_{cons} (g/ml) was calculated after the shear test from the weight of sample in the shear base and shear ring and their known volume (274.89 ml).

Results and discussion

Particulate materials represent a dominant form of substances in various industries, including the pharmaceutical one. The flow and compression behaviour of pharmaceutical powder active substances and excipients affect significantly their manipulation as well as the fluent manufacturing and the quality of final dosage forms. It is generally accepted that the flow properties depend on many factors. Of these, the particle size and shape have a primary effect^{1, 18)}. The main target of this work was the investigation of the influence of the mean particle diameter of the size fractions in a range of 0.080–0.400 mm on the flow and shear behaviour of the free-flowable pharmaceutical excipient for direct compaction, sorbitol.

Figure 1 illustrates the sorbitol particles. Using an optical microscopy with automated image analysis, particle shape was characterized with different descriptors as shown in Table 1. Shape factor which is the ratio of square perimeter and the particle area, and sphericity which is the ratio of the surface area of a sphere having the same volume to that of the measured particle are frequently used characteristics showing how spherical and regular the particle shape is¹²⁾. Generally, more spherical particles have less inter-particle friction and better flowability. In the last column of Table 1, the value of fractal dimension, FD , is listed. As the fractal dimensions of the shape boundaries are scale invariable they do not depend on the particle size (the principle of self-similarity). The average FD value of 1.066 is near to that detected by Zatloukal¹⁷⁾. The slight deviation results from a different method of FD estimation (structured walking over box counting) and different resolution of pictures as fractal dimension is strictly resolution-dependent¹⁹⁾.

In Table 2, Hausner ratio (HR) which relates the bulk density d_c (g/ml) to tapped density d_t (g/ml) both measured in a cylinder is shown. The values of 1.13–1.15 placed the tested sorbitol fractions to the good flowability group in agreement with a general scale for the flow behaviour. In the last column, the average mass flow rate Q_{10} (g/s) calculated from the time for the powder sample to pass through the aperture of the conical hopper having a diameter of 10 mm is summarized. For this orifice size, the best results were previously obtained⁴⁾. A non-linear

relationship between the mean particle size x (mm) and Q_{10} (g/s) was detected. Generally, the cohesive forces between particles decrease with an increase in particle size leading to better flow. In the tested particle size range of 0.080 – 0.400 mm, this was true up to particle size 0.245 mm. Then, Q_{10} (g/s) decreased.

To show the particle size effect in detail, a shear test was performed for the sorbitol size fractions using a translational Jenike shear tester. The method is considered the best fundamental and physical measurement of flow properties. From the yield loci of the shear stress vs. the reduced normal load, the characteristics: the major principal stress σ_1 , unconfined yield strength σ_c , cohesion τ_c , angle of internal friction ϕ_i , effective angle of friction ϕ_e , and flow function ff which is the ratio σ_1/σ_c were obtained using Mohr's circle analysis as listed in Table 3.

The low values of cohesion 0.02–0.16 kPa were noted showing that the frictional forces between the particles are very low. However, it could be seen that cohesion τ_c decreases in a range of 0.16–0.02 kPa up to particle size 0.245 mm and then slightly increases again for the 0.346 mm fraction (0.09 kPa). This reflects well the results of the mass flow rate measurement mentioned above.

Similarly to the general scale of flowability known for angle of repose and/or Hausner ratio (Ph. Eur. 9.0, 2.9.36), the flow function ff can be used for classification of flow behaviour. The smaller the ratio of the unconfined yield strength σ_c to the major principal stress σ_1 the better a bulk solid flows⁷⁾ as written below:

- 10 < ff free flowing
- 4 < ff < 10 easy flowing
- 2 < ff < 4 cohesive
- 1 < ff < 2 very cohesive
- ff < 1 not flowing

The value of the flow function increases for the fractions in order 0.100 mm < 0.158 mm < 0.245 mm reaching the maximum value of 212 for the latest mentioned, then drops again for the fraction 0.346 mm ($ff = 56$). The internal angle of friction represents the additional property of the bulk solids. The values of ϕ_i (Table 3) increased with the particle size up to 22.13° for 0.245 mm fraction. As ϕ_i is equal to the slope of the yield locus⁷⁾, higher values again verify the better flow properties.

Conclusions

In conclusion, the boundary fractal dimension, $FD = 1.066$, was detected for regular crystal particles of a free-flowable pharmaceutical excipient sorbitol for direct compression. While the empirical criterion Hausner ratio did not demonstrate the particle size effect significantly and all obtained values corresponded to good flowability, the flow rate through a hopper orifice was much better criterion. Although all fractions used were free-flowing, a non-linear relationship between the particle size and the mass flow rate Q_{10} (g/s) through the circular orifice with a diameter $D_o = 10.0$ mm was registered with the maximum for the mean particle size

$x = 0.245$ mm. However, only the results of Jenike shear measurement allowed the most precise description of sorbitol fractions flow behaviour. The significant increase in the flow function (212) has been registered for the sorbitol size fraction 0.245 mm again which was in good agreement with the lowest value of the cohesion (0.02 kPa) and the highest value of the angle of internal friction (22.13°). The granulometric influence of the flow rate of particulate matter is not studied very often although, empirically, the manufacturers often use the powder material with narrow particle size distribution. The results of this work show the significance of the choice of a suitable particle size fraction to achieve the best flow behaviour of pharmaceutical particulate material.

The authors thank to the grant No. 322315/2015 of Grant Agency of Charles University and the specific research project 260 291 of Charles University for the financial support.

Conflicts of interest: none.

References

1. **Wu Ch. Y.** Characterization of powder flowability for die filling. *Part. Sci. Tech.* 2012; 30, 378–389.
2. **Schwedes J.** Review on testers for measuring flow properties of bulk solids. *Granul. Matter.* 2003; 5, 1–43.
3. **Zatloukal Z., Šklubalová Z.** Effect of orifice geometry on particle discharge rate for a flat-bottomed, cylindrical hopper. *Part. Sci. Tech.* 2012; 30, 316–328.
4. **Šklubalová Z., Hurychová H.** The effect of the size of a conical hopper aperture on the parameters of the flow equation of sorbitol and its size fractions. *Čes. slov. Farm.* 2015; 64, 14–18.
5. **Beverloo W. A., Leniger H. A., Van de Velde, J.** The flow of granular solids through orifices. *Chem. Eng. Sci.* 1961; 15, 260–269.
6. **Bolhuis G. K., Armstrong N. A.** Excipients for direct compaction – an update. *Pharm. Dev. Tech.* 2006; 11, 111–124.
7. **Schulze, D.** Powders and bulk solids: Behavior, characterization, storage and flow. Berlin: Springer; pp. 517.
8. **Freeman N. R.** Measuring the flow properties of consolidated, conditioned and aerated powders – A compactive study using a powder rheometer and a rotational shear cell. *Powder Technol.* 2007; 174, 25–33.
9. **O'Connor R. E., Schwartz J. B., Felton L. A.** Powders. In: Allen L. V (ed.) Remington: The science and practice of pharmacy, 22nd ed. London: Pharmaceutical Press 2013.
10. **McGlinchey D.** Characterization of bulk solids, 1st ed. Oxford: Blackwell Publishing Ltd. 2005.
11. **Pons M. N., Vivier H., Belaroui K., Bernard-Michel B., Cordier F., Oulhana D., Dodds J. A.** Particle morphology: from visualisation to measurement. *Powder Technol.* 1999; 103, 44–57.
12. **Allen M., Brown G. J., Miles N. J.** Measurement of boundary fractal dimensions: review of current techniques. *Powder Technol.* 1995; 84, 1–14.
13. **Pippa N., Dokoumetzidis A., Demetzos C., Macheras P.** On the ubiquitous presence of fractals and fractal concepts in pharmaceutical sciences: a review. *Int. J. Pharm.* 2013; 456, 340–352.
14. **Bérubé D., Jébrak M.** High precision boundary fractal analysis for shape characterization. *J. Computers & Geosci.* 1999; 25, 1059–1071.
15. **Bandt C., Duy M. T., Mesing, M.** Three dimensional fractals. *Math. Intelligencer.* 2010; 32, 12–18.
16. **Mihryan A., Strømme M.** Fractal aspects of powder flow and densification. *Part. Part. Syst. Charact.* 2007; 24, 223–228.
17. **Zatloukal, Z.** Ovlivnění rychlosti sypání práškových pomocných látek fraktální dimenzí. *Čes. slov. Farm.* 2002; 51, 236–239.
18. **Juliano P., Barbosa-Cánovas G. V.** Food powders flowability characterization: Theory, methods, and applications. *Annu Rev. Food Sci. Technol.* 2010; 1, 211–239.
19. **Landini G.** Fractals in microscopy. *J. Microsc.* 2011; 241, 1–8.