International Journal of Pharmaceutics 662 (2024) 124528

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

A continuous micro-feeder for cohesive pharmaceutical materials

P. Hou [a,b], M.O. Besenhard [c], G. Halbert [a,b], M. Naftaly [d], D. Markl [a,b,*]

[a] Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow G1 1XQ, UK
[b] Centre for Continuous Manufacturing and Advanced Crystallisation (CMAC), University of Strathclyde, Glasgow G1 1RD, UK
[c] Department of Chemical Engineering, University College London, London WC1E 7JE, UK
[d] National Physical Laboratory, Teddington TW11 0LW, UK

ARTICLE INFO

Keywords:
Powder micro-feeding
Continuous feeding
Low dose feeding
Screw feeder
Double-screw agitator

ABSTRACT

Over the past decade, continuous manufacturing has garnered significant attention in the pharmaceutical industry. Still, numerous continuous unit operations need developments, such as powder blending and feeding at low and high throughputs. Especially the continuous and consistent feeding of solid drug substances and excipients at low feed rates remains challenging. This study demonstrates a micro-feeder capable of feeding poorly-flowing pharmaceutical powders at low feed rates. The system performance was investigated using three grades of pharmaceutical powder: croscarmellose sodium (cohesive), magnesium stearate (very cohesive), and an active ingredient, paracetamol (non-flowing). The results show that the micro-feeder can continuously and consistently feed powders at low flow rates (<20 g/h) with low variability (<10 % for non-flowing materials and < 5 % for cohesive materials). Notably, the micro-feeder achieves these results without any feedback control and remains unaffected by refilling, making it a truly versatile and industry-relevant solution. The study's results demonstrate that this micro-feeder system effectively tackles the challenge of consistent and accurate powder feeding at low rates.

1. Introduction

Consistent feeding of powder materials is a critical aspect of the manufacturing process for oral medicines (Besenhard et al., 2017, 2016, 2015; Chen et al., 2012; Fathollahi et al., 2021; Sacher et al., 2021, 2020). Any variations in the feed stream can directly influence the quality of the final drug product (Janssen et al., 2022). This factor becomes even more significant in light of current industry trends, such as smaller batch sizes for clinical trials or smaller patient populations, and the use of high-potency active pharmaceutical ingredients (APIs). For instance, delivering high-potency APIs in doses of milligrams or lower per tablet demands a feeding rate of less than 10 g/h with minimal fluctuation over time (Chamberlain et al., 2022). Achieving consistent and precise powder flow rates in micro-feeding is still challenging in the pharmaceutical and biopharmaceutical industries. To tackle this challenge, innovative manufacturing technologies are needed to ensure the delivery of high-quality products in a sustainable and affordable manner (Nagy et al., 2020; Oladeji et al., 2022).

The primary challenges in achieving consistent powder feeding is the strong dependence of flow rate performance on material properties. Particle size distribution, cohesion force between particles, and adhesion force between particles and the equipment contact surface are critical factors that influence powder feeding. Additionally, equipment design and environmental conditions can also play a role. This challenge is particularly significant given that many new APIs are classified as cohesive or poorly flowing materials (Burcham et al., 2018). Consequently, continuously and consistently feeding micrograms of powder remains challenging (Huang et al., 2022; Janssen et al., 2022; Sacher et al., 2021).

The most common feeders in the pharmaceutical sector are loss-in-weight (LIW) screw feeders. LIW feeders are built on a load cell and rely on gravitational control to attain the preferred powder flow rate and reduce fluctuations through adjusting the screw speed. LIW feeders have been improved through the refinement of the screws (Barati Dalenjan et al., 2015; Engisch and Muzzio, 2014; Santos et al., 2018) and the optimisation of the feedback control system (Blackshields and Crean, 2018). Despite these advancements, conventional LIW feeders cannot achieve consistent feeding at low flow rates, particularly for cohesive materials (Blackshields and Crean, 2018; Burcham et al., 2018; Peterwitz et al., 2022). In addition, refilling LIW feeders remains a challenge due to their dependence on the load cell and the feedback control, resulting in additional variations in the mass flow rate during the

* Corresponding author at: Strathclyde Institute of Pharmacy & Biomedical Sciences, University of Strathclyde, Glasgow, UK.
E-mail address: daniel.markl@strath.ac.uk (D. Markl).

https://doi.org/10.1016/j.ijpharm.2024.124528
Received 19 May 2024; Received in revised form 24 July 2024; Accepted 25 July 2024
Available online 26 July 2024

refilling process. Other difficulties for LIW feeders that affect the consistency and precision of powder feeding include issues such as bridging, adhesion, cohesion, and vibrations (Janssen et al., 2022; Minglani et al., 2020; Peterwitz et al., 2022).

Several other technologies have been developed for feeding at low rates. Besenhard et al. (2017) created a powder pump that utilised a piston in a cartridge to push the powder into a chamber where a rotating scraper would scrub the powder from the cartridge and transfer it to the process. Fathollahi et al. (2021) improved the powder pump by adding a LIW function to enhance its feeding consistency. In contrast, we developed a pneumatic micro-feeder that uses adjustable cross-sectional areas to maintain the entrainment energy, which controls the powder feed (Hou et al., 2023). While both the powder pump and pneumatic micro-feeder show promise in feeding small quantities of cohesive powders, they still have weaknesses, such as the inability to perform long-term continuous feeding operation. This limitation arises because powder cannot be filled or recharged during operation, and the operation time is restricted by the reservoir size.

Only a few commercial feeders have been deployed for dosing or feeding small amounts of pharmaceutical material. The approaches applied for micro-feeding include an auger method (Coperion, 2013; Amouzegar et al., 2000), vibratory channels (Tardos and Lu, 1996), micro-dosing (MG2, 2023; Besenhard et al., 2016), a pneumatic method (DEC Group, 2023; Bellon et al., 2013) or a rotor vane feeder (LCI Corporation, 2020). However, only a few commercial feeders can continuously feed the powder material at very low flow rates (<50 g/h) while the majority of these feeders struggle to handle cohesive or non-flowing materials (Nowak, 2015; Kruisz et al., 2021; Jones-Salkey

Table 1
Existing micro-feeders and their feeding principles.) and (P.

Publication year	Author	Investigated materials	Feed rates	Variation	Concept
Mechanical feeder					
2011 2020	Fernandez, Cleary & McBride, Minglani *et al.*, Li et al.				Applying DEM to study flow behaviour in diverse screw designs can inform the development of an improved screw for powder feeding.
2015	Barati Dalenjan, Jamshidi & Ale Ebrahim	Zinc oxide	72–630 g/h	2–14 %	The screw-brush feeding system utilises a brush conveyor to stabilise the powder flow rate downstream of a single screw feeder.
2017 2020 2021	Besenhard *et al.*, Fathollahi *et al.*,. Fathollahi *et al.*	α-lactose monohydrate powders, API and spray-dried intermediate	1–100 g/h	4–20 %	Powder pump, a cylinder-piston feeder, loads powder into a cartridge and uses a motorised plunger and scraper to control the flow rate via adjustable speed settings.
Vibratory feeder					
2012	Chen, Seyfang & Steckel	Lactose Powder	3.6–36 g/h	< 3 %	Vibrating capillary – Through the employment of a vibrating capillary and modulation of both frequency and amplitude, the regulation of flow rate and variability was achieved.
2012 2014	Zainuddin *et al.*; Horio, Yasuda & Matsusaka	Microcrystalline cellulose	86.4–306 g/h	3–5 %	Vibration shear tube method – The study expelled powder through a narrow gap between a vibrating tube and a flat surface, subjecting each particle to high shear forces to overcome adhesion and friction. The powder flow rate was regulated by controlling the vibration amplitude.
2015 2016	Besenhard et al.	Inhalac 230 Respitose SV003	3.6 – 7.2 g/h	4.6–12 %	Vibratory sieve chute system – to transfer powder from chute to receiver using vibration. The feeder achieved continuous feeding of pharmaceutical materials by regulating frequencies and amplitudes.
2018	Wang et al.	Respitose SV003 Granulac 230	1.4–1.8 g/h	< 12 %	The pulse inertia force was utilised to effectuate the vibration and transportation of the powder, with the flow rate of the powder being regulated by controlling the frequency of the applied force.
Pneumatic/Fluidised feeder					
1986	Wibberley and Phong-Anant	Coal	2.0–97.2 g/h		The study employed a motorised screw jack to narrow the fluidised chamber, while carrier gas was used to fluidise the powder and prevent compaction. Top carrier gas was used to blank the gas-powder mixture.
1991	Burch et al.	Geldart A particles: coal and coal-derived char particles. Geldard C particles: coal-derived ashes and CaO powders	1.2–12 g/h	Short term: < 12 % Long Term: > 15 %	This method strips particles from the powder surface by passing a carrier gas through a narrow gap between a cylindrical piston and the reservoir wall, then carries them through a feed tube when the reservoir is elevated. The flow rate is adjustable through gas flow and reservoir motion.
1999	Tang & Chen	Geldart A particles: coal and coal-derived char particles. Geldard C particles: coal-derived ashes and CaO powders	0.6–31.8 g/h	Short term: < 3 % Long Term: > 5 %	Modified Burch et al. (1991)'s design
2004	Michael Pohořelý et al	Silica sand, g-alumina, ceramsite (fired claystone), digested and dried municipal sewage sludge, and shredded hard wood.	100–1800 g/h	0.14 % – 15 %	Slide feeder – filling two containers with powder and then using two pockets on the side plate to dispense and receive powder into the pneumatic transport pipe. The powder is then transported by constant pressure air.
2009	Suri & Horio	Charcoal, glass beads, Neo beads	36–3852 g/h		The study improved upon Wen & Simons (1959)'s work by using a cartridge as a closed fluidised bed for powder fluidisation from the bottom.
2023	Hou et al.	Microcrystalline cellulose croscarmellose sodium, crospovidone, and paracetamol	0.7 – 20 g/h	5 %–20 %	Using adjustable cross-sectional area in the entrainment zone to entrain the particle. By adjusting the air flow rate to maintain the powder flow rate.

Adapted from (Besenhard et al., 2016; Hou et al., 2023).

et al., 2023; Kerins et al., 2023). Table 1 presents an overview of the feeding mechanisms of various existing feeders and recent advancements in feeding technologies. The screw feeder has seen improvements with twin screws and agitation mechanisms to address flow inconsistency and blockage issues (De Souter et al., 2023; Engisch and Muzzio, 2015; Fernandez et al., 2011; Santos et al., 2018). Vibratory feeders, which rely on vibrations to move powders, have been optimised by adjusting vibration frequency and amplitude to better handle different material characteristics (Besenhard et al., 2016, 2015; Horio et al., 2014; Zainuddin et al., 2012). The screw-brush feeder combines a screw feeder with a brush conveyor to stabilise powder flow, though it faces challenges such as particle grinding and contamination (Barati Dalenjan et al., 2015). Fluidised feeders, using fluidisation principles, provide precise control over feed rates, but issues like segregation and control complexity persist (Hou et al., 2023; Suri and Horio, 2009; Tang and Chen, 1999). Powder pumps, utilising cylinder-piston systems, achieve low flow rates with minimal fluctuation but are less suitable for continuous processes due to powder compaction and refilling needs (Besenhard et al., 2017; Fathollahi et al., 2021, 2020). Slide feeders, employing a double-acting air-driven mechanism, have demonstrated good reproducibility and reliability for various powders (Pohořelý et al., 2004).

This study introduces a new micro-feeder technology that combines an inclined screw feeder with a double-screw agitated hopper to enable highly consistent feeding of typical pharmaceutical materials at rates below 10 g/h. The double screw agitator speed controls the powder flow rate, while the feeding screw speed minimises powder flow rate variation. The effects of feeding screw pitches, agitator speed, and screw speed are investigated. The feeding performance and the mechanisms of the micro-feeder are evaluated and investigated in relation to three common pharmaceutical materials: croscarmellose sodium (CCS, cohesive), magnesium stearate (MgSt, very cohesive), and paracetamol (APAP, non-flowing).

2. Materials and method

2.1. Materials

Three different powders were used: croscarmellose sodium (CCS, JRS pharma, Germany), magnesium stearate (MgSt, LIGAMED MF-2-V from Peter Greven Nederland C.V., Nederland), and an active pharmaceutical ingredient, paracetamol (APAP, Ph Eur Powder from Mallinckrodt Pharmaceuticals, Ireland). Table 2 summarises the powder properties of the investigated materials.

Particle size distribution (reported as D_{10}, D_{50} and D_{90}) and sphericity (S_{50}) of all tested materials were determined using a dynamic imaging instrument (QIC/PIC, Sympatec GmbH, Germany). True density was measured using a gas pycnometer (MicroUltrapyc 1200, Quantachrome instrument, Graz, Austria). Bulk density was measured by weighing a known volume of the material using a 50 mL graduated glass cylinder. The bulk density was then calculated by dividing the material's mass by its volume. Tapped density was determined by Autotap (AT-6, Quantachrome instrument, Graz, Austria) following the USP⟨616⟩ method II. To assess the flowability of the powder materials, a flow function coefficient was determined using a powder flow tester (PFT3230, Brookfield AMETEK, USA). Powders with a higher flow function coefficient are typically more difficult to handle and may cause flow problems such as bridging, rat-holing, or segregation. Based on this powder characterisation, CCS, MgSt and APAP can be classified as cohesive, very cohesive and non-flowing, respectively.

2.2. Micro-feeder design

The inclined screw feeder (Fig. 1) is composed of three key design features: a feeding screw (Fig. 2), a double-screw agitator (Fig. 3) and a piping bag hopper. The feeding screw and double-screw agitator were fabricated from Tough 2000 Resin employing a high-precision stereolithography (SLA) printer (Form 2, FormLab, USA), while the screw housing was manufactured using polylactic acid (PLA) through a fused deposition modelling (FDM) printer (Ultimaker 3, Ultimaker, Netherlands). This fabrication approach enabled the system to be fine-tuned and optimised, providing maximum flexibility in design adjustments. The fundamental screw-based conveying principle is shared with LIW feeders in this design, but several differences in the screw design and overall feeding mechanism contribute to its improved low flow rate feeding performance:

Screw Geometry: The screw in the micro-feeder features a unique geometry designed to enhance the precision of powder delivery. Unlike traditional augers, the screw has no central shaft, reducing friction and improving the consistency of powder flow. Additionally, the design eliminates potential backward flow and inconsistency issues found in spiral screws with a hollow centre. These optimisations minimise pulsation and ensure a smooth, continuous flow of material, as explained in Section 2.2.1.

Surface Treatment: The screw undergoes surface polishing and antistatic spray coating, with optimised pitch and helix angle to reduce friction and adhesion of the powder. This treatment is particularly beneficial for handling fine and cohesive powders and helps maintain

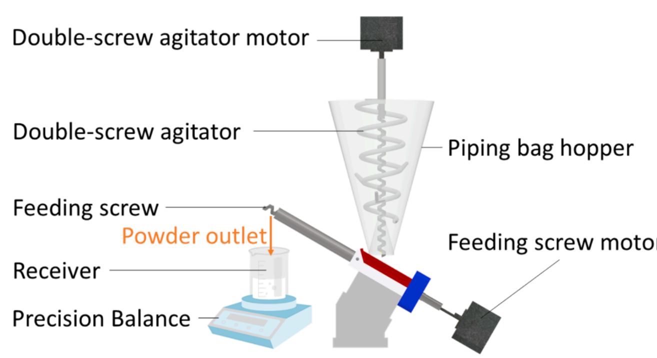

Fig. 1. An overview of a schematic inclined micro-feeder.

Table 2
Material properties of the experimental materials.

Powders	D_{10} (μm)	D_{50} (μm)	D_{90} (μm)	S_{50} (−)	True Density (g/cm^3)	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	Flow function coefficient @1.61 kPa (−)	Flowability
Croscarmellose Sodium (CCS)	29.9 ± 0.1	50.0 ± 0.1	74.2 ± 0.1	0.72 ± 0.003	1.537 ± 0.010	0.529 ± 0.001	0.715 ± 0.001	3.79 ± 0.48	Cohesive
Magnesium Stearate (MgSt)	7.1 ± 0.2	24.4 ± 0.6	48.4 ± 0.6	0.80 ± 0.001	1.074 ± 0.001	0.207 ± 0.007	0.349 ± 0.009	2.23 ± 0.09	Very Cohesive
Paracetamol (APAP)	23.6 ± 0.1	67.9 ± 0.4	178.1 ± 3.8	0.63 ± 0.003	1.291 ± 0.002	0.310 ± 0.003	0.495 ± 0.005	1.63 ± 0.33	Non-flowing

The shown values are the mean ± standard deviation of all measurements in triplicate.
D_{10}, D_{50} and D_{90} are the mean particle sizes below which 10 %, 50 % or 90 % of all particles are contained.
S_{50} is the sphericity below 50 % of all particles contained.

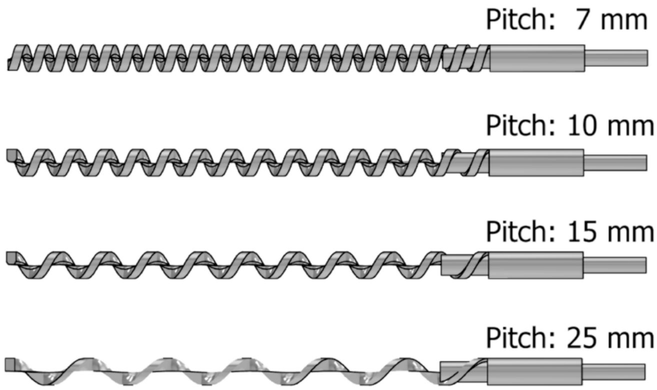

Fig. 2. Schematic diagram of the feeding screws in four pitches: 7 mm, 10 mm, 15 mm and 25 mm.

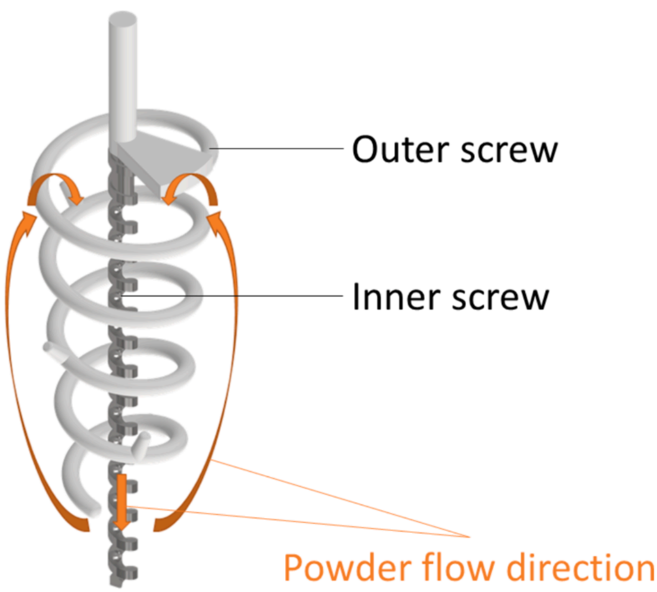

Fig. 3. Schematic diagram of the double-screw agitator.

consistent feeding rates.

Agitator: The double-screw agitator homogenises the powder in the hopper and acts as a regulating valve, controlling the amount of powder fed into the feeding screw (Section 2.2.2).

2.2.1. Feeding screw

The unique feeding screw in this study is a design between an auger and a spiral screw. Unlike the auger screw, it eliminates the need for a central shaft, resulting in an increased screw pocket capacity and reduces powder compression due to shear stress on the wall and shaft. In contrast to spiral screws, this design does not have a hollow shaft, which eliminates the risk of unstable powder feeding caused by a steep drop of the powder flowing back into the screw housing. To investigate the effect of screw pitch on various powder properties, the study examined four screw pitches (7 mm, 10 mm, 15 mm, and 25 mm) to identify the optimal screw pitch.

2.2.2. Double-screw agitator

The double-screw agitator comprises a central feeding screw and an outer spiral screw tapered at 5° and a pitch of 25 mm, printed as two separate components, providing design versatility. This unique design allows the powder to circulate vertically in the hopper, effectively homogenising the bulk density and eliminating common issues such as rat holes and bridging, which are frequently observed in traditional LIW feeders.

2.3. Operation

Initially, the powder must be added to the hopper until it reaches a level exceeding 50 % of its total capacity. Subsequent refilling of the hopper should be initiated when the powder level falls below 20 % of its total capacity, with each refilling involving the addition of approximately 80 mL of powder. To operate the feeder, two process parameters must be configured: the speeds of the feeding screw and the double-screw agitator. Each of these speeds can be regulated using stepper motors connected to an Arduino controller (Arduino Mega 2560). Both speeds can then be set by an operator in a MATLAB-designed graphical user interface (Figure S1 in Supporting Information). The inner screw of the double-screw agitator feeds the powder into the inclined feeding screw within the screw housing. The inclined screw transports the powder to a receiver positioned below the feeding screw outlet. The pre-run involves operating the system with a constant agitator and feeding screw speed until powder is discharged from the outlet. Throughout this study, a powder charging was conducted before each measurement to ensure that the space of the feeding screw was filled with the powder. If the subsequent experiment employs the same parameter setting as the previous one, the pre-run is deemed unnecessary. In this study, the pre-run involves operating the system with a constant agitator and feeding screw speed until powder is discharged from the outlet. This step ensures that the feeding screw is properly filled with powder before the feeder delivers a consistent mass flow rate. In this study, a feedback control loop was not implemented; the motor speed was set to different levels to achieve various feed rates. A lab-scale balance (Sartorius Quintix 125D-1S, Germany) recorded the accumulating powder weight per second, which was then converted to a powder flow rate (g/h). An operator observed the powder level, and manual refilling was conducted when it went below one-fifth of the hopper level.

2.4. Definition of parameters

Numerous parameters are employed to evaluate the micro-feeder's performance, including powder flow rate ($\dot{m}_p$), mean powder flow rate ($\overline{\dot{m}_p}$), standard deviation (σ), relative standard deviation (RSD), mean relative standard deviation ($\overline{RSD}$), repeatability (r) and stability (σ_{RSD}). A comprehensive explanation of these parameters can be found in our prior study (Hou et al., 2023). Within the context of this study, the term "consistent" is explicitly defined to encompass the combined notions of accuracy and precision. Specifically, the term "double-screw agitator speed" refers to the motor rotation rate (rpm) of the double-screw agitator, whereas the feeding screw speed refers to the motor rotation rate (rpm) of the feeding screw.

3. Results and discussions

3.1. Mass flow rate analysis

To analyse the performance of the powder feeding process, the weight of the powder was recorded using a catch scale at a frequency of 1 Hz (Fig. 4). The recorded weight was then used to calculate the mass flow rate, $\dot{m}_p(t) = \Delta m/\Delta t$, which represents the rate of powder mass accumulated within a certain time window, Δt. The experimental mass data exhibited a linear trend, as depicted by the red-dashed line in Fig. 4a.

In continuous powder feeding processes, fluctuating weight measurements can arise from various factors, such as the height of the feeding position (Figure S2 in the Supporting Information) and the weight of the material fed. In this study, measurement noise was identified to be caused by a vibrating spring in the balance due to the initial

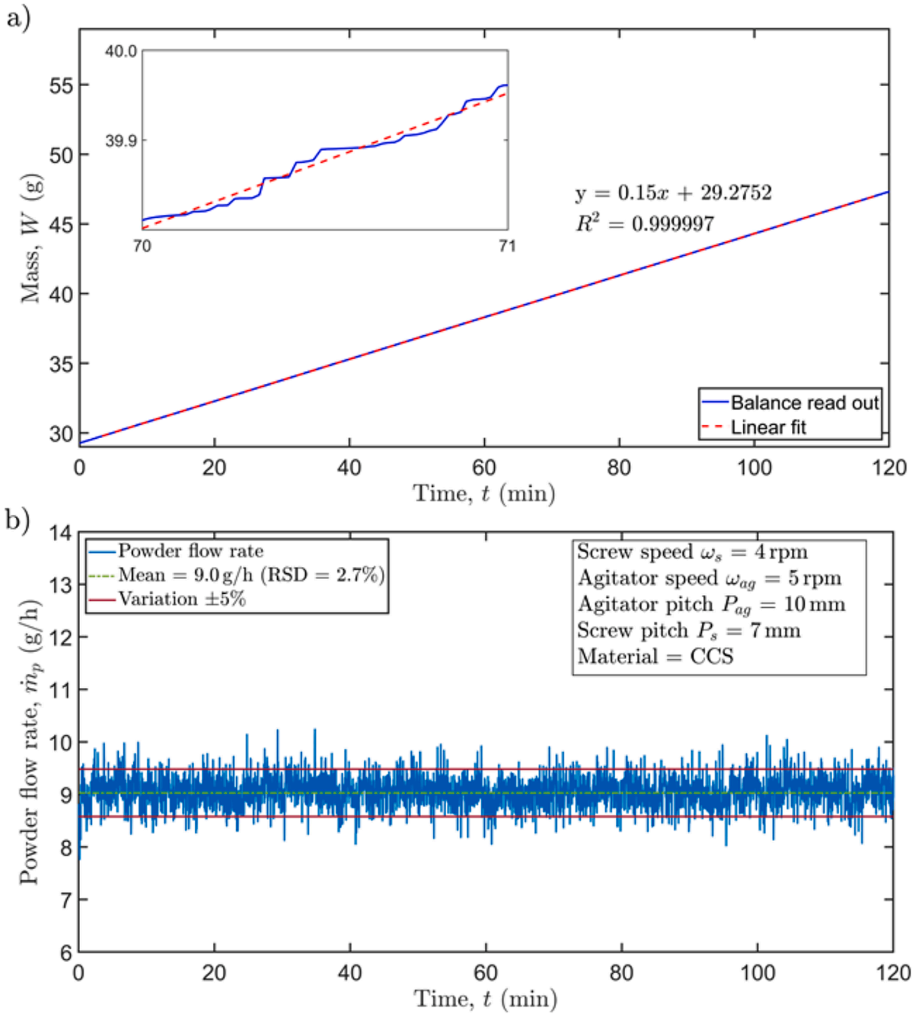

Fig. 4. Data acquisition and analysis of continuous CCS powder feeding at 6 rpm feeding screw speed and 5 rpm double speed agitator speed over 2 h: a) experimental mass acquired at 1-second intervals from the catch scale; b) filtered mass flow rate using a 60-second moving mean window. The green dashed line represents the mean powder flow rate, while the upper and lower solid red lines denote the predetermined range of variation, set at ± 5 % for this particular experiment. The lines depicted in the figure are not continuous; rather, they represent individual points occurring at a rate of one per second. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

and subsequent drops arriving at the balance pan, preventing the balance from reaching a stable equilibrium.

To mitigate the influence of measurement noise on powder feeder performance analysis, a 60-second moving mean filter was employed. This technique, widely used in spectral data and powder feeding analysis in previous studies (Beretta et al., 2023; Bostijn et al., 2019; Fathollahi et al., 2020; Huang et al., 2022; Johnson et al., 2022), was applied to the weight difference of the powder fed per second. While complete elimination of these factors may not be feasible, the implementation of this filter serves to minimise their influence on further analyses. Fig. 4b depicts the CCS powder feeding process with the additional application of a 60-second moving mean window to the generated data (g/s), which was subsequently converted to g/h. This data is then further used to calculate the mean powder flow rate, SD, and RSD.

To ensure the moving mean filter does not remove real variability, 30- and 60-second manual measurement experiments were conducted at identical operational conditions without applying any filter. Fig. 5 depicts an example of APAP feeding over a period of 30 min, with manual measurements taken at one-minute intervals, alongside automatic data acquisition with the implementation of a 1-minute moving mean filter. Fig. 5 provides a comprehensive summary of the outcomes derived from both manual and automatic measurements. The results indicate that the RSDs using the moving mean filter are larger (or equal to the highest CCS flow rate) than the RSD of the manual measurements. The findings reveal that this particular manual measurement variation yields lower results compared to applying a 60-second moving mean. This indicates that using the 60-second moving mean filter does not eliminate genuine data points. In addition, the difference in RSDs between moving mean and manual measurement reduces with increasing powder flow rate. This is attributed to the fact that the time it takes the balance to stabilise has a stronger influence on the RSD at low flow rates. Overall, using a time window of 60 s with the moving-mean filter technique can effectively reduce the measurement noise without compromising the actual data. However, a longer time window of 120 s is necessary when dealing with lower powder flow rates below 2 g/h due to the limited accuracy of the balance. By applying moving-mean, the balance spring vibrations caused by continuous feeding can be minimised, leading to more reliable and accurate measurements.

3.2. *Refilling*

Numerous investigations have explored the influence of hopper refill and fill level on feeding consistency, e.g. Janssen et al. (2022), Van Snick et al. (2017), Hörmann-Kincses et al. (2022), and Tahir et al. (2020). Janssen et al. (2022) conducted repeated lactose feedings (H=1.21, free-flowing material) using a 22 mm double concave screw in volumetric

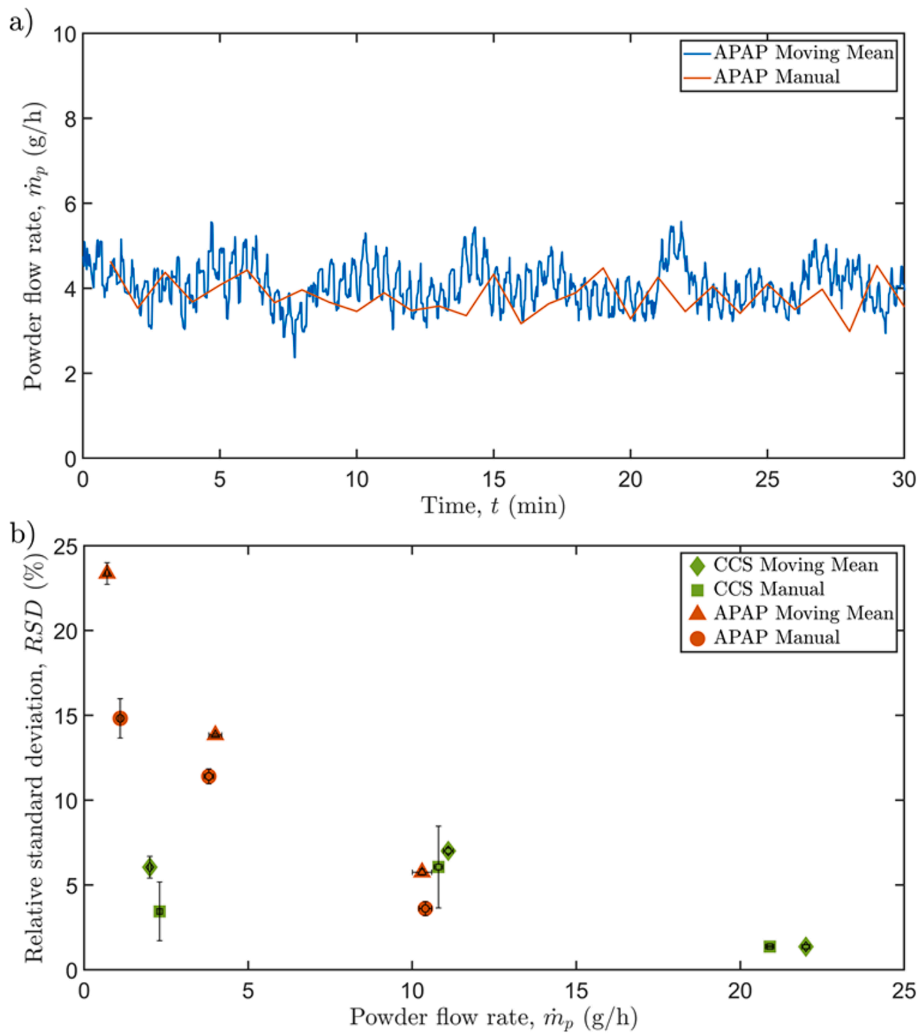

Fig. 5. Effect of powder flow rate on RSD for automated and manual operation with 60-second window measurement, and APAP with lowest powder rate at 120-second window measurement. a) an illustration of APAP feeding conducted over a 30-minute duration, with manual measurements recorded at one-minute intervals, juxtaposed with automatic data acquisition utilising a 1-minute moving mean filter; b) a comprehensive summary of the results obtained from both manual and automatic measurements. Each measurement was done in triplicate ($n = 3$). The vertical error bar represents the standard deviation of relative standard deviations of three repeat experiments. The horizontal error bar represents the standard deviation of powder flow rates of three repeat experiments. The statistical comparison of data set can be found can be found in Table S1 in the Supporting Information.

mode. Tahir et al.'s (2020) illustrates the application of a GEA compact feeder for MgSt feeding with a 20 mm concave screw (Bin# = hopper fill level). Van Snick et al.'s (2017) explored the different powder properties using a concave screw. Hörmann-Kincses et al.'s (2022) investigated the feeding of M200 grade mannitol using various types of feeders. These feeders delivered M200 grade mannitol with a coarse concave screw at 50 % screw speed. The feeders included Coperion-KTron KT20, Compact feeder, Compact feeder with adapted hopper, ZD12FB, and Brabender MT-S.

Consistent findings across all these studies reveal a gradual decrease in the feed factor with changes in the hopper fill level. Compression at the bottom of the powder results in a higher bulk density. As the feeding progresses and the hopper level decreases, the bulk density lowers, resulting in a gradual reduction in the powder flow rate This trend is particularly pronounced in highly compressible powders such as MgSt and APAP. Additionally, materials with poor flow characteristics exhibit lower feed factors due to alterations in powder density within the hopper.

The hopper in this study was refilled approximately every 20 min, with the amount of powder added varying depending on the feed rate. On average, around 80 ml of powder were added to the hopper during each refill. The effectiveness of the refilling process was monitored and analysed through Fig. 6, which captures the feeding process over a period of 2 h for three different materials. The results revealed that no significant excessive variations were observed during the feeding process, indicating that the design of the double-screw agitator used in this study effectively mitigated any variations caused by the refilling. In contrast to current industrial feeders, the double-screw agitator eliminates variations in the mass flow rate induced by refilling.

Bekaert et al. (2022) also indicates that the inconsistent feeding marked by sudden peaks the refill points. Fig. 6 does not exhibit this issue, indicating that the hopper refill does not affect feeding consistency in this design. This is attributed to the action of the agitator, which continuously circulates the powder in the hopper. Upon addition to the hopper, the refill is promptly circulated, preventing the powder compression, which leads to a decrease in bulk density and, consequently, results in a higher feed rate, particularly beneficial for sensitive compressible materials.

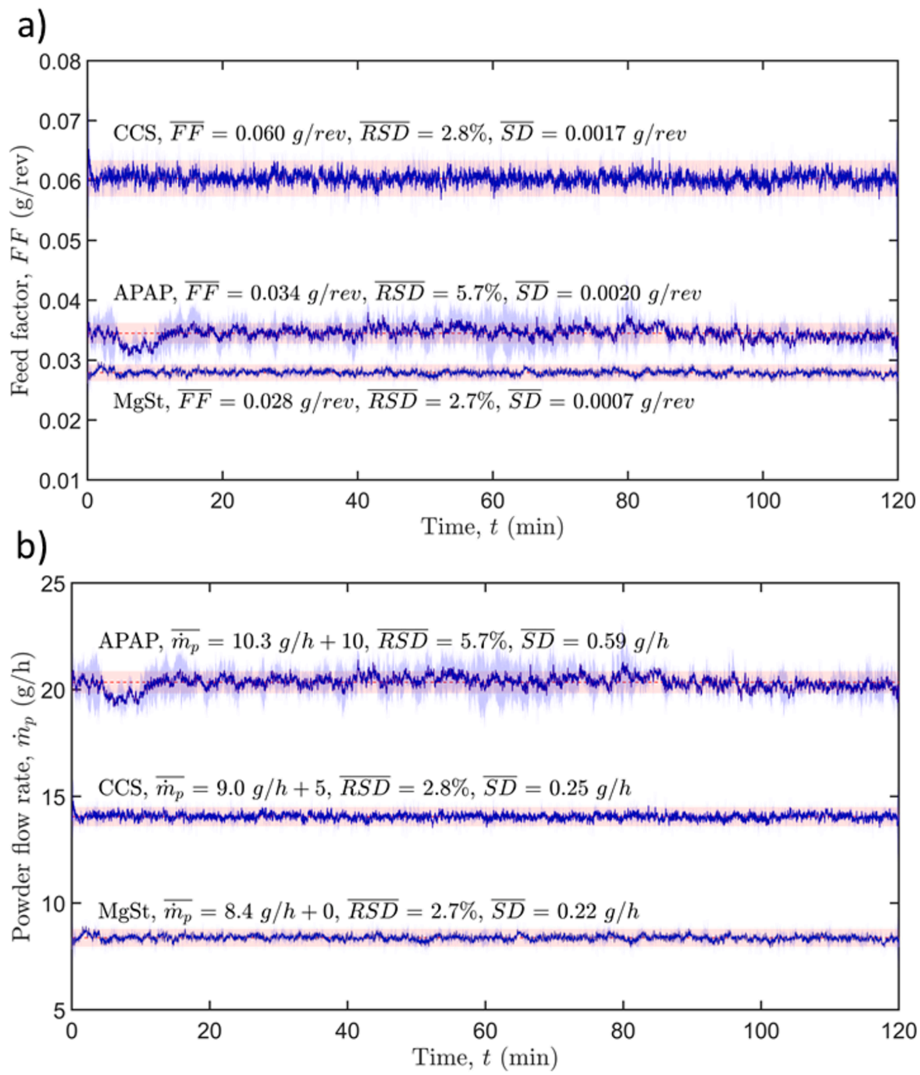

Fig. 6. Refilling every 20 min in continuous feeding demonstrated for three different materials: a) Feed factor over time, b) Changes in powder flow rate with respect to feeding time. All experiments were performed in triplicates (n = 3). The blue line is the mean powder flow rate. The blue shadow represents the SD of three repeated experiments. The red shaded belt represents ± 5 %. The notation "XX g/h + Number" is used to shift the trend up by "Number" g/h for comparison purposes. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

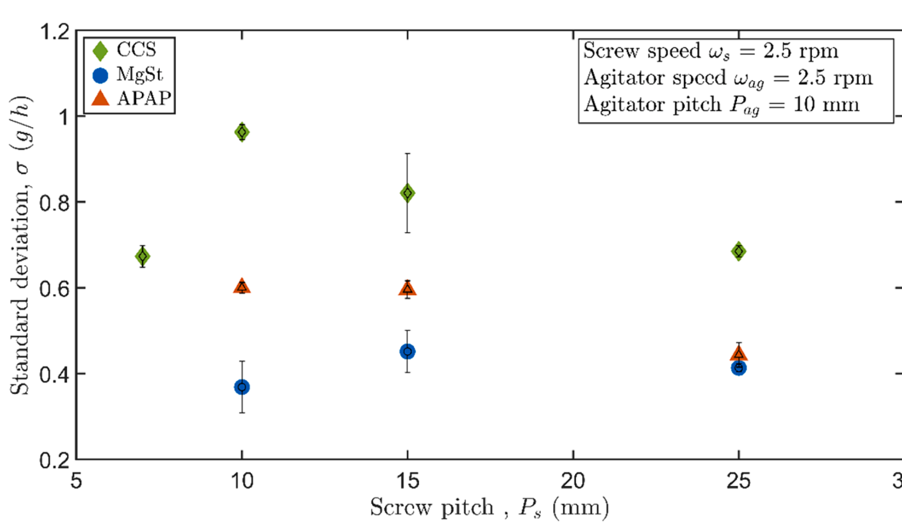

Fig. 7. Standard deviation as a function of screw pitches for CCS, MgSt and APAP. Each measurement was done in triplicate (n = 3).

As a result of the increase in bulk density resulting from powder compression, it also prompts a decrease in screw speed in gravimetric control. In scenarios where refill occurs, the compression and increased bulk density can cause a sudden spike in feed rate, leading to unstable control. In contrast, the absence of an influence on feed rate in our design suggests that the agitator plays a crucial role in homogenising bulk density within the hopper. This, in turn, ensures a more stable and consistent powder feeding experience across various fill levels.

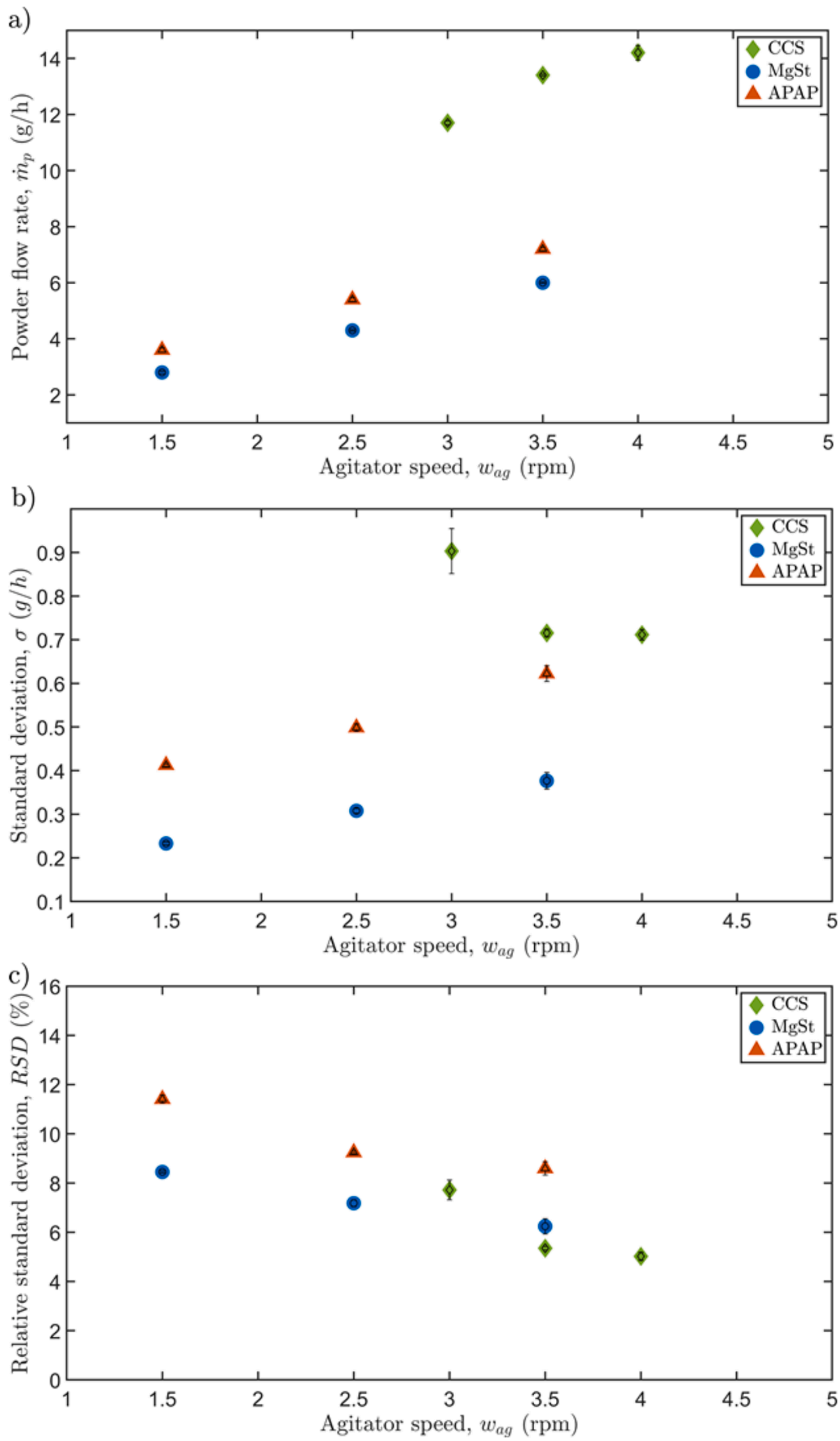

Fig. 8. The effect of double-screw agitator speed on powder flow rate, SD and RSD. a) The mean powder flow rate from three repeated experiments ($n = 3$) is plotted against agitator speed for three different powder properties at a fixed feeding screw speed of 3.5 rpm. b) SD is plotted against agitator speed. c) RSD is plotted against agitator speed.

3.3. Effect of equipment configuration and process parameters on feeding performance

3.3.1. Feeding screw pitch

Fig. 7 presents the effect of screw pitch on feeding the three different powders: APAP, MgSt, and CCS. The results reveal that a screw pitch of 25 mm leads to the lowest SD of 0.44 g/h ± 0.03 g/h for APAP, while a pitch of 7 mm gives the lowest SD of 0.67 g/h ± 0.03 g/h for CCS. Although a pitch of 25 mm yields a higher SD of 0.41 g/h ± 0.009 g/h for MgSt compared to a pitch of 10 mm (0.37 g/h ± 0.06 g/h), it provides better stability ($\sigma_{SD} = 2.3$ %) for MgSt using a 25 mm pitch, whereas 10 mm pitch results in $\sigma_{SD} = 16.3$ %. These findings suggest that using a screw pitch of 25 mm for MgSt can maintain better precision and consistency in the powder feeding process. Furthermore, it is observed that the application of a 7 mm pitch for APAP and MgSt results in screw clogging. Based on these findings, it is recommended that highly cohesive materials such as APAP and MgSt are better suited for larger screw pitches to stabilise the feeding process, while materials with better flowability, like CCS, benefit from smaller screw pitches.

3.3.2. Double-screw agitator speed

Increasing the agitator speed while maintaining a constant feeding screw speed leads to a considerable increase in the powder flow rate (Fig. 8). Moreover, Fig. 8b indicates that with rising agitator speed and powder flow rate, the SD also increases for APAP and MgSt. Conversely, the outcome of CCS feeding reveals a contrasting pattern, whereby an increase in the agitator speed leads to a decrease in the SD. The results also demonstrate that increased agitator speed leads to a decrease in the RSD for the three tested materials (Fig. 8c). Fig. 8 shows that the agitator and feeding screw speeds are critical parameters that influence the powder flow rate and the RSD. However, the effect of these parameters on the powder flow rate and RSD depends on the powder properties and agitator design, necessitating careful consideration when optimising the performance of the inclined screw feeder.

The experimental results confirm the critical role of the agitator in ensuring consistent powder feeding. In the absence of the agitator, issues such as rat holing and bridging arise, making continuous feeding at low rates challenging. The application of a double-screw agitator also helps to overcome the refilling issues that current LIW feeders face.

3.3.3. Feeding screw speed

For optimal process settings, it is vital to understand the effect of various ratios between feeding screw speed and double-screw agitator speed on the stability of the powder flow rate in the system. Fig. 9 indicates that all investigated materials exhibit a close to constant feeding rate with variations below 5 %, indicating stable and consistent feeding.

Fig. 10a shows that the screw speed has a relatively minor effect on the powder flow rate compared to the more significant effect of agitator speeds, as discussed in Section 3.3.2. Nevertheless, it indicates that increasing the feeding screw speed slightly enhances the CCS powder flow rate but has an insignificant effect on the flow rates of MgSt and APAP powders.

Fig. 10b and Fig. 10c, on the other hand, emphasises the notable influence of feeding screw speed variation on SD and RSD while maintaining a constant double-screw agitator speed. The results demonstrate fluctuations in both SD and RSD as the feeding screw speed increases. Nevertheless, the results of these experiments reveal that the system demonstrates the best stable and consistent powder feeding for CCS and APAP when the agitator speed is 0.5 rpm higher than the feeding screw speed. Moreover, MgSt has its optimal point at 2.5 rpm (twice the feeding screw speed). This result suggests the existence of an optimal value for a specific screw speed to agitator speed ratio, and adjusting this ratio can enhance the consistency of powder feeding.

3.4. Performance statistics

An experimental investigation was conducted to determine the optimal ratio of screw speed to agitator speed for a given material. The preliminary experiment, conducted without an agitator, observed occurrences of rat-holing and bridging, resulting in the absence of flow. The summary tables of feeding performance for all tested materials can be found in Tables S2, S3 and S4 in the Supporting Information. Fig. 11 depicts the temporal consistency of powder feeding for the three materials investigated under optimal conditions without the implementation of feedback control. The findings establish that powder feeding maintains consistent performance over time at different powder feed rates. The optimal ratio was found to be when the screw speed was 0.5 rpm higher than the agitator speed for APAP and CCS, while no clear optimal ratio pattern was observed for MgSt. Details on the effect of speed ratio between agitator and feeding screw are provided for each material in the Supporting Information Section 5.

It is important to note that the RSD between the equal (screw speed = agitator speed) and optimal ratios decreases as the powder flow rate increases for all tested materials (Fig. 12). The findings indicate that the powder flow rate remains relatively stable when the agitator speed is held constant, regardless of whether the feeding screw speed is increased or decreased. This observation highlights the dominant influence of the agitator speed, that it controls the powder flow rate, with the screw speed exerting a minor effect, particularly when the powder cohesion is high. These results support the concept that the screw speed governs the screw volumetric efficiency and reduces the powder flow rate variation. The decrease in the RSD gap with increasing powder flow rates can be attributed to the concurrent rise in screw volumetric efficiency, leading to the screw pocket approaching its maximum capacity. During this phase, the influence of screw speed on the variation in powder flow rate diminishes significantly.

The investigation reveals that materials with poor flowing characteristics exhibit good repeatability when subjected to flow rates exceeding 6 g/h (Fig. 13). In terms of stability, the results indicate that satisfactory stability under 0.4 % of standard deviation of RSD is attained when the flow rates are above 2 g/h for all three tested materials. However, stability declines when CCS and APAP are fed at flow rates under 2 g/h. This is because the feeder may have achieved its minimum feed rate at this configuration. A comparison of repeatability and stability of the equal and optimal ratios can be found in Figures S4 and S5 in the Supporting Information.

To sum up the experimental results from the optimal ratios, a linear correlation between the powder flow rate and agitator speed can be observed in Fig. 14. The observed linear relationship between the powder flow rate and agitator speed suggests that adjusting the appropriate agitator speed, tailored to the specific powder properties, enables the attainment of the desired powder flow rate. This relationship can be used to calibrate the agitator speed for a desired powder flow rate, and further for process optimisation or control to maintain the desired flow rate control.

Overall, the inclined micro-feeder presented in this study differentiates from existing technologies through its feeding screw and double-screw agitator design. This configuration not only enhances volumetric efficiency and minimises flow variations but also effectively addresses issues such as rat holing and bridging, commonly encountered

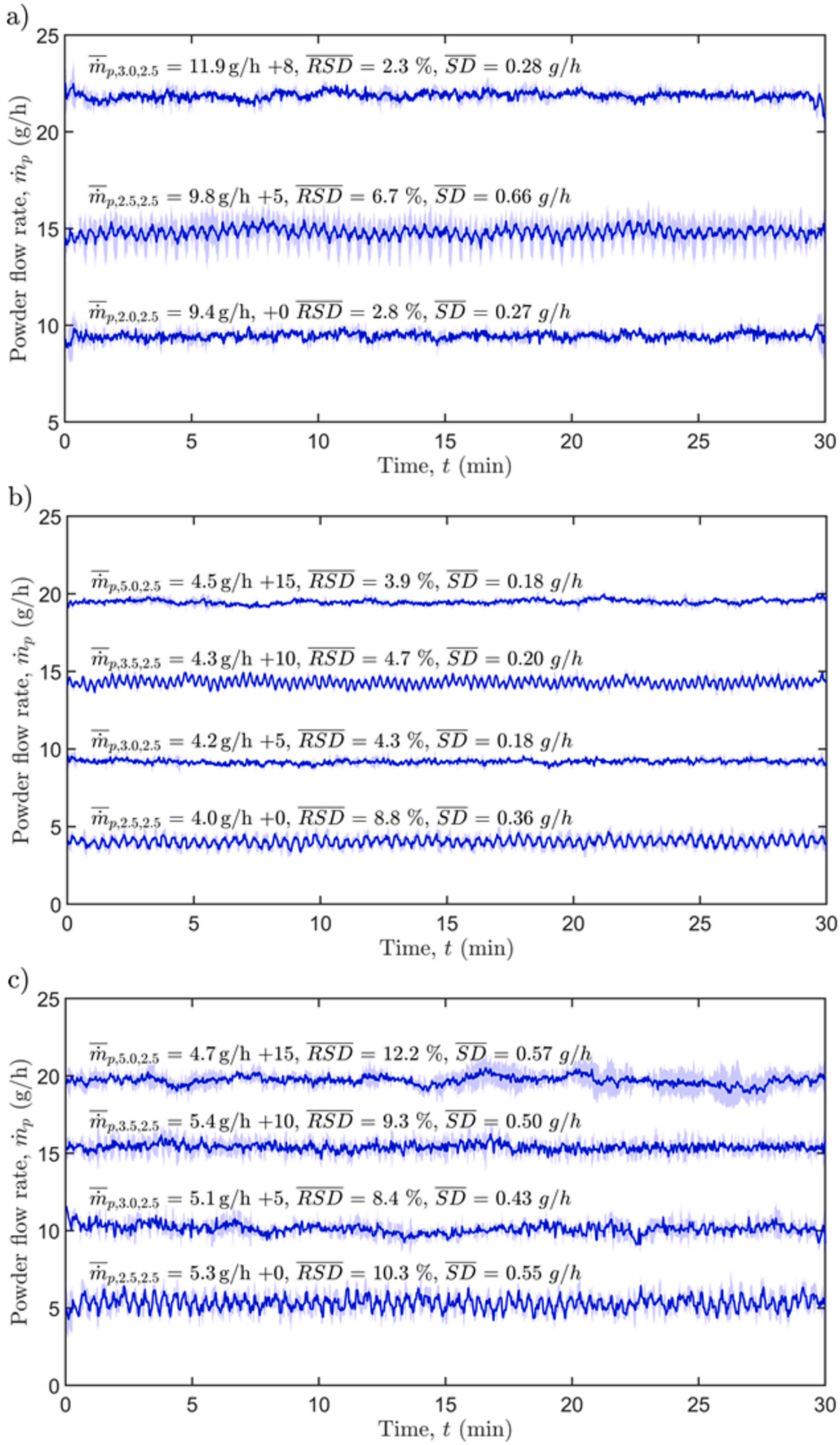

Fig. 9. Effects of feeding screw speed on powder flow rate, SD and RSD for three distinct powder properties. a) CCS; b) MgSt; and c) APAP powder feeding at varying feeding screw speeds and a constant agitator speed of 2.5 rpm. The blue line is the mean powder flow rate. The blue shadow represents the SD of three repeated experiments. The notation "XX g/h + Number" is used to shift the trend up by "Number" g/h for comparison purposes. A hopper refill at 20 min was performed. $\overline{\dot{m}}_{p,\text{1st number, 2nd number}}$ denotes the powder flow rate corresponding to the specified screw speed (1st number) and agitator speed (2nd number) in rpm. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

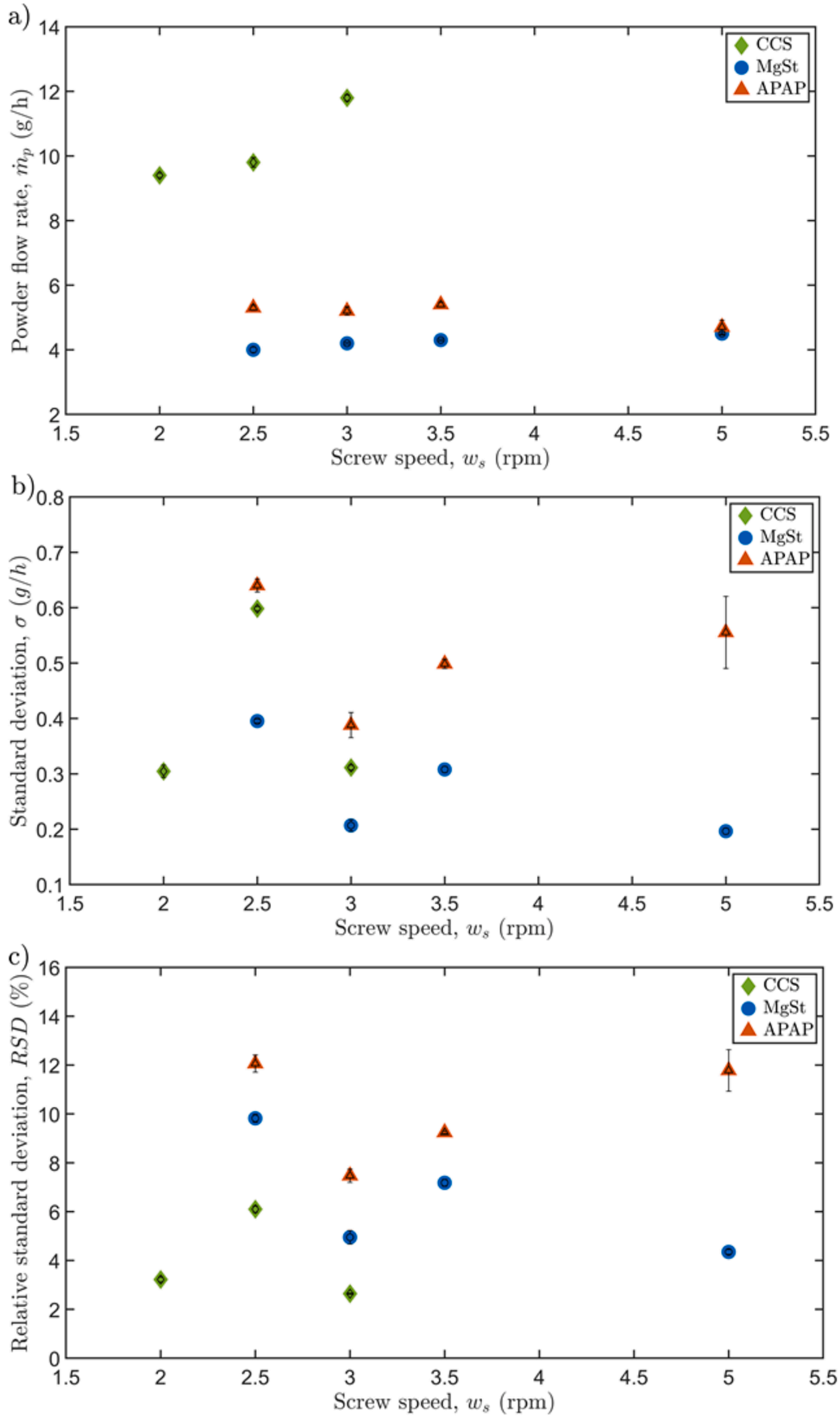

Fig. 10. Effects of feeding screw speed on powder flow rate, SD and RSD for three distinct powder properties. a) Mean powder flow rate of three repeat experiments ($n = 3$) as a function of feeding screw speed for three different powder properties at a constant double-screw agitator speed of 2.5 rpm; b) standard deviation as a function of feeding screw speed at 2.5 rpm of double-screw agitator speed; c) relative standard deviation as a function of feeding screw speed at 2.5 rpm of double-screw agitator speed.

with cohesive powders. Consequently, it ensures more reliable long-term operation without flow interruptions.

Unlike conventional screw feeders and vibratory channels, the agitator homogenises the powder density in the hopper while feeding a consistent rate to the feeding screw. By adjusting the ratio of feeding screw speed to agitator speed, this design minimises powder feed rate variation. Additionally, unlike loss-in-weight (LIW) feeders that rely on feedback control and are sensitive to refilling disturbances, this micro-

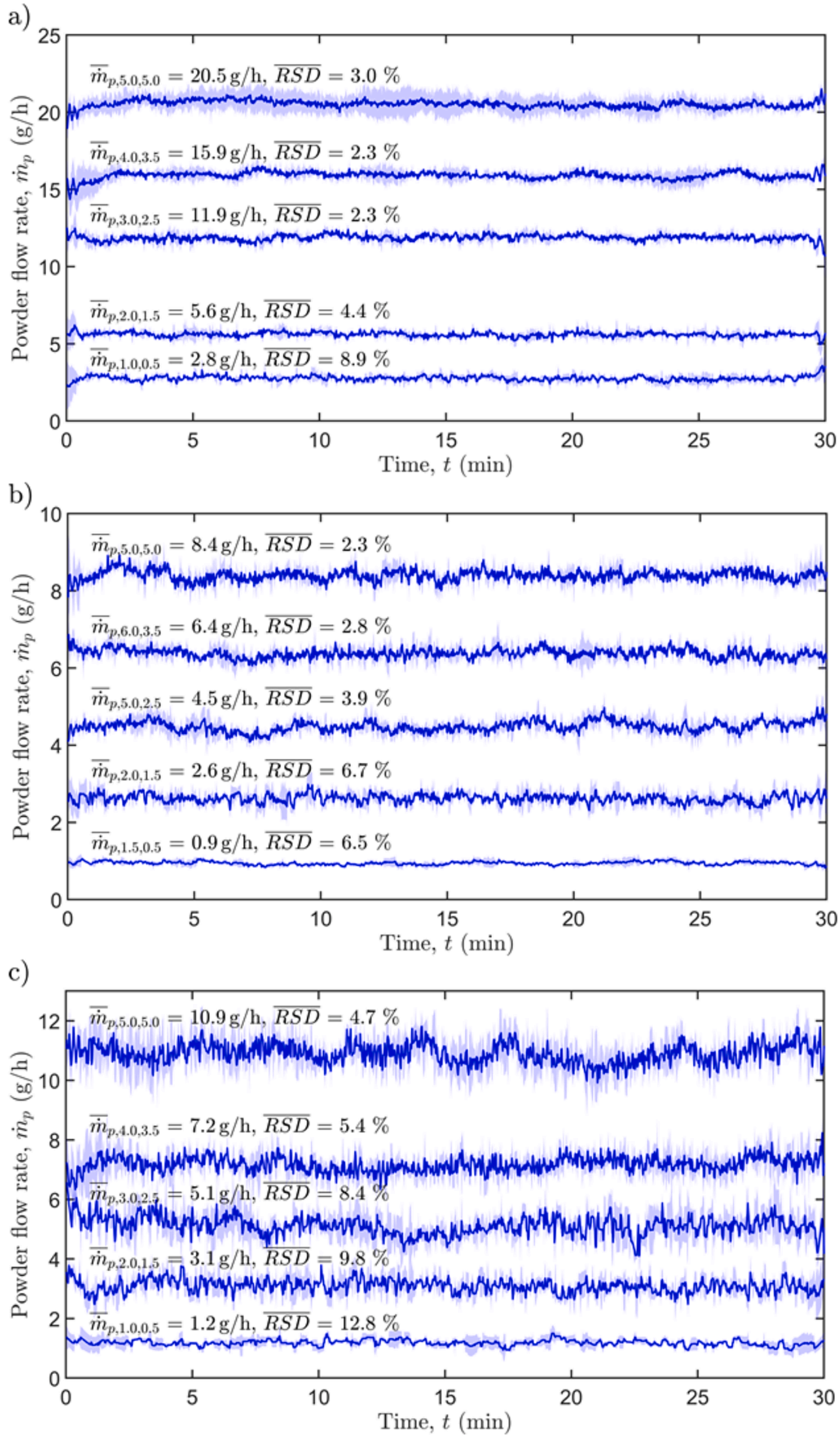

Fig. 11. Consistent feeding of optimal ratios was observed in three repeat experiments without feedback control for (a) CCS, (b) MgSt, and (c) APAP. The blue line is the mean powder flow rate. The blue shadow represents the SD of three repeated experiments. A hopper refill at 20 min was performed. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

feeder maintains consistent performance without feedback control and remains unaffected by the refilling process. This simplifies operation and improves overall reliability.

The micro-feeder achieves improved feeding consistency and accuracy, demonstrated by repeatability below 8 % and stability below 6 %, even at low flow rates. It achieves low feed rates (<20 g/h) with low variability (<5–10 % RSD) for challenging materials, outperforming many existing micro-feeders in this critical low flow rate range. These

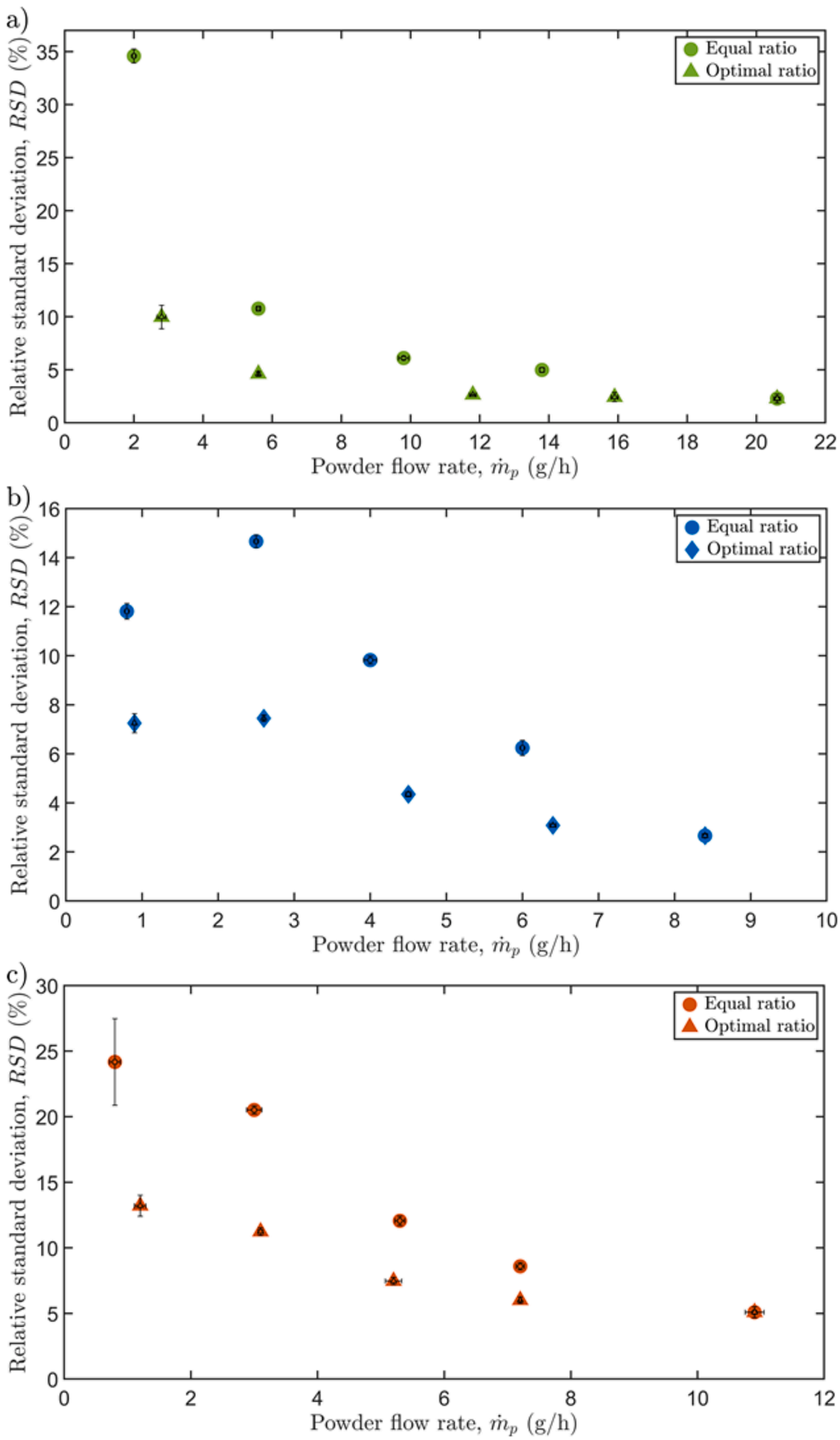

Fig. 12. The summary statistics of the powder flow rates and RSDs for the three materials. RSDs as a function of powder flow rate at the equal and optimal ratio of screw and agitator speed a) CCS – Equal ratio: 20.6 g/h ± 2.3 % to 2.0 g/h ± 34.6 %; Optimal ratio: 20.6 g/h ± 2.3 % to 2.8 g/h ± 10.0 %; b) MgSt – Equal ratio: 8.4 g/h ± 2.7 % to 0.8 g/h ± 11.8 %; Optimal ratio: 8.4 g/h ± 2.7 % to 0.9 g/h ± 7.3 %; c) APAP – Equal ratio: 10.9 g/h ± 5.1 % to 0.8 g/h ± 24.1 %; Optimal ratio: 10.9 ± 5.0 % to 1.2 g/h ± 13.2 %. Horizontal and vertical errors represent the SDs of the powder flow rates and RSDs of triplicate experiments. Each measurement was done in triplicate (n = 3).

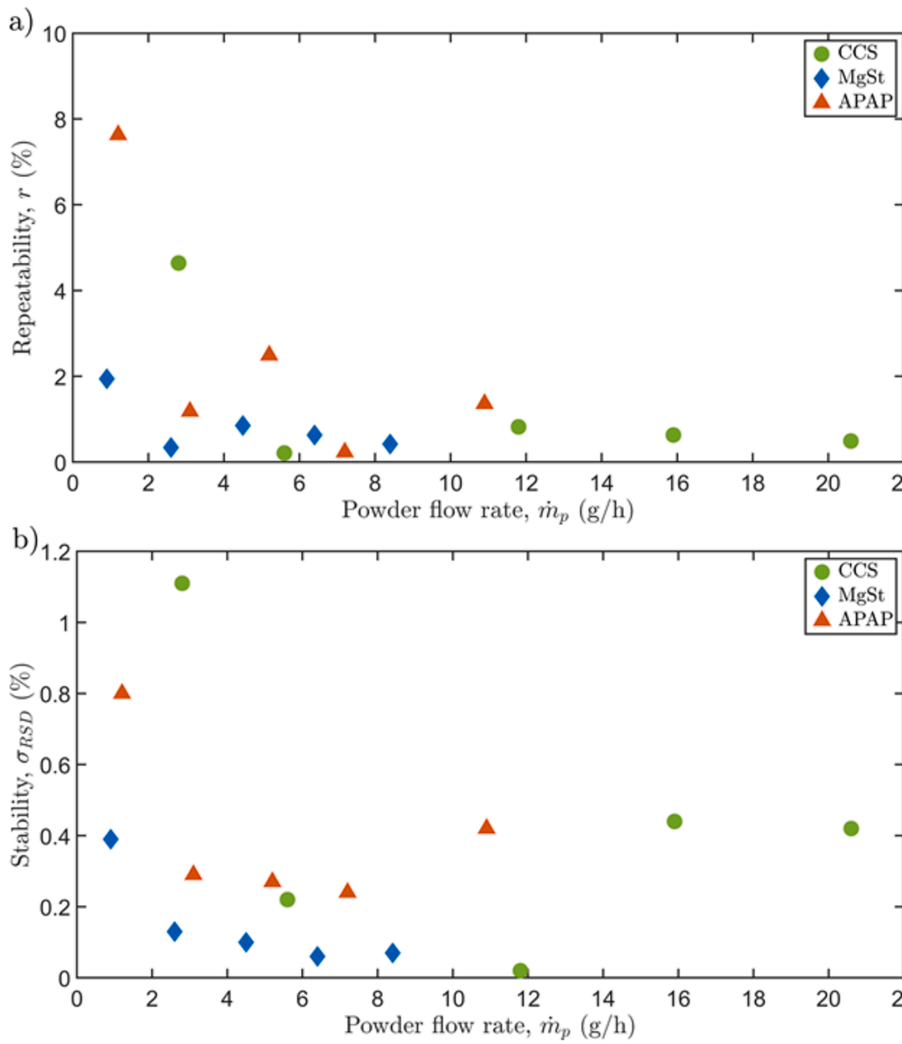

Fig. 13. Repeatability and stability at the optimal ratios were investigated for the three materials. a) repeatability and b) stability as a function of powder flow rate at the optimal ratio. The agitator speed was kept constant rather than the feed rate. Due to the differing physical properties of the three investigated powders, the average feed rate varies at a constant agitator speed.

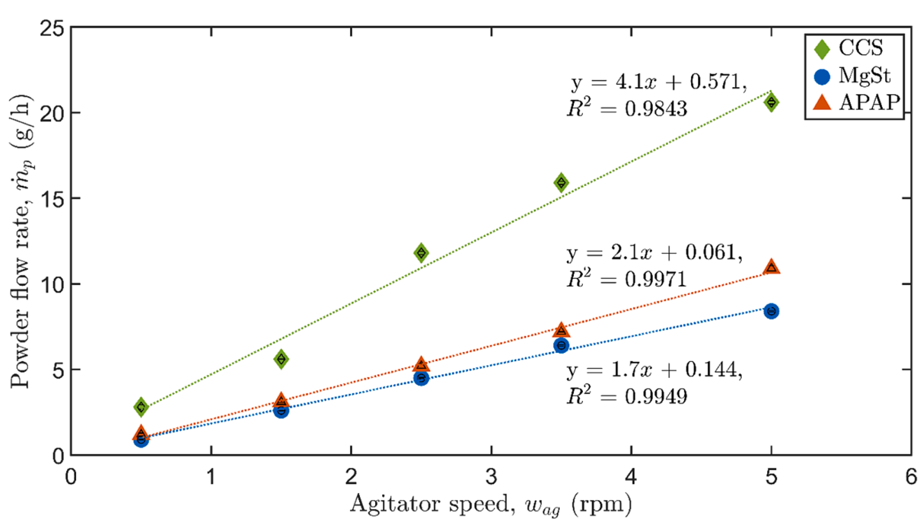

Fig. 14. The summary of the powder flow rate as a function of agitator speed for the three different materials at optimal ratios, demonstrating a linear relationship. Experiments were conducted in triplicate (n = 3).

performance metrics highlight its potential as a reliable and adaptable solution for precise powder feeding across a broad range of industrial applications.

4. Conclusions

This study presents a micro-feeder that can achieve consistent and continuous powder feeding without feedback control and without being affected by refilling. The micro-feeder incorporates a novel design featuring a feeding screw and a double-screw agitator design, which can handle a wide range of powder properties, settle common hopper issues, and maintain high feeding stability and repeatability. The research demonstrates that by adjusting the speeds of the double-screw agitator and feeding screw, feeding accuracy can be optimised, with the double-screw agitator controlling the powder flow rate and the feeding screw minimising variations. The main findings of the study are as follows:

- The micro-feeder's feeding mechanism employs an agitator in combination with screw speed adjustment to enhance screw volumetric efficiency and minimise variations in powder flow rate during the feeding process, distinguishing it from conventional screw feeders.
- The agitator design effectively addresses challenges such as rat holing and bridging that commonly occur when feeding cohesive materials (Figure S3 in Supporting Information).
- The repeatability of all tested materials was found to be below 8 %.
- At low flow rates, the stability of all tested materials was observed to be below 6 %. However, when feeding cohesive materials at high flow rates, stability levels were below 15 %.
- The micro-feeder demonstrates good repeatability and stability in powder feeding without feedback control, ranging from 0.5 g/h to 22 g/h, with very low RSD (<10 % for non-flowing materials and < 5 % for cohesive materials).
- The feeding performance is not influenced by refilling during the process, allowing for long-term operation and enabling recharging without interruptions.
- While the system was only demonstrated to continuously feed powder for 2 h, it is expected to be capable of long-term feeding operation.
- The modular and compact design of this micro-feeder offers enhanced flexibility, enabling easy adaption of the system to handle a wider range of powder properties and cater to various industrial and research applications.

The inclined micro-feeder offers several advantages over the existing feeding mechanisms detailed in Table 1. It achieves low feed rates with similar or better relative standard deviation (RSD) compared to the conventional feeders listed. Additionally, the inclined micro-feeder demonstrates potential for long-term continuous operation, surpassing the durability of some pneumatic, vibration and powder pump feeders. Its modular and customisable design provides greater versatility for different materials and applications, while optimised features ensure reduced friction, improved consistency, and lower maintenance, making it a cost-effective solution compared to more complex systems.

In summary, the optimised inclined micro-feeder provides practical benefits for consistent and reliable powder feeding, particularly for cohesive powders. Its compact design, improved feeding consistency, cost-effectiveness, and scalability make it an option in industry. Future research will aim to further enhance the system's capability to achieve even higher and more consistent flow rates, especially for non-flowing materials.

CRediT authorship contribution statement

P. Hou: Writing – original draft, Validation, Software, Methodology, Formal analysis, Data curation, Conceptualization. **M.O. Besenhard:** Writing – review & editing, Supervision, Conceptualization. **G. Halbert:** Writing – review & editing, Supervision. **M. Naftaly:** Writing – review & editing, Supervision. **D. Markl:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Peter Hou, Gavin Halbert and Daniel Markl have patent #PCT/GB2023/051291 pending to Assignee. Daniel Markl recently accepted to serve on the Editorial Board of IJP and IJP:X in 2024. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Acknowledgements

The authors would like to thank the University of Strathclyde, the Centre for Continuous Manufacturing and Advanced Crystallisation and the National Physical Laboratory for funding this work. The authors would like to acknowledge that this work was carried out in the CMAC National Facility supported by UKRPIF (UK Research Partnership Fund) award from the Higher Education Funding Council for England (HEFCE) (Grant ref HH13054).

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijpharm.2024.124528.

References

Barati Dalenjan, M., Jamshidi, E., Ale Ebrahim, H., 2015. A screw-brush feeding system for uniform fine zinc oxide powder feeding and obtaining a homogeneous gas-particle flow. Adv. Powder Technol. 26, 303–308. https://doi.org/10.1016/j.apt.2014.10.010.

Bekaert, B., Van Snick, B., Pandelaere, K., Dhondt, J., Di Pretoro, G., De Beer, T., Vervaet, C., Vanhoorne, V., 2022. In-depth analysis of the long-term processability of materials during continuous feeding. Int. J. Pharm. 614, 121454 https://doi.org/10.1016/J.IJPHARM.2022.121454.

Beretta, M., Kruisz, J., Hörmann-Kincses, T.R., Magosi, V., Guo, M., Naderi, M., Heupl, S., Kastner, J., Spoerk, M., Paudel, A., 2023. Assessment of tribo-charging and continuous feeding performance of direct compression grades of isomalt and mannitol powders. AAPS PharmSciTech 24, 91. https://doi.org/10.1208/s12249-023-02552-5.

Besenhard, M.O., Faulhammer, E., Fathollahi, S., Reif, G., Calzolari, V., Biserni, S., Ferrari, A., Lawrence, S.M., Llusa, M., Khinast, J.G., 2015. Accuracy of micro powder dosing via a vibratory sieve – chute system. Eur. J. Pharm. Biopharm. 94, 264–272. https://doi.org/10.1016/j.ejpb.2015.04.037.

Besenhard, M.O., Karkala, S.K., Faulhammer, E., Fathollahi, S., Ramachandran, R., Khinast, J.G., 2016. Continuous feeding of low-dose APIs via periodic micro dosing. Int. J. Pharm. 509, 123–134. https://doi.org/10.1016/j.ijpharm.2016.05.033.

Besenhard, M.O., Fathollahi, S., Siegmann, E., Slama, E., Faulhammer, E., Khinast, J.G., 2017. Micro-feeding and dosing of powders via a small-scale powder pump. Int. J. Pharm. 519, 314–322. https://doi.org/10.1016/j.ijpharm.2016.12.029.

Blackshields, C.A., Crean, A.M., 2018. Continuous powder feeding for pharmaceutical solid dosage form manufacture: A short review. Pharm. Dev. Technol. 23, 554–560. https://doi.org/10.1080/10837450.2017.1339197.

Bostijn, N., Dhondt, J., Ryckaert, A., Szabó, E., Dhondt, W., Van Snick, B., Vanhoorne, V., Vervaet, C., De Beer, T., 2019. A multivariate approach to predict the volumetric and gravimetric feeding behavior of a low feed rate feeder based on raw material properties. Int. J. Pharm. 557, 342–353. https://doi.org/10.1016/j.ijpharm.2018.12.066.

Burch, T.E., Conway, R.B., Chen, W.Y., 1991. A practical pulverized coal feeder for bench-scale combustion requiring low feed rates. Rev. Sci. Instrum. 62, 480–483. https://doi.org/10.1063/1.1142091.

Burcham, C.L., Florence, A.J., Johnson, M.D., 2018. Continuous manufacturing in pharmaceutical process development and manufacturing. Annu. Rev. Chem. Biomol. Eng. 9, 253–281. https://doi.org/10.1146/annurev-chembioeng-060817-084355.

Chamberlain, R., Windolf, H., Geissler, S., Quodbach, J., Breitkreutz, J., 2022. Precise dosing of pramipexole for low-dosed filament production by hot melt extrusion applying various feeding methods. Pharm. Technol. 46, 16–20. https://doi.org/10.3390/pharmaceutics14010216.

Chen, X., Seyfang, K., Steckel, H., 2012. Development of a micro dosing system for fine powder using a vibrating capillary. Part 1: The investigation of factors influencing on the dosing performance. Int. J. Pharm. 433, 34–41. https://doi.org/10.1016/j.ijpharm.2012.04.068.

De Souter, L., Waeytens, R., Van Hauwermeiren, D., Grymonpré, W., Bekaert, B., Nopens, I., De Beer, T., 2023. Elucidation of the powder flow pattern in a twin-screw LIW-feeder for various refill regimes. Int. J. Pharm. 631, 122534 https://doi.org/10.1016/J.IJPHARM.2022.122534.

Engisch, W.E., Muzzio, F.J., 2014. Loss-in-weight feeding trials case study: Pharmaceutical formulation. J. Pharm. Innov. 10, 56–75. https://doi.org/10.1007/s12247-014-9206-1.

Engisch, W.E., Muzzio, F.J., 2015. Feedrate deviations caused by hopper refill of loss-in-weight feeders. Powder Technol. 283, 389–400. https://doi.org/10.1016/j.powtec.2015.06.001.

Fathollahi, S., Sacher, S., Escotet-Espinoza, M.S., Dinunzio, J., Khinast, J.G., 2020. Performance evaluation of a high-precision low-dose powder feeder. AAPS PharmSciTech 21. https://doi.org/10.1208/s12249-020-01835-5.

Fathollahi, S., Kruisz, J., Sacher, S., Rehrl, J., Escotet-Espinoza, M.S., DiNunzio, J., Glasser, B.J., Khinast, J.G., 2021. Development of a controlled continuous low-dose feeding process. AAPS PharmSciTech 22, 1–14. https://doi.org/10.1208/s12249-021-02104-9.

Fernandez, J.W., Cleary, P.W., McBride, W., 2011. Effect of screw design on hopper drawdown of spherical particles in a horizontal screw feeder. Chem. Eng. Sci. 66, 5585–5601. https://doi.org/10.1016/j.ces.2011.07.043.

Horio, T., Yasuda, M., Matsusaka, S., 2014. Effect of particle shape on powder flowability of microcrystalline cellulose as determined using the vibration shear tube method. Int. J. Pharm. 473, 572–578. https://doi.org/10.1016/j.ijpharm.2014.07.040.

Hörmann-Kincses, T.R., Beretta, M., Kruisz, J., Stauffer, F., Birk, G., Piccione, P.M., Holman, J., Khinast, J.G., 2022. Predicting powder feedability: A workflow for assessing the risk of flow stagnation and defining the operating space for different powder-feeder combinations. Int. J. Pharm. 629 https://doi.org/10.1016/j.ijpharm.2022.122364.

Hou, P., Besenhard, M.O., Halbert, G., Naftaly, M., Markl, D., 2023. Development and implementation of a pneumatic micro-feeder for poorly-flowing solid pharmaceutical materials. Int. J. Pharm. 635, 122691 https://doi.org/10.1016/J.IJPHARM.2023.122691.

Huang, Y.S., Medina-González, S., Straiton, B., Keller, J., Marashdeh, Q., Gonzalez, M., Nagy, Z., Reklaitis, G.V., 2022. Real-time monitoring of powder mass flowrates for plant-wide control of a continuous direct compaction tablet manufacturing process. J. Pharm. Sci. 111, 69–81. https://doi.org/10.1016/j.xphs.2021.06.005.

Janssen, P.H.M., Kulkarni, S.S., Torrecillas, C.M., Tegel, F., Weinekötter, R., Meir, B., Dickhoff, B.H.J., 2022. Effect of batch-to-batch variation of spray dried lactose on the performance of feeders. Powder Technol. 409, 117776 https://doi.org/10.1016/J.POWTEC.2022.117776.

Johnson, B.J., Sen, M., Hanson, J., García-Muñoz, S., Sahinidis, N.V., 2022. Stochastic analysis and modeling of pharmaceutical screw feeder mass flow rates. Int. J. Pharm. 621 https://doi.org/10.1016/j.ijpharm.2022.121776.

Li, X., Hou, Q., Dong, K., Zou, R., Yu, A., 2020. Promote cohesive solid flow in a screw feeder with new screw designs. Powder Technol. 361, 248–257. https://doi.org/10.1016/j.powtec.2019.08.045.

Minglani, D., Sharma, A., Pandey, H., Dayal, R., Joshi, J.B., Subramaniam, S., 2020. A review of granular flow in screw feeders and conveyors. Powder Technol. 366, 369–381. https://doi.org/10.1016/j.powtec.2020.02.066.

Nagy, Z.K., Hagrasy, A. El, Litster, J., 2020. Book of Continuous Pharmaceutical Processing.

Oladeji, S., Mohylyuk, V., Jones, D.S., Andrews, G.P., 2022. 3D printing of pharmaceutical oral solid dosage forms by fused deposition: The enhancement of printability using plasticised HPMCAS. Int. J. Pharm. 616, 121553 https://doi.org/10.1016/j.ijpharm.2022.121553.

Peterwitz, M., Gerling, S., Schembecker, G., 2022. Challenges in tracing material flow passing a loss-in-weight feeder in continuous manufacturing processes. Int. J. Pharm. 612, 121304 https://doi.org/10.1016/J.IJPHARM.2021.121304.

Pohořelý, M., Svoboda, K., Hartman, M., 2004. Feeding small quantities of particulate solids. Powder Technol. 142, 1–6. https://doi.org/10.1016/j.powtec.2004.03.005.

Sacher, S., Heindl, N., Alberto Afonso Urich, J., Kruisz, J., Khinast, J.G., 2020. A solution for low-dose feeding in continuous pharmaceutical processes. Int. J. Pharm. 591, 119969. Doi: 10.1016/j.ijpharm.2020.119969.

Sacher, S., Fathollahi, S., Khinast, J.G., 2021. Comparative Study of a Novel Micro-feeder and Loss-in-weight Feeders. J. Pharm. Innov. https://doi.org/10.1007/s12247-021-09599-6.

Santos, B., Carmo, F., Schlindwein, W., Muirhead, G., Rodrigues, C., Cabral, L., Westrup, J., Pitt, K., 2018. Pharmaceutical excipients properties and screw feeder performance in continuous processing lines: a Quality by Design (QbD) approach. Drug Dev. Ind. Pharm. 44, 2089–2097. https://doi.org/10.1080/03639045.2018.1513024.

Suri, A., Horio, M., 2009. A novel cartridge type powder feeder. Powder Technol. 189, 497–507. https://doi.org/10.1016/j.powtec.2008.08.001.

Tahir, F., Palmer, J., Khoo, J., Holman, J., Yadav, I.K., Reynolds, G., Meehan, E., Mitchell, A., Bajwa, G., 2020. Development of feed factor prediction models for loss-in-weight powder feeders. Powder Technol. 364, 1025–1038. https://doi.org/10.1016/j.powtec.2019.09.071.

Tang, L., Chen, W.Y., 1999. Improvements on a particle feeder for experiments requiring low feed rates. Rev. Sci. Instrum. 70, 3143–3144. https://doi.org/10.1063/1.1149876.

Van Snick, B., Holman, J., Cunningham, C., Kumar, A., Vercruysse, J., De Beer, T., Remon, J.P., Vervaet, C., 2017. Continuous direct compression as manufacturing platform for sustained release tablets. Int. J. Pharm. 519, 390–407. https://doi.org/10.1016/j.ijpharm.2017.01.010.

Wang, H., Wu, L., Zhang, T., Chen, R., Zhang, L., 2018a. Continuous micro-feeding of fine cohesive powders actuated by pulse inertia force and acoustic radiation force in ultrasonic standing wave field. Int. J. Pharm. 545, 153–162. https://doi.org/10.1016/j.ijpharm.2018.05.006.

Wang, H., Zhang, T., Zhao, M., Chen, R., Wu, L., 2018b. Micro-dosing of fine cohesive powders actuated by pulse inertia force. Micromachines 9. https://doi.org/10.3390/mi9020073.

Wen, C.-Y., Simons, H.P., 1959. Flow characteristics in horizontal fluidized solids transport. AIChE J. 5, 263–267. https://doi.org/10.1002/aic.690050225.

Wibberley, L.J., Phong-Anant, D., 1986. A simple laboratory feeder for fine particles. Combust. Sci. Technol. 49, 93–97. https://doi.org/10.1080/00102208608923904.

Zainuddin, I.M., Yasuda, M., Horio, T., Matsusaka, S., 2012. Experimental Study on Powder Flowability Using Vibration Shear Tube Method 29, 8–15. Doi: 10.1002/ppsc.201100052.