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RESEARCH ARTICLE

The use of novel tools for the assessment of powders and granules flow properties and for the analysis of minitablets compression process

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ABSTRACT

Objective: The purpose of this study was to apply the rheological measurements to assess the flow properties of powders and granules and to compare the results with the standard pharmacopeial tests. Quality by design approach was utilized to better understand the compression of the solids into minitablets.

Significance: Insights are provided regarding the methodology of rheological properties of powders and granules using powder flow analyzer (PFA). The 'six sigma' approach was presented as a tool for assessment of the minitablets manufacturing process.

Methods: Pharmacopeial methods and rheological tests using PFA were performed to assess the flow properties of designed powder and fractionated granule mixtures – placebo and with benzodiazepines. Compression of 2.5 and 3 mm minitablets was carried out and the compression force registered during the process and weight uniformity were statistically analyzed by calculating the capability indices.

Results: The flow rate measurement and cohesion test (PFA test) resulted in the best differentiation between mixtures. Higher values of capability indices were obtained for processes in which granule mixtures with better flow properties were compressed and 3 mm minitablets were produced and the usefulness of QbD tools in assessment of minitablets compression process was confirmed.

Conclusion: Performed study showed that the flow properties are the critical quality attributes determining the performance of minitablets compression. The cohesion test is the most discriminative to distinguish the analyzed mixtures. Capability indices can be used to assess the manufacturing process as a useful tool in pharmaceutical development of minitablets.

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Minitablets; compression process; quality by design; process capability; flow properties

Introduction

Minitablets are solid dosage forms gaining interest in the pharmaceutical industry, especially as an acceptable formulation for patients with swallowing difficulties [1]. In 2007, the Pediatric Regulation came into force in European Union to increase the development and accessibility of products with pediatric indications by mandating the pediatric development for new medicines authorization. Additionally, if pediatric drug formulation is developed according to PUMA (Pediatric-Use Marketing Authorization) it can benefit in 2 years of extra data and market protection [2]. By this regulation appropriate and acceptable medicines for children should be available. Since that time, several scientific studies have shown very good acceptability of minitablets in children, even in neonates [3–10]. Minitablets give a lot of opportunities because they can be swallowed directly or mixed with liquids or soft food before administration [11–13]. They can be also a great solution for elderly people who often struggle with dysphagia, multiple diseases, and require polypharmacy. Recently, European Medicine Agency (EMA) published a paper considering important aspects in development of medicines for elderly [14]. Minitablets offer versatility in product development, they can be used as single or multiple dosage form. With an adequate dosing system, the right number of minitablets can be administered which gives the possibility to set the right dose regarding age or other variabilities in patient population (individualized therapy). On the other hand, a fixed dose of active pharmaceutical ingredient (API) can be closed in a capsule or sachet. Depending on formulation, the release rate of API can be designed as: immediate, delayed, sustained, or controlled [15].

In addition to factors which have to be considered to select the target patient group, very important are also factors connected with the manufacturing process. In manufacturing of tablets they include: composition and physical properties of the tablet mass, equipment, and compression process parameters. Composition of non-modified release formulations can be exactly the same for minitablets as for bigger tablets [16]. However, for sustained release minitablets, some modifications are required. The content of polymer and its viscosity have to be adjusted to produce products with similar dissolution rate [15].

One of the reasons why minitablets are still rarely produced on bigger scale is the presumption that special production requirements has to be secured during the minitableting process. The main issues are connected with equipment and flow properties of tableting blend requirements. Minitablets can be produced using standard rotary presses equipped with proper punches and dies (single or multiple). The use of multiple tooling increases the productivity [17]. There are still few works regarding e.g. flow

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properties and die filling or importance of other process parameters during minitableting [18–21]. According to Tissen et al. [18] the smallest the minitablet, the more difficult the process is. The production scale tablet presses are not designed to produce so small tablets and, for instance, the scrapers have to be modified for 1 mm minitablets because the gap between the die table and the scraper is too large and minitablets can be damaged. The die fill variation during process depends on many factors connected with flow properties of tablet mixtures but also with die filling mechanism. Goh et al. [19] showed that higher weight variations were observed for 1.8 mm minitablets than for 3.0 mm ones but all produced minitablets complied with European Pharmacopeia (Ph. Eur.) mass uniformity criteria regardless of the differences in flow properties. Additionally, in another study Goh et al. [20] demonstrated that in comparison to gravitational feeding better die filling reproducibility can be ensured when the force feeding mechanism was used. The authors also demonstrated that the compression roller displacement can be an in-process indicator of the product quality, because good correlation between roller displacement and weight variation of minitablets was demonstrated. A good flowability is essential for the uniform die filling and granulation is an effective technique to improve the flow properties by increasing the particle size of the blend. However, especially when small tablets are produced the maximum particle size has to be controlled. Zhao et al. [21] indicated that for successful compression of minitablets and good uniformity of a dose appropriate size of the particles in the compressed mixture cannot exceed 1/3 of the die diameter.

To ensure good product quality, flowability of a designed mixture should be assessed and optimized. It is not only important for good performance of the tableting process but also for control of the granulation or mixing process. There is a lot of methods describing properties of powders and granules. There are well known static tests like angle of repose and bulk density or gravitational flow rate measurements described in pharmacopeial monographs. However, new dynamic tests which apply an increasing force to a powder sample are gaining more popularity because of better control of experimental parameters. These tests can be conducted with powder rheometers or shear cells. The most wildly used tests configurations using a shear cell are described in Ph. Eur. 10.0 in the new monograph titled 'Powder flow properties by shear cell methods' [22].

The manufacturing process assessment should be supported by novel approaches like quality by design (QbD). One of the way to assess manufacturing process performance is to calculate its capability using 'six sigma' method. Sigma (σ) represents the population standard deviation (SD), which is a measure of the variation in process data. The term 'six sigma' is defined as having less than 3.4 defects per 1 million performed processes, which means that mean value of quantitative parameters of the process are six SDs from the nearest specification limit. This approach is focused on improving the manufacturing process rather than correction the resulting product [23]. The process capability indices measure the inherent variability of a stable process in relation to the established specification limits (acceptance criteria). However, there is still a need to measure the quality attributes of the products, hence the process capability can be assessed by verifying whether samples generated from the process are capable to meet the established requirements [24].

The aim of the study was to obtain minitablets from powder and granule mixtures designed in accordance with the concept of QbD. The manufacturing process was statistically analyzed to compare compression process performance depending on the flow properties of the blends, which were assessed by various pharmacopeial methods and with new rheological tests performed using powder flow analyzer (PFA) – the cohesion, caking, and flow speed dependence tests.

Benzodiazepines were chosen as model drugs due to some indications in pediatrics and geriatrics, e.g. premedication, anxiety treatment, behavior disorders, insomnia, and epilepsy [25,26] as swallowing difficulties minitablets may be an appropriate dosage form for these patients. Moreover, minitablets allow a flexible dose adjustment in pediatrics for children of different ages. On the market diazepam tablets of 2 mg and 5 mg strength are available, while dosage accuracy of 0.3 mg/kg body weight in children can be required [27]. The results of the study should give more information on minitablets processing what may help in popularization of this challenging dosage form.

Materials

Active ingredients: diazepam and lorazepam were received from Polfa Tarchomin (Warsaw, Poland). The following excipients were used in the powder formulations: silicified microcrystalline cellulose (Prosolv SMCC90, JRS Pharma, Rosenberg, Germany), spray-dried lactose (Flowlac 100, Meggle, Wasserburg, Germany), croscarmellose sodium (Ac-di-sol, FMC Corporation, Newark, NJ) and sodium stearyl fumarate (Pruv, JRS Pharma, Rosenberg, Germany). In the mixtures for compression after wet granulation: microcrystalline cellulose (Avicel 101, FMC Corporation, Newark, NJ), lactose (Sorbolac 400, Meggle, Wasserburg, Germany), hypromellose (Pharmacoat 606, Shin-Etsu, Tokyo, Japan), croscarmellose sodium (Ac-di-sol, FMC Corporation, Newark, NJ), and sodium stearyl fumarate (Pruv, JRS Pharma, Rosenberg, Germany) were used.

Methods

Composition of powders and granules

All formulations were prepared according to the compositions given in Table 1. To prepare powders: placebo (Powd-P) and with diazepam (Powd-D) or lorazepam (Powd-L), the components were weighed and mixed in a cubic mixer for 10 min at 50 rpm. The lubricant (sodium stearyl fumarate) was added last and mixed for 3 min. Placebo (Gran-P) and diazepam (Gran-D) granules were prepared by wet granulation in a high shear mixer using 2% (w/w) solution of hypromellose; afterwards the granules were dried in an oven at 50 °C to reach less than 3% moisture content and screened through 1 mm sieve. The granules were additionally divided into fractions by sieving. The fractions of particles below 250 μm (Gran $<$ 250) and above 250 μm (Gran $>$ 250) were obtained and together with the non-fractionated granules (Gran-non) were tested to evaluate the differences in flow properties.

Table 1. The composition (% w/w) of powders and granules prepared for compression of minitablets.

	Compression after granulation		Direct compression		
Excipients	Gran-P	Gran-D	Powd-P	Powd-D	Powd-L
Diazepam	–	0.5	–	5.0	–
Lorazepam	–	–	–	–	1.0
Prosolv SMCC90		–	57.0	54.0	56.4
Flowlac 100		–	38.0	36.0	37.6
Avicel 101	58.1	56.1		–	–
Sorbolac 400	38.7	37.4		–	–
Pharmacoat 606	1.2	1.0		–	–
Ac-di-sol		2.0			
Pruv		3.0			

Physical tests for powders and granules

Morphological properties

The morphology of the prepared powder and granule mixtures was examined by a scanning electron microscope (SEM, EVO LS25, Carl Zeiss Microscopy, Jena, Germany) with the accelerating voltage of 0.2–30 kV and electron backscatter diffraction detector. Additionally, particle size distribution using the principles of light scattering was measured using LS 13 320 Laser Diffraction Particle Size Analyzer (Beckman Coulter, Brea, CA). The 6 g sample of powders or granules was placed in a sample holder and delivered to the sensing zone in the optical bench by a vacuum (Tornado Dry Powder System).

Compendial methods of flowability assessment

Flow properties of the prepared formulations were evaluated using a pharmacopeial method (Ph. Eur. 9.0) described in the monograph 2.9.36. The flow rate and angle of repose through 15 mm orifice were measured using a manual powder flow tester (Electrolab, Mumbai, India). In the first test, a 100 g sample was placed in a funnel and the time needed to empty the funnel was measured. In the second test, a powder sample from the funnel was poured onto the base with a diameter (d) of 10 cm to form a cone. The height of the cone (h) was measured using height gauge and the angle of repose α (°) was calculated using following equation:

$$\tan(\alpha) = \frac{h}{0.5 \times d} \quad (1)$$

Measurements were done in triplicate, and the results were expressed as mean ± SD. Hausner ratio (HR) was calculated by dividing the bulk density (ρ_{bulk}) by the value of tapped density (ρ_{tapped}). The bulk density was calculated from the volume of 100 g of powder or granule mixture placed gently into a 250 mL graduated cylinder. The tapped density was determined using Erweka SVM tester (Heusenstamm, Germany) by measuring the volume of the solids after 1250 taps.

Non-compendial methods of flow properties assessment

Furthermore, non-pharmacopeial tests were performed using a powder flow analyzer (Stable Micro Systems, Surrey, UK). The tests were conducted using powder or granule samples (30 mL) placed in a cylindrical vessel. A rotor carrying a blade was passed through the sample in a controlled way (at defined speed and angle, depending on the used test). The PFA was assembled to the texture analyzer as it is shown in Figure 1(A).

Before each test two conditioning cycles were conducted to eliminate variations caused by unrepeatable sample loading and to standardize the sample bed in the cylinder. To do so, the rotor moved down through the sample at a tip speed of 50 mm/s and an angle of 175°, and then moved back up through the powder at a tip speed of 50 mm/s and an angle of 178° (Figure 1(B)). Subsequently, the required test sequence was initiated and the blade moved downwards and upwards through the sample according to the test protocol (Figure 2). The tests listed below were performed:

a. The cohesion test, which measures the cohesiveness of powder (the tendency to agglomerate);

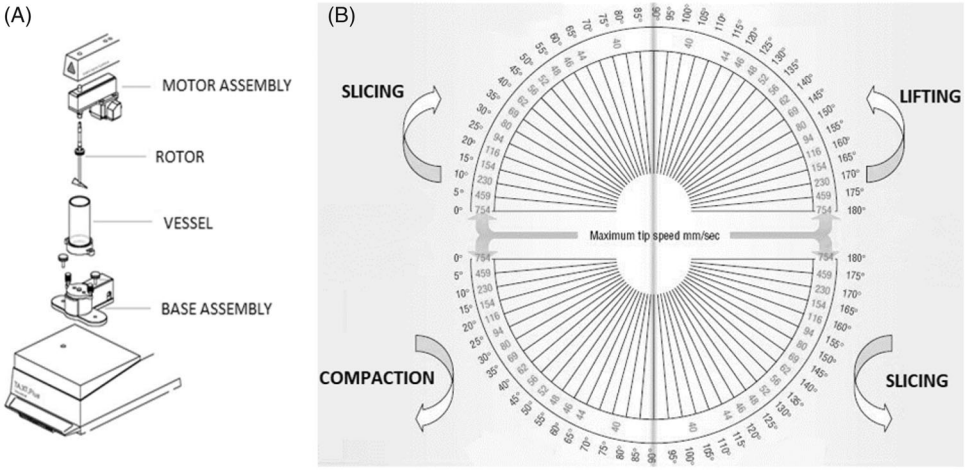

Figure 1. Overview of powder flow analyzer (A) and the action of the rotor movement by angle and direction (B) [28].

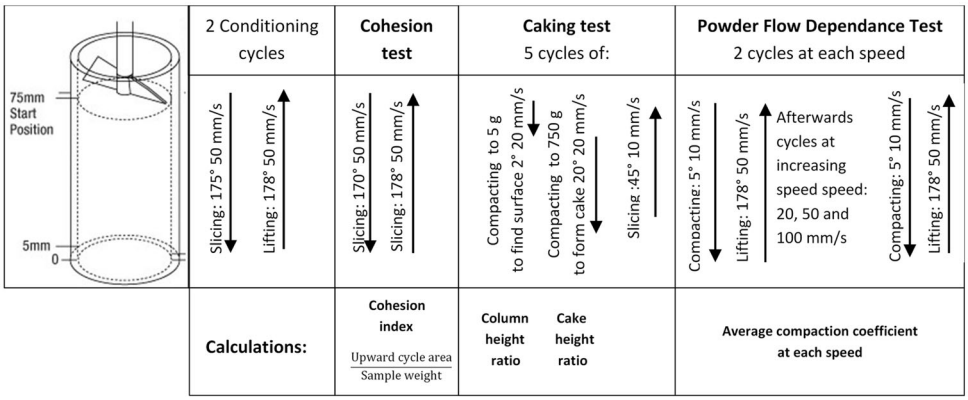

Figure 2. Sequence of blade movement in a single test carried out in PFA [28].

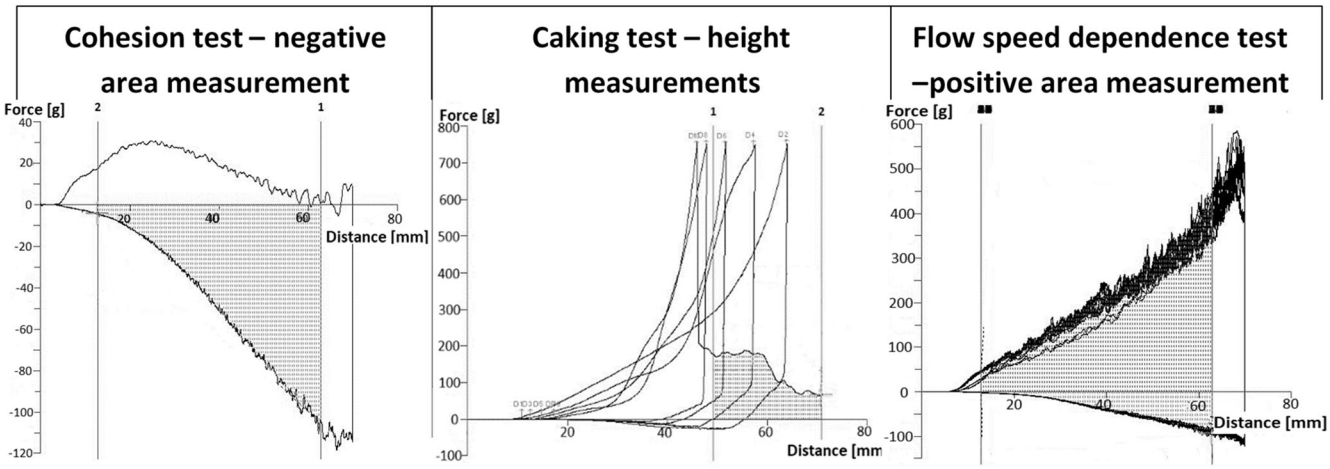

Figure 3. Typical force–displacement profiles for tests in PFA [28].

b. The caking test, which assesses the formation of cakes after gentle compaction;
c. Powder flow dependence test, which measures the resistance of a sample as controlled flow is imposed at different speed.

During each test, the force–displacement profile was plotted as it is shown in Figure 3.

Cohesion test. During the cohesion test, the blade moved to the bottom of the powder or granules bed at 50 mm/s with a path angle of 170° (Figure 2). Cohesion data were recorded on the upward stroke with the blade moving in the same way. The negative area from the force–displacement profile was calculated as the cohesion coefficient (g·mm) (Figure 3). It corresponded to the work required to lift the powder or granules by the moving blade, so it was related to the weight of the sample. Therefore, the cohesion index (CI) was calculated by dividing the cohesion coefficient value (upward cycle area) by the sample weight. Based on the CI, the flow behavior can be characterized [29]. The test was repeated six times for each formulation every time using a fresh sample of the mixture.

Caking test. The sample in a vessel was gently compacted with the blade tip speed 20 mm/s and path angle of 20° until 750 g force was achieved. In that moment, the powder cake height was measured and then the powder was sliced back to the top with the minimum force and speed (Figure 2). This cycle was repeated for five times and the results of the cake height after each cycle were compared to the initial height (cake height ratio). The test was repeated three times for each batch.

Powder flow speed dependence test. The blade moved downwards and upwards in five sets of two cycles at increasing speeds (10, 20, 50, and 100 mm/s) and the last two cycles were carried out again at the lowest speed. The downward path angle was 5° while the return was at 50 mm/s and 178° at each cycle. For each speed, the compaction coefficient (g.mm) was calculated as the positive area under the compaction curves (Figure 3).

Compression process

Minitablets with a diameter of 2.5 mm or 3 mm were prepared from the powder mixture or from the non-fractionated granules with diazepam (Powd-D and Gran-D-non) using a laboratory rotary tablet press (Erweka RTP-D8, Heusenstamm, Germany) equipped with four sets of single concave punches (Adamus SA, Szczecin, Poland). The compression pressure of 150 and 250 MPa was used.

Table 2. Acceptable range of the compression forces during the conducted tableting processes.

Minitablet diameter (mm)	Target compression pressure (MPa)	Compression force (kN)		
		Target value	LSL[a]	USL[a]
2.5	150	0.74	0.59	0.89
	250	1.23	0.98	1.48
3.0	150	1.06	0.85	1.27
	250	1.77	1.42	2.12

[a]LSL: lower specification limit; USL: upper specification limit.

Each compression process was conducted on a laboratory scale using about 200 g of tableting mixture. The turret speed was 25 rpm and the feeder paddles speed was 50 rpm. During the process, the main compression force values were monitored and registered in P.A.D. – Software For Force Evaluation (Ver. 2.16).

Process capability analysis

Statistical analysis of the compression force values registered during the manufacturing process and the mass of compressed minitablets was performed to assess the minitableting process performance. Statistical process control method was used (Statistica 13, Statsoft, Krakow, Poland). In the first step, the normality assumption of the data was tested and the lower specification limits (LSLs) and upper specification limits (USLs) were established. The capability indices were calculated using a suitable method described in detail in the sections 'Process capability based on compression force' and 'Process capability based on minitablets weight'.

Process capability based on compression force

The compression force values were the output of the process used to evaluate the compression process capability. For this purpose, specification limits of the compression force as critical process parameters were established (Table 2). The target value of compression force depended on the compression pressure and the diameter of minitablets. The acceptable range of compression force was ±20% from the target value. The specification limits were selected based on recently published study [19], where a significant linear correlation between variations of the compression roller displacement and weight of the produced minitablets was determined and the authors observed that variability of the

compression roller displacement of 20% resulted in weight deviations not larger than 2%.

The collected data showed a non-normal distribution which was proven by Shapiro–Wilk's test. Therefore, to demonstrate the robustness and consistency of the process, process capability indices (C_p and C_{pk}) were calculated via the percentile method [30] according to Equations (2) and (3). In this method, the specification limits (USL and LSL), median (M) and percentiles: 99.865 (UP) and 0.135 (LP) were used for calculations.

$$C_p = \frac{USL - LSL}{UP - LP} \quad (2)$$

$$C_{pk} = \min\left\{\frac{USL - M}{\left[\frac{UP-LP}{2}\right]}, \frac{M - LSL}{\left[\frac{UP-LP}{2}\right]}\right\} \quad (3)$$

Process capability based on minitablets weight

Twenty minitablets from each batch were weighed and the results were used to assess the compression process capability. The specification limits shown in Table 3 were established according to pharmacopeial requirements (Ph. Eur. 2.9.5).

The data showed normal distribution ($p>.5$ in Shapiro–Wilk's test) and the process capability indices (C_p and C_{pk}) were calculated according to Equations (4) and (5) [32] using specification limits (USL and LSP), mean and sigma values.

$$C_p = \frac{USL - LSL}{6 \times sigma} \quad (4)$$

$$C_{pk} = \min\left\{\frac{USL - mean}{3 \times sigma}, \frac{mean - LSF}{3 \times sigma}\right\} \quad (5)$$

Results and discussion

The prepared mixtures were examined to assess the flow properties, which is an important parameter not only in the design of the formulation composition but, moreover, in the process and equipment design. Among various methods described in the Ph. Eur., the most common are flow rate, angle of repose and bulk and tapped densities measurements. The rheological tests for solid materials are not used routinely in pharmaceutical development, although their advantage is that powder flow assessment is carried out in dynamic conditions (increasing force applied to a sample). From 2020 in Ph. Eur. 10.0, the rheological tests in shear cell are described in more detail in the new monograph titled 'Powder flow properties by shear cell methods' [22]. The principle of this method is to apply to a powder bed different states of consolidation stress and afterwards the compressive while at certain stress the powder starts to flow (state of sample failure). At the moment, various equipment and techniques are proposed but still not widely used in the industrial projects.

In our study, the new rheological tests were performed to assess flow properties of tableting masses used to obtain minitablets. In case of minitablets production, the good flowability of mixtures should be carefully tested because even small variations in die filling could cause a significant change in minitablets weight. The cohesion, caking, and powder flow speed dependence tests were carried out using a patented equipment PFA. During these tests, powder and granules samples were displaced by slicing, shearing, compacting, mixing, and aerating. Exposing the tableting mixtures to different types of stress in the controlled laboratory conditions could be beneficial because during processing the powders or granules are also exposed to similar stress, for instance caused by the feeder paddles. Well-known static tests like bulk density or angle of repose do not show how the flow properties can change while the solids are subjected to mixing and the results are hard to compare because the pretreatment of the sample in the operating procedure influence the results.

The powder and granules, placebo and with benzodiazepines, were prepared. The granules were additionally divided into fractions below and above 250 μm in size and flow properties were analyzed either for non-fractionated granules or for these two fractions separately. The fraction above 250 μm was characterized by d_{90} value 950 μm, and the particle size distribution in the fraction below 250 μm of the granules was similar like determined in the powder mixtures – d_{90} was 230–240 μm (Table 4).

In the first step, pharmacopeial tests were performed, namely flow rate, angle of repose, and HR were obtained and the results are shown in Table 5. No flow through 15 mm orifice for powder mixtures was observed, whereas for all granules a free flow through this orifice was determined (5.3–9.0 s/100 g). For each formulation, the flow rates of the non-fractionated granules and granules with size above 250 μm were similar and significantly greater than in case of the granules fraction below 250 μm (Kruskal–Wallis's test, $p<.05$). Small decrease of the flow rate was observed for Gran-D in comparison to Gran-P; however, it was not statistically significant.

Additionally, the mixtures were examined by an electron scanning microscope to justify the flowability results. The image

Table 3. Acceptable range of the minitablets mass according to Ph. Eur. 2.9.5 [31].

		Minitablets weight (mg)		
Minitablet diameter (mm)	Mixture type	Target value	LSL[a]	USL[a]
2.5	Powder	11.0	9.9	12.1
	Granules	12.0	10.8	13.2
3.0	Powder	17.0	15.3	18.7
	Granules	20.0	18.0	22.0

[a]LSL: lower specification limit; USL: upper specification limit.

Table 4. Particle size distribution of diazepam tableting mixtures (mean values).

	Particle diameter (μm)		
Volume (%)	Powd-D	Gran-D < 250	Gran-D > 250
d_{10}	21.4	59.1	148.0
d_{50}	119.1	126.6	464.9
d_{90}	240.9	227.9	945.8

Table 5. Flow properties of the mixtures – powders and granules.

	Powders			Granules[a]					
				Placebo			Diazepam		
Mixture type	Placebo	Diazepam	Lorazepam	Non-*F*	*F* < 250	*F* > 250	Non-*F*	*F* < 250	*F* > 250
Flow rate (s/100 g)		No flow		5.33 ± 0.2	7.87 ± 0.2	5.57 ± 0.1	6.87 ± 0.1	9.03 ± 0.4	7.73 ± 0.1
Angle of repose (°)	37.7 ± 0.6	39.6 ± 1.0	39.2 ± 0.7	35.6 ± 0.4	35.2 ± 0.6	37.5 ± 1.1	36.3 ± 1.0	36.7 ± 0.3	38.7 ± 0.2
Hausner ratio	1.25	1.25	1.30	1.16	1.26	1.18	1.20	1.26	1.21

[a]Non-*F* (non-fractionated), *F* < 250 (fraction of particles below 250 μm) and *F* > 250 (fraction of particles above 250 μm).

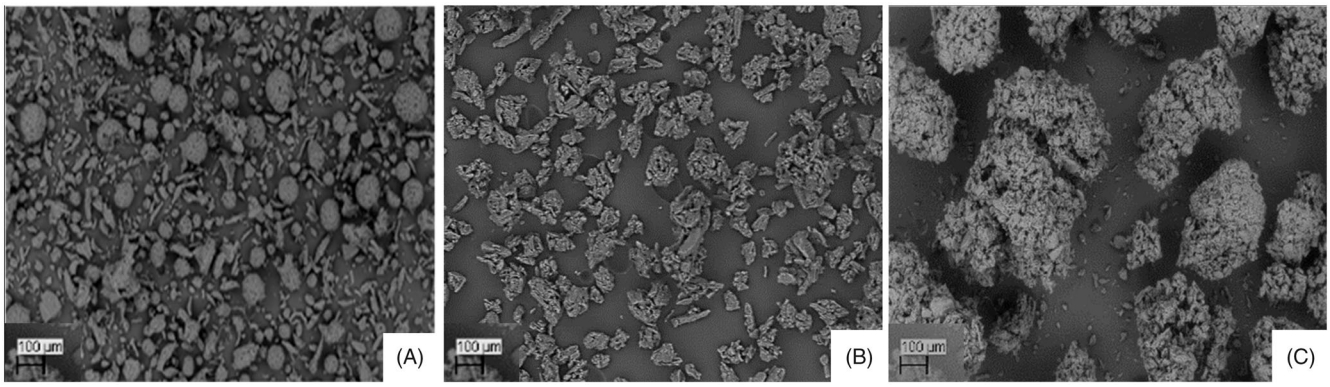

Figure 4. SEM images of powder mixture with diazepam – Powd-D (A), fraction of granules below 250 µm – Gran-D < 250 (B) and fraction above 250 µm – Gran-D > 250 (C).

presented in Figure 4(A) showed a big difference in the particles shape of the powder components. This disproportion could influence the flow properties of the powder. In the image of fractionated granules (Figure 4(B,C)), particles more similar in shape were visible, which allowed improved flowability. The particles above 250 µm had more spherical shape (Figure 4(C)) which justifies the best flow rate of this fraction as well as non-fractionated granules. The particle shape explained that despite similar particle size distribution (Table 4) granules with size below 250 µm showed free flow through orifice as opposed to the powders.

Although the mixtures differed in size and shape of the particles, the angle of repose was in the range of 35–40° for both, powders and granules. According to the pharmacopeial flowability scale, the mixtures were classified as fair flowing, with no aid needed during processing, e.g. tableting, which was not consistent with the observations that the powder mixtures hung up in the funnel. However, it was visible that for powders it was hard to form a sharp ended cone, hence manual measurement of the formed cone height gave inaccurate and unsure results. In this case, dynamic or indirect methods of the angle of repose estimation should have been adopted [33]. Therefore, the obtained results did not differentiate the mixtures but gave some information about cohesiveness of the analyzed mixtures.

From the bulk and tapped densities, HR was calculated. For the granules with particles below 250 µm higher values of HR (1.26), related to worse flowability, were obtained, which was consistent with the significantly slower flow of this fraction through the funnel. However, the test did not distinguish this fraction of granules from powders (HR: 1.25–1.3), although better flow through the 15 mm orifice was observed.

It can be concluded that among the pharmacopeial tests performed only the flow rate measurements showed significant difference between powders and granules, additionally differentiating two fractions of the granules.

The non-pharmacopeial tests were carried out using PFA connected to the texture analyzer, where the principle is a force–displacement measurement through the powder bed. The equipment gives rheological information about dynamic flow properties. The results of the cohesion test presented as CI values in Figure 5 indicated free and easy flow of the granule mixtures (CI < 14) and very cohesive behavior of the powders (CI > 16). These differences were statistically relevant (Tukey's test, $p<.05$). For the non-fractionated granules, the CI was about 10, irrespective of the active substance present. Smaller cohesion was determined for granules above 250 µm (CI – 7) and significantly greater for granules fraction below 250 µm (CI – 13). The fractionated diazepam granules (Gran-D < 250 and Gran-D > 250) had

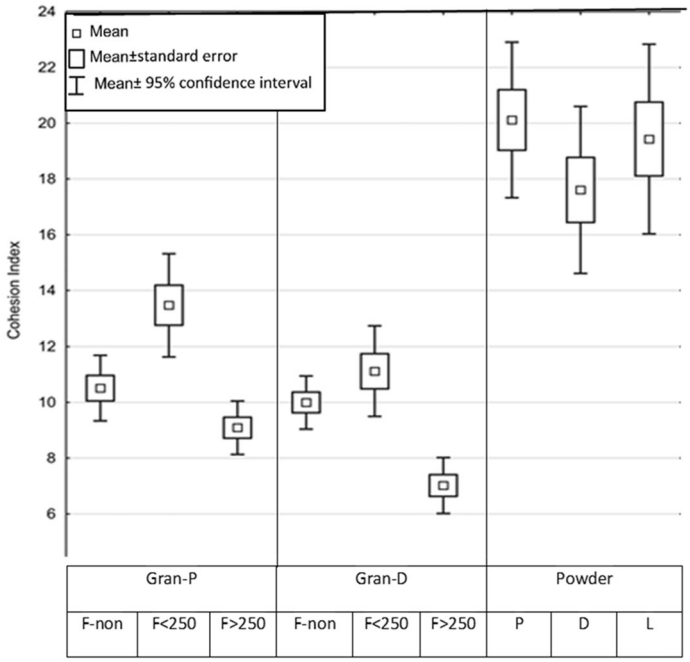

Figure 5. Cohesion index values determined for powder and granule mixtures ($n = 6$).

lower cohesion indices in comparison to corresponding placebo fractions (Gran-$p < 250$ and Gran-$p > 250$). For the powders, similar values of cohesion indices were found for placebo (Powd-P) and for drug containing powders (Powd-D and Powd-L). Despite the fact that the analyzed mixtures differed in the content of the active ingredients (0.5, 1, and 5%), they did not differ significantly from the placebo mixtures. The results showed that the cohesion test is a precise tool which allows to demonstrate differences in flow properties of powders and granules. Furthermore, the results can be compared with the flow rate measurements through the funnel.

The results of the caking test are presented in Figure 6(A) as the cake height ratio after following compaction cycles (from 1 to 5). An increase in the cake height ratio might indicate strong tendency to form cakes during storage. For the analyzed mixtures (granules and powders), the increase of this factor was observed after the second or sometimes the third cycle, however in the next cycles, the ratio decreased or stabilized. It can be seen that larger increase in the cake height ratio is observed for the powders than for the granules. However, similar cake height ratios were observed for all granules, irrespective of the particles size or

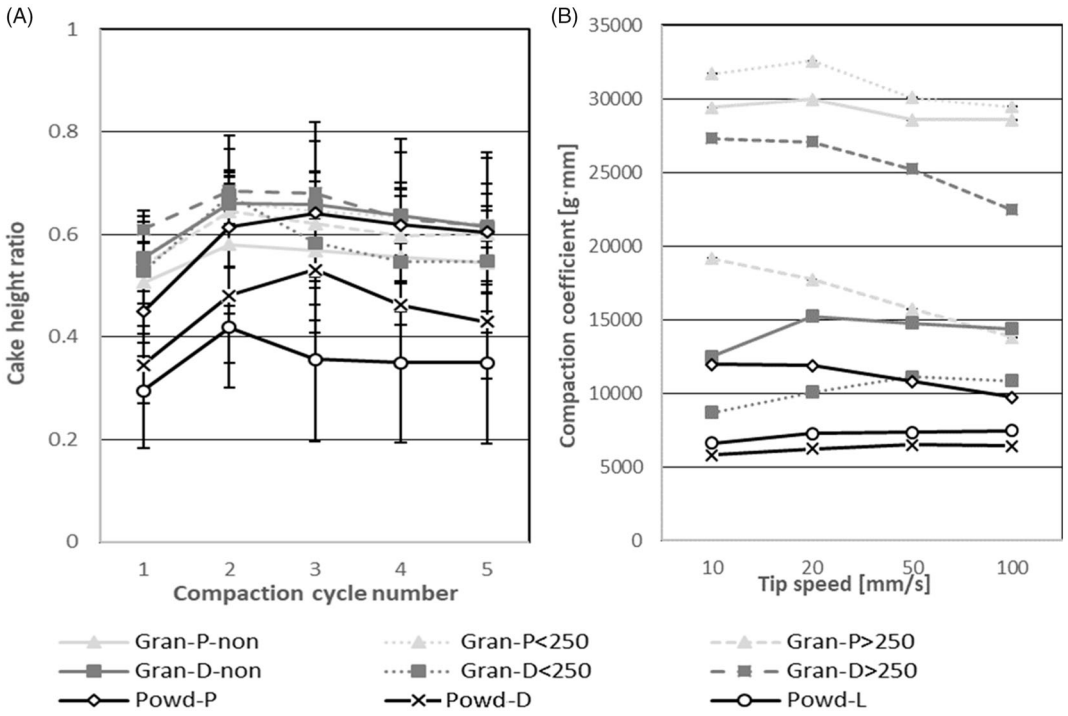

Figure 6. Cake height ratio trends along with subsequent compaction during the caking test (A) and compaction coefficient trend along with increasing tip speed during PFSD test (B) for powder and granule mixtures.

Table 6. Capability indices calculated for the compression process of diazepam minitablets on the basis of compression force acceptance criteria.

Minitablets batch			Compression force (kN)		Process capability indices	
Diameter (mm)	Compression pressure (MPa)	Mixture type	Mean	Sigma (σ)	C_p	C_{pk}
2.5	150	Powder	0.75	0.046	1.05	0.70
		Granules	0.79	0.049	1.25	0.81
	250	Powder	1.22	0.112	0.39	0.28
		Granules	1.18	0.086	1.27	1.16
3.0	150	Powder	1.03	0.069	0.99	0.93
		Granules	1.06	0.055	1.56	1.52
	250	Powder	1.78	0.158	0.75	0.62
		Granules	1.75	0.107	1.24	1.13

API presence. Although the test demonstrated some trends for the analyzed mixtures, the results from three measurements showed large deviations (even 40% for powders), which did not allow further analysis of the results.

The powder properties are not always constant, they can change during processing, e.g. when the feeder or turret speed increases, the tableting mixture may become more resistant to flow (increasing compaction coefficient) or more free flowing (decreasing compaction coefficient), what may result in non-reproducible die filling [29]. This behavior can be predicted by powder flow speed dependence test (Figure 6(B)). For the investigated granules, similar behavior was observed for non-fractionated granules (Gran-non) and for the fraction below 250 μm (Gran < 250). The compaction coefficient was stable with increasing tip speed regardless of the presence of API. However, for the fraction above 250 μm, the course of compaction coefficient was different – it was strongly decreasing which indicated improvement of the flow properties as the tip speed increased during the test. This may result in the overfilling of dies during tableting process. In case of powders, the compaction coefficient values were constant, which demonstrated stable flow properties.

All tests performed, pharmacopeial and non-pharmacopeial, showed that an accurate powder flow assessment is very difficult and multifaceted because it depends on many factors. In effect, it was difficult to make comparisons between different tests because they assessed various aspects of flow properties. From the industrial point of view, the main goal is to find a clear correlation between the flow during tableting and the resulting uniformity of the product. Although some relationships were already reported in the literature, there is still a need to verify them on high speed production tableting [34]. The present studies demonstrated that the best differentiation between the studied mixtures was obtained on the base of flow rate measurements and cohesion test. Moreover, the results from both tests correlated.

Powder and granule mixtures with diazepam (Powd-D and Gran-D-non) were compressed using two levels of compression pressure (150 and 250 MPa) and 2.5 and 3 mm minitablets were obtained. Tableting process was statistically assessed by calculating capability indices based on compression force acceptance criteria (Table 2) and minitablets mass acceptance criteria (Table 3). The results are presented in Tables 6 and 7 and additionally illustrated on histograms in Figure 7. The compression force value is a critical tableting process parameter, which determines the product quality. Statistical analysis of the compression force stability can help to evaluate the process performance. Depending on the tablet press design, the compression force value is influenced by the distance between lower and upper punch and also, what is more important, by the die filling. This design allows to detect changes

Table 7. Capability indices calculated for the compression process of diazepam minitablets on the basis of minitablets mass acceptance criteria.

Minitablets batch			Weight (mg)		Process capability indices	
Diameter (mm)	Compression pressure (MPa)	Mixture type	Mean	Sigma $-\sigma$	C_p	C_{pk}
2.5	150	Powd	11.17	0.11	3.059	2.572
		Gran	12.24	0.19	1.852	1.477
	250	Powd	11.06	0.13	2.480	2.349
		Gran	12.10	0.16	3.063	2.810
3.0	150	Powd	17.07	0.22	2.359	2.267
		Gran	20.24	0.13	5.255	4.644
	250	Powd	17.00	0.26	2.250	2.248
		Gran	20.00	0.20	4.038	4.037

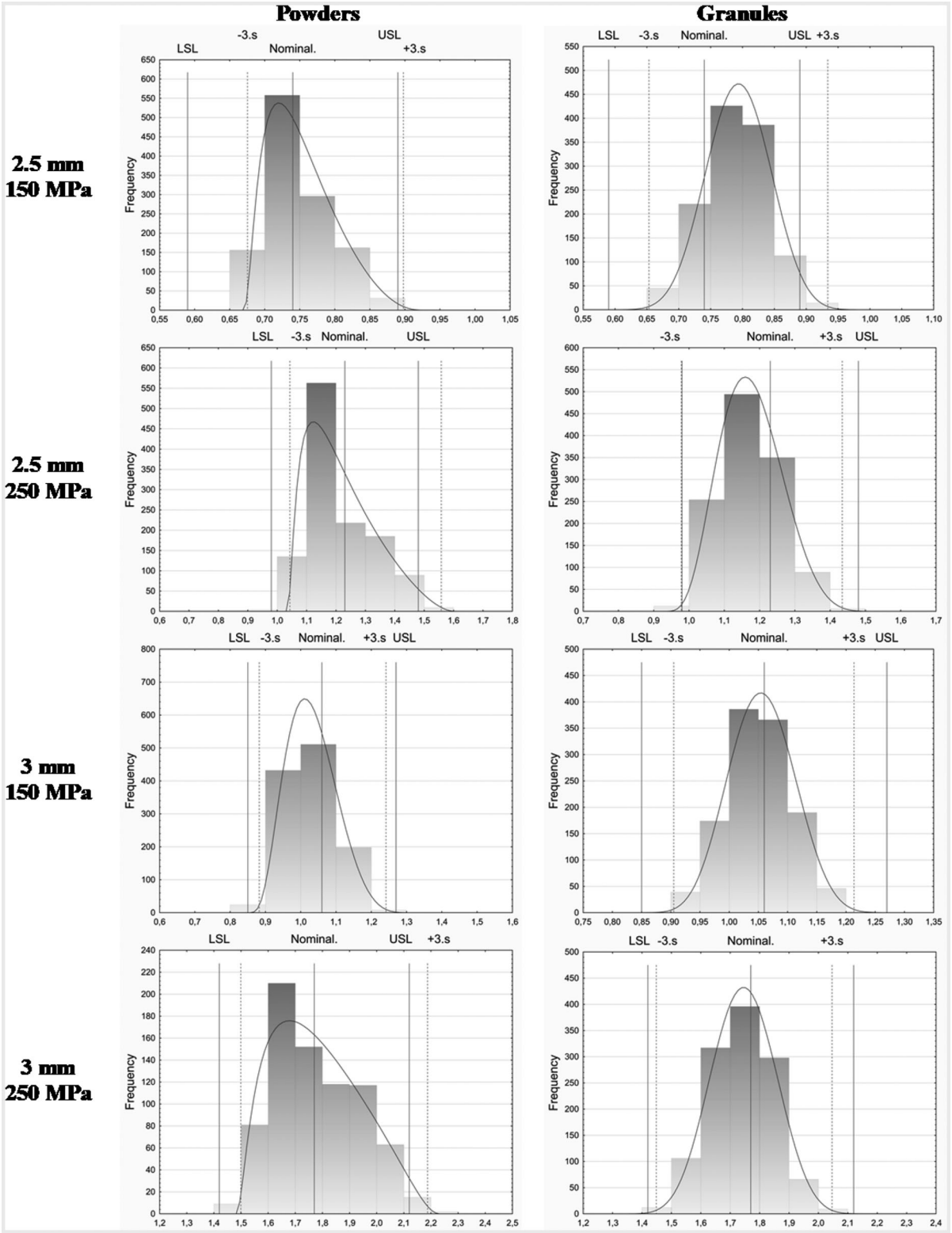

Figure 7. Histograms of compression force distribution depending on tableting mixture type, minitablet diameter, and compression pressure.

in the die filling by variations in compression force during the process, in contrast to checking tablet weights at given intervals which do not guarantee that all tablets fulfill weight specification [35]. Analysis of the compression force might be a QbD tool to assess product quality during the manufacturing process [36]. The process is capable when the C_p value is greater than 1. However, the higher the capability index, the better the process is. The C_{pk} value refers to the process centering and when it is equal to C_p the process is perfectly centered within the specification limits [37].

The capability indices based on compression force data showed that more capable and more stable were the processes where the tableting masses were granulated (C_p=1.24–1.56). The best process robustness was obtained for 3 mm Gran-D minitablets compressed with pressure of 150 MPa and for this process the best fitting into specification requirements ($C_p \approx C_{pk}$) was determined. On the other hand, tableting process of the powder mixtures when lower compression force was used (150 MPa) showed better robustness (C_p about 1) in comparison to 250 MPa.

Based on the weight uniformity specifications, all processes exhibited very good capability (C_p>1.8). In most cases, the compression of granules was characterized by significantly greater robustness. However, tableting process of Gran-D 2.5 mm minitablets compressed with lower compression pressure had capability indices lower than compression of powder mixture. The highest C_p was determined for Gran-D 3 mm/150 MPa minitablets, as it was also established based on the compression force variations. For the granules, better process capability was determined during manufacturing of larger 3 mm minitablets. In the study, only 20 minitablets were weighed to determine the mass, hence it was much less data than in the case of compression force value which was registered for each tablet (about 1200 recordings).

The statistical assessment of minitablets manufacturing process showed better process capability when free flowing and non-cohesive materials were used. However, it was possible to obtain minitablets with acceptable mass uniformity from the cohesive powders, even when the compression force was characterized with high variation. Nevertheless, the use of mixtures with lower flowability may result in a reduced production efficiency and greater risk of product faults during the scale-up and increasing the tableting speed. Additionally, better robustness was demonstrated for 3 mm minitablets than for 2.5 mm, what indicates that producing of smaller minitablets is more challenging.

Development of oral solid dosage forms appropriate especially for pediatric patients can be achieved with the minitablets. This study showed how new methods of flow properties assessment can be used to provide information about tableting mixtures. Additionally, the compression process can be assessed by calculating the capability indices which can be a useful tool in product quality maintenance.

Conclusion

The flow properties are the quality attributes of the tableting masses which have to be defined in order to properly design the manufacturing process. It seems to be especially important in case of minitablets because of their small sizes and difficulty in reproducible filling of small, 2–3 mm, dies. However, an accurate assessment of the flow properties is very demanding and the static tests based only on gravitational flow of the material do not describe these properties precisely. The study showed that non-compendial dynamic tests with changing speed and shear force can provide more reliable information. In the study, it was proved the most useful test was the cohesion test, which allows to distinguish the analyzed mixtures in the terms of cohesiveness.

Determination of critical process parameters and defining the acceptance criteria can help to ensure the product quality by better understanding of the manufacturing process. The performed studies showed that the compression force variations can be used to predict the manufacturing process performance, which fits into the concept of QbD in pharmaceutical development. The results of the study showed the usefulness of 'six sigma' concept in assessment of minitablets production by calculating the capability indices. The study proved that manufacturing of small tablets can be successful which hopefully increase the interest of pharmaceutical industry in minitablets.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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