International Journal of Pharmaceutics 597 (2021) 120344

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Effect of colloidal silicon dioxide and moisture on powder flow properties: Predicting in-process performance using image-based analysis

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ARTICLE INFO

Keywords:
Powder flow
Colloidal silicon dioxide
Moisture
Lactose
Cohesive powders
Image analysis
Tablet manufacture

ABSTRACT

The effect of colloidal silicon dioxide (CSD) on powder flow properties of poor-flowing excipient lactose 200 M was investigated. Binary mixtures of different ratios of CSD as glidant were examined using a modern image-based flow measuring technique. Special attention was placed to subtle variations in powder flow from small changes in glidant concentration (0.025% w/w). Understanding the modes of interaction of particles and their effects on flowability using the method predicted the die filling performance during tablet manufacture. In addition, the importance of moisture content on powder flow properties was empirically underlined. A more efficient range of CSD was detected from 0.10 to 0.50% w/w in most of the tested conditions, which revealed a significant improvement in powder flow performance compared to higher amounts typically handled in the pharmaceutical industry.

1. Introduction

Poor powder flow is a frequently encountered challenge in pharmaceutical drug manufacturing (Tan et al., 2015; Prescott and Barnum, 2000). Thus, a considerable effort has been directed towards overcoming flow problems. During formulation development, the flow of a blend may affect the selection of excipients and it may dictate whether direct compression is used or if some form of granulation is required (Sarfaraz K.Niazi, 2009). Contrary to granulation processes, direct compression requires fewer processing steps and less equipment (Shanmugam, 2015; Jivraj et al., 2000), which reduces production times and costs. This and other considerations make direct compression the preferred choice and the most economical method for tablet manufacturing in the pharmaceutical industry. Although the principles governing direct compression have been well known for many years, the technique has only recently become more popular/attractive as a result of the introduction of certain grades of excipients specifically designed for direct compression (Li et al., 2017).

Colloidal silicon dioxide (Aerosil® Pharma) has been used as a pharmaceutical adjuvant since the early days of direct-compression tableting (York, 1975). Classified as a nanomaterial with an average particle size around 30 to 40 nm, it is an amorphous solid consisting of highly pure silicon dioxide. Its different applications (Ekijäat and Koo. , 2016; Zimmermann et al., 2004) include the absorption of substances (carrier application) and the formulation of gels from liquids through the formation of a network of aggregates (rheology control). The adhesion of CSD aggregates to the pharmaceutical powder was evaluated in this study. This mode of action enhances powder flow over the pure excipient (glidant application). The type and concentration of CSD depends on the physical properties of the powder, i.e., composition, particle shape and size, and the processing equipment (Zimmermann et al., 2004).

Powder flow properties refer to the behaviour of the bulk material and arise from the collective forces acting on individual particles like van der Waals forces, liquid bridging, electrostatic charge, mechanical interlocking, friction and gravity. The forces are derived from the physical properties of the material and are also influenced by the operating conditions such as relative humidity (Prescott and Barnum, 2000; Duran, 2000). CSD helps to improve powder flow properties by counteracting these different mechanisms (Everett, 1979). Firstly, small CSD aggregates adhere to the surface of the material, thereby filling the voids and irregularities on the particles surface and reducing mechanical interlocking and friction. Van der Waals forces and electrostatic attractions decrease consequently by increasing the distance between individual particles. Additionally, the hydrophilic nature of some types of CSD retains moisture, which helps to reduce liquid bridges between solid particles that hinder powder flow.

Moisture adsorbs on the surface of CSD by the formation of siloxane

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https://doi.org/10.1016/j.ijpharm.2021.120344
Received 9 September 2020; Received in revised form 29 January 2021; Accepted 30 January 2021
Available online 2 February 2021
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bonds (≡Si–O–Si≡) and silanol groups (≡Si–OH), which are capable of forming numerous hydrogen bonds, thus affecting the collective forces between individual particles. The adsorbed water can alter the surface conductivity by decreasing the electrostatic forces, or it may condense creating capillary forces (especially liquid bridging and occasionally solid bridges between particles) adversely affecting powder flow. The effect of moisture on powder flow depends on the physicochemical properties of the material, such as roughness, specific surface area (SSA) or particle composition, which affects interfacial tension and capillary pressure (Hiestand, 1966). Relative humidities (RH%) above 60% are rarely used in the pharmaceutical industry -except in specific manufacturing processes such as wet granulation-, considering the multiple challenges involved (e.g., microbiological stability, caking process, recrystallization and deposition of solid bridges). Conversely, RH below 20% are not normally recommended assuming increased electrostatic charges in the system (Bhatt, 2010). Deficiency or excess of moisture content, which depends on the physicochemical properties of the material and the pharmaceutical manufacturing conditions, results in poor powder flow properties. Therefore, the level of moisture required for the compression process is largely governed by the degree of hydrophilicity of the components in the formulation. No agreement exists to optimal humidity conditions in drug manufacturing (Sarfaraz K. Niazi, 2009). However, to ensure production quality, Good Manufacturing Practices (GMP) establish certain limits on humidity conditions, for example, in the tableting process a range of 25–35 RH% is recommended (Bhatt, 2010).

X-ray photoelectron spectroscopy (XPS) has been successfully used to measure the optimal amount of CSD for glidant purposes (Jonat et al., 2006). However, there is no generally accepted method for evaluating glidant effectiveness and the selection of the glidant and its concentration are often empirical (Morin and Briens, 2013). As a consequence, glidant usage is often ascertained on a trial and error basis through inaccurate predictions, such as angle of repose (AOR), Carŕs Index or conventional flow rate through an orifice (York, 1975; Pingali et al., 2011; Chang et al., 1999; Zimmermann et al., 2004). This has several limitations including reproducibility, predictability and sensitivity, and the analysis is often time-consuming and user-dependent (Tan et al., 2015; Vasilenko et al., 2011). Powder rheometry and shear-cell are well established in the powder-flow analysis technology, but they become inefficient when measuring subtle variations in powder flow (Blanco et al., 2020) and single determinations require large amounts of sample (typically>50 g). Furthermore, it has been suggested that current powder flow parameters are not able to fully predict the die filling performance and the measurement technique that best simulates the tableting process should be selected (Goh et al., 2017).

Mixing conditions strongly influence powder flowability (Parvizi et al., 2016). CSD is delivered in the form of agglomerates, which need to be broken down to maximize efficiency. Preferred mixers are free-fall (gravity) mixers or mechanical mixers that apply only low shear forces such as Turbula® mixer (Parvizi et al., 2016). Long mixing times are not recommended. In the pharmaceutical industry, the amount of CSD used as glidant is between 0.1 and 1.0% w/w based on the total formulation (Rowe et al., 2009). Aerosil® manufacturer recommends that a concentration of 0.5% w/w is used initially and the amount be adjusted up or down to find the optimum concentration. This quantity would be defined as the surface concentration of CSD that covers enough of the powder particles, i.e., prevent direct contact and thus obtain better bulk powder flow properties. Being under or over coverage of the particles negatively influences powder flow (Zimmermann et al., 2004).

The effect of CSD concentration and RH on powder flow properties was examined in this study using unique image-based analysis technology of powder flow through an orifice. Previous studies demonstrated the high sensitivity of the method to characterize different powdered materials with a strong correlation with tablet manufacture (Blanco et al., 2020).

2. Materials and methods

2.1. Materials

α-lactose monohydrate (Pharmatose 200 M milled lactose, Ph.Eur grade, DmV-Fonterra Excipients, Veghel, The Netherlands) was selected as a model filler based on its very poor-flowing properties, low hygroscopicity and excellent physical and chemical stability (Rowe et al., 2009). Moreover, as an electrical insulator, relative humidity is critical to its flow behaviour.

High-purity amorphous CSD (Aerosil® 300 Pharma, Evonik Industries, Essen, Germany) was used as glidant to evaluate the effect on powder flow of small changes in sample physicochemical characteristics. Classified as a hydrophilic CSD, it was conceived specially for applications requiring a very high specific surface area (average particle size of 7 nm). The manufacturer describes CSD as a more efficient glidant in the case of nonporous materials and often requires concentrations of<0.5% w/w CSD (Industries, 1424).

Magnesium stearate (Orion Pharma, Finland) contributed to better lubricity during the tableting process, lowering ejection forces and die-wall friction.

2.2. Blending and sample acclimatization

Binary mixtures of lactose 200 M and CSD were prepared in triplicate using Turbula® mixer (Turbula T2C, W.A. Bachofen, Switzerland), a 2L glass container with a 50% filling ratio (batch size ± 500 g) and medium rotation speed (67 rpm). To ensure a homogeneous distribution of the components of the mixture, the mixing time was defined at 20 min (Zimmermann et al., 2004), considering the wide particle size distribution of lactose 200 M. Both materials were screened through a 750 μm sieve to remove possible lumps derived from consolidation during storage and to ensure an efficient mixing process. This also prevented re-agglomeration of CSD during mixing, since smaller agglomerates are more effective in enhancing flowability (Rumpf, 1974). The weighing operation was conducted directly into the mixing container to avoid possible losses during handling. To evaluate the effect of CSD on powder flow properties, different percentages by weight (% w/w) were added to the mixture (0.00, 0.05, 0.075, 0.10, 0.125, 0.15, 0.175, 0.20, 0.25, 0.50, 1.00 and 2.00% w/w). Lactose without CSD (0% w/w CSD) was used as reference compound to determine the effect of CSD on powder flowability. Sample preparation and weighing were conducted at 30 ± 0.5% RH for all samples.

Powder flow characterization was conducted prior to tablet production, without the addition of lubricant, to evaluate the effect of CSD alone, which was the primary aim of this study. The flow performance in the press was subsequently evaluated to scale up from the predicted to the real-processing conditions.

2.2.1. Sample preparation: Flow characterization

The mixtures were stored at different RH to simulate diverse manufacturing conditions. First, six samples of each mixture (average mass: 87 ± 1 mg) were weighed and stored separately in polystyrene antistatic weighing-dishes for 5 days in four different humidity-adjusted desiccators, at 25 °C (23% RH: CH_3CO_2K; 33% RH: $MgCl_2$ $6H_2O$; 43% RH: K_2CO_3; 53% RH: $Mg[NO_3]_2$). This single-sample preparation minimized the moisture exchange during the analysis. Additionally, the concentration of CSD in the analytical samples was blinded until the end of the determination, when data collection and analysis were conducted. Humidity was monitored over the conditioning time with thermo-hygrometers (F007TH Wireless Thermo-Hygrometer Ambient Weather; Chandler, AZ, USA).

2.2.2. Sample preparation: Tableting studies

A fixed amount of Magnesium stearate (MgSt; 1% w/w) was added prior to the tableting step to ensure that the tablet was properly ejected

from the press die. Tableting mixtures were prepared by combining the binary mixtures with MgSt for another 5 min. As a boundary layer lubricant, MgSt forms a film around particles affecting the friction through modified particle–particle contact. This becomes especially important in ternary component powder systems like this one, where lubricant efficiency of MgSt depends on the CSD concentration (Sabir et al., 2001; Rowe, 1988). The mixing order, amount of MgSt and mixing time were selected based on previous studies (Sabir et al., 2001).

2.3. Powder physical properties: Size, morphology and bulk/tapped/true density

Particle size distribution (PSD) and true density were measured in triplicate and are reported in Fig. 1. True density was tested at all RH for pure lactose. PSD was determined using the dry dispersion technique with a laser diffraction Malvern Mastersizer 3000 instrument (Malvern Instruments Ltd., Worcestershire, U.K.). Dry powder samples were analyzed using the Aero S dry powder disperser, equipped with a micro volume sample tray (2–10 g), applying 3 bar dispersive air pressure and 50% vibration feed rate. MS3000 software (v3.5) generated particle size distribution data. True density was quantified using a Helium Pycnometer (Model 1305 Multivolume, Micromeritics Instrument Corporation, Norcross, USA). Particle morphology of pure lactose was examined using a scanning electron microscope (Quanta FEG250 SEM, ThermoFisher, OR, USA) equipped with a large field low vacuum SED (LFD) detector, where samples were sputtered with gold prior to examination.

Bulk and tapped densities were determined in triplicate for each tableting mixture (Ph.Eur 10th Ed. 2.9.36) using Erweka SVM equipment (Erweka Apparatebau GmbH, Germany). This data was used to calculate Carŕs Index and the theoretical tablet weight for optimal filling of a known die-cavity volume. RH% remained within a 30–35% range during the whole process.

2.4. Powder flow characterization

Powder flow properties were characterized using a dynamic flow-testing method developed at the University of Helsinki, Finland (Blanco et al., 2020). The image-based flowability system employs unique technology for measuring the resistance of the powder to flow. It consists of a sample cuvette mounted on a stepper motor, which is controlled with a custom-made software. These two components are the core of the method.

The cuvette consisted of two horizontally positioned chambers separated by an orifice (d = 6 mm). The chambers were illuminated from below and the progress of powder flow was monitored by real-time from above. The powder sample (0.2 cm^3) was placed in the left chamber and then the cuvette was subjected to a specific acceleration profile, consisting of a slow acceleration and rapid deceleration when moving to the right. Consequently, based on Newtonian mechanics, the sample moved to the opposite chamber through the orifice where a pivot disturbed the powder flow stream. This resulted in the creation of unique patterns depending on the material flow properties.

The flow was defined as a single parameter -Flowability Index (FI%)- dependent upon the variation of luminous intensity and the movement of powder inside the measurement cuvette. Both images (final flow pattern and empty cuvette) were compared on their grey-scale values pixel by pixel. In case the analyzed pixel showed a darker value when compared to the background pixel (empty cuvette), it was colored black, assuming powder particles absorb certain light intensity. Otherwise, the pixel was considered "clear" and was colored white. The resulting binary image was used to obtain the FI% parameter as a function of the area covered by powder.

The optical evaluation or visual inspection of powder flow was useful to support quantitative data and helped the analyst to understand the materiaĺs behaviour in real manufacturing conditions. Additionally, the method was compared with the current methodology and showed a significant improvement in sensitivity when evaluating powder flowability in tablet compression (Blanco et al., 2020). Differences in processing time and the amount of sample required were also significant compared to other methods. An average of 5 min and 200 mg per measurement (n = 3) was reported using the method. In the present study, the measuring system was enclosed in a sealed chamber with a humidity-controlled environment. A customized medical nebulizer ensured that humidity conditions during the analysis were precisely adjusted (StDev: ±3 RH%) and an air blowing system homogeneously distributed moisture in the air. Remote controlled hygrometry (Testo 440 kit -resolution 0.1%RH-, West Chester, PA, USA) was used for monitoring purposes. To reduce moisture exchange between the samples and the environment during the analysis, samples were directly transferred from the desiccator to the humidity-controlled environment for the powder flow determination. This was considered important to ensure reliable results due to the extremely fluctuating moisture on the surface of powdered materials (Sandler et al., 2010; Emery et al., 2009), which particularly affects small sample amounts. The flowability of every powder mixture was analyzed six times (n = 6) for each humidity. The flow images presented throughout the study were selected to precisely describe the average flow values.

2.4.1. Tableting studies

Powder compression was performed on an eccentric tablet press (EK 0, Korsch, Berlin, Germany) equipped with a flat single-punch (diameter (Ø): 9 mm) in a stationary die and a moving-forced feeder, which translates over the die at a defined speed of 60 tablets $minute^{-1}$. Powder filled the hopper to approximately 3 cm from its top. Die-cavity volume and compression force were adjusted so that tablets exhibited acceptable

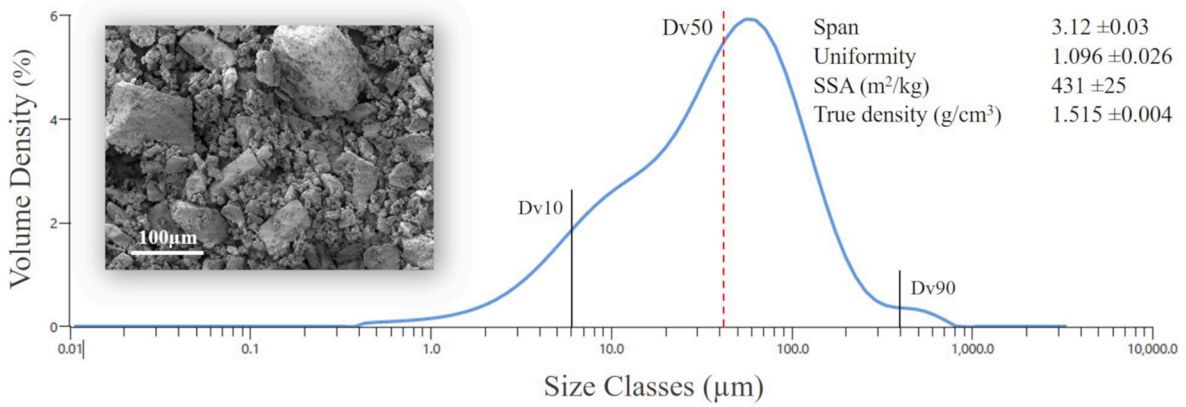

Fig. 1. Physical properties of lactose 200 M. SEM-micrograph and PSD analysis.

thickness and strength to remain intact during the collecting and handling processes. Between batches, the equipment was cleaned and the process of loading and filling the feeder was repeated from the start. Tablets were collected in the order of release (100 units per batch), and the average, standard deviation and relative standard deviation (RSD) of tablet weight were calculated and compared with the bulk density-derived tablet weight (i.e., the ideal or theoretical weight for an optimal die filling). This helped to determine individually the die filling efficiency (experimental weight/ideal weight *100) for each CSD ratio as a reliable descriptor of powder flow (Mills and Sinka, 2013; Sinka et al., 2004). RH remained within 30–35% during the whole process. All measurements were made in triplicate, three batches for each CSD concentration.

2.5. Data analysis

MatLab (v.2018b, Mathworks Inc., Natick, Massachusetts) program was used to calculate statistical significance between datasets. One-way analysis of variance (ANOVA) statistical model analyzed the differences among means in a dataset (e.g., a selected RH). Multiple comparison test (Tukeýs Honest Significant Difference) explored the differences between datasets determining the contrast of observing the experimental results at different humidities.

3. Results and discussion

SEM-micrographs and laser diffraction analysis described a broad PSD population composed of non-spherical, nonporous lactose particles (see Fig. 1), which conferred a high bulk density on the material. Furthermore, a considerable amount of fines produced during the milling process (Paques and Lindner, 2019) contributed to a significant degree of mechanical interlocking and therefore poor-flowing properties.

3.1. Effect of CSD on powder flow properties

Quantitative and qualitative powder flow characterization described the motion-response performance of the mixtures at constant room humidity (30–35%RH). Special attention was placed on subtle variations in powder flow from small changes in glidant concentration (0.025% w/w CSD). Powder flow experimental data supported the theoretical behaviour for CSD aggregates when mixed with the poor-flowing excipient lactose 200 M. The flow dataset shown in Fig. 2 differentiates three general phases: 1) The flowability increases progressively and uninterruptedly until, 2) the plateau or optimal glidant range is reached. 3) Then the flowability slightly decreases. This flow behaviour is reported supporting the numerical data in the flow pattern images or visual inspection of powder flow. Thus, facilitates the analyst to investigate explanations of the interaction of particles and the characteristic flow effects of different quantities of CSD that cannot be elucidated only from data analysis.

CSD aggregates adhere to the surface of lactose enhancing powder flow properties at a certain range of concentration (glidant application). At low concentrations, CSD aggregates fill the voids and irregularities of powder particles, reducing friction and mechanical interlocking. Therefore, the agglomerate-forming phenomenon decreases with CSD (Zimmermann et al., 2004; Everett, 1979), as noted in Fig. 2 *(a.)*. Moreover, sequentially increasing the amount of CSD in the mixture improves particle roundness and sphericity (Cruz-Matías et al., 2019) and thus increases the interparticular distance or direct contact between particles. This prevents intermolecular forces, i.e., Van der Waals and electrostatic forces. This was evidenced in the progressive enhancement in powder flow data. Once those anti-cohesive mechanisms reach their maximum, the effectiveness of the glidant is in maximum too. This stage was characterized by a homogeneous distribution of components and a low population of CSD agglomerates in the mixture, as exemplified in the 0.15% CSD flow-pattern image in Fig. 2. Certainly, it corresponded to the most favorable flow behaviour. Further addition of CSD to the mixture adversely affects powder flow (Zimmermann et al., 2004). Free CSD aggregates tend to group into larger aggregates as the lactose particle surface is now coated. These agglomerates act as foreign objects in the powder bed increasing the cohesiveness and thus decreasing the flowability (Chang et al., 1999). This phenomenon was first observed at 0.25% CSD as occasional darker areas in the powder flow pattern, as depicted in Fig. 2 *(b.)*, and became more evident as the amount of CSD increased.

Jonat et al. (Jonat et al., 2006), achieved similar CSD concentrations when improving flowability of common pharmaceutical powders using X-ray photoelectron spectroscopy surface-analysis on microcrystalline cellulose (Avicel® PH 101) and pregelatinized starch (Starch 1500®). The Si 2p signals (Silicon spectra) of the CSD indicated that the optimal coverage of the excipient surface corresponded to a higher degree of de-agglomeration of the aggregates in the powder bed. This was characteristic in a range of 0.125–0.25% w/w CSD, depending on the mixing conditions.

Note that all the mechanisms of action of CSD occur simultaneously during the mixing process and are also present in the subsequent preparation. The limited number of repetitions ($n = 6$) proved to be sufficient

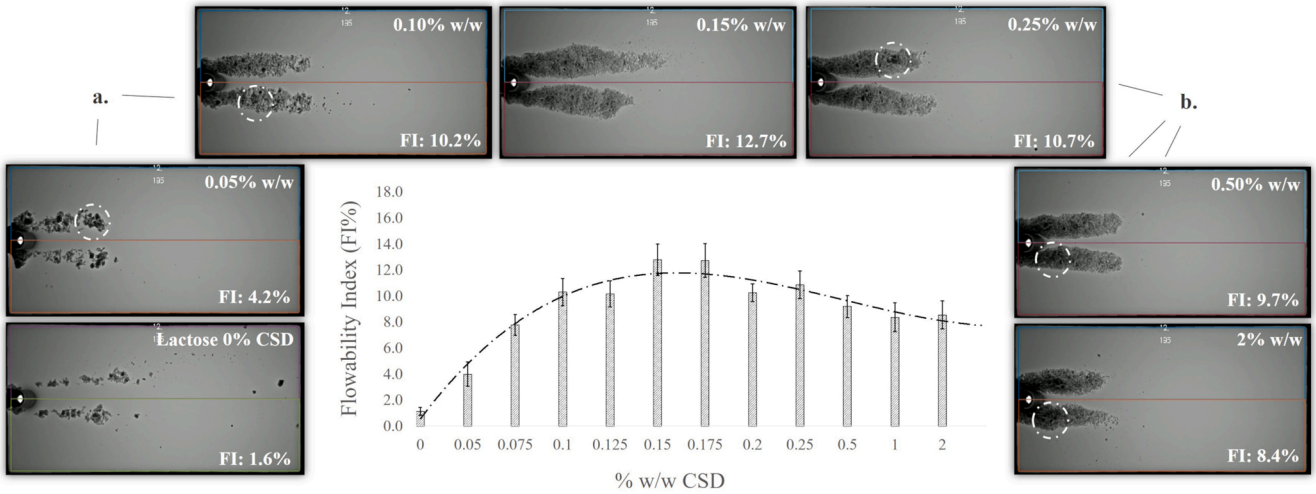

Fig. 2. Lactose 200 M powder-flow response for different ratios of CSD at 33(±3%) RH. **a.** Agglomerate-forming phenomenon decreases. **b.** Free CSD aggregates tend to group into larger agglomerates that result in powder cohesion. *Third-grade polynomial function describes the flow trend.* StDev ($n = 6$).

to achieve good sensitivity using the method. The amount of CSD to produce better flow properties was consistent with the literature recommendations (0.1–1.0% w/w) (Rowe et al., 2009). There is strong evidence that the very high SSA of approximately 300 m2/g (compared to 200 m2/g for Aerosil® 200 Pharma and 50 m2/g for Aerosil® 50) and small aggregate size might be highly effective for crystalline non-porous materials with small particle size such as lactose (Johansson and Nicklasson, 1987). This was recognized in the limited amount needed to produce acceptable powder flow results in small particle size excipient lactose 200 (0.1–0.25% w/w). However, further research on the efficiency of different grades of CSD is needed to support such comparisons.

3.1.1. *Effect of moisture on powder flow.*

CSD positively influences powder flow at different humidity levels. The hydrophilic nature of Aerosil® 300 Pharma compensates the low hygroscopicity of lactose and reduces interparticular cohesion by limiting the formation of liquid bridges within certain limits of moisture (Zimmermann et al., 2004; Everett, 1979). This buffering effect became evident by preserving the flow properties of the mixtures as the moisture was increased. CSD saturation was observed at 53% RH, where overall flowability declined (see Table 2*)*. In addition, most of the flow dataset at 53% RH was significantly different to other humidities ($p \langle 005$) according to multiple comparison test. ANOVA test revealed a better flow performance from 0.10 to 1.00% w/w CSD for most humidities ($p < 0.05$), as shown in Table 2. However, higher amounts of CSD (>0.5% w/w) did not positively affect powder flow in any of the tested conditions and, consequently, a range of 0.10–0.50% CSD was selected for glidant purposes.

The visual inspection of powder flow patterns provided description of the materiaĺs physicochemical properties according to the moisture content. This offered an opportunity to explore possible rationale for powder behaviour. For that purpose, a constant CSD concentration was evaluated at two different humidities (23 and 53%), assuming that the effect of powder flow, largely governed by the moisture content, is in close relation to CSD modes of action. Three replicates of each test (n = 6) were collected for the selected humidities and CSD concentration and are compared in Fig. 3.

A humidity range from 23 to 43% positively affected powder flow compared to higher humidities (see Table 2) and preserved the glidant properties of CSD. Water on the particle surface acted as a lubricant by decreasing friction. In this respect, the water adsorbed on the CSD reduced particle micro-irregularities and electrostatic charges (Bravo-Osuna et al., 2007). Nonetheless, powders stored at low RH are known to facilitate electrostatic charges and a larger amount of fines (Omar et al., 2016), therefore RH below 20% are not normally recommended (Bhatt, 2010). When the RH is low, particle friction induces the appearance of electrical charges (Rescaglio et al., 2017).

Electrostatic charges appeared at 23% RH, as exemplified in Fig. 3 *(b.)*, inducing certain repulsion between particles in low density areas such as the terminations of the flow pattern. This might be facilitated by the larger amount of fines in the mixture. However, further analysis of the powder electrostatic properties would be needed to ultimately rationalise this phenomenon. This must be considered when entering large-scale production, where electrostatic forces are a challenging aspect of powder processing (Duran, 2000; Sarfaraz K.Niazi, 2009). Electrostatic repulsion decreased in higher humidities levels (>23% RH); it was partially detected at 33% RH and disappeared at 43% RH.

At 23% RH, moderate cohesiveness characteristic of lactose material was identified on powder flow (fluffy) consistency. In addition, some agglomerates of unfragmented CSD, typically found in low-shear mixing processes (Parvizi et al., 2016), were detected and are depicted in Fig. 3 *(a.)*. This flow behaviour remained similar up to 53% RH, where the excess of moisture was adsorbed onto the particle surface reinforcing the liquid bridges and negatively influencing flowability (Emery et al., 2009). This particularly affects the powder flow of nonporous materials such as lactose, since water hardly absorbs inside the particle and then adsorbs onto CSD aggregates. As a result, strong capillary forces between powder particles were apparent in numerous agglomerate formations (Omar et al., 2016), as detailed in Fig. 3 *(c.)*. This was evidenced in the irregular and discontinuous flow pattern due to cohesion, as exemplified in Fig. 3 *(d.)*. The negative impact of high humidity conditions emphasized the significance of moisture content on powder flow. Considering both effects (electrostatic charging and agglomerate formation) caused by deficiency or excess of moisture content, the powder flow properties improved for the intermediate RH values, i.e., between 35 and 50%. These results correlate with recent research on the effect of moisture on lactose flowability (Omar et al., 2016; Rescaglio et al., 2017).

3.2. *Powder flow and weight uniformity of dosage units*

Tablet compression was considered to investigate the influence of CSD concentration on the die filling process in real-manufacturing conditions, i.e., flow requirements. Representative fractions of CSD (0.00, 0.05, 0.10, 0.15, 0.20, 0.25, 0.50, 1.00 and 2.00% w/w) were selected and conditioned for tableting by adding a fixed amount of MgSt (1% w/w). Over the production time, the powder bed consolidates at the hopper due to mechanical tapping (Hildebrandt et al., 2019). This was evidenced in the high inter-tablet weight variation at the beginning of each production cycle, when the tablets were collected in order.

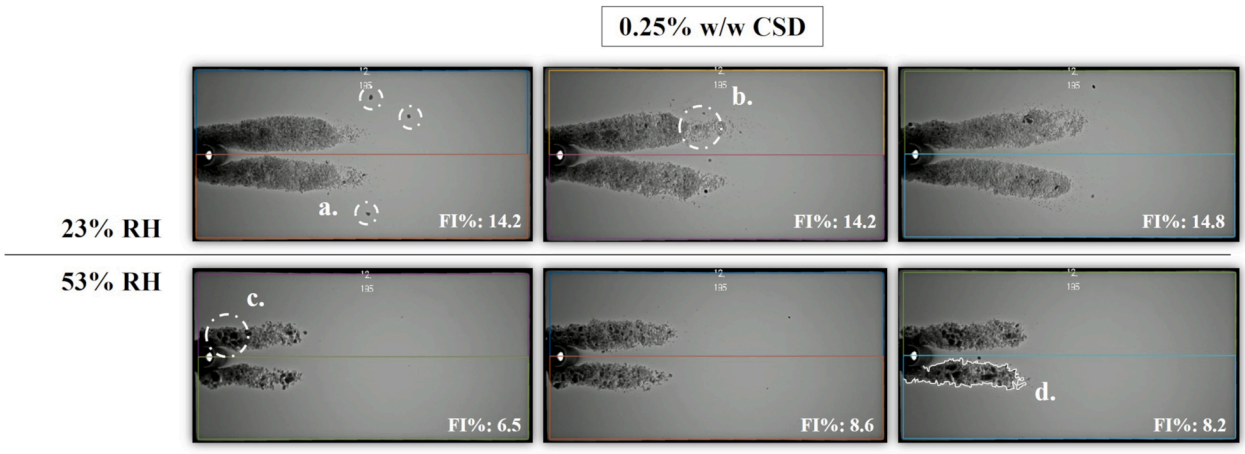

Fig. 3. Effect of moisture on powder flow for 0.25% CSD. **a.** Occasional CSD agglomerates. **b.** Electrostatic repulsion. **c.** Agglomerate-forming phenomenon. **d.** Irregular flow pattern due to cohesion. *Flowability Index (FI%) attached to the pictures.*

Table 1
Summary of bulk and tapped densities in tableting mixtures (1% w/w MgSt). StDev ($n = 3$).

	Lactose	0% CSD	0.05% CSD	0.10% CSD	0.20% CSD	0.50% CSD	1% CSD	2% CSD
Bulk density (g/cm3)	0.457 ± 0.034	0.551 ± 0.009	0.570 ± 0.008	0.583 ± 0.007	0.612 ± 0.004	0.619 ± 0.008	0.612 ± 0.004	0.546 ± 0.009
Tapped density (g/cm3)	0.761 ± 0.029	0.857 ± 0.008	0.862 ± 0.012	0.874 ± 0.009	0.904 ± 0.009	0.904 ± 0.006	0.838 ± 0.016	0.821 ± 0.013
Carŕs Index (CI)	40 (Very Poor)	36 (Very Poor)	35 (Very Poor)	33 (Poor)	32 (Poor)	32 (Poor)	27 (Poor)	33 (Poor)

Table 2
Data table of average flow values (FI%) at different humidities (n = 6). Nonsignificant differences in powder flow for each humidity is in bold ($p < 0.05$).

	23% RH	33% RH	43% RH	53% RH
Lactose 0% CSD	1.3	1.1	1.7	1.4
0.05% CSD	5.9	4.0	5.4	2.8
0.10% CSD	**11.0**	**10.3**	**11.8**	**7.3**
0.15% CSD	**10.8**	**12.8**	**14.8**	**9.3**
0.20% CSD	**13.0**	**10.3**	**10.8**	**10.1**
0.25% CSD	**13.2**	**10.9**	**12.3**	**7.8**
0.50% CSD	**10.4**	9.2	**10.3**	**8.1**
1.00% CSD	**10.4**	8.4	**10.2**	**7.9**
2.00% CSD	6.3	8.6	6.5	7.3

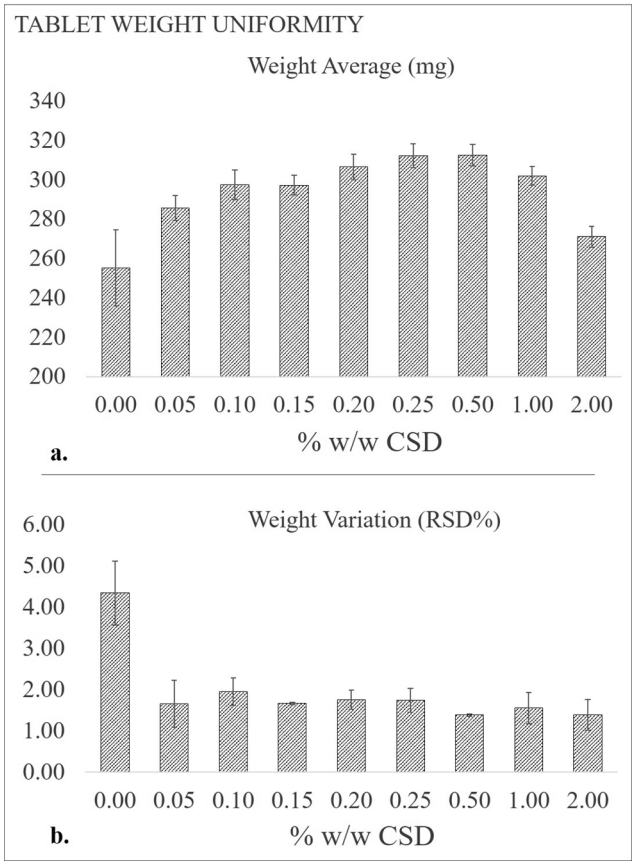

Fig. 4. Weight uniformity studies; StDev ($n = 3$). **4a.** Tablet weight averages. **4b.** Tablet weight variation (RSD%).

Therefore, the first 30 tablets (out of 100 uds per batch) were removed from the statistical analysis to increase the sensitivity of the compression data.

Although the primary role of lubricants is to improve tableting, some lubricants can also improve powder flow. Faqih et al. (Faqih et al., 2007) examined the avalanche behaviour of commonly used pharmaceutical powders mixed with MgSt and observed a significant increase in the flow of regular lactose (glidant properties). This became apparent in the increased bulk density when MgSt was added to lactose alone (see Table 1), exhibiting acceptable, though inefficient, processing in the press. Carŕs Index inadequately defined the optimal CSD concentration at 1% w/w and classifies every mixture as a poor/very poor-flowing powder.

Accuracy of dosage is an important requirement for the production of quality tablets, which demand a constant delivered volume of powder into the die. The factors influencing the tablet uniformity are numerous, however, the concentration of CSD was the main variable in this operation. The compression results showed weight average values distributed according to powder flow properties (FI%), as distinguished in Fig. 4a. Tablet weight variation (RSD) or reproducibility of die fill during tablet production decreased with the addition of 0.05% w/w CSD, as seen in Fig. 4b., and remained constant throughout the remaining CSD concentrations. Contrary to expectations, no decrease in inter-tablet weight variability was observed in correlation with powder flow properties. This was attributed to the poor flowing nature of lactose, which has been found to achieve more uniform die fill than better flowing powders (Mills and Sinka, 2013; Monedero Perales et al., 1996; Sinka et al., 2004). However, a larger sample amount (presumably thousands of tablets) would be necessary to rationalize this behaviour.

Multiple comparison test on die-filling efficiency dataset statistically defined a better CSD range using three lots of data per product, as shown in Fig. 5. Non-significant differences in the die filling efficiency data were found between 0.15, 0.20 and 0.50% CSD ($p < 0.05$) and higher values were detected at 0.10 and 0.25%. In addition, non-significant differences between 0.05, 1.00 and 2% CSD were detected and therefore considered suboptimal CSD concentrations. The poor flowing nature of lactose mixtures was recognized in the irregular and incomplete filling of the die (<90%) for all the samples.

Various studies (Sabir et al., 2001; Johansson and Nicklasson, 1987) have reported that CSD aggregates coat the MgSt particles and prevent the formation of a lubricant film on the powder blend. Therefore, at certain concentrations, when lactose particle surface is coated and there is a fraction of free CSD, the lubricant efficiency is reduced. Then both the presence of CSD agglomerates and the formation of MgSt-CSD complexes reduce the die filling efficiency and the tablet weight average values. The flowability method and the tablet compression studies determined these concentrations to be above 0.5% w/w CSD. In contrast, concentrations above 0.10% w/w CSD were required to significantly improve flow properties.

4. Conclusions

The effect of colloidal silicon dioxide (CSD) on powder flow properties of the poor-flowing excipient lactose 200 M was determined using sample sizes less than 100 mg (0.2 cm^3). Quantitative and qualitative analysis comprehensively described subtle variations in powder flow from small changes in glidant concentration. The method demonstrated unprecedented sensitivity in the characterization of particle flow at small-scale. This brought new insights into the required amount of CSD to improve powder flow properties. Inadequate amounts of CSD adversely affected powder flow.

Accordingly, the die filling performance during tablet manufacture was precisely characterize using the method. The significance of moisture on powder flow properties was also recognized. The optical evaluation identified certain physicochemical phenomena that can affect powder flow, such as agglomerate formation or electrostatic charging, depending on the moisture content. Consequently, powder flow

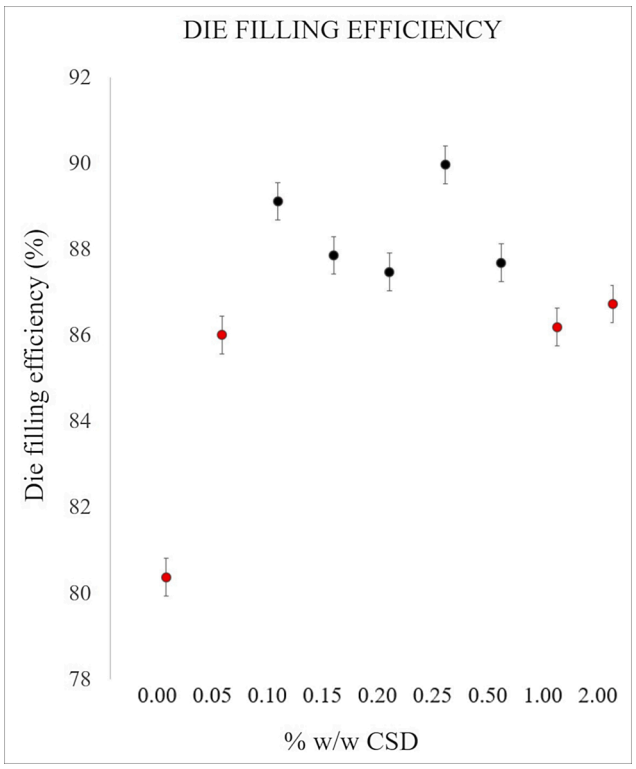

Fig. 5. Weight uniformity studies: Multiple variable analysis on the die-filling efficiency (Calculated from experimental weight/ideal weight *100). *Suboptimal CSD concentrations ($p < 0.05$) are colored in red.*

characterization using image analysis technologies demonstrated to be an additional tool in pharmaceutical tablet manufacture to predict in-process performance and to detect flow problems before the powder is introduced in the processing equipment.

CRediT authorship contribution statement

David Blanco: Methodology, Investigation, Writing - original draft. **Osmo Antikainen:** Formal analysis. **Heikki Räikkönen:** Conceptualization. **Jouko Yliruusi:** Supervision. **Anne Mari Juppo:** Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors gratefully acknowledge financial support from the Finnish National Agency for Education (EDUFI) -Opetushallitus- [Grant Number TM-19-11041, 2019]. R.F. y T.B.

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