12 Přílohy

Příloha 1

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 (1-2), s. 14-18, ISSN (online):1805-4439

Vliv průměru kruhového otvoru kónické nerezové násypky D_0 (cm) v rozmezí 0.6-1,5 cm na hmotnostní rychlost sypání Q (g/s) byl studován u sorbitolu pro přímé lisování (Merisorb 200, MS 200) a jeho velikostních frakcí v rozmezí 80-400 µm. Platnost některých matematických modelů je omezena hranicí 500 µm, příp. 200 µm, a proto byla nelineární závislost mezi Q a D_0 modelována pomocí mocninné rovnice autorů Jones&Pilpel (JP rovnice), která takovou limitaci neuvádí. Pro jednotlivé frakce byly z grafické závislosti mezi komplexní proměnnou $(Q/24,6 \cdot d_b)$ a D_0 určeny parametry JP rovnice (A a exponent n) a studována přesnost zpětného odhadu rychlosti sypání s cílem návrhu optimálního průměru otvoru s nejnižší procentní odchylkou mezi experimentálně zjištěnou a predikovanou hodnotou Q. Pro polydisperzní sorbitol a jeho čtyři velikostní frakce se odchylka pohybovala v rozmezí 2,5-12,6 %, s nejnižší průměrnou odchylkou 2,5 % pro otvor o průměru 1,0 cm. V použitém rozsahu průměru otvorů byl pro testování rychlosti sypání doporučen pro další experimenty otvor 1,0 cm.

ORIGINAL ARTICLE

The effect of the size of a conical hopper aperture on the parameters of the flow equation of sorbitol and its size fractions

Vliv velikosti otvoru kónické testovací násypky na parametry rovnice sypání sorbitolu a jeho velikostních frakcí

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Summary

Determination of the rate of gravitational flow through a hopper aperture is one of the most widely used methods for the evaluation of flowability properties of pharmaceutical materials. This work studies the influence of the diameter of a conical hopper aperture in the range of 0.6–1.5 cm on the mass flow rate *Q (g/s)* of the pharmaceutical excipient, sorbitol, for direct compression (*Merisorb 200, MS 200*) and its size fractions in the range of 0.080–0.400 mm in order to recommend the appropriate aperture size for testing. Non-linear dependence of the flow rate on the aperture diameter is modeled by the Jones-Pilpel power equation. Using the actual parameters of the power equation, the precision of the mass flow rate prediction was the basic criterion in optimization of the orifice diameter. It was detected experimentally that for the evaluation of the flow rate of *MS 200* and its size fractions in the range used a 1.0 cm aperture is recommended, which allows the most precise prediction of the flow rate.

Key words: particulate material • excipient, flow equation • conical hopper • size fraction

Souhrn

Stanovení rychlosti gravitačního sypání otvorem testovací násypky je jednou z nejpoužívanějších metod pro hodnocení sypných vlastností farmaceutických materiálů. V této práci je studován vliv průměru otvoru kónické násypky v rozmezí 0,6–1,5 cm na hmotnostní rychlost sypání *Q (g/s)* farmaceutické pomocné látky sorbitolu pro přímé lisování (*Merisorb 200, MS 200*) a jeho velikostních frakcí v rozmezí 0,080–0,400 mm s cílem doporučit pro testování vhodnou velikost otvoru. Nelineární závislost rychlosti sypání na průměru otvoru je modelována mocninnou rovnicí Jones-Pilpel. S využitím aktuálních parametrů mocninné rovnice byla základním kritériem optimalizace průměru otvoru přesnost zpětného odhadu rychlosti sypání. Na základě experimentu bylo zjištěno, že pro hodnocení rychlosti sypání *MS 200* a použitých velikostních frakcí lze doporučit otvor 1,0 cm, který umožňuje nejpřesnější odhad rychlosti sypání.

Klíčová slova: partikulární materiál • pomocná látka • rovnice sypání • kónická násypka • velikostní frakce

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Introduction

An important characteristic of pharmaceutical powders is flowability, which expresses the ability of powder substances to flow. The flow behavior is dependent not only on the material's characteristics such as particle size and shape, adhesiveness, moisture content, etc.[1–4], but also on the conditions in which the flow behavior is specified, e.g. external conditions and equipment used.

It is possible to observe different kinds of flow behavior of particulate matter during the flow. During the unloading of the hopper a variety of different flow problems can take place. Detailed information provided, e.g., by the authors Prescott & Barnum[5]. The conditions for each material, in which the flow experiences no significant problems, should be experimentally determined.

The correct description of the flowability properties is important not only for handling, storage and transportation of powder materials, but in pharmaceutics

it is very important for the processes of blending, homogenization and dosing of active substances and excipients in the manufacturing of dosage forms, such as tablets or gelatin capsules. If, during filling, the mixture of powder substances has inappropriate flowability properties, then tablets or divided powder in gelatin capsules fail to comply with the requirements of content or mass uniformity. In pharmaceutical technology, the inappropriateness of flow of powder materials is solved, e.g., by adding lubricating substances or increasing the size of particles by granulation process.

Flow behavior of powders depends on their physicochemical and mechanical properties, and its characterization is very difficult, because the individual test methods are not able to sufficiently and, above all, completely, describe the properties of powders. The results of the flowability evaluations carried out in different laboratories are therefore often significantly varied, which is mainly due to large quantities of wide-spread methodologies of measurement, different types of measuring instruments, and especially the lack of a standardized measuring procedure. In pharmaceutical technology, the flowability evaluation is performed using pharmacopoeial methods of powder assessment (Ph. Eur., 2.9.36.), such as angle of repose[6], expression of the compressibility index and the Hausner ratio and the rate of flow through the aperture. Other assessment methods are used in technical testing and evaluating flow such as shear and avalanching behavior of powder materials[4–5, 7–9].

The mass flow rate *Q (g/s)* through the hopper aperture is considered one of the best methods of flowability evaluation. This method is suitable for free-flowing materials. The condition is to achieve a uniform flow of material with minimal amount of failures. The literature also recommends optimum geometry of the test hopper to achieve this state. Normalized geometry takes into account the relationship between the diameter of the hopper D, the hopper aperture diameter D_0, the particle diameter x and the height of the hopper H.

It is recommended that: $D > 2.5D_0$, $D - D_0 > 30x$, $D_0 > 6x$, $H > D$, $H > D_0$ with a choice of different aperture diameter[10]. The optimal (uniform) flow rate is not set and the success of an accurate estimate of the flow rate for a variety of hoppers is limited[11]. Increasing the accuracy of the estimation of the flow rate is therefore a constant focus for a number of research teams.

As already mentioned, the flow rate is primarily influenced by the diameter of the hopper aperture, the particle diameter and bulk density. The relationship between these variables is described by the flow equation. One of the most frequently used ones is the Brown and Richards power equation [1] which describes the flow rate of monodisperse particulate materials through the hopper aperture[12],

$$\frac{Q}{\left(\frac{\pi}{4}\right) \cdot g^{1/2} \cdot d \cdot (D_0 - kx)^{5/2}} \qquad [1]$$

where Q is the mass flow rate (g/s), d is the true powder density (g/ml), g is the acceleration of gravity (cm/s^2), x is the particle diameter (cm) and D_0 is the diameter of the hopper circular aperture (cm), k (dimensionless) is the empirical shape coefficient and $\pi/4$ is quadrature of the circle (dimensionless). The expression (k . x) is interpreted as the *"empty annulus"* and describes the corrected influence of the hopper wall. Dependence of the flow rate on the diameter of the hopper is transformed by a constant exponent *5/2*. It was discovered that the shape coefficient is usually in the range of $1 \leq k \leq 2$[13].

The Beverloo et al equation [2][14], which is also frequently used, is derived from equation [1].

$$Q = C \cdot d_b \cdot g^{1/2} \cdot (D_0 - kx)^{5/2} \qquad [2]$$

The parameters of the equations are empirical discharge coefficient $C \sim \pi/4$ (dimensionless), and the previously mentioned shape coefficient whose value k = 1.4 is used as a constant. Instead of the true powder density, the equation introduces bulk density d_b, which describes the behavior of powders during flow and is more easily measurable. It is usually stated that the validity of equations [1] and [2] is limited to particles greater than 0.500 mm, respectively 0.200 mm[15].

In pharmaceutical technology, the Jones & Pilpel empirical equation [3] can also be used[16],

$$D_0 = A\left[\frac{4Q}{\pi \cdot d_b \cdot g^{1/2}}\right]^{1/n} \qquad [3]$$

where A and n (the reciprocal value of the exponent) are dimensionless parameters of the equation, d_b is the powder bulk density (g/ml) and g, D_0 and Q were as already mentioned above.

This work evaluates the effect of the diameter of the conical hopper aperture on the mass flow rate Q (g/s) of sorbitol for direct compression (*MS 200*) and its fractions in the range of 0.080–0.400 mm with the goal of recommending the appropriate diameter for the hopper aperture D_0 (cm) to achieve the highest precision of the reverse prediction of the flow rate.

Experimental part

Materials

Sorbitol for direct compression (*Merisorb 200, Tereos Syral SAS Nesle*), of pharmaceutical quality was used. Sample *MS 200* was characterized by a mean particle diameter x_{50} = 0.123 mm and x_{90} = 0.214 mm by the analytical sieving methods (Vibratory Sieve Shaker AS 200 basic, RETSCH, Germany) in accordance to European Pharmacopoeia (Ph. Eur., 2.9.38); the moisture content in the material of 0.79% ± 0.03% was determined (N = 3) gravimetrically (XM60, PRECISA, Switzerland).

The *MS 200* size fractions were obtained by sieving (Vibratory Sieve Shaker AS 200 basic, RETSCH, Germany) with the use of the following sieves: 0.080 mm, 0.125 mm, 0.200 mm, 0.300 mm, and 0.400 mm. In Table 1, the particle diameter x (mm) is referred to as geometric mean of the used range of the sieves.

Table 1. The effect of the size of a conical hopper aperture D_0 (cm) on the mass flow rate Q (g/s) of MS 200 and its fractions. The relative standard deviations (RSD) in % are provided in brackets

Size fraction (mm)	x (mm)	d_b (g/ml)	D_0 (cm)			
			0.6	0.8	1.0	1.5
0.080–0.125	0.100	0.588	1.81 (2.45)	4.56 (1.97)	6.58 (2.79)	18.43 (2.76)
0.125–0.200	0.158	0.611	2.29 (3.26)	5.83 (1.67)	9.18 (1.38)	25.53 (2.59)
0.200–0.300	0.245	0.619	2.46 (0.93)	6.55 (2.08)	10.25 (1.26)	29.41 (0.00)
0.300–0.400	0.346	0.639	2.36 (0.99)	6.66 (0.95)	10.27 (1.74)	31.25 (0.00)
	MS 200	0.631	2.32 (0.94)	5.97 (0.94)	9.60 (1.42)	25.13 (1.66)

Methods

All measurements were carried out at a temperature in the range of 21 °C ± 1°C and relative air humidity in the range of 29% ± 2%.

Bulk density

The bulk density of *MS 200* and its size fractions was determined by Scott's volumeter (COPLEY, SOTAX, UK) in accordance with the European Pharmacopoeia (Ph. Eur., 2.9.34). The powder was layered into a cylindrical stainless cup with volume of 25.00 ml ± 0.05 ml. The distance between the powder heap and the cylindrical stainless cup was 1.9 cm. The excess powder was carefully removed so as to avoid any compression, tapping or losses of powder from the cup. The bulk density d_b (g/ml) was calculated from a known volume of the cylindrical cup, and the weight of the powder. Table 1 lists the means for ten repetitions of measurements, the relative standard deviations (RSD) were less than 1%.

The flow rate Q (g/s) through the test hopper aperture

To measure the flow rate of *MS 200* and its size fractions the Automated Powder and Granulate Testing System was used (PTG S3, PHARMATEST, Germany). The mass flow rate Q (g/s) was determined by measuring the time it took to empty a 50.0 g of powder through a stainless steel conical test hopper with a capacity of 300.0 ml. For the measurements, the following sizes of the aperture diameter were used: 0.6 cm, 0.8 cm, 1.0 cm, and 1.5 cm. The selected aperture was fixed on the bottom part of the hopper. After unblocking the aperture, the pass-through time was measured automatically with an accuracy rating of 0.1 s. The uniform mass flow rate was detected by graphical registration. The flow rate of *MS 200* and its fractions was then calculated from the discovered pass-through time. Table 1 lists the means for ten repetitions of measurements, the relative standard deviations (RSD) in % are provided in brackets.

Mathematical model

The results have been modeled using the equation [3]. The accuracy of the reverse prediction of the flow rate Q_p (g/s) was expressed as the percentage deviation Δ (%) between the experimentally noted flow rate and that calculated by the generated flow equation.

Results and discussion

Particulate materials are the most common materials used in the manufacturing of dosage forms. The exact description of their flow behavior is essential to ensure the continuity of the production process and the quality of the final products. An appropriate method of evaluation is measuring the flow rate Q through the test hopper aperture. Achieving uniform flow without faults is a main requirement. In order to achieve this, the appropriate diameter of the hopper aperture D_0 should be determined experimentally.

Table 1 summarizes the overview of properties of sorbitol for direct compression (*MS 200*). The size fractions are characterized by the particle diameter x (mm), the bulk density d_b (g/ml) and the mass flow rate Q (g/s) depending on the diameter of the circular aperture of the conical test hopper D_0 (cm). Geometrical requirements for the test hopper and the progress of measurement have been in compliance with the recommendation[10–11]. The uniformity of flow was monitored by using a graphical record of the quantity of poured material in time. No malfunctions were observed during the flow for the tested size fractions, not even for the smallest fraction with a mean diameter of 0.100 mm.

With increasing the size of the aperture, the flow rate increases non-linearly. This dependency can be mathematically described by a power equation, which is usually referred to as the flow equation. The experimentally determined flow rates Q (g/s) of *Merisorb 200* and its size fractions (Table 1) were modeled using the Jones-Pilpel power equation [3][16].

Calculation of the parameters of the equation A and n is possible due to the graphical dependencies between $(Q/\sqrt{g.\pi/4.d_b})$ and the size of the aperture D_0 (cm). The parameters of the flow equation [3] A and n are given in Table 2. The results are supplemented by the correlation

Table 2. The parameters of the Jones-Pilpel flow equation for MS 200 and its size fractions

x (mm)	d_b (g/ml)	A	n	r
0.100	0.588	1.3443	2.4944	0.9950
0.158	0.611	1.2042	2.6015	0.9966
0.245	0.619	1.1529	2.6745	0.9959
0.346	0.639	1.1527	2.7832	0.9950
MS 200	0.631	1.2148	2.5760	0.9957

Table 3. The effect of the diameter of an aperture D_0 (cm) on the accuracy of the prediction of the flow rate Q_p (g/s)

D_0 (cm)	x (mm)	Q (g/s)	Q_p (g/s)	Δ (%)	Average Δ (%)
0.6	0.100	1.81	1.93	6.65	7.7
	0.158	2.29	2.45	7.06	
	0.245	2.46	2.65	7.82	
	0.346	2.36	2.55	8.43	
	MS 200	2.32	2.52	8.62	
0.8	0.100	4.56	3.96	–13.25	12.6
	0.158	5.83	5.18	–11.12	
	0.245	6.55	5.73	–12.59	
	0.346	6.66	5.69	–14.56	
	MS 200	5.97	5.29	–11.43	
1.0	0.100	6.58	6.91	4.92	2.5
	0.158	9.18	9.26	0.86	
	0.245	10.25	10.40	1.45	
	0.346	10.27	10.59	3.08	
	MS 200	9.60	9.39	–2.14	
1.5	0.100	18.43	18.99	3.05	4.6
	0.158	25.53	26.59	4.14	
	0.245	29.41	30.76	4.58	
	0.346	31.25	32.72	4.71	
	MS 200	25.13	26.70	6.24	

coefficient r in the range of 0.9950–0.9966 which demonstrates that the mathematical model describes experimental data with a high degree of accuracy. Parameter A (dimensionless) expresses the correction of the influence of the hopper wall and its values are in the range of approximately 1.15–1.34. The values of the exponent n are in the range of approximately 2.5–2.8, with a mean value of 2.6.

When testing the flow, it is usually necessary to first select an appropriate diameter of the aperture. The criterion for the proposal of the optimal diameter of the hopper aperture can be the precision of the individual reverse estimates of the flow rate Q_p (g/s) of *MS 200* and its size fractions through the individual test hopper aperture D_0 (cm). In the used range of D_0 = 0.6–1.5 cm, the flow equation parameters A and n (Table 2) were used in the estimation of Q_p (g/s) according to the equation [4],

$$Q_p = \left(\frac{D_0}{A}\right)^n \cdot \left(\frac{\pi}{4}\right) \cdot g^{1/2} \cdot d_b \qquad [4]$$

Comparing the reverse estimate of the flow rate with the experimentally obtained value of Q, percentage deviations Δ (%) between the two values could be subsequently expressed. The results are listed in Table 3. The accuracy of the reverse estimate of the flow rate for all of the hopper apertures (i.e. without discern to the aperture diameter) for polydisperse *MS 200* is approximately 7% and is comparable with the precision for monodisperse fractions in the range of 0.080 mm – 0.400 mm, which ranges from 5.5% to 7.7%. The mean deviation in the last column of Table 3 allows for an expression of the optimal diameter of the hopper aperture D_0 (cm) for the flow of *MS 200* and its size fractions in the studied range of 0.080–0.400 mm. Regardless of the fraction size and the minus or plus sign, the lowest mean deviation has been recorded for the aperture of 1.0 cm as is evident from Table 3.

Conclusions

The mass flow rate of sorbitol and its size fractions through the conical hopper aperture is non-linearly influenced by the size of the test hopper aperture D_0. On the basis of the experimental results, it is possible, for evaluation of flow rate of sorbitol *MS 200* and its fractions in the studied range of 0.080–0.400 mm and in the used range of aperture diameters of 0.6–1.5 cm, to recommend aperture of 1.0 cm, for which a mathematical model used allows the most precise estimate of the flow rate (g/s), characterized by the lowest average deviation from the experimentally observed flow rate of 2.5%.

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Conflicts of interest: none.

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Příloha 2

HURYCHOVÁ, H., LEBEDOVÁ, V., ŠKLUBALOVÁ, Z., DZÁMOVÁ, P., SVĚRÁK, T., STONIŠ, J. Fractal aspects of the flow and shear behaviour of free-flowable particle size fractions of pharmaceutical directly compressible excipient sorbitol, *Čes. slov. Farm.*, 2016, 65 (6), s. 221-225, ISSN (online): 1805-4439

Byl sledován vliv velikosti částic čtyř velikostních frakcí sorbitolu v rozmezí 80-400 µm na hmotnostní rychlost sypání Q (g/s) kruhovým otvorem nerezové kónické násypky o průměru 1,0 cm, a na smykové chování. Pomocí optické mikroskopie (SW analySIS auto 5.1) byly částice charakterizovány základními granulometrickými údaji (ekvivalentní průměr, Feretův průměr, tvarový faktor, sfericita), včetně lineární fraktální dimenze částic (*particle fractal dimension,* pD_F) určené Minkovského metodou. Velikost částic neovlivnila fraktální dimenzi pD_F, která se pohybovala v rozmezí 1,061-1,069 s průměrnou hodnotou 1,066. Ve sledovaném rozmezí velikostních frakcí byl detekován významný vliv (ANOVA, $p < 0{,}0001$) středního rozměru částic x (µm) na rychlost sypání Q (g/s) jednotkovým otvorem s maximem pro frakci 245 µm. Výsledky testování sypnosti korelovaly s výsledky smykového testování s využitím Jenikeho smykového přístroje a potvrdily vliv velikosti částic na kohezi τ_c (kPa), určenou z Mohrovy analýzy kružnic, a tokovou funkci ff_c, vypočítanou z podílu většího hlavního napětí a tlakové pevnosti. Minimální hodnota koheze (0,02 kPa) a nejvyšší hodnota tokové funkce $ff_c = 212$ frakce 245 µm korelovala se zjištěným maximem rychlosti sypání. Závěrem je doporučeno využití rychlosti sypání otvorem a smykového testování pro výběr optimální velikostní frakce s nejlepšími tokovými vlastnostmi.

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

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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 granulometricaly 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 dominant[1)].

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

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compare the results directly; it is necessary to collect the conclusions of more methods in order to describe the material properties completely[2]. 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 well[5]. 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 smaller[6].

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 one[7] and the powder rheometer[8] 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 perimeter[11]. 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 structures[15]. In pharmaceutical technology, fractals are mostly used to describe the dissolution kinetic[13] 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 ± 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.

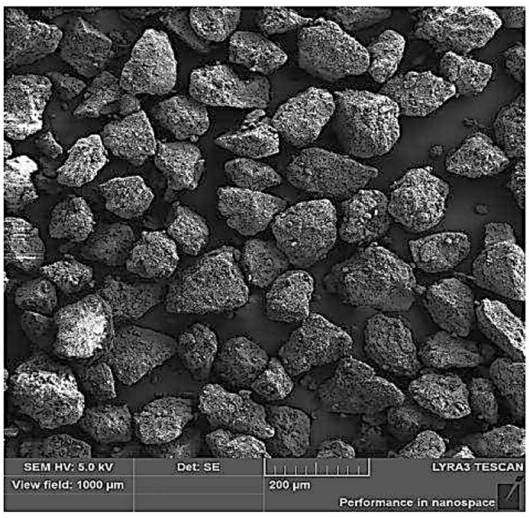

Figure 1. SEM picture of sorbitol particles

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 is[12]. 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 Zatloukal[17]. 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-dependent[19].

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 obtained[4]. 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 flows[7] 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 locus[7], 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_0 = 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.

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Conflicts of interest: none.

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Příloha 3

HURYCHOVÁ, H., ONDREJČEK, P., ŠKLUBALOVÁ, Z., VRANÍKOVÁ, B., SVĚRÁK, T. The influence of stevia on the flow, shear and compression behaviour of sorbitol for direct compaction, *Pharm. Dev. Technol.*, 2018, 23 (2), s. 125-131, doi: 10.1080/10837450.2017.1315132, ISSN (online): 1097-9867, $IF_{2016} = 1{,}860$

Článek se zabývá vlivem přídavku nového alternativního sladidla, stévie (Rebaudioside A, Reb-A), v koncentraci 0,2 % a 0,5 % na sypné, smykové a kompaktační vlastnosti volně sypného sorbitolu pro přímé lisování (Merisorb 200, MS). Pro hodnocení sypného chování byly využity standardní metody statického testování, jako je Hausnerův poměr (*HR*), index stlačitelnosti (*CI*) a sypný úhel (*SA*). I když bylo zaznamenáno mírné zvýšení *HR*, empirické metody neumožnily rozlišit vliv přídavku Reb-A a chování všech směsí odpovídalo dobrým tokovým vlastnostem. Pro dynamické hodnocení sypnosti se využilo testování gravitační rychlosti sypání otvorem kónické testovací násypky o průměru 1,0 cm. Bylo prokázáno významné snížení (ANOVA, $p < 0{,}0001$) hmotnostní rychlosti sypání Q (g/s) sorbitolu vlivem přídavku stévie; vliv byl přímo úměrný koncentraci Reb-A. S využitím Jenikeho smykového přístroje byly směsi hodnoceny za podmínek konsolidovaného stavu. Hodnoty koheze τ_c (kPa), určené metodou Mohrovy analýzy kružnic, a tokové funkce ff_c sorbitolu a jeho směsí s Reb-A, vypočítané z podílu většího hlavního napětí a tlakové pevnosti, potvrdily významný (ANOVA, $p < 0{,}0001$) vliv přídavku stévie již v koncentraci 0,2 % na sypné vlastnosti sorbitolu a kohezivní vlastnosti Reb-A.

Pomocí tradiční metody záznamu "síla-dráha" (*force-displacement*) byl sledován vliv přídavku stévie na průběh lisování sorbitolu. Pro podchycení efektu Reb-A nebyla použita mazadla. Přídavek Reb-A zvýšil energii E_1 (fáze předlisování) a energii E_2 (fáze lisování), zatímco energie elastické deformace (E_3) byla snížena. To ukazuje na zhoršení ochoty směsi se přeskupit díky zvýšenému tření mezi částicemi a na zvýšení tvorby mezičásticových vazeb. Tablety se stévií také vykazují nižší relaxaci ve fázi dekomprese. Výsledky byly porovnány s vlastnostmi tablet. Přídavek stévie v tabletách způsobil signifikantní, koncentračně závislé, zvýšení pevnosti (ANOVA, $p < 0{,}0001$) a prodloužení doby rozpadu tablet (ANOVA, $p < 0{,}0001$).

Závěrem je konstatováno, že přídavek kohezivní složky může i ve velmi malém množství signifikantně zhoršit tokové chování volně sypné pomocné látky a její lisovatelnost. Vzhledem k tomu, že stévie se svým tvarem a velikostí částic (mikronizované částice jehličkovitého tvaru) podobá léčivým látkám, jsou výsledky praktickou ilustrací nedostačující citlivosti empirických metod při hodnocení sypnosti některých farmaceutických práškových směsí a nezbytnosti využití dynamického, příp. smykového testu pro predikci sypného chování.

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RESEARCH ARTICLE

The influence of stevia on the flow, shear and compression behavior of sorbitol, a pharmaceutical excipient for direct compression

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ABSTRACT

Good flow and compaction properties are necessary for the manipulation of particulate material in the pharmaceutical industry. The influence of the addition of an alternative sweetener, rebaudioside A, in a concentration 0.2% w/w and 0.5% w/w on the flow, shear and compaction properties of sorbitol for direct compaction, Merisorb® 200, was investigated in this work. Rebaudioside A worsened the flow properties of sorbitol: the Hausner ratio, the compressibility index and the mass flow rate through the aperture of a model hopper. Using a Jenike shear cell revealed a significant increase in cohesion leading to the decrease of the flow function; moreover, the addition of rebaudioside A increased the total energy for compression of tablets and plasticity estimated by the force–displacement method. Finally, the tablets showed a higher tensile strength and needed longer time to disintegrate compared to the tablets made of sorbitol itself. In view of the results for the free-flowable excipient, sorbitol, the effects of stevia even for a 0.2% w/w concentration have to be carefully considered, particularly whenever used in pharmaceutical formulations of poor flow properties.

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Sorbitol; rebaudioside A; flowability; Jenike shear tester; force–displacement method; tablets

Introduction

Powders are widely used materials in many different industries including the food industry and production of pharmaceuticals. The packing and cohesive properties of a powder affect the storage and flow necessary for continuous processing of bulk material and its compaction (McGlinchey 2005; Augsburger & Hoag 2008). Irregular flow leads to unevenness in filling the matrix during production of tablets and to high mass deviations; moreover, the products do not meet uniformity of mass (and/or content of the active ingredient) requirements.

The flowability and compressibility of powders depend on the properties of particles, for example, their particle size and shape, surface topography, particle density and moisture content, as well as on the external conditions such as room temperature and relative air humidity, and further, by using testing and/or production machines (Prescott & Barnum 2000; Schwedes 2003). A careful examination of the flow and compaction behavior of the particulate material is, therefore, essential for the production of solid pressings such as tablets.

There are many methods describing the flow and compaction properties of powders. However, no individual method can fully describe them and it is often necessary to collect and compare the results of different methods to characterize the powder properties satisfactorily (Schwedes 2003; McGlinchey 2005; Qiu et al. 2009). Of these, the measurement of the static and/or dynamic angle of repose, the expression of Hausner ratio and/or compressibility index and the measurement of the flow rate are popular.

In particular, monitoring the discharge rate through a hopper orifice under gravity has been proposed as one of the most useful methods for the evaluation of flow properties of a free-flowing powder material. To obtain a uniform mass flow (Prescott & Barnum 2000), the hopper geometry must follow general guidelines for the relationship between the diameter of a hopper, the diameter of the hopper orifice and the material particle diameter (Nedderman et al. 1982; Xie & Puri 2006).

Using a translational shear cell allows the measurement of the force needed to shear the bed of preconsolidated powder which corresponds to the forces acting between the particles of the inner layer. A wide variety of parameters can be obtained such as the shear stress–shear strain relationship (yield loci, YL), the cohesion, internal friction angle, flow function and many others (McGlinchey 2005; Schulze 2008). The method is mostly used to determine the critical parameters of the hoppers and to predict flow problems.

Direct compression is a relatively simple method of producing tablets, which involves only dry mixing of powders and subsequent compacting. However, the material must meet specific requirements, for example, particle size and size distribution, porosity, moisture content, good flow and compaction properties (Parikh 2005; Augsburger & Hoag 2008). On the other hand, the flow of tableting material can be worsened by some additives, for example, flavors and sweeteners (Mullarney et al. 2003). Before the manufacturing of tablets, knowledge of the material compaction properties is, therefore, necessary. The force–displacement (FD) record method allows correlation of the parameters of the energy for the phase of compression and decompression (relaxation) with the deformation and tablet-forming properties of material from measurements of upper punch force and displacement (Augsburger & Hoag 2008; Gad 2008, Ragnarsson 1996). Further, this can be correlated with the tablet strength or disintegration time. In relation to material deformation properties (e.g. elasticity, plasticity), the critical parameters of compression process and batch-to-batch variability can be studied.

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For the acceptability of the orally applied products, taste is one of the most important factors. In order to modify the unpleasant taste, sweeteners are widely included in the formulation (Sohi et al. 2004). Sorbitol is among the most commonly used sugar alcohols for taste correction, as a filler/dry binder for direct compression of tablets, a wet granulation agent, a plasticizer for coated tablets and in chewable tablets; the crystalline or spray dried form of sorbitol represents an example of a free flowable excipient (Bolhuis & Chowhan 1996; Nabors 2012; Grembecka 2015). Generally, sugar alcohols have lower sweetening power than sucrose, but they have the advantage of similar sensation properties and are therefore often combined with other sweeteners. Recently steviosid, the natural sweetener, is in the forefront of interest.

The highly refined preparations of Stevia rebaudiana, that is, steviol-glycosides (rebaudioside A) can be considered GRAS (Generally Recognized as Safe) and have been approved by the FDA. Of approximately 100 different compounds, stevioside and rebaudiosides A to E are the most important (Goyal et al. 2010; Nabors 2012). Rebaudioside A (Reb-A) has a pleasant sweet taste, higher water solubility and better stability in comparison with stevioside; a sweet taste starts off slowly and a slightly bitter aftertaste or licorice flavor can be suppressed by mixing with other sweeteners (Caracostas et al. 2008; Goyal et al. 2010; Nabors 2012; O'Donnell & Kearsley 2012).

In this work, the influence of the addition of rebaudioside A 0.2% w/w and/or 0.5% w/w on the bulk (angle of repose, apparent bulk and tapped densities, Hausner ratio and compressibility index), dynamic (the flow rate) and shear (cohesion, the angle of internal friction, the flow function) properties of sorbitol for direct compaction, Merisorb®200, was investigated. The effect on the compaction behavior was studied by the force–displacement method and the tablets were tested for tensile strength and disintegration time.

Materials and methods

Materials

Sorbitol for direct compaction (Merisorb®200, MS; Tereos Syral SAS Nesle) and rebaudioside A 97% (Stevia Reb-A 97 powder, Reb-A; NP Sweet A/S) were used.

The particle morphology of MS (Figure 1(a)) and Reb-A (Figure 1(b)) was investigated using scanning electron microscopy (SEM) with a FEG electron gun (FIB-SEM TESCAN LYRA3GMU) at an acceleration voltage of 5 kV. To conduct the measurements, the samples were placed on a carbon-conductive tape. Subsequently, approximately 10 nm thick gold layer was sputtered on the sample surfaces. The particle size distribution of substances (Figure 2) was estimated by Malvern Mastersizer 2000 (Malvern Instruments Ltd, UK) using the Mie theory for light scattering. The measurements were carried out in a dry mode (air dispersion). The median particle diameter x_{50}=250.38 µm and/or 4.23 µm was noted for MS and/or Reb-A, respectively.

Methods

All measurements and manipulations were carried out at a controlled ambient temperature of 22 ± 1 °C and relative air humidity of 37 ± 5% (Hygrometer 608-H1, Testo, China).

Preparing of mixtures

The mixtures of MS and 0.2% w/w (MSReb-A 0.2) and/or 0.5% w/w of Reb-A (MSReb-A 0.5), respectively, were prepared by

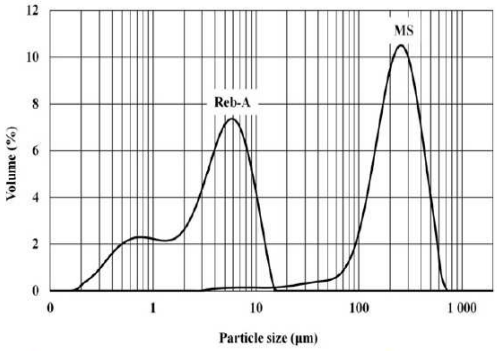

Figure 2. Particle size distribution of sorbitol (MS) and rebaudioside A (Reb-A).

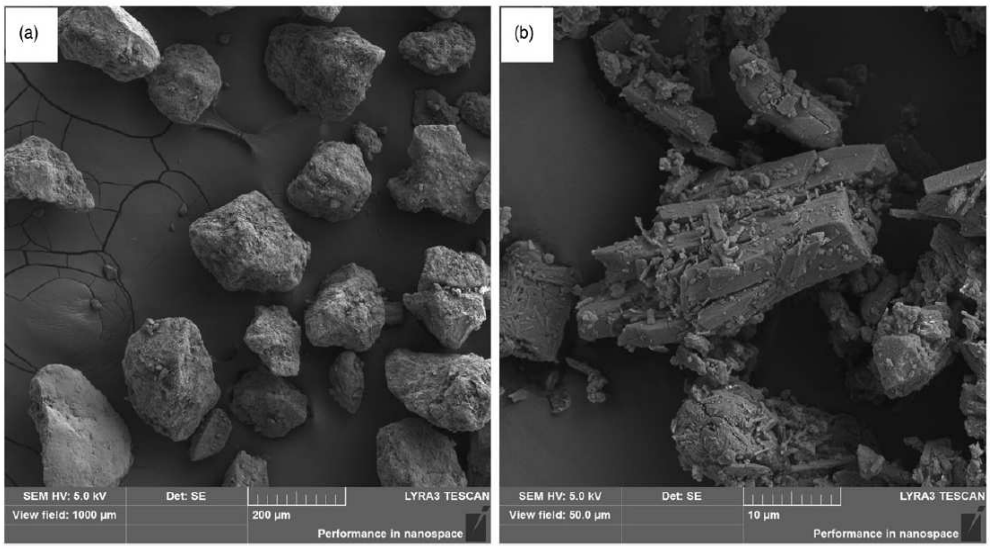

Figure 1. Scanning electron micrograph of sorbitol (a) and rebaudioside A (b).

mixing the substances for 2.5 min at 18 rpm in a cube mixer (Erweka, Germany).

Measurement of moisture content

In order to characterize the samples, the moisture content was measured gravimetrically at 70 °C (Moisture Analyser XM60, Precisa, Switzerland) before and after experiments using 1.000 g of the powder.

Measurement of bulk and tapped density

The density of samples was measured using a tapped density tester (Erweka, Germany) in compliance with the European Pharmacopoeia 9.0 (2. 9. 34). Fifty grams of powder was carefully poured into the 100.0 mL graduated cylinder and the bulk density d_c (g/mL) was calculated from the mass and the volume of the powder. After 1250 taps (250 ± 15 taps/min from a height of 3 ± 0.2 mm) the volume of powder was measured and the tapped density d_t (g/mL) was estimated. Table 1 lists the means of ten measurements; data are completed with standard deviation (SD).

The Carr compressibility index, CI (%), and Hausner ratio (HR) were calculated using Equations (1) and (2) where V_0 is the bulk volume (mL) and V_t is the tapped volume (mL).

$$CI = \frac{(V_0 - V_t)}{V_t} \times 100 \quad (1)$$

$$HR = \frac{V_0}{V_t} \quad (2)$$

Measurement of angle of repose

The static angle of repose (AOR) of powder samples was measured in compliance with European Pharmacopoeia 9.0 (2. 9. 36) and ASTM (C1444–00). A base with a fixed diameter of $d = 10.0$ cm and a protruding outer edge was used to retain a layer of powder upon which the cone is formed. In order to avoid any segregation, consolidation and/or aeration of the powder, the cone was carefully formed by raising the 200.0-mL stainless steel conical hopper having an internal angle wall inclination of 40° and a circular aperture with a diameter of 1.0 cm. The angle of repose AOR (°) was calculated using Equation (3) from the height of the pile h (cm) and the diameter of the base d (cm). Table 1 summarizes the mean for 10 repetitions of measurements with the SD.

$$tg\ AOR = \frac{h}{0.5 \times d} \quad (3)$$

Estimation of the flow rate

To measure the flow rate of powder samples, an automated powder and granulate tester (Erweka, Germany) with the same hopper and aperture as above was used. The hopper was uniformly filled with the sample of tested powder. The mass flow rate was measured in discrete samples such that the time (s) for 100.0 g of powder to pass through the aperture was recorded and the mass flow rate Q (g/s) was calculated. The mean of ten measurements with the SD are presented in Table 1.

Shear cell measurement

All measurements were performed with a translational Jenike shear tester (a home-made model with a diameter of the shear base 100.0 mm and the total volume of shear cell 274.8 mL) in compliance with the recommendations of ASTM (D6128–16). A constant speed of 4 mm/min was used for the force-measuring pin. The consolidated sample (consolidating normal stress σ of 10.15 kPa, 20 twists) was subsequently subjected to shear at the same normal stress to achieve steady state (preshear point, *P*). To measure the actual values of shear stress τ, the normal stresses were reduced to 7.62 kPa, 5.21 kPa and 2.72 kPa to obtain the shear points. The measurements were repeated three times, each time using a fresh powder sample.

To evaluate the results, the yield locus of the shear stress vs. the reduced normal load was obtained using Mohr's circle analysis (GeoGebra SW) from which the basic characteristics of the samples were determined. Table 2 shows the average of three measurements for each powder as the values were similar. The flow function *ff* was calculated as the ratio σ_1/σ_c, where σ_1 is the major principal stress (kPa) and σ_c is the unconfined yield strength (kPa).

Table 1. Properties of sorbitol (MS) and its mixtures with rebaudioside A (Reb-A) 0.2% w/w and 0.5% w/w.

	d_c[a] (g/mL)	d_t[b] (g/mL)	CI[c] (%)	HR[d]	Q[e] (g/s)	AOR[f] (°)
MS	0.666 ± 0.01	0.752 ± 0.02	11.48	1.13	9.71 ± 0.07	33.8 ± 0.24
MSReb-A 0.2	0.647 ± 0.01	0.736 ± 0.01	12.11	1.14	9.59 ± 0.04	33.8 ± 0.26
MSReb-A 0.5	0.643 ± 0.00	0.736 ± 0.00	12.67	1.15	9.43 ± 0.03	33.8 ± 0.20

Data are completed with standard deviation.
[a]d_c=bulk density.
[b]d_t=tapped density.
[c]CI = compressibility index.
[d]HR = Hausner ratio.
[e]Q=mass flow rate.
[f]AOR = angle of repose.

Table 2. The shear characteristics of sorbitol (MS) and its mixtures with rebaudioside A (Reb-A) 0.2% w/w and 0.5% w/w.

	d_{cons}[a] (g/mL)	σ_1[b] (kPa)	σ_c[c] (kPa)	τ_c[d] (kPa)	φ_i[e] (°)	φ_e[f] (°)	ff[g]
MS	0.598	15.17	0.13	0.05	20.50	20.74	117
MSReb-A 0.2	0.592	15.78	0.25	0.08	27.44	27.74	63
MSReb-A 0.5	0.589	17.18	0.36	0.11	27.58	28.00	48

[a]d_{cons}=consolidated density.
[b]σ_1=major principal stress.
[c]σ_c=unconfined yield strength.
[d]τ_c=cohesion.
[e]φ_i= angle of internal friction.
[f]φ_e=effective angle of friction.
[g]ff = flow function.

Preparation of tablets

Tablets without facets and breaklines (diameter of 13.00 ± 0.02 mm, height of 3.76 ± 0.02 mm, mass of 0.5000 ± 0.0010 g) were compacted using the compaction punches (Adamus HT, Machine Factor Group, Poland) in the material testing equipment T1-FRO 50 Zwick/Roell (Zwick GmbH & Co., Germany). The machine was adjusted as follows: distance of jaws 13 mm, rate of compaction 0.5 mm/s, preload 2 N, rate of preload 0.5 mm/s and compaction pressure of 75.34 MPa. Twenty tablets were compacted out of each powder sample; tablets were stored in closed plastic tubes. No glidants or lubricants were used. The evaluation of tablet properties (see below) was carried out at least 24 h after the compaction.

During the compaction, the values of energy parameters for the force–displacement record (Ragnarsson 1996; Gad 2008) were automatically registered and statistically processed using the computer program testXpert V 9.01 (Zwick GmbH & Co., Germany). The energy consumed during precompression E_1 (J), the energy of

Table 3. Energy profile values of compression and tablet properties for sorbitol (MS) and its mixtures with rebaudioside A (Reb-A) 0.2% w/w and 0.5% w/w.

	E_1[a] (J)	E_2[b] (J)	E_3[c] (J)	PL[d] (%)	TS[e] (MPa)	DT[f] (sec)
MS	9.04 ± 0.20	6.13 ± 0.04	1.65 ± 0.01	78.74 ± 0.19	1.12 ± 0.04	43.50 ± 1.22
MSReb-A 0.2	9.34 ± 0.27	6.26 ± 0.03	1.63 ± 0.01	79.37 ± 0.11	1.28 ± 0.04	48.17 ± 2.64
MSReb-A 0.5	9.61 ± 0.22	6.26 ± 0.03	1.63 ± 0.01	79.37 ± 0.06	1.34 ± 0.02	70.67 ± 2.50

Data are completed with standard deviation.
[a]E_1=energy of precompression.
[b]E_2=energy of plastic deformation.
[c]E_3=energy of decompression.
[d]PL = plasticity.
[e]TS = tensile strength.
[f]DT = disintegration time.

plastic deformation E_2 (J), the energy of elastic deformation E_3 (J), and plasticity PL (%) are listed in Table 3 with the SD.

Measurement of the resistance to crushing and the tensile strength of tablets

The resistance to crushing was measured by the destruction force for 10 tablets using a Schleuniger apparatus (Dr. Schleuniger Pharmatron AG, Switzerland) according to the European Pharmacopoeia 9.0 (2.9.8). The tensile strength of tablets TS (MPa) was subsequently calculated according to the Equation (4) (Fell & Newton 1970), where CF is the force needed to disrupt the tablet by crushing (*N*), *D* is the diameter of the tablet (mm), and *H* is the height of the tablet (mm). The mean value and the SD are presented in Table 3.

$$TS = \frac{2 \times CF}{\pi \times D \times H} \quad (4)$$

Disintegration time of tablets

The disintegration test (without discs) was performed on a basket-rack apparatus Erweka ZT 301 (Erweka, Germany) for six tablets in compliance with the European Pharmacopoeia 9.0 (2.9.1). Each tablet was placed into the basket and immersed in purified water, maintained at 37 °C ± 1 °C. The time to complete disintegration (no fragments remaining on the sieves of the apparatus) of all the units was recorded. The mean of six measurements and the SD are presented in Table 3.

Mathematical and statistical processing of results

To evaluate the results of shear tests and determination of the basic characteristics of materials, the GeoGebra software was used (GeoGebra Inc., https://www.geogebra.org). The values of energies and plasticity were statistically processed by the computer program testXpert V 9.01 (Zwick GmbH&Co, Germany) during compaction. The results of the resistance to crushing and disintegration time of tablets were statistically processed by means of the computer programs Excel and QCexpert (TriloByte Statistical Software, s.r.o., Czech Republic). For the evaluation of the influence of the addition of Reb-A, analysis of variance (ANOVA) at a significance level of 0.05 was employed.

Results and discussion

Powders represent a large amount of materials in various industries. Their flowability and compressibility significantly determine their manipulation. However, the properties of the powder substance itself can be easily influenced by the addition of further powders and additives. The main aim of the present paper is to study the effect of rebaudioside A (Reb-A) addition on the flowability and compactability of free-flowable sorbitol for direct compaction.

Flowability is not a physical property of the powder substance itself, but a complex characteristic which is influenced by the particle properties as well as by environmental and processing factors (Prescott & Barnum 2000; Schwedes 2003; Qiu et al. 2009). Generally, regular and round particles produce better flow, while the small ones have a tendency to agglomerate that increases the friction force and reduces their ability to flow. As can be seen from Figure 1(a), particles of sorbitol are relatively regular, slightly rough surface crystals; the median size x_{50} = 250.38 µm was estimated experimentally (Figure 2). In contrast, Reb-A has very small, irregular and agglomerated particles (Figure 1(b)) with a median size x_{50} of only 4.23 µm (Figure 2). If the particles are very small (<50 µm), generally, the cohesional forces are higher than the gravitational force decreasing flowability (Prescott & Barnum 2000; McGlinchey 2005). A decrease in flowability, however, can be expected in advance after mixing free-flowable sorbitol with stevia powder.

Since the moisture content is another factor which influences the flow significantly (Crouter & Briens 2013) and both sorbitol and stevia are described as hygroscopic materials (Bolhuis et al. 2009; Nabors 2012; O'Donnell & Kearsley 2012), stable experimental conditions were used and the loss on drying was checked throughout the experimental time period in this work. A slightly higher content was observed in the mixtures with stevia in direct proportion to the concentration used but the moisture content in all mixtures studied did not exceed approximately 1% w/w.

The bulk properties of mixtures

The static angle of repose (AOR) represents a simple and fast flowability test that relates the interparticulate friction between particles or resistance to movement to flow properties. However, the results depend on the way the pile of powder was formed on the base (Geldart et al. 2006). Apparatus in which the height of the funnel may be varied as the cone forms was used to avoid any compaction of material or distortion caused by impact. In the concentration range used, no effect of Reb-A on the sorbitol AOR (33.8°) was noted (Table 1) and good flow properties were detected in agreement with the general scale of flowability for AOR (Carr 1965).

In Table 1, the values of the bulk and tapped densities of powder samples are summarized. Of the samples, the lowest bulk density of 0.643 g/mL was found for 0.5% w/w of Reb-A which is the result of the increase in the cohesion and the higher friction between the particles (Abdullah & Geldart 1999). However, the change in density during manipulation, that is, densification by tapping is necessary to know before the production of tablets. The ratio of the bulk density (apparent, aerated) to tapped density

(packed) is, therefore, a useful characterization of material cohesion in prediction of the compression rate of powders (Carr 1965; Qiu et al. 2009; Traina et al. 2013). The larger value of the Carr compressibility index and/or Hausner ratio, the worse the compressibility of the material. The values of the CI and/or HR in a range of 11.48–12.67% and/or 1.13–1.15, respectively, were detected (Table 1). The results of all mixtures tested were located in a "good flow character" group in agreement with the general scale for flowability. However, the weakness of the empirical criteria CI and HR is that they are calculated from the bulk volume including the voids between particles in which the filling method plays a crucial role (Abdullah & Geldart 1999). The standard procedure for the routine measuring of the powder bulk and tapped densities (European Pharmacopoeia 2.9.36 Powder flow) was used in this work. Although the differences in CI and HR were insignificant (ANOVA, $p \leq .05$), an increase in values was observed for both used concentrations of Reb-A illustrating the effect of the particle cohesion due to the stevia addition.

The dynamic and shear properties of mixtures

The mass flow rate through an orifice of the hopper which is considered more illustrative method to evaluate the dynamic flow properties of powders (Prescott & Barnum 2000; Schwedes 2003) was measured in order to investigate the blends behavior in detail. An aperture of diameter 1.0 cm was used and the time taken for 100.0 g of powder to pass was registered for all samples. For this orifice size, the best results were previously obtained for sorbitol and its size fractions (Šklubalová & Hurychová 2015). As can be seen in Table 1, the mass flow rate decreased significantly (ANOVA, $p \leq .05$) from 9.71 g/s for sorbitol itself to 9.59 g/s and/or 9.43 g/s in proportion to the concentration of Reb-A demonstrating the cohesive properties of Reb-A.

To show the stevia effect at particulate level, a shear test was performed using a translational Jenike shear tester. The yield loci (YL) and Mohr's circles acquired from σ-τ relationship (Schulze 2008) for MS, MSReb-A 0.2 and MSReb-A 0.5 were used to obtain the powders' characteristics (Table 2). For sorbitol, a low value of cohesion τ_c (kPa) was detected proving its noncohesive behavior. In contrast, this characteristic was increased in mixtures with Reb-A; a detailed view of the cohesions of samples as the intercept of the YL lines is shown in Figure 3. The increased friction between particles which was found to depend both on particle size and shape for the unlubricated powders (Podczeck & Miah 1996) resulted in higher values of the angle of internal friction (Table 2). Finally, the value of the flow function is higher for sorbitol (117) than that of 63 and/or 48 found for MSReb-A 0.2 and/or MSReb-A 0.5, respectively, showing the significant (ANOVA, $p \leq .05$) reduction of sorbitol flowability after the addition of stevia. Similarly to the general scale of flowability known for AOR and/or HR, the flow function *ff* can be used for classification of flow behavior (Schulze 2008). Although for all tested samples a $ff > 10$ was noted, a considerable influence of Reb-A on the flow function of free-flowable sorbitol was exhibited. This effect would be more evident whenever stevia is processed with poor flowing tableting mixtures or pharmaceutical excipients. Therefore, its deteriorating effect on the flow properties should be carefully taken into consideration during formulation.

The compressibility properties of the mixtures and tablet properties

A compressibility test was performed using the force-displacement method (FD). A plots of upper punch force versus upper punch displacement during the compression and decompression (Ragnarsson 1996) were recorded. To characterize the properties of the tableting material itself, no glidants or lubricants were used. Each tablet was made separately. The mass of MS or its mixture with Reb-A was weighed on an analytical balance, carefully filled into the die and compacted. The values of energy parameters were registered automatically and they are summarized in Table 3.

In the first column of Table 3, the energy consumed during precompression, E_1 (J), is shown. The visibly higher values of E_1 9.34 J and/or 9.61 J for MSReb-A 0.2 and/or MSReb-A 0.5, respectively, were noted in comparison to sorbitol itself (9.04 J). The energy E_1 is associated with the rearrangement of powder bed and reduction of the interparticulate voids at the beginning of the compression process (Ragnarsson 1996; Augsburger & Hoag 2008). It is therefore directly connected to the bulk properties of the powder and the density change if the powder bed is packed. The results are consistent with the bulk properties of samples and the increased HR and CI values (Table 1) mentioned earlier. The efficiency of bulk volume reduction is also directly related to the

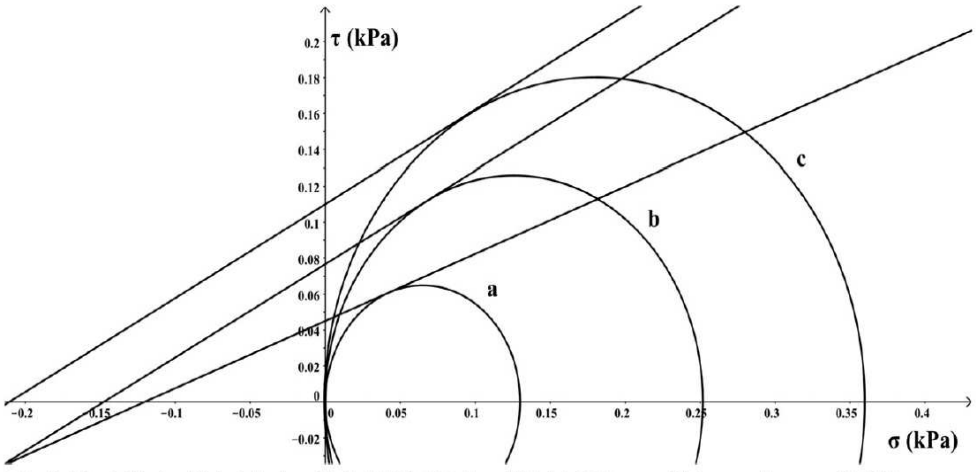

Figure 3. Detail of the yield loci and Mohr circles for sorbitol (a), MSReb-A 0.2 (b) and MSReb-A 0.5 (c) at consolidating normal stress σ of 10.15 kPa.

interparticulate friction. The more friction, the higher energy input is needed for material to be densified (Augsburger & Hoag 2008). The E_1 parameter, therefore, should be as small as possible. In this context, the increase in the E_1 values also relates well to the worsening of the mass flow rate (Table 1) and the shear characteristics (Table 2) due to the presence of stevia.

A further reduction in powder bed volume results in particle elastic, viscoelastic and plastic deformation which is associated with their fragmentation or breakage, the elimination of voids and the formation of interparticular bonds when forming a compact (Ragnarsson 1996; Augsburger & Hoag 2008). The energy accumulated by the tablet after compression, E_2 (J), shows the work used in the formation of the compact and the work needed to overcome die wall friction. The energy E_2 was increased (Table 3) for the mixtures with Reb-A (6.26 J for both concentrations used) compared to sorbitol itself (6.13 J) indicating stevia behavior similar to that of binders which are known to increase the resistance to deformation (Bastos et al. 2008).

The energy of elastic deformation, E_3 (J), is measured during the decompression phase. The value of E_3 for MS was very low (1.65 J) and decreased with the addition of stevia (1.63 J), that is, stronger bonds between particles were created during compaction and less energy was released during decompression.

Finally, the total energy of compression E_{max} (J), which is the sum of all energies needed during the tableting process, and plasticity PL (%) which is the ratio of the energy used to form the compact to the total energy input (Ragnarsson 1996) were estimated. E_{max} of 16.82 J, 17.23 J and 17.5 J and/or plasticity 78.74%, 79.37% and 79.37% for MS, MSReb-A 0.2 and MSReb-A 0.5, respectively, were detected showing that more energy input was utilized in irreversible deformation of the material, i.e. plastic deformation and forming bonds in the presence of stevia.

The force–displacement record results can be correlated with the tablet strength or disintegration time (Ragnarsson 1996). As can be seen in Table 3, the tensile strength as well as the disintegration times were significantly increased (ANOVA, $p \leq .05$) with the addition of Reb-A even for the 0.2% w/w concentration.

Conclusions

In conclusion, the addition of Reb-A 0.2% w/w or 0.5% w/w resulted in the increase in Carr compressibility index and Hausner ratio in comparison to sorbitol itself. However, the empirical tests cannot demonstrate the effect significantly and all values obtained for mixtures corresponded to good flowability. On the other hand, the significant decrease of the mass flow rate through a circular orifice 1.0 cm of a model conical hopper, the twofold increase in the cohesion resulting in the significant increase in the angle of internal friction, and the approximately 50% decrease of flow function showed the higher cohesivity of mixtures even after the addition of Reb-A 0.2% w/w which is usually used in tablets for sweetening effect. In view of the differences in flow and shear properties observed by adding stevia to the pharmaceutical free-flowable excipient, sorbitol, it is quite possible that other tableting mixtures or pharmaceutical excipients would be prone to suffering from poor powder performance once stevia had been added.

The binder behavior of Reb-A was detected using the force–displacement record leading to the increase in the total energy input for compression E_{max} and plasticity of the tableting mixture. As a result, the tablets containing stevia had significantly higher tensile strength and a longer disintegration time. Due to the fact that the disintegration time directly influences the release of the drug from the dosage form, stevia could affect drug bioavailability after oral administration. However, this needs to be confirmed by the future testing of other pharmaceutical formulations.

Disclosure of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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Příloha 4

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Pro rozsáhlý soubor celkem 19 vzorků farmaceutických pomocných látek rozdílných sypných vlastností, velikostních frakcí a modelových směsí byly využity statické a dynamické metody hodnocení sypných vlastností a sledováno jejich ovlivnění fraktalitou částic a práškového lože. Mezi vzorky patřily běžné excipienty používané v pevných lékových formách i moderní materiály s upraveným povrchem.

Pomocí optické mikroskopie (SW analySIS auto 5.1) byly pro pomocné látky určeny granulometrické charakteristiky a lineární fraktální dimenze částic (*particle fractal dimension,* pD_F) Minkovského metodou. Použití statických metod hodnocení sypnosti (Hausnerův poměr, *HR*, a statický sypný úhel, *SA*) dovolilo rozdělit testované materiály do skupin podle sypného chování. Pro některé kohezivnější materiály však byly zaznamenány experimentální problémy, které pro absenci toku otvorem násypky při měření *SA* znemožnily získat potřebné výsledky.

Stanovení hmotnostní rychlosti sypání *Q* (g/s) otvorem kónické násypky o průměru 1,0 cm prokázalo rozdíly v dynamickém sypném chování sedmi použitých druhů laktosy získaných rozdílným technologickým postupem přípravy. U tří vzorků (bezvodá laktosa, potravinářská laktosa a GranuLac 70) došlo k tvorbě klenby nad výsypným otvorem a blokádě otvoru. To se projevilo také u modelových směsí volně sypné a kohezivní laktosy. Ve zmíněných případech nebylo možné experimentální výsledky *Q* získat.

Tradiční metody byly doplněny lavinovým testováním v rotujícím bubínku s dynamickou analýzou obrazu. Na základě lavinového chování byly testované materiály rozděleny do tří skupin vykazujících sesuvné (*slumping*), kaskádové (*cascading*) a peřejové (*cataracting*) proudění. Dobré tokové vlastnosti práškových vzorků byly potvrzeny nižšími hodnotami dynamického sypného úhlu, lavinové energie a krátkými dobami lavinového času; pro kohezní prášky byl zaznamenán opak.

Byla prokázána výhodnost testování v bubínku zejména pro kohezivnější látky, u nichž nebylo možné určit tradičními metodami experimentální hodnoty.

Obrazová analýza povrchu vrstvy prášku během lavin umožnila určit povrchovou fraktální dimenzi (*bulk fractal dimension, bD_F*). Byly zkoumány korelace mezi rychlostí sypání, parametry lavinového chování a fraktální dimenzí částic pD_F a práškového lože bD_F. Vysoká korelace (*PCC* a *SRCC* 0.97 (p = 0,0000) příp. 0.95 (p = 0,0001)) byla zjištěna mezi bD_F a lavinovou energií; vyšší hodnoty byly detekovány pro kohezivnější vzorky. Ačkoliv byla zjištěna relativně silná záporná korelace mezi pD_F a rychlostí sypání, nebylo možné vyvodit zobecňující závěry pro chování látek, protože korelace s rychlostí sypání byla zkomplikována absencí experimentálních hodnot pro některé vzorky.

Závěrem bylo lavinové testování doporučeno pro dynamické hodnocení sypnosti, neboť rotující válec umožnil měřit i sypné vlastnosti kohezivních materiálů, které byly tradičními statickými i dynamickými metodami obtížně měřitelné nebo neměřitelné. Vzhledem ke komplexnosti ovlivnění tokového chování partikulárních materiálů na částicové (mikroskopické) i „bulk“ (makroskopické) úrovni nebyla prozatím mezi hodnotami lineární fraktální dimenze a povrchové fraktální dimenze pozorována významná korelace. Fraktalita částic i jejich vrstvy patří mezi prediktory toku a špatné tokové vlastnosti byly spojeny s členitější konturou vrstvy, a tedy i vyšší hodnotou bD_F. Vzájemné vztahy budou dále studovány.

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ORIGINAL ARTICLE

Fractal Aspects of Static and Dynamic Flow Properties of Pharmaceutical Excipients

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Abstract

Purpose Characterisation of powder flow is important for pharmaceutical processing and manufacturing. This work aims at a better understanding of how fractal particle and bulk properties affect the static and dynamic flow of excipients.

Methods Traditional methods of flowability testing, e.g. the angle of repose or the flow through an orifice, were complemented by avalanching in a rotational drum. Dynamic image analysis provided a fractal contour line dimension of the powder bulk in the drum (bD_F). This was compared to the contour line fractal dimension of particles (pD_F) as obtained from the box-counting method. Avalanche testing was able to measure also cohesive materials that were otherwise difficult or not measurable at all using the classical methods.

Results The values of the avalanche energy were in good agreement with the different flow properties of the samples. These flow properties showed good correlations with bD_F in that poor flow properties were associated with a more rugged contour line of the bulk and hence higher bD_F.

Conclusions Interestingly, there was no correlation observed between pD_F and bD_F, which may suggest that a distinct bulk structure typically emerges from the particles under dynamic flow. Future research should further clarify how fractal powder aspects affect pharmaceutical manufacturing processes.

Keywords Flowability · Avalanching · Dynamic behaviour · Rotating drum · Particle fractal dimension · Bulk fractal dimension

Introduction

Handling of particulate materials is an essential part of various unit operations in pharmaceutical manufacturing. The manipulation of powders includes the transport, storage, sieving, mixing, flow through hoppers, die-filling and compaction. However, the multifactorial behaviour of powders can significantly influence the quality parameters of the final products [1]. To avoid technical problems in pharmaceutical processing of solid dosage forms and to comply with pharmacopoeial requirements, it is particularly important to analyse and specify the characteristics of powder flow.

The ability of a particulate material to flow is directly influenced by (i) the characteristics of the individual particles such as the particle size and shape, its density, the surface area, the moisture content, the electrostatic charge, etc. and (ii) their bulk properties. This includes also its ability to dissipate captured air because a powder generally represents a two-phase system (solid/air). Moreover, (iii) the environmental factors, e.g. temperature, air humidity or storage time, and (iv) the testing method used and equipment can affect results of powder flow testing significantly [2–4]. Thus, this multifaceted nature of powder flow behaviour makes the description of flowability using only one simple method difficult so that results of different analyses may have to be compared.

Teaser The article contributes to a better understanding of how fractal particle and bulk properties affect static and dynamic flow of pharmaceutical powder excipients.

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In powder flowability testing, the characterisation of the bulk and tapped densities, the Hausner ratio and/or compressibility (Carr's) index [5] and the angle of repose ranking provide fast methods (Ph. Eur. 9.0, 2.9.36) that give an initial assessment of how a powder flows and consolidates. However, such simple indicators may not act as reliable markers of powder flow because of the complex nature of flow that depends on material as well as external factors. It is therefore necessary to also study dynamic powder behaviour, for example, by evaluation of discharge rate through an orifice [6, 7]. More recently, avalanche testing can be considered as an alternative method [8].

The evaluation of powder flow rate through a hopper orifice by the force of gravity necessitates to some extent a reproducible, uniform powder flow. This method is therefore generally recommended for free-flowable materials showing no significant failures in flow pattern. General guidelines for cylinder hopper geometry can be inferred from Ph. Eur. (2.9.36): (i) the diameter of a cylinder is greater than twice the diameter of the orifice and (ii) the diameter of the hopper orifice is greater than six times the diameter of the particle. The flow is virtually independent of the powder head if the height of the powder bed is much greater than the diameter of the orifice. This phenomenon in known as the hourglass theory [6, 7, 9, 10]. Although a cylindrical, flat-bottomed hopper is generally recommended, commercial testers mostly employ a funnel.

Not all powders can be measured through an orifice. In cohesive powders, the formation of craters, arches or blockage of the outlet can occur [3]. To measure such powders, shear cells are therefore the preferred instruments. In principle, the force needed to shear the bed of a consolidated powder is measured. Because this directly corresponds to the forces acting between the particles of the inner layer, a good representation of flow/friction at a particulate level is expected. A translational Jenike shear tester and annular tester are examples of traditional equipment [11]. The shear measurements enable the detection of considerable cohesive properties of some pharmaceutical additives even in very small amounts that are undetectable by traditional methods as reported, for example, by Hurychová et al. [12] for stevia mixtures with free-flowing sorbitol. Recently, powder rheometry [13] represents a progressive technique that can determine traditional shear characteristics as well as obtain various unconfined flow indices as demonstrated for binary blends of pharmaceutical excipients with glidants by Majerová et al. [14]. The use of a relatively small sample amount is another benefit in comparison to other classical techniques.

It is generally accepted that the particle size, shape and surface structure are key factors in particle flow behaviour [2]. Besides the granulometric characteristics as for example the mean diameter, shape factor, sphericity and aspect ratio, the regularity/irregularity of a particle boundary can be described by a boundary fractal dimension pD_F [15–20]. In two-dimensional projection, a fractal dimension is related to the outline perimeter:

$$P = N \cdot \lambda^{-pD_F} \quad (1)$$

where P is the particle perimeter, N is the number of steps having the length λ and pD_F is the particle fractal dimension [15].

In pharmaceutical technology, fractal theory is often used to describe properties of crystals, particles and aggregates of the solid material as well as the kinetics of their dissolution [21, 22]. Moreover, it can be a predictor of powder flow as described, e.g. by Kaye [17, 18], and the differences in the particle fractal dimension were related to the flow pattern of the pharmaceutical excipients. Thus, higher pD_F was associated with flow irregularities [23].

The study of powder flow in a rotating drum is still considered a rather non-standard method even though early reports had already appeared in the 1990s [24]. This first generation of powder avalanching instruments had only a small photocell area, and therefore, a quite limited part of the moving powder bulk was analysed. It was possible to detect kinetics of avalanching, which was used to characterise, for example, pharmaceutical excipients [8, 25, 26]. The method appeared to be even suitable to measure rather cohesive powders [27]. More recently, a second instrument generation is available that is capable of full-scale dynamic image analysis, which was used to measure different excipients and their mixtures with drugs [28, 29].

The new imaging capabilities also enabled the detection of the fractal dimension of the moving bulk, bD_F, from the contour line of the dynamic shadow images in the rotating drum. This fractal property of the bulk was recently found to be a main determinant of powder flow for a range of excipients [30]. The use of fractal concepts is gaining increasing momentum in pharmaceutics [22]. Even though the application of fractal concepts to powder flow was already proposed by the pioneer Brian Kaye [17, 18], the rotating drum methods have changed over the years as well as the parameters that were obtained. One should in particular differentiate characteristics and fractal dimensions obtained from individual particles as compared to emerging bulk properties like bD_F. Analysis of the boundary fractal dimension of individual particles pD_F is a different approach [23] and has been applied recently to characterise free-flowable size fractions of sorbitol [31].

There is a need to study a wider range of different pharmaceutical materials with an emphasis on fractal aspects and their effects on static and dynamic flow properties. A particular area of research is interested in clarifying the role of pD_F and bD_F on flow properties of more or less cohesive pharmaceutical samples. Accordingly, the aim of the current work was to characterise such a range of powder samples by classical methods as well as by using powder avalanching. The fractal

contour dimensions on the level of individual particles pD_F as well as of the bulk bD_F were determined to study a potential correlation between themselves as well as relationships with the obtained flowability parameters.

Experimental: Materials and Methods

Materials

In this work, powder flow behaviour of individual substances, powder size fractions and the powder blends was assessed. Ten pharmaceutical powder excipients of different flow properties were used: Neusilin US2 (N) Fuji Chemicals Industries, Co., Ltd., Japan; Rebaudioside A 97% (RA) NP Sweet A/S, German; Merisorb® 200 ~ Sorbitol (S), Tereos Syral SAS Nesle, France; Excipress™ GR150 (EP) Armor Pharma, France; Lactopress® Granulated (LPG) DFE Pharma, Germany; Tablettose® 80 (TB80) Meggle, Germany; SpheroLac® 100 (SL100) Meggle, Germany; Granulac® 70 (GL70) Meggle, Germany; Lactose PP 60-80 mesh (LPP) Lactalis ingredients, Italy; and Lactopress® Anhydrous (LPA) DFE Pharma, Germany.

Four particle size fractions of sorbitol of 80–400 μm were obtained using a vibratory sieve shaker AS 200 basic (Retsch, Germany). The fractions were labelled with the mean size as the geometrical mean of the screens used, i.e. S100, S158, S245 and S346 for the fractions 80–125, 125–200, 200–300 and 300–400 μm, respectively.

The five powder mixtures were prepared: the blends of Sorbitol and 0.2% *w/w* (S-0.2RA) and/or 0.5% *w/w* (S-0.5RA) of Rebaudioside A, respectively, and the mixtures of Excipress and Lactopress Anhydrous in the ratios 3:1 (3EP-1LPA), 1:1 (1EP-1LPA) and 1:3 (1EP-3LPA). The powder components were mixed in a cube mixer (Erweka, Germany) for 2.5 min at 18 rpm.

Methods

All measurements and manipulations were carried out at a controlled ambient temperature of 24 ± 2 °C and relative air humidity of 27 ± 3% (Hygrometer 608-H1, Testo, China).

Loss on Drying

In accordance with the European Pharmacopoeia 9.0 (2.2.32), the loss on drying (%) was measured gravimetrically (Moisture Analyser XM60, Precisa, Switzerland) for 1.000 g of powder at 105 °C. For Sorbitol, temperature 70 °C was used. The measurement was repeated five times for each powder sample ($n = 5$).

Particle Size Distribution

Particle size distribution (PSD) was determined by a Malvern Mastersizer 3000 (Malvern Instruments Ltd., UK) using the Mie theory of static light scattering. The dispersing agents were water (N), heptane (S) and isopropanol (RA, EP, LPG, TB80, SL100, GL70, LPP and LPA). Particle sizes of x_{10} (μm), x_{50} (μm) and x_{90} (μm) were detected for 10, 50 and 90% of the cumulative frequency, respectively. De Brouckere mean diameter $d_{(4/3)}$ (μm) and "span" value characterising the width of the particle size distribution were determined.

Microscopy

The particle shape for ten used powder excipients was examined using the scanning electron microscopy (SEM) Phenom Pro (Phenom-World B.V., Netherlands) at magnification of ×300 with the backscattered detector at an acceleration voltage of 10 kV. To conduct the measurements, the samples were placed on a carbon conductive tape. Subsequently, an approximately 10-nm-thick gold layer was sputtered on the sample surfaces.

The particle fractal dimension (pD_F) was estimated using an optical microscope BX 51 (Olympus, Japan) that was equipped with a digital camera DP72 (resolution of 4140 × 3096 pixel) and video (resolution of 1360 × 1024 pixel). A small amount of a dry powder was laid uniformly on a glass slide without agglomerates. Using an automatic software detection (SW analySIS auto 5.1), pD_F was obtained by means of box-counting, i.e. the Minkowski principle [16, 20], for about 200 particles at a magnification of an objective ×10 (pixel size of 0.2164 μm). The individual particles were detected and recorded. The particles were lined (a line having the width of 1 pixel) and then enveloped using 20 steps. The binary images were obtained from digitalized images using a relative grey level threshold of 40% and the pixel connectivity of 4. All results involving less than 20 steps were eliminated to reduce bias.

Bulk Properties of Samples

In accordance with the European Pharmacopoeia 9.0 (2.9.34), the bulk density d_c (g/mL) of the nonconsolidated powder was estimated in a graduated cylinder as the ratio of the mass of the powder to its volume 100.0 mL. Subsequently, the tapped density was determined using the density tester SVM 102 (Erweka, Germany). After 1250 taps (250 ± 15 taps/min from a height of 3 ± 0.2 mm), the volume of powder V_t (mL) was measured and the tapped density d_t (g/mL) was calculated. The Hausner ratio (HR) was computed from the ratio of the bulk volume V_0 (mL) and the tapped volume. The measurement was repeated ten times for each powder sample ($n = 10$).

Static Angle of Repose

Measurement of the static angle of repose, SA (°), was performed for the individual powders, the sorbitol size fractions and the powder blends in accordance with the European Pharmacopoeia 9.0 (2.9.36) and the recommendations of ASTM (C1444-00). The powder cone was formed on a base with a diameter of $d = 10.0$ mm. The base was filled with a layer of the same material to carefully build the cone. The distance between the stainless steel conical hopper (200.0 mL) and the cone tip was slowly increased as the cone was formed avoiding vibration. A circular aperture with a diameter from 6.0 to 15.0 mm was used; the smallest diameter of an orifice through which the powder sample flowed freely was chosen for each sample experimentally to avoid any segregation, consolidation and/or aeration of the powder heap. The static angle of repose, SA (°), was calculated using Eq. (2) from the height of the cone h (mm) and the diameter of the base d (mm).

$$tgSA = \frac{h}{0.5 \cdot d} \tag{2}$$

The measurement was repeated ten times for each powder sample ($n = 10$).

Mass Flow Rate Through the Orifice

In accordance with the European Pharmacopoeia 9.0 (2.9.36), the mass flow rate of each powder sample was measured using an automated powder and granulate tester (Erweka, Germany) with the stainless steel conical hopper (200.0 mL) having an internal angle wall inclination of 40°. The general guideline that the dimension of the opening should be six times greater than the diameter of the particle was taken into consideration [6, 10]. The time (in seconds) was estimated for a 100.0 g powder sample to pass through a circular aperture with the diameter of 10.0 mm. The mass flow rate Q_{10} (g/s) was then calculated. The average of ten measurements for each powder sample was expressed ($n = 10$).

Avalanche Testing

The dynamic flow properties were measured in a rotating drum using the Revolution powder analyser (Revolution®, Mercury Scientific Inc., USA) with a digital camera (resolution of 648 × 488 pixel) for scanning of moving of powder during the avalanching and a computer software (Revolution® V3.00, Mercury Scientific Inc., USA). A drum consisting of an anodised aluminium ring and two borosilicate transparent glass plates and having a diameter of 110.0 mm and a width of 35.0 mm was used [28, 32]. The drum was filled with the constant sample volume of 118.3 mL using a calibrated cell. A sample was filled into the drum and inserted into the test instrument to initially rotate for 60 s (a preparation time) before the analysis was started for standardisation purposes. A drum rotation speed of 0.5 rpm was selected and the images were recorded at a rate of 10 frames/s. The data collection was set to 2048 data points (run time was 264 s). The avalanche angle, AA (°), from the centre point on the powder edge to the top of the powder edge was registered at the maximum position just before the avalanche occurrence started as illustrated in Fig. 2. The avalanche time, AT (s), was recorded as the average time between powder avalanche events. The avalanche energy, AE (kJ/kg), was calculated from the difference in the energy of the powder before and after the avalanche.

In addition, the surface fractal number was determined from the avalanche contour line of powder shadow images. Then, the bulk fractal dimension, bD_F, was determined: bD_F = (surface fractal number/100) + 1 [30, 33]. The average of the values detected for each avalanche was calculated and measurements were repeated with $n = 5$ for each powder sample.

Statistical Analysis

Data were processed in MS Excel in the standard way. The analysis of variance (ANOVA) at a significance level α of 0.05 was used for the evaluation of the influence of the addition of Rebaudioside A to Sorbitol or Lactopress Anhydrous to Excipress, respectively. Additionally, Tukey's multiple comparisons test was applied to these data (GraphPad Prism 7, version 7.03, GraphPad Software, Inc., USA). The calculation of the Spearman's rank correlation coefficient (SRCC) and Pearson correlation coefficient (PCC) were based on Statgraphics® Centurion XVI (version 16.2.4) (StatPointTechnologies Inc., USA).

Results and Discussion

In line with the objective to study powder flow by using a fractal approach, ten powder excipients of different flow characteristics were selected. The selected materials are used in pharmaceutical technology for the production of solid dosage forms (e.g. tablets and capsules). The samples included an aluminium metasilicate, Neusilin US2 (N), that is a promising carrier for liquisolid systems [34]; fillers for tablet compression: Sorbitol (S), a spray-dried lactose Excipress (EP), a granulated lactose Lactopress Granulated (LPG), a spray-agglomerated lactose Tablettose 80 (TB80), an anhydrous lactose Lactopress Anhydrous (LPA), for filling of capsules and sachets: a sieved lactose SpheroLac 100 (SPL100), for wet and dry granulation: a milled lactose GranuLac 70 (GL70) or a Lactose PP (LPP) used in food industry. Finally, a new

alternative sweetener, Rebaudioside A, with a very high sweetening power [35], was included too.

In order to study the influence of particle size on the flow properties, four particle size fractions (in a range of 80–400 μm) were prepared for the free flowable excipient Sorbitol. Moreover, powder blends of Sorbitol and Rebaudioside were prepared in a concentration of 0.2% *w/w* (S-0.2RA) and/or 0.5% *w/w* (S-0.5RA), respectively. Furthermore, mixtures of lactose of good (Excipress) and poor (Lactopress Anhydrous) flow properties were also tested to analyse the impact on the flow properties and to compare with the pure substances.

Generally, higher moisture content increases the cohesivity of powders and reduces the flowability [4]. Because some pharmaceutical powders are hygroscopic, the moisture content was measured by a loss on drying (LOD) method. Apart from Neusilin US2 and Rebaudioside A, the LOD (%) was always less than 1.0% ($n = 5$). Percentages of moisture content of N and RA of 3.9 and 3.1%, respectively, were registered. All analytical and preparation work was carried out as mentioned above at a controlled ambient temperature and relative humidity.

Powder Properties of Samples

The static light scattering method was used to determinate the particle size and size distribution, PSD, of excipients used. The particle size and shape are well-known key factors for good powder flow. Irregular, small, fine and agglomerated particles as well as samples having a large particle size distribution generally result in flow difficulties [2, 11]. The particle sizes x_{10}, x_{50} and x_{90} of powder samples are summarised in Table 1. Data are completed with the span showing the width of particle size distribution. The mean particle size x_{50} in the range of 125–248 μm was detected for eight out of ten powders evaluated; a mean particle size of 94 μm was noted for GranuLac 70. The largest spans were registered for LPP and LPA (2.07 and 2.38, respectively) showing a large distribution of particle size. The finest particles ($x_{50} = 8$ μm) were observed for RA whose span of 2.95 appeared to be a function of the small median particle.

Data in Table 1 are completed with the Brouckere mean diameter $d_{(4/3)}$ (μm). The values of $d_{(4/3)}$ were similar to that of x_{50} for all substances investigated excluding that of RA. As the volume mean diameter of particles, it is affected by the sphericity of particles [36]. Therefore, the irregular and columnar particle habitus of Rebaudioside A exhibited a $d_{(4/3)}$ that was about twice that of x_{50}. In the last column of Table 1, the particle shape of powder excipients is described and this morphology is also illustrated in the SEM micrographs given by Fig. 1a–j.

Particle static and dynamic flow properties are of special importance in pharmaceutical manufacturing. However, flow characterisation methods analyse flow properties essentially for given testing conditions. Flow is influenced by the properties of a powder as well as by the external conditions used [3, 4]. This should be differentiated from powder properties that are static but may hold for a predictor of powder flow.

Pharmaceutical powders are, for example, characterised by bulk and tapped densities. The average results of ten measurements of d_c (g/mL) and d_t (g/mL) for powder substances are listed in Table 2 with the standard deviations (SD) in brackets. However, the bulk density is directly associated with the particle size, their structure, size distribution and the arrangement in a powder bed [37, 38]. Being an apparent density, it includes the void volume between the particles and the contribution of the inter- and intraparticular pores. Generally, finer particles agglomerate and entrap a high portion of air, which decreases bulk density. However, similarly sized particles may organise less efficiently than distributions with a wider range of particle sizes as has been shown, for example, with microcrystalline celluloses [39]. Out of ten powders evaluated, the lowest value of d_c was noted for Neusilin US2 (0.160 g/mL), a highly porous aluminium metasilicate (Fig. 1a), and Rebaudioside A (0.355 g/mL), a very fine powder (Fig. 1b).

The Hausner ratio (HR) obtained from the ratio of tapped to bulk density is one of the classical measures of powder flow. According to the detected HR in the range of 1.13–1.30 (Table 2), the evaluated powder excipients can be divided into three categories of flow behaviour. The first group with good flow properties included Neusilin US2, Sorbitol and Excipress. The middle category of fair flow included Lactopress Granulated, Tablettose 80, SpheroLac 100, GranuLac 70 and Lactose PP. Finally, a third group of relatively poorer but still acceptable flow properties consisted of small and cohesive particles of Rebaudioside A and Lactopress Anhydrous. For the latter, the highest change in volume after tapping was observed. As mentioned above, HR is often a useful measure of powder packing efficiency, but it is necessary to compare results with other methods to fully assess powder flow.

Results for four size fractions of Sorbitol in a range of 80–400 μm (S100, S158, S245 and S346) are summarised in Table 3. No effect of particle size on the values of the Hausner ratio (1.13–1.15) was observed. On the other hand, addition of fine, cohesive RA (0.2%, 0.5%) caused a slight increase of the HR when compared to Sorbitol itself although the blends are included in a group with good flow properties (Table 3). In Table 3, the results for mixtures of LPA and EP are also shown. The worsening effect of LPA addition on bulk and flow properties of EP was directly proportional to the increasing amount of LPA in the mixture due to the fine, agglomerated LPA particles.

The static angle of repose (SA) represents the most common simple demonstration of flow behaviour. The powder should flow freely onto the base from the hopper until a cone

Table 1 Granulometric characteristics of used powder substances. Standard deviations for particle fractal dimension, pD_F, in brackets ($n \cong 200$)

Material	x_{10} (μm)	x_{50} (μm)	x_{90} (μm)	span	$d_{(4/3)}$ (μm)	pD_F	Shape and structure
N	60	129	234	1.35	139	1.088 (0.015)	Regular, rounded, porous surface
RA	2	8	26	2.95	16	1.072 (0.012)	Irregular, columnar, agglomerated
S	119	248	445	1.31	283	1.064 (0.008)	Regular, angular, rough surface
EP	49	178	304	1.43	180	1.069 (0.008)	Regular, rounded, rough surface
LPG	60	155	280	1.42	164	1.064 (0.007)	Regular, rounded, rough surface
TB80	53	190	372	1.68	202	1.075 (0.013)	Regular, rounded, rough surface
SL100	32	135	221	1.40	134	1.069 (0.006)	Regular, angular, smooth surface, sharp-edged
GL70	14	94	179	1.76	95	1.074 (0.012)	Regular, angular, rough surface, sharp-edged
LPP	18	130	287	2.07	146	1.075 (0.014)	Regular, angular, smooth surface, sharp-edged
LPA	11	125	308	2.38	144	1.071 (0.007)	Regular, angular, rough surface, sharp-edged, agglomerated

is completely formed. The results for the powder samples are listed in Table 2. In agreement with the general flowability scale [5], excellent flow properties (SA = 30°) were detected only for Neusilin US2. The excipients used in direct compression, Sorbitol and Excipress, demonstrated good flow properties indeed (SA approximately 34° and 35°, respectively), whereas rather fair flow properties were observed for LPG, TB80, SL100, GL70 and LPP. As can be seen in Table 2, a high variability of SA was detected for GL70 (SD = 1.79) and LPP (SD = 2.06). Typical problems of passage through a hopper orifice were observed for these materials, i.e. formation of craters and occasional blockage of the flow, which entails the necessity to tap the hopper. In the case of Rebaudioside A and LPA, the estimation of SA was impossible because of the creation of arches above the orifice due to particle cohesion.

Values of static angle of repose for four particle size fraction of Sorbitol are summarised in Table 3. A slightly higher value of SA was detected for the smallest size fraction (S100) due to finer and more cohesive particles in comparison to the other size fractions (S158, S245, S346). When the mixtures were studied, however, the addition of RA to Sorbitol did not affect the formation of a powder cone of Sorbitol. In contrast, increased values of SA were noted for blends of LPA with EP as the amount of LPA in the mixture was increased. The gradual increase in the cohesive effect of LPA particles led finally to blockage of the flow for 1EP-3LPA and the estimation of SA was again impossible.

Evaluation of Flow Rate

The evaluation of flow rate through a hopper orifice represents a classical method for flowability testing [3, 38] which is primarily recommended for free-flowing powders that exhibit a uniform flow without failures. In this work, a 200.0-mL conical stainless steel hopper was uniformly filled with 100.0 g of powder. In the case of Neusilin US2, however, only 20.0 g could be used, as this is a very voluminous material. In order to compare the discharge rate of powder samples investigated, the same orifice size having a diameter of 10.0 mm

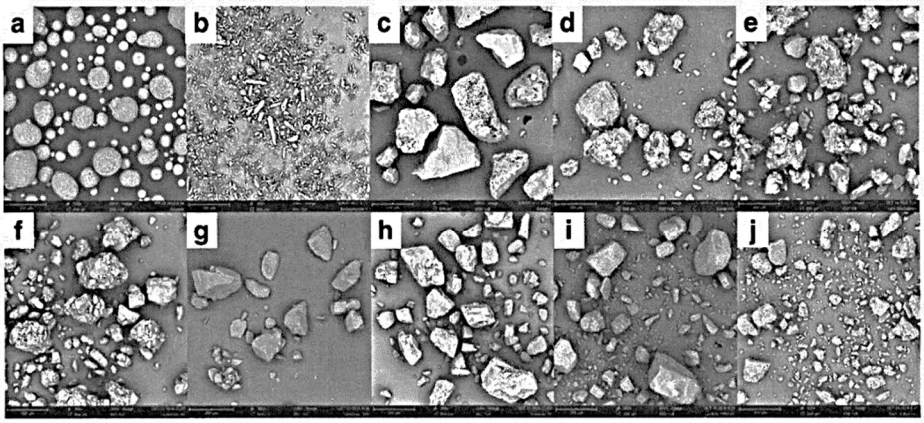

Fig. 1 SEM pictures (magnification of ×300) of **a** Neusilin US2, **b** Rebaudioside A, **c** Sorbitol, **d** Excipress, **e** Lactopress Granulated, **f** Tablettose 80, **g** SpheroLac 100, **h** GranuLac 70, **i** Lactose PP and **j** Lactopress Anhydrous

Table 2 Bulk and flow characteristics of powder substances with standard deviations in brackets ($n = 10$)

Code	d_c (g/mL)	d_t (g/mL)	HR	SA (°)	Q_{10} (g/s)
N	0.160 (0.002)	0.182 (0.001)	1.14 (0.02)	30.2 (0.44)	0.49 (0.01)
RA	0.355 (0.006)	0.458 (0.005)	1.29 (0.02)	NF	NF
S	0.666 (0.006)	0.752 (0.015)	1.13 (0.02)	33.8 (0.24)	9.71 (0.07)
EP	0.658 (0.006)	0.773 (0.003)	1.17 (0.01)	35.4 (0.42)	4.79 (0.14)
LPG	0.527 (0.002)	0.650 (0.003)	1.23 (0.01)	37.6 (0.23)	5.22 (0.04)
TB80	0.590 (0.006)	0.728 (0.003)	1.23 (0.01)	38.0 (0.43)	4.72 (0.08)
SL100	0.667 (0.008)	0.831 (0.003)	1.25 (0.01)	37.6 (0.16)	5.32 (0.13)
GL70	0.697 (0.008)	0.866 (0.007)	1.24 (0.01)	37.2 (1.79)	NF
LPP	0.738 (0.013)	0.905 (0.010)	1.23 (0.02)	40.2 (2.06)	NF
LPA	0.590 (0.017)	0.767 (0.008)	1.30 (0.03)	NF	NF

NF no flow

was used. The mass discharge rate Q_{10} (g/s) was calculated from the registered time in seconds.

In the last column of Tables 2 and 3, the average of ten measurements of Q_{10} (g/s) is presented for the powder substances and/or size fractions and mixtures, respectively. Excellent flow was noted only for Sorbitol (9.71 g/s). In the order of SL 100 > LPG > EP > TB80, a decrease in flow rate was registered for lactose powders. In the case of GL 70, LPP, LPA and RA, an uneven flow pattern or occasional arch formation above the hopper orifice was observed due to the cohesive forces between particles and the powder did not pass through the orifice diameter used.

The particles of Neusilin US2 were spherical (Fig. 1a) with a mean particle size of 129 μm (Table 1), and therefore, a good powder flow would be expected. Interestingly, the discharge rate Q_{10} (g/s) of a rather moderate 0.48 g/s was recorded. This was likely due to the very low density ($d_c = 0.160$ g/mL) associated with the porous structure and the release of the entrapped air from the material bulk that flow under gravity conditions was complicated. Moreover, the electrostatic forces between the particles also reduced the flow through the hopper orifice.

As can be seen in Table 3, the mass flow rate increased with the particle size of Sorbitol fractions. A non-linear dependence between the mean particle size and the flow rate was registered previously having the maximum of Q_{10} for particles of 245 and 346 μm [31].

In Table 3, the results of the mass flow rate estimation are summarised for all mixtures tested as well. The significant (ANOVA, p value < 0.0001 at $\alpha = 0.05$), concentration-dependent influence of adding Rebaudioside A on the gravitational flow rate of Sorbitol was noted; the flow rate decreased in order 9.71 g/s (S)–9.59 g/s (S-0.2RA)–9.43 g/s (S-0.5RA). The results were additionally tested using Tukey's multiple comparisons test, which resulted in the same conclusion (p value < 0.0001 at $\alpha = 0.05$). Similarly, to the results of angle of repose measurement, a higher proportion of Lactopress Anhydrous resulted in relatively lower Q_{10}. Finally, blockage of the hopper orifice was observed (no flow) for the mixture 1EP-3LPA due to the cohesive forces induced by LPA small particles.

Avalanching with Dynamic Image Analysis

Following a characterisation with the more classical methods of powder flow, avalanche testing and fractal bulk properties were evaluated in line with the study objectives. The employed test instrument was equipped with a dynamic image

Table 3 Bulk and flow characteristics of size fractions and mixtures. Standard deviations in brackets ($n = 10$)

Code	d_c (g/mL)	d_t (g/mL)	HR	SA (°)	Q_{10} (g/s)
S100	0.561 (0.003)	0.647 (0.003)	1.15 (0.00)	34.5 (0.26)	6.69 (0.08)
S158	0.602 (0.004)	0.681 (0.006)	1.13 (0.00)	33.6 (0.36)	9.28 (0.03)
S245	0.621 (0.005)	0.707 (0.005)	1.14 (0.00)	33.8 (0.36)	10.3 (0.14)
S346	0.642 (0.003)	0.726 (0.005)	1.13 (0.00)	33.7 (0.51)	10.4 (0.10)
S-0.2RA	0.647 (0.005)	0.736 (0.008)	1.14 (0.01)	33.8 (0.26)	9.59 (0.04)
S-0.5RA	0.643 (0.004)	0.736 (0.003)	1.15 (0.01)	33.8 (0.20)	9.43 (0.03)
3EP-1LPA	0.673 (0.007)	0.799 (0.010)	1.19 (0.02)	36.8 (0.20)	3.59 (0.06)
1EP-1LPA	0.662 (0.016)	0.822 (0.020)	1.24 (0.02)	38.8 (0.20)	2.83 (0.13)
1EP-3LPA	0.645 (0.007)	0.819 (0.009)	1.27 (0.02)	40.3 (0.27)	NF

NF no flow

analysis of the entire drum as used before to characterise pharmaceutical materials by Nalluri and Kuentz [28] and Nalluri et al. [29]. The present study used a drum size of 110.0 mm that was filled with a constant volume of powder (118.3 mL), which occupied 36.0% of the total drum volume. A constant rotational speed of 0.5 rpm was selected for all material samples. In Tables 4 and 5, the average of five measurements of the avalanche parameters: the avalanche angle AA (°), the avalanche time AT (s) and the avalanche energy AE (kJ/kg), are presented for ten powder excipients, four sorbitol size fractions and five powder mixtures.

As a result, different avalanche regimes from slumping, cascading to cataracting [40, 41] were observed for the 19 samples tested. This enabled the classifying of materials into three groups as illustrated in Fig. 2a–e. Slumping behaviour was found for Sorbitol (Fig. 2a), its size fractions S245 and S346 and its mixtures with Rebaudioside A (S-0.2RA, S-0.5RA). Cascading behaviour was observed for most of the samples: SpheroLac 100 (Fig. 2b), Excipress, Lactopress Granulated, Tablettose 80, Neusilin US2 (Fig. 2c), the sorbitol size fractions S100 and S1580 and the 3EP-1LPA mixture. Finally, the cohesive powders: Lactopress Anhydrous (Fig. 2d), GranuLac 70, Lactose PP and Rebaudioside A (Fig. 2e) as well as the mixtures 1EP-1LPA and 1EP-3LPA exhibited cataracting behaviour.

The avalanche angle AA (°) at the maximum position just before the avalanche (see Fig. 2) and the time between avalanches AT (s) during a total experimental run of 264 s were automatically recorded. From the difference in the energies of the powder before and after the avalanche, the avalanche energy AE (kJ/kg) was calculated. The results are summarised in Tables 4 and 5. An increase in AA and AE and a relatively lower number of avalanches per time interval (i.e. increase in avalanche time AT) can be expected for cohesive particles, which is in line with previous work using multivariate analysis [30, 32, 33, 42]. The values of AA of samples in the range of 37.08°–59.62°, the AE in the range of 9.60–51.10 kJ/kg and the AT in the range of 2.02–5.42 s are listed for the different samples.

Table 4 Dynamic parameters of powder substances with standard deviations in brackets ($n = 5$)

Code	AA (°)	AE (kJ/kg)	AT (s)	bD_F
N	41.0 (0.3)	9.60 (0.35)	2.02 (0.08)	1.015 (0.000)
RA	46.8 (1.7)	51.10 (5.86)	5.42 (0.59)	1.084 (0.007)
S	37.9 (0.1)	15.48 (0.25)	2.54 (0.05)	1.016 (0.000)
EP	48.0 (0.6)	18.47 (0.92)	2.80 (0.14)	1.016 (0.000)
LPG	49.6 (0.4)	18.81 (0.83)	2.78 (0.13)	1.018 (0.001)
TB80	49.1 (0.2)	19.55 (0.51)	2.88 (0.08)	1.017 (0.000)
SL100	51.5 (0.6)	20.06 (0.67)	2.62 (0.08)	1.020 (0.001)
GL70	58.5 (0.8)	26.53 (2.04)	3.08 (0.26)	1.032 (0.002)
LPP	54.4 (0.5)	23.03 (1.02)	2.92 (0.13)	1.022 (0.001)
LPA	59.6 (1.0)	36.88 (1.79)	4.28 (0.18)	1.047 (0.001)

Table 5 Dynamic parameters of size fractions and mixtures with standard deviations in brackets ($n = 5$)

Code	AA (°)	AE (kJ/kg)	AT (s)	bD_F
S100	45.6 (0.5)	12.37 (0.66)	2.54 (0.11)	1.015 (0.001)
S158	39.4 (0.7)	12.45 (1.14)	2.58 (0.13)	1.014 (0.001)
S245	37.7 (0.3)	15.96 (0.76)	2.60 (0.10)	1.016 (0.000)
S346	37.1 (0.1)	16.99 (0.15)	2.72 (0.04)	1.017 (0.000)
S-0.2RA	37.9 (0.2)	15.03 (0.49)	2.50 (0.07)	1.016 (0.000)
S-0.5RA	38.0 (0.2)	15.12 (0.76)	2.52 (0.11)	1.016 (0.000)
3EP-1LPA	52.6 (0.5)	20.51 (0.68)	2.60 (0.12)	1.023 (0.001)
1EP-1LPA	56.6 (0.7)	25.77 (1.27)	3.06 (0.15)	1.030 (0.002)
1EP-3LPA	59.3 (1.0)	31.05 (1.41)	3.62 (0.08)	1.040 (0.002)

The correlation between the avalanche energy AE (kJ/kg) and the avalanche time AT (s) is shown in Fig. 3. It is visible that the powder samples are positioned according to their avalanching pattern as explained above. The materials that exhibit slumping (circles) are located in the bottom part, the cascading ones (crosses) in the middle (with the exception of Neusilin US2 and two sorbitol fractions as discussed below) and the cataracting ones (squares) in the upper part of Fig. 3. In order to describe how well the experimental data correlate, Spearman's rank correlation coefficient (SRCC) and Pearson correlation coefficient (PCC) were estimated. The former is a non-parametric measure that can also test for non-linear relationships, whereas the latter Pearson correlation is a test for linear association that can be also more sensitive to individual outliers. Relatively high values were detected for SRCC and PCC of 0.68 ($p = 0.0041$) and 0.74 ($p = 0.003$), respectively. Powders with increasing cohesivity obviously resulted in more pronounced avalanche events of higher energy.

The lowest AE (9.60 kJ/kg) as well as the shortest AT (2.02 s) was interestingly observed for Neusilin US2. This was in line with the excellent flow properties that were expected from particle morphology and marks a difference in the flow conditions through the hopper orifice, for which other flow results were obtained. However, the interparticle electrostatic forces were considered to cause a slight tendency to form cascades (Fig. 2c). In contrast, an avalanche time of 5.42 s was detected for Rebaudioside A located at the top of Fig. 3.

Direct proportionality between the particle size and AA was evidenced for Sorbitol size fractions; AA decreased from 45.6° to 37.1° (Table 5). This was in close agreement with higher cohesive forces for smaller particles detected previously using the Jenike shear tester [31]. Interestingly, the larger particle size fractions resulted here in higher avalanche parameters AE and AT (Table 5). Reducing the particle size with an increase of voids and pores may have led to a reduced density of aggregates that were in turn dominating flow so that

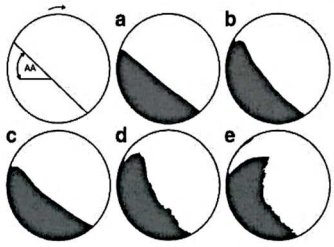

Fig. 2 Measurement of avalanche angle, AA (°). Schematic avalanche regimes of **a** Sorbitol (slumping), **b** SpheroLac 100 (cascading), **c** Neusilin US2 (cascading), **d** Lactopress Anhydrous (cataracting) and **e** Rebaudioside A (cataracting)

avalanching likely becomes less energy-consuming [43]. Another aspect is that initial particle size of the materials can differ from in situ generated aggregates that are relevant for powder flow. Thus, different mechanisms can play a role depending on a given material and flow conditions applied.

For the mixtures with Sorbitol, no detectable effect of adding RA 0.2 and 0.5 *w/w* % was observed (Table 5) and all samples showed slumping flow. This confirmed our previous results that effects of cohesive materials in very small amounts might be difficult to demonstrate with traditional testing methods [12]. On the contrary, more energy is needed to break down a powder bulk when increasing the proportion of Lactopress Anhydrous in the EP mixtures, which led to the expected increase in AA and AE, and prolonged AT (Table 5).

To compare the results of the static angle of repose measurement with the avalanche angle, the corresponding data are plotted in Fig. 4. The three groups of materials are arranged based on the obtained avalanche regimes (as discussed above) showing good correlation of the static and dynamic experimental results. Unfortunately, some data are missing because no SA was detected for RA and LPA (Table 2).

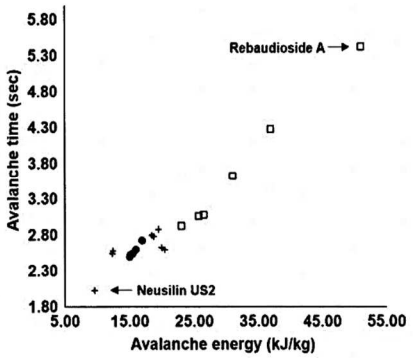

Fig. 3 Scatterplot of avalanche energy (kJ/kg) and avalanche time (s). The graph shows a slumping (black circle), cascading (cross) and cataracting (white square) regime of studied powders

Particle and the Bulk Fractal Dimension

It is well accepted that bulk flow properties are influenced by the individual particle characteristics. However, bulk flow is essentially an emerging property so the influence of individual particles can be for example less pronounced when more representative particle aggregates exist that dominate overall flow.

For individual particles, roughness of the surface boundary can be described by the fractal dimension [15–19]. The fractal dimension can be obtained from optical, scanning electron or atomic force microscopy using different methods, of which the structured walk technique or the box-counting method is often used [16, 19, 20, 44, 45]. A newer method of measuring a fractal dimension is by image analysis of the dynamic powder contour line in a rotating drum. The surface fractal contour dimension or the related number provides information about the roughness of bulk powders but, however, not about the individual particles [30].

In this work, the influence of the particle linear fractal dimension pD_F obtained from the box-counting method [16, 19, 20] (using an optical microscope with a digital camera) and the bulk fractal dimension, bD_F, obtained from powder avalanching was investigated.

The average values of pD_F are listed in Table 1. The pD_F is connected to the particle boundary and relates to its surface structure. For the available samples, there was a correlation with particle flow rate Q_{10} noted with PCC of -0.851 ($p = 0.032$) and a borderline SRCC of -0.853 ($p = 0.056$). However, some care is needed regarding final conclusions because Q_{10} was not measurable with all samples (Tables 2 and 3) so that the dataset was comparatively limited. Thus, the bulk fractal dimension became the focus of our study as it describes the structure of the powder bed surface. For the excipients tested, the results of bD_F values are summarised in Tables 4 and 5.

The extent of cohesive forces between particles was likely very important for higher values of bD_F. However, rather low values were found for most samples displaying slumping and cascading avalanche. The contour line of powder bulk is here rather smooth and not rugged (Fig. 2a–c), resulting in better

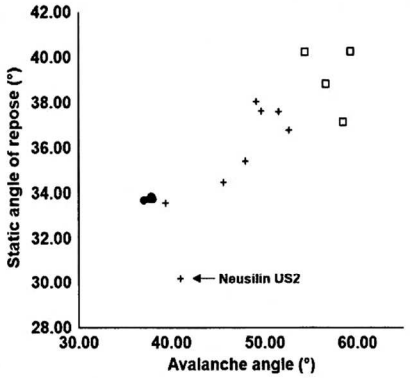

Fig. 4 Scatterplot of avalanche angle (°) and static angle of repose (°). The graph shows a slumping (black circle), cascading (cross) and cataracting (white square) regime of studied powders

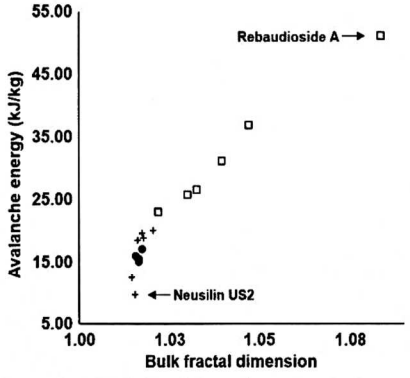

Fig. 6 Scatterplot of bulk fractal dimension and avalanche energy (kJ/kg). The graph shows a slumping (black circle), cascading (cross) and cataracting (white square) regime of studied powders

flow properties. In addition, no effect of particle size on bD_F (1.014–1.017) was observed for sorbitol fractions (Table 5), which was in agreement with the previous results for pD_F [31]. Values of 1.022, 1.032, 1.047 and 1.084 were detected for Lactose PP, GranuLac 70, Lactopress Anhydrous and Rebaudioside A, respectively, for which a cataracting avalanche was observed. In Fig. 2d, e, a rough and jagged contour line of bulk powder is illustrated. The cohesive forces between particles, particularly the small ones (Table 1), distinctly worsened the flow.

In the case of the studied powder mixtures, no noticeable effect of the addition of Rebaudioside A was observed on the bulk fractal dimensions of Sorbitol (1.016). On the other hand, the addition of Lactopress Anhydrous significantly influenced (ANOVA and Tukey's multiple comparisons test, p value < 0.0001 at $\alpha = 0.05$) the bD_F of Excipress (EP). With the increase in the amount of cohesive LPA, an increase in the bD_F was registered (Table 5). In consequence, the transition from a cascading (3EP-1LPA) to a cataracting avalanche (1EP-1LPA, 1EP-3LPA) occurred thereby reducing the flowability as mentioned above.

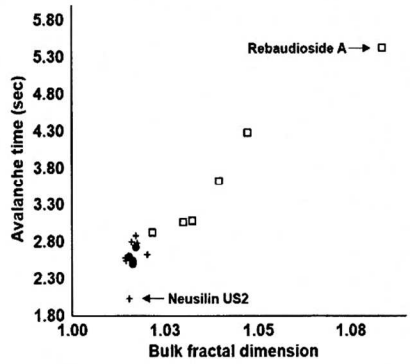

Fig. 5 Scatterplot of bulk fractal dimension and avalanche time (s). The graph shows a slumping (black circle), cascading (cross) and cataracting (white square) regime of studied powders

The relationship between the mass flow rate Q_{10} (g/s) and the bulk fractal dimension was studied. In accordance with the results in Tables 2 and 3, however, the highest values of Q_{10} were noted for the slumping samples with lowest values of bD_F, the contrary was true for the cataracting samples. Unfortunately, the flow rate data were incomplete again, as the cohesive samples did not pass through the 10.0-mm orifice. It seems that more data of Q_{10} would be needed and it is interesting to note that a previous study of powder flow testing identified bD_F as the most dominant influence on flow behaviour by using multivariate data analysis [30].

A relatively high linear coefficient (PCC) of 0.74 (p = 0.0003) was detected between the bulk fractal dimension bD_F and the avalanche time AT (s) for 19 studied powder excipients as illustrated in Fig. 5. The Spearman's rank correlation coefficient (SRCC) was lower 0.61 ($p = 0.0091$), which was expected for a non-parametric test describing the association of how values are ranked. In Fig. 6, a high positive correlation between the avalanche energy AE (kJ/kg) and the bulk fractal dimension is shown. The close association between the variables for all samples was documented with PCC and SRCC equal to 0.97 ($p = 0.0000$) and 0.95 (p = 0.0001), respectively.

In order to describe the relationship between the particle boundary surface structure and the bulk powder one for the excipient samples, the correlation between the fractal dimensions pD_F and bD_F was lastly investigated. Interestingly, no significant correlation was observed. In light of the previous findings, it seems that bD_F is an emergent property of dynamically moving particle assemblies (a macroscopic property), which is likely affected by a number of parameters but a relevant influence of pD_F (a microscopic property) was not observed here.

Conclusions

In conclusion, 19 pharmaceutical excipients including the particle size fractions and the powder mixtures of various flow behaviours were studied using different methods for flowability testing. The results of the standard test methods (e.g. Hausner ratio, the static angle of repose and the discharge rate through the hopper orifice) and the more recent method of dynamic image analysis in powder avalanching were compared. The main benefit of the latter method is that even more cohesive samples could be analysed, which was not the case with all classical methods, such as flow through an orifice. The relationship between avalanche energy and avalanche time was investigated and the data correlated well with the results of the flow properties of studied samples. The good flow properties of the powders were confirmed by low values of the avalanche energy and the short values of the avalanche time; the opposite was true for the cohesive powders. A high correlation was observed between the bulk fractal dimension estimated from the contour line of the powder bulk (at the moment of avalanching) and the avalanche energy. The higher values of bD_F as well as that of avalanche energy were detected for materials showing cohesive properties. In line with the main objective to study fractal aspects on flow properties, it was also interesting to compare pD_F with bD_F. The lack of a significant correlation underlined the emerging character of the dynamic geometric bulk properties under flow. Accordingly, bD_F is obviously not easy to predict from contour properties of individual particles. Finally, powder flow is certainly a multifactorial event for which fractal bulk properties merit further investigation. More research is also needed to better understand how the geometric aspects of the bulk are generated under different dynamic flow conditions.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Nomenclature AA avalanche angle (°), AE avalanche energy (kJ/kg), AT avalanche time (s), d diameter of the base (mm), d_c bulk density (g/mL), d_t tapped density (g/mL), $d_{(4/3)}$ volume mean diameter; De Brouckere mean (μm), h height of the cone (mm), HR Hausner ratio (−), LOD loss on drying (%), P perimeter (μm), Q_{10} mass flow rate for diameter of a hopper orifice of 10 mm (g/s), SA static angle of repose (°), V_0 bulk volume (mL), V_t tapped volume (mL), x_{10} particle dimension corresponding to 10% of the cumulative distribution (μm), x_{50} mean particle dimension corresponding to 50% of the cumulative distribution (μm), x_{90} particle dimension corresponding to 90% of the cumulative distribution (μm), λ length of steps (μm)

Abbreviations α level of significance, ANOVA analysis of variance, bD_F bulk fractal dimension, n number of replicas, N number of steps, p p value, PCC Pearson correlation coefficient, pD_F particle fractal dimension, PSD particle size distribution, SEM scanning electron microscopy, SD standard deviation, *span* width of the particle size distribution, SRCC Spearman's rank correlation coefficient

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Příloha 5 Postery

1. TRPĚLKOVÁ, Ž., **HURYCHOVÁ, H.,** ONDREJČEK, P., ŠKLUBALOVÁ, Z. Charakterizace tokového chování a lisovatelnosti celet, slibných nosičů léčiv, Technologické dni, Témy: Nové trendy v oblasti výskumu a vývoja liekov a Inovácie v oblasti zdravotníckych pomôcok, 25. - 27. 10. 2017, Štrbské Pleso

CHARAKTERIZACE TOKOVÉHO CHOVÁNÍ A LISOVATELNOSTI CELET, SLIBNÝCH NOSIČŮ LÉČIV

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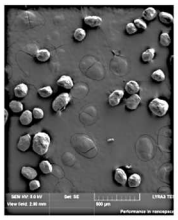
ÚVOD

Celety jsou považovány za ideální částice pro další technologické zpracování díky jejich kulatému tvaru, hladkému povrchu a úzké distribuci velikosti částic. Při jejich využití jako nosičů léčiv může být léčivá látka součástí pelety, nebo je na inaktivní jádro nanášena ve formě roztoku, anebo je k povrchu jádra přitahována adhezivními silami vznikajícími při tvorbě interaktivní směsi. Tato studie se zaměřuje na detailní charakterizaci celet – pelet vyrobených z mikrokrystalické celulosy.

MATERIÁLY



V této práci byly použity celety (Cellets® 100, Process-Center GMBH&Co. KG, Německo), které mají většinu částic v rozmezí 100-200 μm (1).

Obr. 1: SEM snímek Cellets® 100 (zvětšeno 140x)

METODY

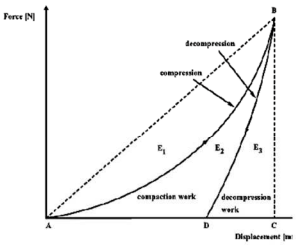
Distribuce velikosti částic byla stanovena pomocí analyzátoru velikosti částic Malvern Mastersizer. Tvar a povrch částic byl pozorován s využitím skenovacího elektronového mikroskopu TESCAN Lyra 3 GMH (Obr. 1). Na sušicích vahách Kern MLB 50-3 byl z 10 měření stanoven průměrný obsah vlhkosti v procentech.

Sypné vlastnosti

Sypná hustota (d_0) celet byla stanovena na Scottově volumetru. Setřesná hustota (d_{1250}) po 1250 sklepnutích byla určena na přístroji Erweka SVM 102. Následně byl spočítán index stlačitelnosti (*CI*) a Hausnerův poměr (*HR*) (2). Sypný úhel byl vypočítán z výšky a průměru kužele vytvořeného v souladu s Evropským lékopisem (Ph. Eur. 9.0, 2.9.36). Dynamické chování celet bylo hodnoceno v rotujícím bubínku Revolution® s digitální kamerou (rozlišení 648x488 pixel) pro snímání pohybu prášku během lavin. Rychlost sypání (Q) byla změřena na přístroji Erweka GT. Byla stanovena doba, za kterou došlo k vyprázdnění násypky obsahující 100.0 g látky. Byly použity otvory násypky s průměrem 6.0, 8.0, 10.0, 11.3 a 15.0 mm. Všechna měření byla opakována 10x.

Lisování tablet

Po kompletní charakterizaci suroviny byly z celet lisovány tablety o hmotnosti 500 mg a průměru 13.0 mm na přístroji pro testování materiálu Zwick/Roell T1 FRO 50. Tablety byly lisovány silou 10 kN a lisovací proces byl popsán metodou záznamu síla-dráha dle Ragnarssona (3). Při této metodě je nastaven určitý lisovací tlak (v tomto případě 10 kN), po jehož dosažení se lisovací trn začne vracet do své výchozí pozice. Výsledky lze poté zpracovat do grafu závislosti lisovací síly na dráze lisovacího trnu (Obr. 2).



A→B...stlačování materiálu
B→D...uvolnění a relaxace tablet
E_1 .....energie předlisování
E_2 .....energie plastická
E_3 .....energie elastická

Obr. 2: Metoda záznamu síla-dráha

Po kompaktaci byly tablety nechány 24 hodin v klidu, aby se vyrovnaly energie a síly vzniklé při lisování. Následně byl dle lékopisu zjištěn oděr tablet ve friabilátoru Sotax FT 2. Pevnost tablet byla vyjádřena jako radiální síla podle stanovení Fella a Newtona (4). Drticí síla byla měřena na přístroji pro testování pevnosti tablet Tablet Tester 8M.

PODĚKOVÁNÍ

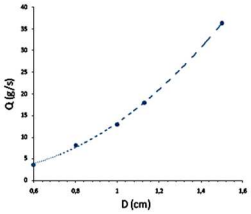
Tento výzkum byl podpořen z Grantové agentury Univerzity Karlovy grantem č. 322315/2015 a studentským projektem SVV 260 401.

VÝSLEDKY A DISKUZE

Základní naměřené charakteristiky jsou shrnuty v tabulce č. 1.

Tab. 1: Základní charakterizace Cellets® 100

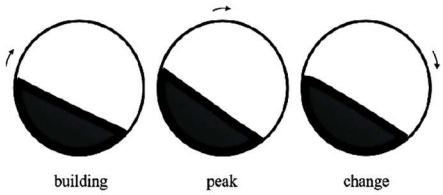
vlhkost (%)	5.35
x_{50} (μm)	142.50
AOR (°)	28.77
Q_1 (g/s)	12.92
d_0 (g/ml)	0.738
d_{1250} (g/ml)	0.858
HR	1.16
CI	13.97
AA (°)	33.78
AE (kJ/kg)	20.47



Obr. 3: Závislost rychlosti sypání na průměru otvoru násypky

Cellets® 100 mají kulatý tvar, hladký povrch a úzkou distribuci velikosti částic (span 0.5). Obsah vlhkosti odpovídal údajům uváděným výrobcem. Naměřený sypný úhel řadí tyto celety mezi látky s výborným tokem. Dle získaných hodnot Hausnerova poměru a indexu stlačitelnosti je však jejich tok charakterizován jako dobrý (ČL 2009). Rychlost sypání stoupá se zvětšujícím se otvorem násypky (Obr. 3); pro standardizaci rychlosti sypání lze doporučit otvor o velikosti 1 cm (Q_1).

Také v rotujícím bubínku vykazují částice celet velmi dobré tokové vlastnosti (slumping avalanche regime) s nízkým lavinovým úhlem (*AA*) a nízkou spotřebou energie (*AE*) (Obr. 4).



Obr. 4: Grafický záznam z měření v rotujícím bubínku

Uvedené velmi dobré tokové vlastnosti celet také korelovaly s nižší spotřebou energie při lisovacím procesu hodnoceném metodou záznamu síla-dráha. Po nasypání do matrice se celetové částice snadno uspořádají, a proto není potřeba dodávat velké množství energie k jejich přeskupení (Tab. 2).

Tab. 2: Energetické parametry ze záznamu síla-dráha

E_P(J)	3.10 (0.16)
E_L(J)	6.35 (0.04)
E_E(J)	1.85 (0.04)

Bohužel, u tablet vylisovaných z celet byla zjištěna velmi nízká radiální pevnost 0.287 MPa a nevyhovující 100% oděr. Tablety se rozpadaly již při testování ve friabilátoru.

ZÁVĚR

Výsledky této práce ukázaly, že Cellets® 100 mají výborné tokové vlastnosti, které vycházejí z jejich tvaru, povrchu a výsledků sypných charakteristik částicových materiálů. Jejich tokové chování se následně projevilo i v nižší spotřebě energie při lisovacím procesu. Avšak díky velmi nízké pevnosti tablet a vysokému oděru nelze dané celety použít jako samostatné plnivo při přípravě tablet. Abychom mohli využít jejich vynikající sypné vlastnosti a použít částice jako nosiče léčiv ve výrobě tablet, je potřeba přidat ještě jiná plniva, např. některá s vyšší plasticitou jako je mikrokrystalická celulosa, a získat tak směs s optimálními vlastnostmi pro lisování.

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2. STONIŠ, J., **HURYCHOVÁ, H.,** SKOŘEPOVÁ, Z., ŠKLUBALOVÁ, Z., ONDREJČEK, P., SVAČINOVÁ, P. Effect of new micronized silica excipient on promoting a disintegration time of orodispersible tablets, 11th Central European Symposium on Pharmaceutical Technology, 22nd-24th September, 2016, Belgrade, Serbia

EFFECT OF NEW MICRONIZED SILICA EXCIPIENT ON PROMOTING A DISINTEGRATION TIME OF ORODISPERSIBLE TABLETS

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INTRODUCTION

Orodispersible tablets (ODT) are innovative dosage forms. ODT disintegrate in mouth within 3 minutes (1). The most important parameters of ODT are disintegration time (DT) and tensile strength (TS) (2). These parameters have to be balanced well, so the ODT would disintegrate in mouth quickly and they would not need a special packing. In this research work, the focus was placed on disintegration time and its promotion. New excipient on the basis of micronized silica, Syloid 244 FP (3), was used as a glidant. ODT were prepared by direct compression of the granular powder made by fluid bed granulation process from different starches.

MATERIALS

Potato starch (PS) (Škrobárny Pelhřimov, Czech Republic), Corn starch (CS) (Roquette, France), Croscarmellose (CMC), Sodium starch glycolate (SSG) (Primellose, resp. Primojel generously gifted by DFE Pharma, Germany), PVP (Kollidon 25, BASF, Germany), Micronized silica (SY) (Syloid 244 FP, generously gifted by Grace, USA.

METHODS

Mixture of starch and superdisintegrant (10 %) was prepared. Granular powder was produced using the UniGlatt fluid bed granulator (Glatt GmbH, Germany) in a batch size of approximately 550 g, with the use of Kollidon 25 (10% aqueous solution). Four batches were prepared – CS CMC, PS CMC, CS SSG, PS SSG (Table 1).

The granular powder (Figure 1) was mixed with glidant (0.5 %) and and used for preparation of tablets having the mass 0.1 g and the diameter (D) 7 mm on material testing machine T1 FRO 50 (Zwick/Roell, GmbH, Germany). Tablets were pressed with different compression force (CF), to have the same innitial tensile strength of 1 MPa. (Table 2).

The mass (Analytical balance, precision 0.1 mg, HR 120, A&D, Japan), the diameter and the height (H) of tablets were estimated as well as the crushing force (CRF), tensile strenght (Tablet tester SCHLEUNIGER 8M, Pharmatron AG, Switzerland) and the disintegration time (Tablet disintegration tester ERWEKA ZT 301, Erweka GmbH). Results are listed in Table 2.

RESULTS AND DISCUSSION

Tablets were measured for disintegration time and for tensile strength after 24 hours. Syloid 244 FP decreases disintegration time of tablets and tablets compressed with SY as a glidant can be produced with lower compression force (Table 2), they are also possessing higher tensile strength after 24 hours after compression. Namely batches PS CMC SY and PS SSG SY showed best the results with satisfactory TS and DT ratios (Figure 2 a, b).

Table 1: Composition of prepared batches

Batch	CS	PS	CMC	SSG	PVP
PS CMC	-	+	+	-	+
PS SSG	-	+	-	+	+
CS CMC	+	-	+	-	+
CS SSG	+	-	-	+	+

Table 2: Parameters of produced tablets

Batch	CF (kN)	H (mm)	D (mm)	CRF (N)	TS (MPa)	DT (s)
CS CMC SY	3.00	2.29	6.97	19.25	0.77	79.00
PS CMC SY	5.00	2.07	6.94	24.00	1.07	81.83
CS SSG SY	3.00	2.34	6.97	18.00	0.70	70.33
PS SSG SY	2.50	2.33	6.94	15.75	0.62	34.83

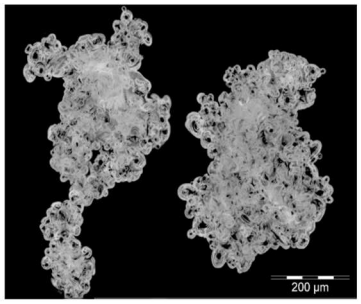

Figure 1: Microscopic picture of granular powder PS SSG produced by fluid bed granulation.

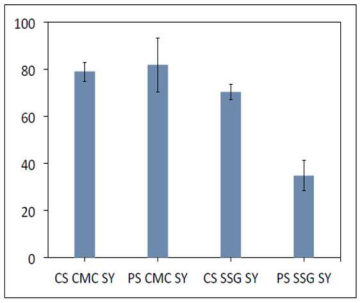

Figure 2 a: Disintegration time (s) of produced tablets

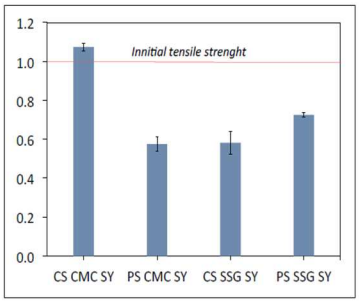

Figure 2 b: Tensile strenght (MPa) of produced tablets

CONCLUSIONS

Experimental data confirmed, that tablets with micronized synthetic amorphous silica gel (Syloid 244 FP), which was used as a glidant in the formulation, can be used as substitution for classic glidants such as Magnesium Stearate. Its influence on promoting disintegration time in comparisson with classic glidants will be further studied.

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ACKNOWLEDGEMENTS

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CESPT, BEOGRAD, 22nd to 24th September 2016

3. **HURYCHOVÁ, H.,** ŠKLUBALOVÁ, Z., SVĚRÁK, T., STONIŠ, J. The influence of magnesium stearate on the mass flow rate and shear behavior of Merisorb®200, 10th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, 4th-7th April, 2016, Glasgow, United Kingdom

THE INFLUENCE OF MAGNESIUM STEARATE ON THE MASS FLOW RATE AND SHEAR BEHAVIOR OF MERISORB®200

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INTRODUCTION

Evaluation of the flow and shear properties is very important for the handling, storage and transportation of particulate material as well as for the processes of blending, homogenization and dosing of active substances and excipients in production of solid dosage forms. To avoid any discharge problems, determination how material flows is necessary. To increase the flow of powders, glidants such as magnesium stearate is usually used.

The flow behaviour of powders mostly depends on the internal friction between individual grains of the material. For evaluation of the flow behavior of powders, various methods can be used.[1] Out of the standard pharmacopoeial methods (Ph. Eur., 2.9), the measurement of the mass flow rate through an orifice of the hopper is believed one of the best. Recently, the particulate materials are also described using the avalanching[2,3] and shear[4] behavior. Shear cell methodology has been used intensively to obtain a wide variety of the flow parameters, including the cohesion, the angle of internal friction, the flow function, etc.

This work studies the influence of magnesium stearate (MgSt) 0.5 wt% and/or 1.0 wt%, respectively, on the mass flow rate Q (g/s) of sorbitol for direct compression, Merisorb®200 (MS 200), through a circular orifice of the conical stainless-steel hopper were evaluated. The influence of the concentration of MgSt on the flow function and cohesion of MS 200 was studied using Jenike shear tester.

EXPERIMENTAL METHODS

MATERIALS

Sorbitol for direct compression (Merisorb® 200, MS 200; Tereos Syral SAS Nesle) and magnesium stearate (MgSt; Acros Organics) were used. The sample morphology of MS 200 was investigated using scanning electron microscopy (SEM) with a FEG electron gun (FIB-SEM TESCAN LYRA3GMU) at acceleration voltage of 5 kV (Figure 1).

The mixtures of MS 200 and MgSt 0.5 wt% and 1.0 wt%, respectively, were prepared by mixing the substances for 2.5 min at 18 rpm in the cube mixer (Erweka, Germany). Each powder mixture was prepared in total amount of 400 g.

METHODS

The measurement conditions were in accordance with the European Pharmacopoeia (8.8) for measuring the bulk density and the mass flow rate through the circular orifice of a hopper. All measurements and manipulations were carried out at a controlled ambient temperature of 21.5 ± 0.5 °C and relative air humidity of 30.0 ± 1.0 %.

MEASUREMENT OF BULK DENSITY

The bulk density of MS 200 and its mixtures with 0.5 wt% and 1.0 wt% of MgSt was determined by Scott's volumeter (Copley, United Kingdom) in accordance with the European Pharmacopoeia (Ph. Eur., 2.9.34). The powder was layered into a cylindrical stainless cup (25.00 ± 0.05 ml). The bulk density d_b (g/ml) was calculated from a known volume of the cylindrical cup, and the weight of the powder. Table 1 lists the average for ten repetitions of measurements with the relative standard deviations (RSD) of less than 1.0 %.

MEASUREMENT OF THE MASS FLOW RATE

In accordance with the European Pharmacopoeia (Ph. Eur., 2.9.36), the mass flow rates of MS 200 and its mixtures with 0.5 wt% and 1.0 wt% of MgSt were measured using a stainless steel conical hopper with a capacity of 200.0 ml having an internal angle wall inclination of 40° (Granulate tester GTB, Erweka, Germany). The time it took for 50.0 g of powder was pass-through the circular aperture with the diameter of 1.0 cm was estimated. The mass flow rate Q (g/s) was then calculated from the measured pass-through time. The mean for ten repetitions of measurements, the relative standard deviations of which were less than 2.0 %, is presented in Table 1.

BULK PROPERTY MEASUREMENT BY JENIKE SHEAR TESTER

The Jenike shear tester (Figure 2) was used for measuring the flow and shear properties of MS 200 and its mixtures with 0.5 wt% and 1.0 wt% of MgSt in accordance with the recommendations of ASTM (D6128-14). The geometry of the shear tester is referred to in Table 2. The constant speed of 4 mm/min was used for the force-measuring pin.

The shear test proceeded in the three phases. As first, the powder was over-filled into the standard shear tester and correctly consolidated using the normal stress σ of 10.36 kPa and twenty twist cycles. The consolidated sample was subsequently subjected to shear at the same normal stress to achieve steady state (preshear point, P). To measure the actual values of shear stress τ, the normal stresses with decreasing values of the normal stress in sequence of 7.87 kPa, 5.37 kPa and 2.87 kPa were used. Three shear points (S_1-S_3) were identified. To evaluate of the results, a yield locus of this shear stress vs. the reduced load was obtained using the Mohr's circle analysis (GeoGebra SW) from which the basic characteristics of the samples were determined. The shear parameters are listed in Table 1.

RESULTS AND DISCUSSION

The flowability of powder materials is usually influenced by the addition of glidants such as magnesium stearate or colloidal silica. Sorbitol is general considered as a free-flowing excipient. Under such circumstances, a lubricant (e.g. MgSt) is used particularly to prevent adhesion of tablets on the die or punch wall.[5]

In the left part, Table 1 summarizes the bulk density d_b (g/ml) and the mass flow rate Q (g/s) through a circular orifice of the conical hopper for MS 200 and its mixtures with MgSt. The orifice diameter of 1.0 cm was used which is the most often used in testing of flowability in the pharmaceutical technology. Although sorbitol is free-flowable, the positive effect of MgSt can be observed. The higher Q was noted with the addition of MgSt 0.5 wt% than 1.0 wt%. This result is in the agreement with the literature.[6]

Figure 3 illustrates the analysis of Mohr's circles of the σ-τ relationship for MS 200 showing the shear points (S_1-S_3), the preshear point (P), the major principal stress (σ_1), the yield locus (YL), and the effective yield locus (EYL). In Figure 4, the detail of the Mohr's circles analysis of the σ-τ relationship for MS 200 is illustrated with the unconfined yield strength (σ_c), the cohesion (τ_c), the angle of internal friction (Φ_i), the effective angle of friction (Φ_e), the yield locus (YL), and the effective yield locus (EYL). In the right part of Table 2, shear parameters are summarized.

Generally, excipients for direct compression are expected to be free-flowable, non-cohesive materials. For MS 200 and its mixtures with MgSt, the very low values of the cohesion were detected. This is in a good agreement with the obtained flow function (ff_c) values greater than 10. The best results were observed with the addition of 0.5 wt% of MgSt again.

Table 1. The mass flow rate and shear characteristics of MS 200 and its mixtures with 0.5 wt% and 1.0 wt% of MgSt.

	d_b (g/ml)	Q (g/s)	σ_1 (kPa)	σ_c (kPa)	τ_c (kPa)	Φ_i (°)	Φ_e (°)	ff_c
MS 200	0.631	9.60	14.92	0.052	0.018	21.76	20.87	286.92
MS 200-0.5 wt% MgSt	0.695	11.06	14.50	0.022	0.008	22.03	22.04	655.88
MS 200-1.0 wt% MgSt	0.683	10.46	14.56	0.050	0.017	20.26	20.40	294.14

Table 2. Characteristics of the shear tester.

	Base	Shear ring	Shear cover
Diameter (m)	0.100	0.100	0.099
Height (m)	0.0190	0.0160	0.002
Weight (kg)	0.3166	0.1136	0.0980
Volume (m^3)	0.0001492	0.0001256	---
Area (m^2)	0.007850	---	0.007694

CONCLUSION

The flowability of a bulk solid depends on the cohesive forces between individual particles. Free-flowable excipients are preferred in the direct compression of the tablets, however, lubricants are used to reduce the friction during compression and ejection process. The very low values of the cohesion and very high values of the flow function for MS 200 were detected. We verified the excellent flow properties of MS 200. MgSt increased the mass flow rate of MS 200 through the opening of a conical hopper and the flow function and decreased the cohesion properties. The better results were observed with 0.5 wt% addition of MgSt.

Figure 1. SEM picture of MS 200.

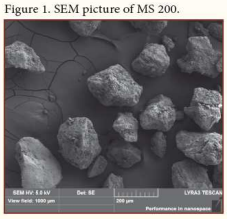


Figure 2. The Jenike shear tester.

Figure 3. The Mohr's circle analysis of the σ-τ relationship for MS 200.

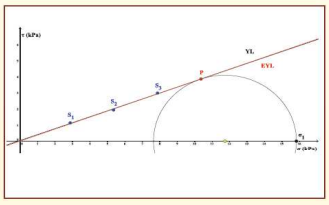
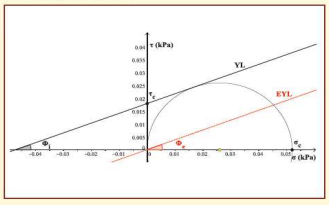


Figure 4. Detail of the Mohr's circle analysis of the σ-τ relationship for MS 200.



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4. STONIŠ, J., ŠKLUBALOVÁ. Z., ONDREJČEK, P., SVAČINOVÁ, P., **HURYCHOVÁ, H.** Evaluation of water absorption rate of tablets by using enslinneff, poster, Technologický den, 3. 9. 2015, Farmaceutická fakulta, Veterinární a farmaceutická univerzita Brno

EVALUATION OF WATER ABSORPTION RATE OF TABLETS BY USING ENSLIN-NEFF

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INTRODUCTION

Orodispersible tablets (ODT) are recently very popular dosage forms. Ease of administration, quick effect, economical and efficient production are main advantages of the ODT. The good mechanical strength and the fast disintegration are the most important properties of ODT for a producer. To evaluate ODT, the same test methods as for classic tablet can be used. Except for the latter, further methods, such as water absorption rate, can be useful to evaluate the tablet properties.

In the water absorption rate test, time and the volume of liquid, that tablet absorbs, are measured. The method proposed by Bi et al.[1] or the apparatus for measuring disintegration time of vaginal tablets and suppositories can be used. In this work, the Enslin-Neff device (Figure 1), generally used in testing of clays and soils in geology [2], is utilized. Main aim of the research work was to evaluate correlation between water absorption rate data with data gathered from friability, the disintegration time and the radial strength measurements.

Figure 1: Detail of Enslin-Neff device

MATERIALS

Corn starch, food grade, (Roquette, France); food grade Lactose (Lactalis, Italia); povidone (Kollidon® 25, BASF GmbH, Germany); and Magnesium stearate (JRS Pharma GmbH and Co KG, Germany).

EXPERIMETAL METHODS

All the measurements were performed at the controlled ambient conditions (24 ± 1°C, relative air humidity of 46 ± 4%).

Corn starch (500 g) was dyed with an aqueous solution of purple red (300 g, 0.4%), using a fluid bed granulator (UniGlatt, Glatt GmbH, Germany) with a Wurster adaptor. Solution was sprayed with speed 7.1 g/min and air flap was set in position 80 – 70° (Temperature of granulation chamber 50 – 60 °C and outlet temperature 25 – 35 °C). Three batches of the dyed corn starch were produced. The dyed corn starch was then mixed with lactose (ratio 1:1); magnesium stearate (0.5%) was added finally.

In parallel, dyed corn starch was mixed with lactose (1:1, 500g) and granulated (Figure 2) in the fluid bed granulator using an aqueous solution (300 g, 10%) of Kollidon® 25, which was top sprayed with speed 9.14 g/min and air flap position set to 75 – 65° (temperature in granulation chamber 50 – 60 °C and outlet temperature 25 – 35 °C). Finally, magnesium stearate (0.5%) was added to the granules.

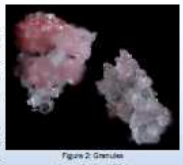

Figure 2: Granules (magnification 100x)

Three batches of tablets were prepared from the granules (FG 1-3) and powder mixture without granulation (DC 1-3), (Figure 3) using the material testing machine (Zwick Roell press, Zwick Roell GmbH, Germany). Tablets were produced with compression force 4 kN, with weight of 0.1000 g and diameter 7 mm. Disintegration time, friability and radial strenght of tablets were measured according to the European Pharmacopeia (Monographies 2.9.1 A, 2.9.7 and 2.9.8)[3].

Figure 3: Compressed tablets

The Enslin-Neff device was carefully filled with the dyed water (methylene blue). The tablet was layed down on a glass filtre and measuring of the absorption time (s) was started. Water absorption time was measured until liquid had reached the top of the tablet. The volume of absorbed water (µl) was recorded. The tablet was afterwards removed from device and weighted immediately. Water absorption rate (µl/s) was then calculated. Absorbed liquid weight as a difference between the weight of a dry and a wet tablet was measured as wet.

RESULTS AND DISCUSSION

In Table 1, the summary of tablet properties can be seen. The experimental data show, that the tablets produced from the granules (FG) have higher radial strenght in the comparison to the directly compressed tablets (DC). They have also significantly longer disintegration time. On the other hand, they compiled with the requirements of Pharmacopoeia having friability lower than 1% in comparison to the directly compressed tablets with the friability higher than 4%.

Because tablets have same composition and were produced with same compression process parameters, the differences in the properties between the granulated and directly compressed tablets can be caused by the addition of povidone in granulated tablets. Generally, povidone increases the radial strenght, decreases weight loss during friability test and prolongs the disintegration time in the case of granulated tablets. [4]

Results gathered from experimental work with Enslin-Neff device are shown in the Figure 4. Tablets produced from granules as well as directly compressed tablets absorbed almost the same amount of water between 0.03 and 0.04 ml (Figure 4.a). However, the tablets pressed from granules have significantly longer water absorption time (Figure 4.b) leading to the slower water absorption rate in comparison with directly compressed tablets. (Figure 4.c).

As was stated above, both groups of tablets were compressed with same compression proces parameters and except for addition of povidone in granulated tablets, their composition is same. Povidone could cause longer water absorption time and lower water absorption rate of tablets produced from granules. These findings correlate well with the radial strenght, friability and the disintegration time data. The addition of povidone could also influence the porosity of tablets. [4] Porosity of the tablets will be studied in further experiments.

Table 1: Tablet properties

		Mass (g)	Diameter (mm)	Height (mm)	Crushing force (N)	Radial strenght (MPa)	Disintegretion time (s)	Friability (%)
FG 1	AV	0.1009	7.03	2.09	22.90	0.99	80.17	0.86
	SD	0.0006	0.01	0.03	1.91	0.09	11.09	
FG 2	AV	0.1009	6.98	2.02	36.00	1.65	115.17	0.87
	SD	0.0006	0.03	0.07	2.49	0.07	32.98	
FG 3	AV	0.0999	6.97	1.97	36.90	1.71	120.67	0.63
	SD	0.0007	0.02	0.02	1.20	0.05	29.46	
DC 1	AV	0.1002	7.02	2.03	7.90	0.35	20.67	4.36
	SD	0.0015	0.01	0.04	0.67	0.03	0.52	
DC 2	AV	0.1003	7.01	2.01	11.20	0.51	20.00	4.76
	SD	0.0008	0.01	0.01	1.62	0.07	0.00	
DC 3	AV	0.1005	7.03	2.06	8.30	0.36	21.17	4.22
	SD	0.0006	0.01	0.02	0.48	0.02	1.47	

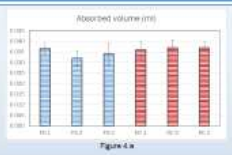

Figure 4.a

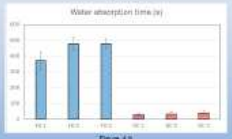

Figure 4.b

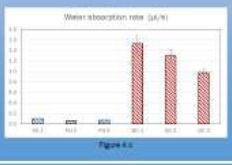

Figure 4.c

CONCLUSIONS

The Enslin – Neff device can be used for measuring the water absorption rate of the tablets. From the volume difference of the absorbed liquid and the wetting time, the water absorption rate can be calculated. Preliminary results shows, that the radial strength and the water absorption time correlates with each other. This relationship would be further studied.

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5. **HURYCHOVÁ, H.,** AZAR, M., ŠKLUBALOVÁ, Z., STONIŠ, J. Study of the influence of the diameter of a conical hopper orifice on the parameters of the flow equation for size fractions of sorbitol granules, 7th Granulation Workshop, Granulation Conference, 1st-3rd July, 2015, University of Sheffield, UK

STUDY OF THE INFLUENCE OF THE DIAMETER OF A CONICAL HOPPER ORIFICE ON THE PARAMETERS OF THE FLOW EQUATION FOR SIZE FRACTIONS OF SORBITOL GRANULES

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INTRODUCTION AND THE AIM

Pharmaceutical powders and granules are the dominant materials used in the pharmaceutical industry. The knowledge of their flow properties is very important not only for the handling and processing into solid dosage forms but also for the standardization of production processes and the quality of the final product. Flow properties of pharmaceutical powders and granules are primarily affected by properties of their particles and conditions of measurement (Hoag & Augsburger, 2008). Generally, Pharmacopoeial methods (Ph. Eur.) could be used in evaluation of flow properties; however, attention is also paid to methods which evaluate the shear and avalanche behaviour of the particulate matter (Schwedes, 2003; Hoag & Augsburger, 2008; Nalluri & Kuentz, 2010).

Wet granulation, in which the solid material is mixed with a liquid phase in order to obtain agglomerates resistant to mechanical stress, i.e. granules, is widely applied in the pharmaceutical industry. The change in particle size and shape leads to improved flow properties as well as better compressibility of pharmaceutical powders (Ennis, 2010).

To evaluate flowability, a number of methods have been proposed (Schwedes, 2003). Measurement of the flow rate Q (g/s) through the aperture of a hopper is considered to be one of the best methods. In order to describe the relationship between variables (D, x, d_b), a power law function is used. In pharmaceutical technology, the Jones & Pilpel power equation (1) is employed (Jones & Pilpel, 1966; Kachrimanis et al., 2005)

$$D = A \cdot \left[\frac{4 \cdot Q}{\pi \cdot d_b \cdot g^{1/2}}\right]^{\chi} \qquad (1)$$

Q	(mass) flow rate	g/s
D	diameter of the hopper circular aperture	cm
d_b	the powder bulk density	g/ml
g	the acceleration of gravity	981.0 cm/s^2
A	parameter of the equation	dimensionless
n	parameter of the equation, the reciprocal value of the exponent	dimensionless

This work studies the influence of the diameter of a conical hopper circular aperture on the mass flow rate Q (g/s) of size fractions of sorbitol in the range of 0.300-0.710 mm. A non-linear dependence of the flow rate on the aperture diameter D (cm) is modelled by the Jones-Pilpel power equation (1) (Jones & Pilpel, 1966) and using the proposed power law equation in which the intercept represents the estimate of the particle flow rate through an orifice of unit diameter. The precision of the reverse estimation of the mass flow rate Q_y (g/s) was the main criterion in evaluation of the mathematical model's suitability.

EXPERIMENTAL

Methods

Preparation of sorbitol granules

Sorbitol granules were prepared by wet granulation mixing of sorbitol for direct compression (Merisorb® 200, MS; Tereos Syral SAS Nesle) with purified water in the ratio of 1:10. The mixture was manually extruded through a 1.0 mm sieve. The granules were dried at room temperature. The moisture content 0.8 % was determined (N = 3) gravimetrically (Moisture analyser XM60, PRECISA, Switzerland).

For the evaluation of sorbitol granules, the following methods were used:

1. Particle size by sieve analysis
2. Optical microscopy
3. Bulk density
4. Mass flow rate

All measurements were carried out at a temperature in the range 23.0 ± 1.0 °C and relative air humidity in the range of 22.0 ± 3.0 %.

Particle size and shape

An optical microscope with a digital camera (Olympus BX 51, Germany) was used to observe the particles. The size and the shape of the sorbitol granules are illustrated by photomicrographs at ten times magnification (Figure 1-3). The finished granules can be characterized as crusting agglomerates of irregular shape.

A mean particle diameter x_{50} = 0.270 mm and x_{90} = 0.620 mm of granules were estimated by the analytical sieving method (Vibratory Sieve Shaker AS 200 basic, RETSCH, Germany) in accordance with European Pharmacopoeia (Ph. Eur., 2.9.38).

The granule size fractions were obtained using vibrating screens of 0.300 mm, 0.400 mm, 0.500 mm, 0.630 mm and 0.710 mm size. In Table 2, the particle diameter x (mm) is referred to as the geometric mean of the range of the sieves used.

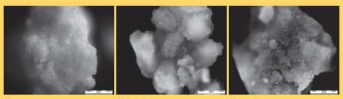

Figure 1 *Figure 2* *Figure 3*

Bulk density

The bulk density of the size fraction of the sorbitol granules was determined by Scott´s volumeter (COPLEY, SOTAX, UK) in accordance with the European Pharmacopoeia (Ph. Eur., 2.9.34). The bulk density d_b (g/ml) was calculated from the known volume of the cylindrical cup and the weight of the sample. Table 1 lists the average for ten repetitions of measurements with the relative standard deviations (RSD) of less than 1.5 %.

Mass flow rate

The flow rate of the size fractions of the sorbitol granules was measured using a stainless steel conical hopper with a capacity of 200.0 ml having an internal angle wall inclination of 40° (Granulate tester GTB, ERWEKA, Germany). The mass flow rate Q (g/s) was determined by measuring the time it took to empty 50.0 g of granules through the circular aperture with diameter D = 0.6 cm, 0.8 cm, 1.0 cm, 1.13 cm, and 1.5 cm. The flow rate was then calculated from the measured pass-through time. Table 1 lists the means for ten repetitions of measurements, the relative standard deviations (RSD) of which were less than 4.5 %.

RESULTS AND DISCUSSION

In the pharmaceutical industry, the improving of flowability of powders is often necessary to achieve optimal process conditions. Out of the possible methods, wet granulation is frequently used in solving poor flow properties of pharmaceutical powders. A fast method for testing of flow rate is generally required. The measurement of the flow rate through a hopper aperture is an easy and illustrative method. However, the choice of a suitable orifice diameter needs to be optimized.

It is known, that the mass flow rate increases non-linearly with an increase in the size of the aperture. This dependency can be modelled by the power function with the constant exponent n = 2.5. The Beverloo equation is an example (Beverloo et al., 1961). In this work, the JP equation (1) (Jones & Pilpel, 1966) with the variable n (a reciprocal value of the exponent) was used to study the relationship of the mass flow rate Q (g/s) of the size fraction of sorbitol granules in a range of 0.300–0.710 mm on the diameter D (cm) of the model testing hopper in a range of 0.6 to 1.5 cm.

The estimation of the parameters A and n is possible by plotting a complex variable $(Q/g^{1/2}\cdot\pi/4\cdot d_b)$ against the diameter of the aperture D (cm). In the equation, parameter A (dimensionless) expresses the influence of the hopper wall. The results in Table 2 are arranged for the size fractions x (mm) in relation to the apertures of the hopper D (cm).

To evaluate the precision of the flow rate prediction, the mean relative percentage deviation Δ (%) between the measured flow rate Q (g/s) and that calculated Q_y (g/s) was expressed using the actual parameters of the equation (1). Data are summarized in Table 3. In the last row, it can be seen that the JP equation allowed the prediction of the flow rate with an average value of Δ = 4.5 %.

Proposed mathematical model

The experimental data from Table 1 were similarly modelled using the proposed power law equation (2)

$$Q = Q_1 \cdot D^n \qquad (2)$$

where n is an exponent and Q_1 is an intercept which represents the flow rate Q (g/s) through the aperture with the diameter D = 1.0 cm. The parameters of the equation n and Q_1 are estimated due to the graphical dependency between the experimentally obtained value of Q and the orifice diameter D. Using the actual equation parameters detected, the precision of the flow rate prediction Q_y (g/s) was calculated again (Table 5). Non-significant differences between Δ (%) 4.4 % and that mentioned above for JP equation were observed.

CONCLUSION

In Table 2 and 4, the correlation coefficients r demonstrates that both mathematical models fit the experimental data well. The differences in the average values of precision for the estimate of the flow rate are insignificant. However, the clear meaning of the parameters makes the proposed power equation (2) beneficial for possible use in pharmaceutical technology in fast, routine testing of particulate matter flow behaviour, e.g. during formulation procedures.

Table 1. Mass flow rate Q (g/s) of the size fractions of sorbitol granules

Size fraction	x	d_b	D (cm)				
(mm)	(mm)	(g/ml)	0.6	0.8	1.0	1.13	1.5
0.300 – 0.400	0.346	0.577	1.93	5.28	10.1	14.4	43.9
0.400 – 0.500	0.447	0.542	1.67	4.48	8.57	12.6	37.4
0.500 – 0.630	0.561	0.545	1.51	4.04	7.85	12.1	33.6
0.630 – 0.710	0.669	0.555	1.40	3.64	7.35	11.6	33.3

Table 2. The parameters of the flow equation (1) of the size fractions of sorbitol granules

x (mm)	d_b (g/ml)	A	n	r
0.346	0.577	1.095	3.36	0.9982
0.447	0.542	1.123	3.35	0.9986
0.561	0.545	1.154	3.36	0.9994
0.669	0.555	1.175	3.45	0.9992

Table 3. Accuracy Δ (%) of the flow rate prediction Q_p (g/s) for the flow equation (1)

D (cm)	x (mm)	Q (g/s)	Q_p (g/s)	Δ (%)	Average Δ (%)
0.6	0.346	1.93	1.89	2.07	2.5
	0.447	1.67	1.63	2.40	
	0.561	1.51	1.49	1.32	
	0.669	1.40	1.34	4.29	
0.8	0.346	5.28	4.97	5.87	3.5
	0.447	4.48	4.28	4.46	
	0.561	4.04	3.91	3.22	
	0.669	3.64	3.62	0.55	
1.0	0.346	10.1	10.5	3.96	5.4
	0.447	8.57	9.04	5.48	
	0.561	7.85	8.29	5.61	
	0.669	7.35	7.83	6.53	
1.13	0.346	14.4	15.9	10.4	6.1
	0.447	12.6	13.6	7.94	
	0.561	12.1	12.5	3.31	
	0.669	11.6	11.9	2.59	
1.5	0.346	43.9	41.1	6.38	5.2
	0.447	37.4	35.2	5.88	
	0.561	33.6	32.4	3.57	
	0.669	33.3	31.7	4.80	
				Average	4.5

Table 4. The parameters of the flow equation (2) of the size fractions of sorbitol granules

x (mm)	Q_1 (g/s)	n	r
0.346	10.5	3.34	0.9982
0.447	9.04	3.34	0.9986
0.561	8.28	3.35	0.9994
0.669	7.83	3.44	0.9992

Table 5. Accuracy Δ (%) of the flow rate prediction Q_p (g/s) for the flow equation (2)

D (cm)	x (mm)	Q (g/s)	Q_p (g/s)	Δ (%)	Average Δ (%)
0.6	0.346	1.93	1.91	1.04	1.8
	0.447	1.67	1.64	1.80	
	0.561	1.51	1.50	0.66	
	0.669	1.40	1.35	3.57	
0.8	0.346	5.28	5.00	5.30	3.1
	0.447	4.48	4.29	4.24	
	0.561	4.04	3.92	2.97	
	0.669	3.64	3.64	0.00	
1.0	0.346	10.1	10.5	3.96	5.4
	0.447	8.57	9.04	5.48	
	0.561	7.85	8.28	5.48	
	0.669	7.35	7.83	6.53	
1.13	0.346	14.4	15.9	10.4	6.1
	0.447	12.6	13.6	7.94	
	0.561	12.1	12.5	3.31	
	0.669	11.6	11.9	2.59	
1.5	0.346	43.9	40.8	7.06	5.7
	0.447	37.4	35.0	6.42	
	0.561	33.6	32.2	4.17	
	0.669	33.3	31.6	5.11	
				Average	4.4

Acknowledgement

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STUDIUM SYPNÝCH VLASTNOSTÍ A STLAČITELNOSTI GRANULÁTU PŘIPRAVENÉHO FLUIDNÍ GRANULACÍ

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ÚVOD

Důležitou vlastností farmaceutických prášků a granulátů je **sypnost**, která podmiňuje homogenitu přípravku a správné dávkování ve výrobě lékových forem, a **lisovatelnost**. Sypnost látek je primárně ovlivněna vlastnostmi částic a vazbami mezi nimi, které mimo jiné závisí na obsahu vlhkosti. (HOAG, W. S., AUGSBURGER, L. L. (Eds): *Pharmaceutical dosage forms: Tablets*, vol. 1, 3rd Ed., 2008, New York: Informa Healthcare, 75-100).

Výsledky měření jsou rovněž ovlivněny použitým zařízením. Ve farmaceutické technologii se pro hodnocení sypnosti a lisovatelnosti prášků a granulátů využívá celá řada metod (PRESCOTT, J. K., BARNUM, R. A., *Pharm. Technol.*, 2000, 24 (10), 60-84).

Fluidní granulace je metoda výroby granulátu nástřikem tekutiny (vlhčivo, pojivo, léčivá látka) na částice plniva ve vznosu. Vzniklý granulát je následně v témže kroku i sušen. V závěru procesu lze granulát smísit s kluznou látkou. Ve výrobním procesu jsou automaticky přednastaveny parametry výroby, ukončení procesu je však závislé na pracovnících obsluhy a může se promítnout do teploty, při které se ke granulátu přidává kluzná látka.

CÍLE PRÁCE

Hodnocení **sypnosti** a **lisovatelnosti** dvou šarží komerčního granulátu připraveného metodou fluidní granulace a porovnání s vlastnostmi sorbitolu, jako vstupní suroviny. Použité šarže granulátu se lišily koncovou teplotou výroby (**G1** - 27°C, **G2** - 29°C). Byl sledován vliv **velikosti částic** a **velikosti otvoru** násypky na **hmotnostní rychlost sypání** Q (g/s) a **sypný úhel** (AOR).

MATERIÁLY A METODY

Ve fluidním granulátoru (Hurtlin Pilotlab L, GmBH A BOSCH) byly připraveny dvě šarže granulátu (**G1, G2**) rozprašováním 50%ního vodného roztoku panthenolu na částice sorbitolu (S). V závěru granulace byl přidán stearan hořečnatý (2,4 %).

Použité suroviny a vstupní podmínky pro výrobu granulátu fluidní granulací:

D-Panthenol 100 %	Dexpanthenol	Teplota v komoře	40°C
Čištěná voda	Aqua purificata	Rychlost průtoku roztoku	0.100 kg/min
Sorbitol	Merisorb®200	Průměr trysek pro nástřik	0.80 mm
Stearan hořečnatý	Ligamed MF-2-V	Relativní vlhkost v komoře	35 %

Pro hodnocení granulátu a sorbitolu byly využity následující **metody**:

1. Hodnocení obsahu vlhkosti
2. Hodnocení velikosti částic sítovou analýzou (ČL 2.9.38)
3. Mikroskopické hodnocení velikosti částic (ČL 2.9.37)
4. Sypná a setřesná hustota (ČL 2.9.34)
5. Stlačitelnost (ČL 2.9.34)
6. Měření sypného úhlu (ČL 2.9.36)
7. Rychlost sypání (ČL 2.9.36)

Měření byla realizována za standardních laboratorních podmínek (T 24 ± 1°C; RH 37 ± 5 %).

VÝSLEDKY A DISKUZE

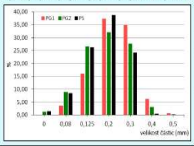
1. OBSAH VLHKOSTI

Obsah vlhkosti (%) byl sledován sušením 1,0 g vzorku v analyzátoru vlhkosti do konstantní hmotnosti při 50°C (G1, G2) a 80°C (S).

Obsah vlhkosti zjištěný (n = 3 ± SD) pro sorbitol byl 0,77 % ± 0,03; po výrobě granulátu byl 0,46 % ± 0,02 pro G1 a 0,51 % ± 0,04 pro G2. Během skladování a manipulace se postupně ustálil na hodnotě cca 0,8 % pro S a 1 % pro G. Ve srovnání s granulátem připraveným vlhkou granulací je mnohem nižší.

2. SÍTOVÁ ANALÝZA

Velikostní frakce granulátů a sorbitolu byly získány vibračním sítováním (Vibratory Sieve Shaker AS 200 basic, RETSCH, Německo) s použitím sít 0,080; 0,125; 0,200; 0,300; 0,400 a 0,500 mm.

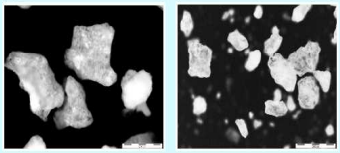


Je patrné rozšíření distribuce se zvýšením počtu částic nad 0,3 mm pro granulát.

Vysoký obsah prachového podílu (pod 0,2 mm) však přesahuje obvykle doporučovaný limit 10 %.

3. MIKROSKOPICKÉ HODNOCENÍ VELIKOSTI ČÁSTIC

Suchý vzorek o hmotnosti cca 0,005 g byl nanesen na podložní sklíčko, rozptýlen a pozorován při 10-tu násobném zvětšení v optickém mikroskopu (Olympus BX 51, Praha). Velikost a tvar vzniklého granulátu ilustrují mikroskopické snímky.



Při nástřiku vodného roztoku léčiva, může docházet k částečnému rozpuštění a spojení částic sorbitolu srůstem krystalů v proudu teplého vzduchu. Výsledný granulát je možné charakterizovat jako krustovitý, nepravidelného tvaru.

4. SYPNÁ A SETŘESNÁ HUSTOTA

Sypná hustota byla určena pomocí Scottova volumetru (COPLEY, GB).

Přístroj umožňuje rozvolnit shluky částic vzorku pomocí sítek o rozměru 1,0 mm nebo 2,0 mm. Při studiu vlivu velikosti sítka byl zjištěn významný vliv ($p \geq 0,01$) na sypnou hustotu. Jsou uvedeny průměry pro n = 10 (SD) pro sítko 1,0 mm.

Setřesná hustota byla stanovena mechanickým sklepáváním v odměrném válci (Tapped Density Tester, ERWEKA, Německo) Metodou 1 (ČL 2.9.34). Jsou uvedeny průměry pro n = 10 (SD).

5. STLAČITELNOST

Index stlačitelnosti a **Hausnerův poměr** byly vypočítány ze sypného a setřesného objemu (ČL 2.9.34, Metoda 1).

6. SYPNÝ ÚHEL

Sypný úhel (AOR) byl určen z výšky a průměru kužele prášku nasypaného na podložku (Granulate Tester GTB, ERWEKA, Německo).

7. RYCHLOST SYPÁNÍ

Rychlost sypání Q (g/s) byla určena měřením času pro vysypání konstantního množství vzorku (50,0 g) otvory násypky (Granulate Tester GTB, ERWEKA, Německo) o velikostech 6,0; 8,0; 10,0; 11,3 a 15,0 mm (n = 10).

VLASTNOSTI GRANULÁTŮ A SORBITOLU

V tabulce jsou částice charakterizovány středním rozměrem x_{50} (mm) pro 50% kumulativní četnost, podílem prachových částic (%), sypnou hustotou ρ_b (g/ml), setřesnou hustotou ρ_T (g/ml), indexem stlačitelnosti (CI) a Hausnerovým poměrem (HR).

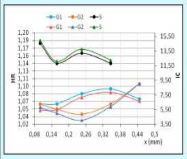
	x_{50} (mm)	podíl prachu (%)	ρ_b (g/ml)	ρ_T (g/ml)	CI	HR
G1	0,204	18,96	0,674 (0,008)	0,705 (0,004)	6,50	1,07
G2	0,166	36,75	0,668 (0,003)	0,744 (0,001)	6,66	1,07
S	0,146	36,27	0,639 (0,004)	0,737 (0,001)	10,63	1,12

Hodnoty ρ_b, ρ_T, CI a HR se využívají k porovnání interakcí částic prášku (granulátu) a hodnocení jeho lisovatelnosti. Čím je vyšší rozdíl mezi sypným a setřesným objemem (hustotou), tím se lisovatelnost zhoršuje (CARR, R. L.: Evaluating flow properties of solids, *Chem. Eng.*, 1965, 72, 163-168).

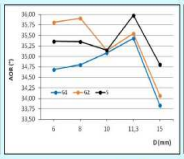
V obou případech měly granuláty lepší lisovatelnost než vstupní sorbitol.

Byl sledován také úhel nasypání (n = 10). Hodnoty AOR jsou tradiční mírou sypnosti prášků.

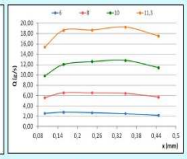
STUDIUM VLIVU VELIKOSTI ČÁSTIC A OTVORU NÁSYPKY



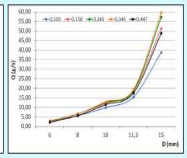
Vliv velikosti částic na index stlačitelnosti a Hausnerův poměr.



Vliv velikosti otvoru násypky D (mm) na úhel nasypání granulátů a sorbitolu.



Vliv velikosti částic x (mm) na rychlost sypání Q (g/s) granulátu G1 jednotlivými otvory násypky.



Vliv velikosti otvoru násypky D (mm) na rychlost sypání Q (g/s) velikostních frakcí granulátu G1.

Byly zjištěny nelineární vlivy velikosti částic, případně velikosti otvoru násypky na sledované vlastnosti granulátů a sorbitolu. To je v souladu s literárními poznatky (BROWN, R. L., RICHARDS, J. C., *Trans. Instn. Chem. Engrs.*, 1960, 38, 243-256. PITKIN, C. G., MITRA, A. K., PITKIN, Jr, C. G., *J. Pharm. Sci.*, 1973, 62, 693). **Tyto závislosti budou dále studovány.**

ZÁVĚRY

1. Granulací se zvýšilo procentuální zastoupení frakcí nad 0,3 mm oproti sorbitolu. Granulát má nízký obsah vlhkosti (do 1 %), vysoký obsah prachového podílu (nad 18 %) a lze ho charakterizovat jako krustovitý s nepravidelným tvarem.

2. Použité sítko Scottova volumetru má na sypnou hustotu významný vliv ($p \geq 0,01$).

3. Granulát má nižší sypnou hustotu ve srovnání se sorbitolem. Nižší hodnoty HR (< 10) a CI (< 1,11) ve srovnání se sorbitolem dokumentují lepší lisovatelnost.
S výjimkou prachového podílu a x_{50} nebyly zjištěny významné rozdíly ve vlastnostech G1 a G2.

4. Velikost částic významně nelineárně ovlivňuje
sypnou a setřesnou hustotu, tj. také Hausnerův poměr a index stlačitelnosti
hmotnostní rychlost sypání

5. Velikost otvoru násypky významně nelineárně ovlivňuje
úhel nasypání
hmotnostní rychlost sypání

6. Rychlost sypání velikostních frakcí granulátů je vyšší než rychlost sypání velikostních frakcí sorbitolu. To může být způsobeno vlivem přidané kluzné látky, ale i obecně lepšími sypnými vlastnostmi částic granulátu.

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