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4 **Pharmaceutical excipients properties and screw feeder performance in**
5 **continuous processing lines: a Quality by Design (QbD) approach**
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Pharmaceutical excipients properties and screw feeder performance in continuous processing lines: a Quality by Design (QbD) approach

Screw feeder performance is a critical aspect in continuous manufacturing processes. Pharmaceutical excipients, such as mannitol, microcrystalline cellulose, lactose monohydrate and anhydrous dibasic calcium phosphate can present problems in ensuring a continuous stable feed rate due to their sub-optimal flow properties. In alignment with Quality by Design (QbD) goals, the aim of this work was to identify and explain critical sources of variability of some powder excipients delivery by screw feeding, in particular to continuous processing lines. Pharmaceutical excipients with a wide range of material properties were selected and the impact of their flow and density properties on screw feeder performance was investigated. The analysis of the powder conveying by the screws was performed at different hopper fills and different screw speeds. A multivariable model involving bulk density (CBD) and parameters from FT4 dynamic downwards testing (SI) and dynamic upwards testing (SE) explained 95.7% of excipients feed rates ($p < 0.001$). The study gathers valuable information about the screw feeder performance and input materials properties that can help process understanding and QbD-based development of solid dosage forms in continuous processing lines.

Keywords: Pharmaceutical Excipients, Solid Dosage, Materials Properties, Powder Flow, Screw Feeder, Continuous Manufacturing, Quality by Design.

1. Introduction

Over the last decade, pharmaceutical industry has been investing huge efforts and resources in the development of continuous manufacturing. Although there have been some benefits, the enormous potential of continuous manufacturing is not yet fully realised and several technical challenges remain and must be addressed [1, 2]. Some of these challenges are related to powder flow, feeding build-up over long run times and maintaining mass flow balance. These challenges are most evident with cohesive/poor flow materials and low-dose products [1, 3, 4]. A workable approach for the transition to continuous manufacturing technologies should be developed. In addition, a Quality

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3 by Design (QbD) approach should be applied to continuous manufacturing processes.
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5 Using QbD, pharmaceutical quality is assured by understanding and controlling
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7 (designing) formulation and manufacturing variables, not just by end quality by testing
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9 (QbT) method [5-7].
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11 Powder flow is a potential critical quality attribute (CQA) for many pharmaceutical
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13 powders and has been widely investigated within the context of the QbD methodology
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15 [3, 5]. Intrinsic and external factors can affect powder flow, including particle and bulk
16
17 properties, experimental and environmental conditions. There are many material
18
19 properties affecting the flow. However, to date, investigations focus on a few[4] and
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21 key excipients in many solid dosage forms were not investigated. An effort is needed to
22
23 correlate powder properties with critical quality parameters of a feeding process for
24
25 enhance process understanding [3, 4].
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28 Screw feeders are widely used in different pharmaceutical manufacturing processes
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30 to consistently feed bulk materials from the container or hopper to other downstream
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32 processes [8]. Screw feeders are a key part of the operation of continuous processing
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34 equipment such as continuous twin screw wet granulation, roller compression, hot melt
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36 extrusion, sachet packaging and micronization. The screw feeder accuracy can have a
37
38 major impact on the output and control of these downstream processes.
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41 Excipients, such as mannitol (MA), microcrystalline cellulose (MCC), lactose
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43 monohydrate (LAC), anhydrous dibasic calcium phosphate (CaP) and others can present
44
45 problems in ensuring continuous and reproducible feed rate due to their powder
46
47 properties. MA is a key excipient as filler/diluent-binder in many solid dosage forms,
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49 especially for the production of popular orodispersible or dispersible formulations [9-
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51 11]. It is widely used in pharmaceutical formulations due to its chemical stability, non-
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53 hygroscopicity, safety, excellent compatibility with drugs and spray-dried quality for
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3 direct compression [9-11]. MCC is available as an odorless, tasteless, white crystalline
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5 powder of porous particles. There are different particle sizes, flowability properties and
6
7 moisture grades of this material, which leads to different characteristics and applications
8
9 [12-14]. MCC is widely used as a binder/diluent in oral tablet and capsule formulations
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11 where it can be used in both direct-compression and wet-granulation [14-17]. LAC
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13 occurs as a white to off-white crystalline particles or powder. It is widely used as a filler
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15 and diluent in tablets and capsules and it is commercially available in different grades
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17 with different particle size distribution and flow characteristics [12]. CaP is a white
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19 crystalline powder [12]. It is used both as a source of calcium in nutritional
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21 supplements and as a tableting aid. It is an insoluble filler but can also control
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23 dissolution profiles [18].
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27 Compaction properties and the good flow properties of the coarse-grade material
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29 make it an important excipient in pharmaceutical products [19-21]. Milled material is
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31 typically used in wet-granulated or roller-compacted formulations. The coarse-grade
32
33 material is typically used in direct compression formulations. It is a non hygroscopic
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35 material and cannot be rehydrated to form the dehydrate [12] under normal
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37 manufacturing conditions.
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40 Very little scientific literature has been published on the interplay between screw
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42 feeder performance and input materials properties despite the importance of this subject
43
44 to industry. Optimisation of powder conveying by screw feeders remain based on trial
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46 and error approach. A systematic approach to evaluate the relationship between CQAs
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48 and critical process parameters (CPPs) would allow better understanding of the process
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50 and for cost reduction in the development and manufacture of new pharmaceutical
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52 products [6].
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3 In alignment with QbD goals [6], the aim of this work was to identify and explain
4 critical sources of variability of some powder excipients delivery by screw feeding, in
5 particular with continuous processing lines. The interactions of flow and density
6 attributes of different excipients and screw feeder performance were investigated to
7 gather valuable information for process design understanding, which would reduce
8 product variability thereby increasing process capability.
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15 16 **2. Material and methods**

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18 Different pharmaceutical excipients with a wide range of material properties were
19 selected (Table 1): MA (Pearlitol®, Roquette, Lestrem, France); MCC (Ceolus®, Asahi
20 Kasei, Tokyo, Japan and Avicel®, FMC BioPolymer, Philadelphia, PA, USA); LAC
21 (Lactochem® Regular Powder, DFE Pharma, Goch, Germany); an inorganic powder,
22 CaP (Emcompress® Anhydrous Powder, JRS Pharma, Rosenberg, Germany) and a
23 mixture of MA and MCC.
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31 32 **2.1. Evaluation of powder properties**

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34 *Ring Shear Tester analysis.* The Ring Shear Tester RST-XS (Dietmar Schulze,
35 Germany) was used to measure the shear stress at different normal stresses applied on
36 the powder. The powder was pre-consolidated at 0.6 kPa in a large volume cell (d [cm]
37 iD 4.60; aD 8.60). This low stress value was proposed for a better correlation with
38 screw feeder experiments. Samples were analysed in duplicate. A Mohr's diagram was
39 constructed using the control software RST-CONTROL 95 and the program RSV 95
40 (Dietmar Schulze, Germany) from which several parameters were obtained, namely,
41 maximum principle stress (σ_1), unconfined yield stress (σ_c), flow function coefficient
42 (FFc) and bulk density (RHOB). FFc is defined as the ratio of consolidation stress to the
43 unconfined yield stress and is commonly used for pharmaceutical powder flow
44 characterisation [22].
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3 *Powder Rheometer analysis.* The powder flow properties were characterised using
4 the FT4 Powder Rheometer (Rotational shear tester, Freeman Technology, Tewkesbury,
5 UK), to measure dynamic flow, bulk and shear properties. All tests were carried out
6 using 48 mm accessories in a 50 mm bore, borosilicate test vessel, as described by
7 Freeman (2007) and by Fu and co-workers (2012) [23, 24].
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13 *Tapped and Bulk Density (TBD).* Cylinder method was used for determining tapped
14 and bulk density [25]. After weighing, powder was poured into the cylinder and the
15 bulk volume was measured. Then the cylinder was subjected to a given number of taps
16 until the difference between the volume measurements was less than 2%, then the
17 tapped volume was recorded. The mass of the powder was divided by the volume
18 occupied by the powder in the cylinder for both conditions to determine the bulk (ρ_b)
19 and tapped density (ρ_t). Samples were analysed in duplicate. Carr's index is used as a
20 measure of the compressibility of a powder; it is calculated using the formula,
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$$31 \text{ Compressibility/Carr Index (\%)} = \frac{100 (\rho_t - \rho_b)}{\rho_t}$$

32 where ρ_b is the bulk density and ρ_t is the tapped density [26].
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36 **2.2. Screw feeder and hopper flow analysis**

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39 A Brabender MiniTwin feeder (twin concave screw = 12/12 mm, hopper volume =
40 3.0 dm³; speed max = 140 rpm; Brabender Technologie, Germany) was used for the
41 experiments (Figure 1). The automated sampling and recording of the weight in each 10
42 seconds interval were carried out using a precision scale Mettler Toledo PJ400
43 (Columbus, OH, USA) with output to a computer and a data collection program written
44 to automate the sampling method. All samples were collected for 12 minutes or 300
45 grams (the necessary weight to achieve approximately 25% of hopper content) to
46 minimise hopper fill influence on the powder conveying by screws. The first and last
47 data points were removed from the analysis to ensure that data at steady state were
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3 obtained. The analysis of the powder conveying by the screws was performed under the
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5 following conditions: constant screw speed (50% of full screw speed) at different
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7 hopper fill (100, 75, 50, 25%, Figure 1) and at different screw speeds (25, 50, 75, 100%
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9 of full screw speed) at the intermediate range of hopper content (from 75 to 25%). Flow
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11 behaviour can be influenced by external factors [3], such as air relative humidity (RH),
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13 temperature (T), and storage time conditions. Hence the screw feeder performance was
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15 evaluated in controlled environment conditions ($T = 20\text{ }^{\circ}\text{C}$; $\text{RH} = 40\%$). The material
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17 flow within the hopper was also observed for each sample. Pictures were taken during
18
19 the experiments to record the hopper flow.
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22 ***2.3. Statistical analysis***

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25 Multivariate regression analysis was conducted using JMP® (version 11.2.1)
26
27 statistical discovery software from SAS (US) to model the relationship between powder
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29 properties and screw feeder performance.
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32 **3. Results and discussion**

33 ***3.1. Evaluation of powder flow and density***

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36 Powder flowability is an important attribute in developing and manufacturing solid
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38 dosage forms [27]. Multiple technologies have been used over the years to characterize
39
40 powder flowability, such as the cylinder method, the Ring Shear Tester RST-XS and
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42 FT4 Powder Rheometer that can be used to determine flow properties of bulk solid [24,
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44 27, 28]. Powder flow and density attributes obtained for each material are shown in
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46 Table 2.
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51 The bulk densities obtained from cylinder method (BD), Schulze shear cell analysis
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53 (RHOB) and FT4 analysis (Conditioned Bulk Density, CBD). CBD is related with the
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55 bulk density of powder submitted to a gentle disturbance to prepare for testing using a
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3 slicing helix downwards and a lifting helix upwards [23]. A linear correlation was
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5 observed comparing CBD with RHOB (R-square = 0.99). Good correlations were also
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7 obtained comparing BD and RHOB (R-square = 0.982) and BD and CBD (R-square =
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9 0.988). All MA samples have higher density than MCC samples. The highest bulk
10
11 density was observed for CaP, an inorganic excipient, followed by LAC.
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14 Compressibility index or Carr index (CI, Table 2) measures the propensity of a
15
16 powder to be compressed or their ability to be settle and permits an assessment of
17
18 interparticulate interactions [26]. It was calculated from the bulk and tapped density
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20 obtained by cylinder method and the flow properties were classified accordingly to the
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22 range of CI (%) described in USP Powder Flow [26]. MA-25C, MA-50C and MA-160C
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24 have very to very, very poor flow character. Spray dried grades (MA-100SD and
25
26 200SD) have fair to passable flow. MCC-C1000 showed the worst flow (CI = 53%;
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28 very, very poor flow). MCC-C101, MCC-A101 have very poor flow and MCC-A102
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30 showed poor flowability. MCC-A200 has flowability comparable to MA-200SD (fair).
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32 Mix MA:MCC, CaP and LAC have very to very, very poor flow character. For more-
33
34 poorly flowing materials, there are frequently greater interparticulate interactions, and a
35
36 greater difference between the bulk and tapped densities will be observed.
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40 Among the samples analysed, only for MCC-C1000, the CI represents the influence
41
42 of the bulk density. MCC-C1000 has the lowest bulk density and the highest CI (very,
43
44 very poor flow).
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47 Compared to the cylinder method, shear cell methodology in general is a greater
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49 degree of experimental control and a wide variety of parameters can be obtained [26],
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51 including the flowability index (FFc from Schulze and FF from FT4). Flow function
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53 values (FFc and FF) were obtained at low pressure (0.6 kPA), approximating the
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55 analysis to the condition into hopper. FFc values (Table 2) indicated easy-flowing for
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3 MA-100SD, MA-200SD, MCC-A102 and MCC-A200. MA-50C, MA-160C, MCC-
4 C1000, MCC-C101, MCC-A101, Mix and CaP showed cohesive flow and MA-25C and
5 LAC indicated very-cohesive flow [29].
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9 FF values (Table 2) indicated free-flowing for MA-200SD; easy-flowing for MA-
10 100SD, MCC-C1000, MCC-C101, MCC-A101, MCC-A102 and MCC-A200; cohesive
11 flow for MA-160C, Mix, CaP and LAC and very-cohesive flow for MA-50C and MA-
12 25C. Comparing CI, FFC and FF values it could be noted that MA-100SD, MA-200SD,
13 MCC-A102 and MCC-A200 presented the best flowability profile among all samples.
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17 Comparing the flow function measured by annular (FFc) and rotational (FF) shear
18 cell, a linear correlation was observed. Equation 1 demonstrates the relation between
19 FFc and FF (RSq=0.774, p<0.0001). The model does not fit MCC-A200 data.
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27 Equation 1. $FFc = 1.1866779 + 0.4020586 \cdot F$
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30 Considering FFc results, MCC-A200 showed the best flowability in disagreement
31 with FT4 analysis that showed the higher FF value for MA-200SD. For free flowing
32 powders, such as MCC-A200 and MA-200SD, the pre-conditioning process that occurs
33 before the shear analysis using FT4 rheometer could increase their flow function. For
34 cohesive and very-cohesive powders such as CaP, LAC, MA-50C and MA-25C, this
35 pre-conditioning stage could not be enough to increase their flow [23, 24, 30, 31].
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39 Cohesion is the shear strength at zero normal stress for an applied normal
40 consolidation stress[23]. In Table 2, the cohesion values for the consolidation stress of
41 0.6 kPa ($C_{0,6}$) is ranging from 0.02 kPa to 0.37 kPa for the least and most cohesive
42 powders. MA-25C showed the highest cohesion value (0.37 kPa) followed by MA-50C
43 (0.23 kPa). MA-160C, Mix MA:MCC, CaP and LAC showed cohesion values between
44 0.2 and 0.1 kPa. All other samples showed cohesion values lower than 0.01 kPa. The
45 spray dried samples of mannitol (100SD and 200SD) showed the lowest $C_{0,6}$ values.
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3 The effective angle of internal friction (ϕ_e and AIFe) is shown in Table 2. In
4 previous report [32], the angle of internal friction was correlated to both particle size
5 and shape in a nonlinear manner. The highest values of effective angle of internal
6 friction were observed for MA-25C which presents the smallest particle size and a
7 needle shape (S1 and S2, Supplemental material), opposing the spray dried samples of
8 mannitol (100SD and 200SD) with the lowest internal friction angles and largest
9 particles with spherical shape (S1 and S2).
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18 Dynamic testing using FT4 Powder Rheometer provides parameters as Flow Rate
19 Index (FRI), Specific Energy (SE), Basic Flowability Energy (BFE) and Stability Index
20 (SI) as showed in Table 2.
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24 FRI can be defined as the factor by which the flow energy is changed when the flow
25 rate (tip speed) is reduced by a factor of 10 during downwards testing and SE is the
26 energy per gram needed to displace conditioned powder during upwards testing [23].
27 Analyzing FRI and SE values for all materials it can be observed that they are inversely
28 proportional to FF, free-flowing or easy-flowing materials showed small values of FRI
29 and SE. They are good parameters to predict powder flowability [23, 24]. The smallest
30 FRI and SE values were observed for the spray dried mannitol samples (MA-100SD and
31 MA-200SD) and MCC-A200 which have high FF values.
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41 BFE measures the energy needed to displace a conditioned powder sample during
42 downwards testing at specific consolidating conditions. Many variables reflect in BFE
43 values, such as particle size and shape, cohesivity, density and moisture content, being
44 complex to interpret. The way in which these variables interact commands the flow
45 properties varying from powder to powder. Therefore, BFE is not necessarily related to
46 how a powder flows through a given process [23, 24]. MA-160C showed the highest
47 BFE value (2385.67 mJ) while the smallest values were observed for MCC-C1000 and
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3 CaP (802.00 and 873.50 mJ, respectively). Comparing MA-160C with CaP, they have
4 high bulk densities and the FF values are similar (2.79 and 2.57, respectively), however
5 their BFE values are extremely different (2385.67 and 871.50 mJ, respectively).
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9 SI measures flow energy changes during repeated testing or processing [23]. The
10 highest values of SI were observed for MA-160C and CaP (1.25 and 1.27, respectively)
11 and MA-25C showed the lowest SI value (0.82) followed by MA-50C (0.91). MA-25C
12 and MA-50C showed the highest cohesion and AIFE and the lowest FF and SI values.
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14 All the other powders showed SI values closer to 1, having a stable rheology.
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19 20 ***3.2.Screw feeder performance*** 21

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23 Flow out of the hopper during screw feeding depends on the powder material
24 properties, the feeder hopper and screws conveyor designs. To ensure that the screw
25 feeder delivers a constant mass flow, different hopper and screws designs may be
26 required depending on the material used. Although appropriate selection of the hopper
27 and screws for the screw feeder must be taken into account for a successful feeding
28 performance [33], these variables were not explored in this manuscript. The hopper and
29 screws designs used in this investigation are illustrated in Figure 1.
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38 39 ***3.2.1. Evaluation of hopper flow*** 40

41 The pictures illustrating the hopper flow taken during the experimental runs are
42 shown in Figure 2. MA-100SD, MA-200SD and MCC-A200 showed good funnel flow,
43 followed by a mass flow with all powder in motion including that near the walls.
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47 As can be seen in Figure 2, MA-160C, MCC-C101, MCC-A101, MCC-A102, Mix
48 MA:MCC and CaP showed rat-holing effect due to the funnel/core flow behaviour. The
49 powder near the walls remains stagnant, while the material at the centre of the silo is
50 being discharged through the screws. Although the hopper has one steep wall, which
51 promotes flow, the flat walls in the face of the outlet zone and lateral favour the funnel
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3 flow [28]. In previous work, MCC-A102 was fed successfully in a K-Tron KT35 feeder
4
5 with a cylinder hopper [34].
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7 For MA-25C, MA-50C, MCC-C1000 and LAC, an arching/bridging effect (Figure
8
9 2) was observed, restricting the flow of material from the hopper to the feed screws.
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11 3.2.2. Evaluation of powder conveying by screws

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14 The feed rate (mass per 10 seconds) was recorded for different screw speeds (25, 50,
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16 75 and 100%) and hopper levels (25, 50, 75 and 100%). To minimise the impact of
17
18 hopper design, analysis of powder conveying by screws was undertaken only when rat
19
20 holing or bridging were not present.
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23 Figure 3 represents the feed rate based on the 60 consecutive samples of 10 seconds
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25 at 50% of maximum screw speed and different hopper levels for each material, while
26
27 the feed rate average, standard deviation and relative standard deviation considering
28
29 these runs are summarized in Table 2.
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31 MA-25C, MA-50C, MCC-C1000 and LAC showed poor repeatability and stability
32
33 (RSD > 15%; Figure 3 and Table 2). MA-25C, MA-50C and MCC-C1000 showed the
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35 lowest feed rate values (0.31, 1.35 and 0.76 g/10 sec, respectively) with largest RSD
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37 (47.43, 15.89 and 25.87%, respectively). Although LAC showed high feed rate value
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39 (4.04 g/10 sec), its RSD was large (19.92%). As can be observed in Figure 3c for LAC,
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41 at runs with 50% and 75% hopper level the feed rate has decreased probably because
42
43 the air pocket/bridging effect observed. MA-50C and MCC-C1000 also showed a
44
45 gradual decrease of the feed rate during the 10 minutes (Figure 3), probably because of
46
47 the air pocket/bridging influence [34].
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51 MA-160C, MA-100SD, MA-200SD, MCC-A200, CaP and Mix MA:MCC showed
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53 consistent feed performance with RSD < 3.0% (Figure 3 and Table 2). CaP showed the
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3 highest feed rate values (8.38 g/10 sec, RSD 2.19%), probably because of its high true
4
5 density, showing consistent feed rate in function of time (Figure 3d).
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7 MA-160C and Mix MA:MCC showed good capacity to be conveyed by screws at
8
9 the intermediate range of hopper content (75 and 50%). They did though show feed rate
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11 decrease over the last 2 minutes (Figures 3a and 3c) corroborating with the rat-holing
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13 effect and so hopper flow limitation.
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16 The feed rate values of spray dried grades MA-200SD (3.90 g/10 sec, RSD 2.84%)
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18 and MA-100SD (4.16 g/10 sec, RSD 1.97%) were lower than MA-160C. For MA-
19
20 200SD, the feed rate was stable during the 10 minutes for all hopper levels (Figure 3a).
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22 However, MA-100SD showed unstable feed rate (Figure 3a) for runs at 100% (feed rate
23
24 increase over the first 2 minutes) and 25% (feed rate decrease over the last minute) of
25
26 hopper content.
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29 Comparing all MCC grades, MCC-A200 showed the highest feed rate value (3.31
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31 g/10 sec, RSD 2.96%) and also stable feed rate during the 10 minutes for all hopper
32
33 levels (Figure 3b). MCC-A102, MCC-A101 and MCC-C101 showed feed rates values
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35 varying from 2.46 to 3.31 g/10 sec and RSD between 3.0 and 5.0%. For MCC-A102 the
36
37 feed rate was more stable for all hopper levels comparing with MCC-A101 and MCC-
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39 C101, that have showed small variations of feed rate along the runs (Figure 3b). MCC-
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41 A101 and MCC-C101 are obtained from different suppliers but they are similar
42
43 materials, showing similar characteristics. MCC-C1000 showed small and inconsistent
44
45 feed rate (0.76 g/10 sec, RSD 25.87%) for all hopper levels. This inconsistency is
46
47 probably because the air pocket influence. Although MCC-C1000 has the same nominal
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49 particle size as MCC-C101 and MCC-A101, it presented the smallest bulk density and
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51 the most pronounced acicular habit (data not shown) among all materials.
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54 55 3.2.3. Linearity 56 57 58 59 60

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3 Feed rate linearity at different screw speeds (25, 50, 75 and 100% of full speed) was
4 investigated with intermediate range of hopper level for each material (Figure 4). The
5 linearity results for mannitol samples are all in agreement with their conveying
6 capacity: MA-25C and MA-50C have smallest feed rate and showed poor linearity (R^2
7 = 0.341 and 0.627, respectively). MA-160C ($R^2 = 0.999$), MA-100SD ($R^2 = 0.996$) and
8 MA-200SD ($R^2 = 0.994$) have highest feed rate and showed excellent linearity (Figure
9 4a). The linearity is a result of the hopper flow and the conveying capacity. If the
10 powder presents some phenomena such as rat holing and bridging into the hopper, no
11 material would enter the screw, thereby stopping the flow. Otherwise, some powders
12 may stick to the screw, that becomes coated, adding resistance and increasing the torque
13 needed to continue pushing the powder through the holes [34]. For MA-25C and 50C,
14 both effects are added together, resulting in their poor linearity.
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28 MCC-A200, MCC-A102, MCC-A101 and MCC-C101 showed excellent linearity
29 ($R^2 > 0.99$; Figure 4b). MCC-C1000 and LAC, that have presented smaller feed rate and
30 larger RSD, also showed poor linearity ($R^2 = 0.9726$ and 0.8652 , respectively) (Figures
31 4b and 4c). CaP showed good conveying capacity and good linearity ($R^2 > 0.99$; Figure
32 4c). Mix MA: MCC showed good linearity ($R^2 > 0.99$; Figure 4c).
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40 ***3.3. Influence of powder properties on screw feeder performance***

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42 The effect of materials properties on screw feeder performance was investigated.
43 Several factors can define powder flow and the capacity for screw conveying. These are
44 not a result of a single material property [3, 35]. Simple and multiple linear regression
45 analysis were carried out to observe the effect of flow and density data (Table 2) on
46 feed rate.
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53 A simple linear model (Equation 2) using bulk density (BD) to explain the feed rate
54 (FR) produced an R-square of 60.8% and $p=0.002$. MA-25C and MA-50C are outliers
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3 in this model; the feed rates of these materials are overestimated (residuals of – 3.02 and
4
5 -2.70, respectively) due their high bulk densities. MA-160C and CAP showed the
6
7 highest values of bulk density and feed rate.

8
9 Equation 2. $FR = -0.705707 + 8.9774949 \cdot BD$

10
11 No linear correlation was observed between CI or flow function (FFc and FF) and
12
13 feed rate. Including a flow parameter in the previously model (Equation 2), a 2-variable
14
15 analysis to observe the effect of CI and BD on feed rate (R-square = 0.637 and p=0.007,
16
17 Equation 3) do not significantly improve the previously model. MA-25C and MA-50C
18
19 are still the outliers; their feed rates are overestimated, however small residuals were
20
21 observed of - 2.81 and -2.54, respectively.
22
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24
25 Equation 3. $FR = 0.5357556 + 8.9018117 \cdot BDF - 0.036234 \cdot CI$

26
27 MA-160C and its sieved/ground grades MA-25C and MA-50C have poor flow
28
29 character, CI values ranging from 32 to 44, and high bulk densities (0.590, 0.430 and
30
31 0.535 g/cm³, respectively, Table 2). These variations of both flow and bulk density
32
33 values do not justifies their feed rate differences (from 0.31g/10 sec for MA-25C to 5.37
34
35 g/10 sec for MA-160C).
36

37
38 Although MA-160C, MA-25C and MA-50C appear similar in terms of particle
39
40 shape, being more elongated and needle-shaped (S1 and S2), it is possible to
41
42 discriminate these samples by particle size distribution. The volume of fine particles is
43
44 much larger for MA-25C and MA-50C than MA-160C (S1). For smaller particles such
45
46 as MA-25C and MA-50C, the interparticle interactions are stronger due to their higher
47
48 contact area. Van der Waals are the dominating and most common intermolecular forces
49
50 in pharmaceutical powders and are primarily responsible for particle-particle
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52 interactions [36]. Hydrogen bonding (HB) is considered to be a relatively strong inter-
53
54 particle bonding [36]. Mannitol acts as a donor and an acceptor for six hydrogen bonds.
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3 The OH groups have different conformations conform to the different polymorphs of
4 mannitol and resulting different HB scheme [37].

5
6 Also, for MA-25C and MA-50C, the irregular particles (S1 and S2) favours the
7 tendency to mechanical interlocking, denoting hooking and twisting of particles
8 together compared with smooth spherical ones, such as spray-dried (MA-100SD and
9 MA-200SD) grades [36]. The acicular habit combined to bimodal size distribution with
10 a high amount of fine particles influences the poor flow/cohesivity and the wall friction
11 in hoppers (arching effect) of these powders.
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20 For powders with a good/fair flow character, the interparticulate interactions are less
21 significant, and the bulk and tapped densities will be closer in value, as in the case of
22 MA-200SD and MCC-A200 (Table 2). Comparing MA-200SD and MCC-A200, they
23 have the same compressibility index (CI = 18), and bulk densities completely different,
24 ranging from 0.377 g/cm³ for MCC-A200 to 0.500 g/cm³ for MA-200SD, which
25 influence on their feed rates. At the same time, comparing MCC-A101 and MA-160C
26 feed rates (2.46 and 5.37 g/10 sec, respectively), it can be observed a small variation in
27 CI values (34 and 32, respectively) and a huge difference between BD values (0.317
28 and 0.590 g/cm³, respectively), which justifies their feed rates.
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39 As expected by the results from CI and BD analysis, a 2-variable model using flow
40 function (FFc/FF) and bulk density (RHOB/CBD) to explain the feed rate did not
41 significantly improve the feed rate explanation (Equation 4 and 5; R-square = 0.686 and
42 0.668, respectively; p=0.005). MA-25C and MA-50C continue to be outliers; the
43 models are overestimating their feed rates.
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50 Equation 4. $FR = -3.356686 + 9.272033 \cdot RHOB + 0.6087218 \cdot FFc$

51
52 Equation 5. $FR = -2.375537 + 8.7026812 \cdot CBD + 0.2537029 \cdot FF$
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3 From FT4 dynamic upwards testing, the SE parameter is more dependent on the
4 inter-particulate forces and less influenced by other factors, such as compressibility [23,
5 24]. SE provides a cohesion indication of the powder under low stress conditions [23,
6 24], such its behavior in the hopper. A weak linear relationship were observed between
7 SE and feed rate (R-square = 0.265, $p < 0.07$). MA-50C, MA-25C, MCC-C1000 and
8 MA-160C showed the highest values of SE, ranging from 13.10 to 10.73 mJ/g (Table
9 2). The high SE value observed for these samples is correlated to their poor flow
10 behavior into the hopper. The high bulk density of MA-160C has major impact on its
11 ability to be conveyed by screws (high feed rate), however its hopper flow (rat-holing
12 effect, Figure 2) is a bottleneck and needs to be overcome for its successful
13 performance.
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26 No simple linear correlation was observed between effective angle of internal
27 friction (ϕ_e and AIFe) or cohesion values and feed rate. In this investigation, the
28 analysis of powder conveying by screws was undertaken only when rat holing or
29 bridging were not present to minimise the impact of hopper design on the feed rate
30 values. The effective angle of internal friction and cohesion values were well correlated
31 to the hopper flow. For the powders with poor hopper flow MA-50C, MA-25C, MCC-
32 C1000, MA-160C and LAC, high values of effective angle of internal friction were
33 observed, and, except for MCC-C1000, all these powders showed high cohesion values
34 ($C_{0.6} > 0.15$ kPa) (Table 2). LAC showed an arching behaviour into the hopper which
35 reflects in its large RSD (19.92%) even with high feed rate value (4.04 g/10 sec).
36
37 Likewise, for powders with good flow into the hopper, such as MA-100SD, MA-200SD
38 and MCC-A200, low SE, effective angle of internal friction and cohesion values were
39 observed.
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3 Regarding to FT4 dynamic downwards testing, no simple linear correlation was
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5 observed between BFE or FRI and feed rate. However, a simple linear regression using
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7 the SI to explain the feed rate produced an R-square of 65.6% and $p=0.0008$. SI
8
9 measures the stability of flowability energy requirement during repeat testing in a
10
11 constant blade tip speed. A value close to 1 suggests a stable rheology.
12

13 For MA-160C, CaP, MA-25C and MA-50C, low levels of repeatability of BFE
14
15 during the downwards test indicated that they have a more unstable rheology than the
16
17 others. The others samples showed SI values closest to 1. Changes in density during
18
19 repeat testing may result these unstable rheology. For these powders, density has greater
20
21 impact on their feed rates. A possible explanation for the linear correlation between SI
22
23 and feed rate is that changes in density occur similarly into the conveyor casing, as
24
25 consequence of the stress applied by the screws to the powder.
26
27

28 The highest values of SI were observed for MA-160C and CaP (1.25 and 1.27,
29
30 respectively, Table 2), powders with the highest feed rates. The smallest value of SI
31
32 (0.82) was observed for MA-25C followed by MA-50C that showed the smallest feed
33
34 rates and the highest RSD, except for MCC-C1000. Differently from MCC-C1000 ($C_{0.6}$
35
36 = 0.08 kPa), MA-25C and MA-50C are more cohesive powders ($C_{0.6}$ = 0.36 kPa and
37
38 0.23, respectively). It suggests that flow does not propagate for these cohesive powders,
39
40 occurring only in the limited shearing zone with low transmissibility of forces from
41
42 particle to particle. The flow energies (BFE) required for these samples are larger than
43
44 for MCC-C1000. Cohesive powders contain considerable air within their particles. BFE
45
46 is measured during the downward blade movement and a possible explanation is that the
47
48 air is being lost during the test, increasing its density and the energy required to flow
49
50 [23]. In addition, MA-25C and MA-50C stick to the screw that becomes coated,
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52 reducing conveying capacity of the screws consequently powder feed rates [34].
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Hence, bulk density, SI and SE showed to be linearly correlated to the feed rate behaviour. A multiple linear regression model involving bulk density (CBD) and parameters from FT4 dynamic downwards testing (SI) and dynamic upwards testing (SE) showed a strong correlation between these variables and the feed rate for the samples investigated, explaining 95.7% of the variation ($p=0.001$; Equation 6). Mix MA:MCC is an outlier in this model (residual = 1.16). The homogeneity of this mixture was not verified and its properties may not be well represented.

Equation 6. $FR = -4.090258 + 3.9548423 \cdot CBD + 8.7281322 \cdot SI - 0.357974 \cdot SE$

4. Conclusion

This study was designed to investigate critical sources of variability in powder delivery using screw feeders. Pharmaceutical excipients with a wide range of properties were investigated. The effect of flow and density properties on conveying capacity was investigated using linear regression analysis.

MA-200SD, MA-100SD and MCC-A200 showed the best screw feeder performance combining hopper flow and conveying by screw analysis. The highest flow function and lowest specific energy, effective angle of internal friction and cohesion values were observed for these powders.

Although MA-160C and CaP showed the highest feed rate values (5.37 and 8.38 g/10 sec, respectively) due to their bulk densities, their hopper flow (rat-holing effect) is a bottleneck and needs to be overcome for their successful performance. According to their SI values, their resistance to forced flow decreases favouring the conveying capacity of the screws.

MA-25C, MA-50C and MCC-C1000 showed the smallest feed rate values, poor repeatability, poor linearity and poor stability. The highest values of SE and effective angle of internal friction were observed for these samples. Except for MCC-C1000,

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2
3 these powders showed high cohesion values. High values of effective angle of internal
4
5 friction and cohesion were also observed for LAC. Although LAC showed high feed
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7 rate value (4.04 g/10 sec), its RSD was large (19.92%) due to an arching behaviour into
8
9 the hopper.

10
11 MCC-C101, MCC-A101 and MCC-A102 showed critical hopper flow and poor
12
13 stability ($3.0 < \text{RSD} < 5.0\%$), otherwise they demonstrate good linearity. Mix MA:MCC
14
15 showed consistent feed performance ($\text{RSD} < 3.0\%$) and good linearity.

16
17 A multivariable model involving bulk density (CBD) and parameters from FT4
18
19 dynamic downwards testing (SI) and dynamic upwards testing (SE) explained 95.7% of
20
21 excipients feed rates ($p < 0.001$). The study gathers valuable information about the screw
22
23 feeder performance and input materials properties that can help process understanding
24
25 and QbD-based development of solid dosages forms in continuous process lines. We
26
27 carried out a carefully investigation to not neglect the proportionality between variables
28
29 and feed rate, avoiding an over-fit model. The multivariable model presented correlates
30
31 the flow and density properties to the feed rate of the pharmaceutical excipients
32
33 investigated, do not covering all necessary properties to be responsive/predictive for all
34
35 types of powders. Therefore, while the findings are useful, there is a need for more
36
37 studies, using more samples and exploring more materials properties to build a
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39 predictive model.
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46 Abbreviations: ϕ_e and AIFe, effective angle of internal friction; BD, bulk density
47
48 obtained from cylinder method; BFE, Basic Flowability Energy; CBD, Conditioned
49
50 Bulk Density obtained from FT4 analysis; CI, compressibility index or Carr index; FF,
51
52 flowability index obtained from FT4 shear cell analysis; FFc, flowability index obtained
53
54 from Schulze shear cell analysis; FR, feed rate; FRI, Flow Rate Index; RHOB, bulk
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3 density obtained from Schulze shear cell analysis; SE, Specific Energy; SI, Stability
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5 Index.

6
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List of Tables

Table 1. List of the pharmaceutical excipients used, including their abbreviation (Abb.) and supplier information.

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Figure 4. Feed rate linearity based on the average of 60 consecutive samples of 10 seconds at different screw speeds (25, 50, 75 and 100% of full speed) and intermediate range of hopper levels (50-75%) for mannitol (a), microcrystalline cellulose (b) and mixture, calcium phosphate and lactose (c).

List of Supplemental material

S1. Particle size distribution (PSD) by volume (V10, V50 and V90%), moisture content (MC) and particle shape (habit) for each grade of mannitol.

S2. Optical microscopy images of the five different grades of Mannitol.

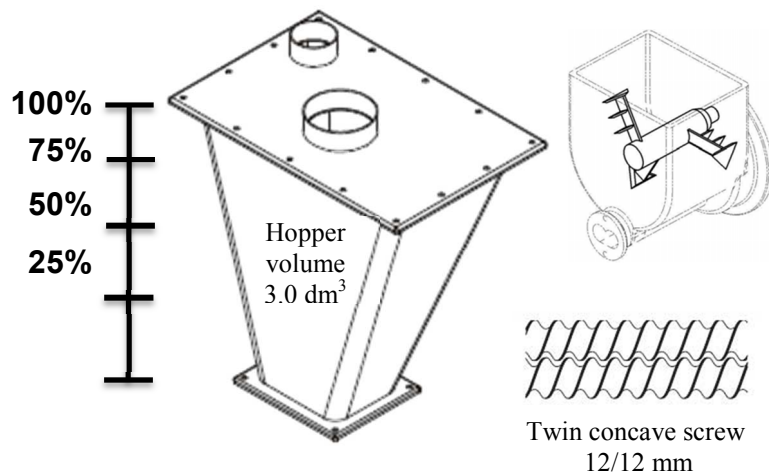


Figure 1. Hopper (powder levels 100, 75, 50 or 25%), stirring agitator and screw design used in the experiments.

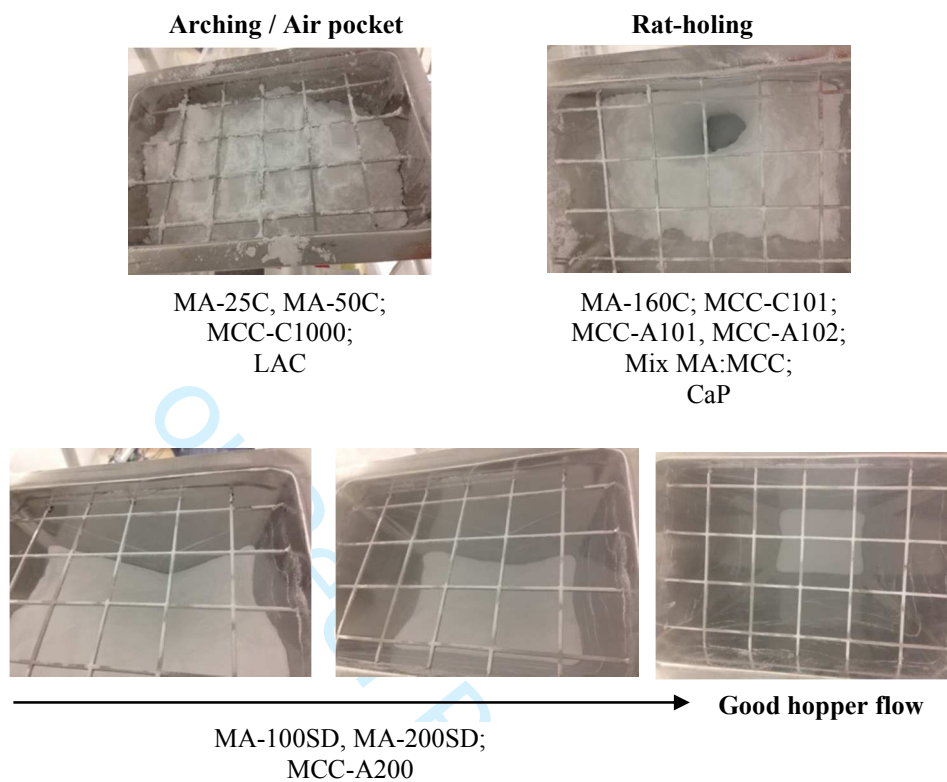


Figure 2. Hopper pictures representing the flow of the pharmaceutical excipients evaluated.

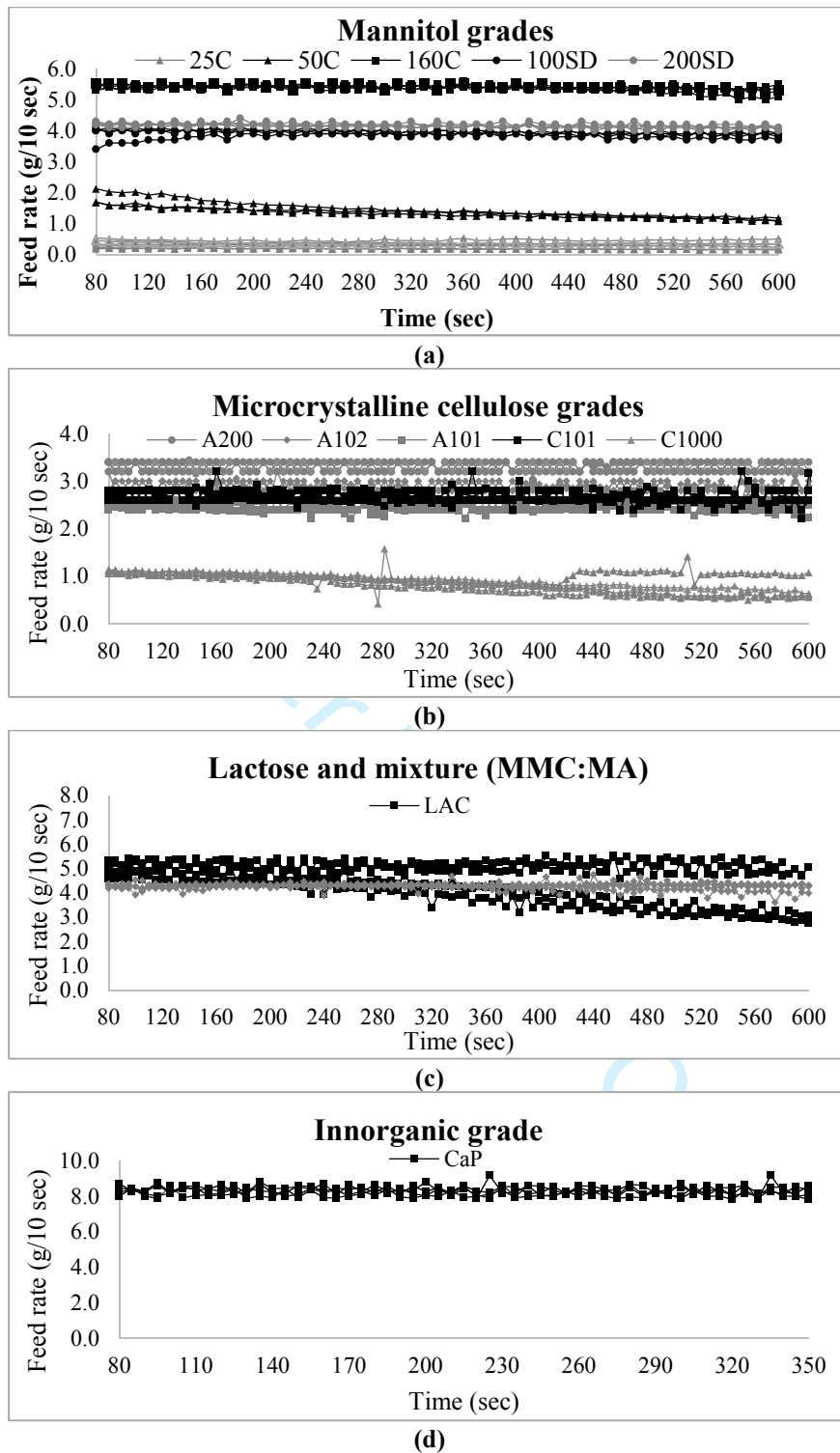


Figure 3. Feed rate based on the 60 consecutive samples of 10 seconds at 50% of full screw in different hopper levels (100, 75, 50 or 25%) for mannitol (a), microcrystalline cellulose (b), mixture and lactose (c) and calcium phosphate (d).

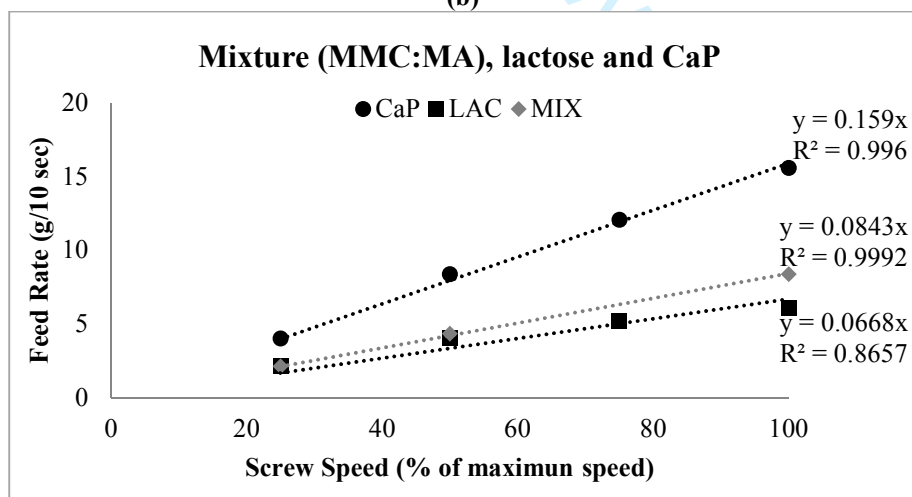
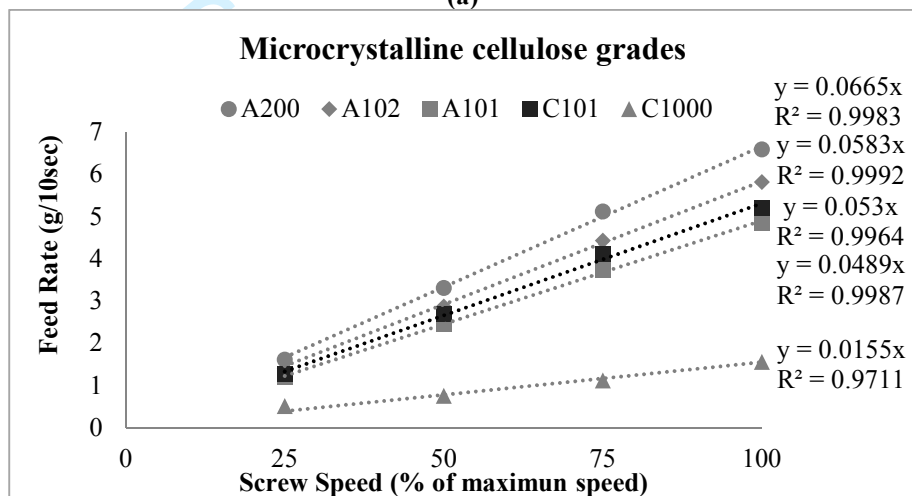
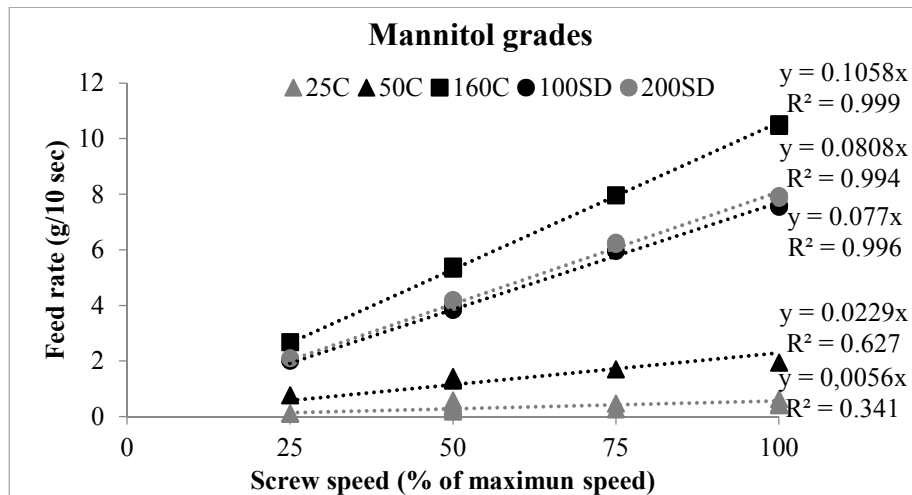


Figure 4. Feed rate linearity based on the average of 60 consecutive samples of 10 seconds at different screw speeds (25, 50, 75 and 100% of full speed) and intermediate range of hopper levels (50-75%) for mannitol (a), microcrystalline cellulose (b) and mixture, calcium phosphate and lactose (c).

Table 1. List of the pharmaceutical excipients used, including their abbreviation (Abb.) and supplier information.






	Pharmaceutical excipients	Abb.	Supplier information	
			Nominal PS (μm)	Powder type
Mannitol (MA)	Pearlitol [®] 25C	MA-25C	25	crystalline; sieved/ground
	Pearlitol [®] 50C	MA-50C	50	crystalline; sieved/ground
	Pearlitol [®] 160C	MA-160C	160	crystalline
	Pearlitol [®] 100SD	MA-100SD	100	granular; spray dried
	Pearlitol [®] 200SD	MA-200SD	180	granular; spray dried
Microcrystalline cellulose (MCC)	Ceolus [®] KG1000	MCC-C1000	50	crystalline; sieved/ground
	Ceolus [®] PH 101	MCC-C101	50	crystalline; sieved/ground
	Avicel [®] PH 101	MCC-A101	50	crystalline; sieved/ground
	Avicel [®] PH102	MCC-A102	100	crystalline; sieved/ground
	Avicel [®] PH 200	MCC-A200	180	crystalline; sieved/ground
Mixture	Pearlitol [®] 160C:Avicel [®] PH101 (2:1)	Mix MA:MCC	N/A*	N/A*
Inorganic	Calcium Phosphate Emcompress [®] Anhydrous Powder	CaP	<50	crystalline
Lactose	Lactochem [®]	LAC	100	crystalline/amorphous; milled and sieved

* N/A: not applicable

Table 2. Summary of powder properties and feed rate average (\bar{X}), standard deviation (SD) and relative standard deviation (RSD) in different hopper levels (100, 75, 50 or 25%) for each material at 50% of full screw speed.

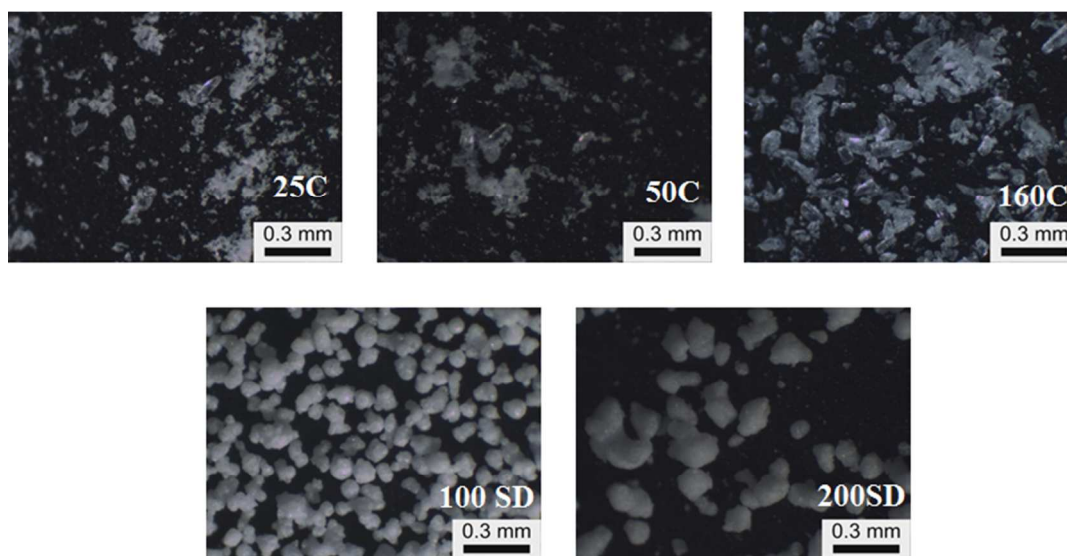
Pharmaceutical excipients	Density (g/cm ³)					Powder flow							Screw feeder				
	Cylinder method		Schulze	FT4	Cylinder method	Schulze		FT4					Feed rate (g/10 sec)				
	BD	TD	RHOB	CBD	CI (%)	FFc	ϕ_c (°)	FF	AIFe (°)	FRI	SE (mJ/g)	BFE (mJ)	SI	C _{0.6} (kPa)	\bar{X}	RSD (%)	
MA	MA-25C	0.430	0.770	0.527	0.540	44	1.38	61.25	1.33	63.60	1.66	13.05	1228.50	0.82	0.37	0.31	47.43
	MA-50C	0.535	0.855	0.622	0.624	38	2.18	49.95	1.86	56.50	1.43	13.10	1528.00	0.91	0.23	1.35	15.89
	MA-160C	0.590	0.865	0.657	0.673	32	2.38	50.00	2.79	51.35	1.18	10.73	2385.67	1.25	0.14	5.37	2.21
	MA-100SD	0.445	0.560	0.486	0.486	21	4.28	37.65	8.39	36.50	1.00	5.48	1308.00	0.95	0.03	3.90	2.84
	MA-200SD	0.500	0.610	0.528	0.549	18	4.94	37.20	11.50	34.55	1.06	5.73	1533.50	0.93	0.02	4.16	1.97
MCC	MCC-C1000	0.132	0.282	0.192	0.163	53	2.75	51.50	4.73	50.75	1.58	12.40	802.00	0.96	0.08	0.36	25.87
	MCC-C101	0.317	0.476	0.370	0.357	33	3.10	44.00	5.50	38.80	1.44	9.14	1184.00	0.95	0.06	2.70	4.58
	MCC-A101	0.290	0.442	0.339	0.328	34	3.05	46.00	4.31	38.80	1.48	9.41	1234.50	0.99	0.08	2.46	4.03
	MCC-A102	0.341	0.479	0.366	0.362	29	4.20	44.50	8.49	41.45	1.25	7.52	1616.00	0.98	0.04	2.87	3.19
	MCC-A200	0.377	0.457	0.377	0.387	18	6.73	40.00	8.63	35.75	1.05	5.55	1180.50	0.95	0.04	3.31	2.96
Mix MA:MCC	0.463	0.713	0.519	0.511	40	2.90	45.00	3.47	45.70	1.34	8.03	1625.00	0.93	0.95	4.32	1.94	
CaP	0.883	1.503	1.011	1.025	41	2.05	47.00	2.57	42.30	2.35	8.16	871.50	1.27	0.13	8.38	2.19	
LAC	0.602	1.010	0.707	0.680	35	1.90	48.50	2.13	49.05	1.58	9.24	1336.50	1.01	0.17	4.04	19.92	

S1. Particle size distribution* (PSD) by volume (V10, V50 and V90%), moisture content** (MC) and particle shape (habit) for each grade of mannitol.

Mannitol grades	PSD μm V(10%)	PSD μm V(50%)	PSD μm V(90%)	MC (%w/w)	Habit
MA-25C	20	41	280	0.041	elongated 
MA-50C	28	63	153	0.035	elongated 
MA-160C	43	121	299	0.044	elongated 
MA-100SD	72	111	158	0.020	spherical 
MA-200SD	106	173	273	0.077	spherical 

**Particles' shape and size analysis.* A SympaTec image analysis sensor (QICPIC/R2, SympaTec, Germany) was equipped with the RODOS/L dry dispersing unit (0.5 Bar, 50% feed rate gap 2.0 mm) to evaluate particle size and shape (measuring range M6: 5-1705 μm) of MA samples. Particle size data was evaluated using size parameter EQPC (Diameter of a Circle of Equal Projection Area) and all distributions are by volume. Samples were analysed in triplicate.

***Moisture content.* The samples were measured for moisture content by using a highly sensitive balance in thermogravimetric analysis (TGA) mode. For TGA, samples (10 mg) were heated at 10 $^{\circ}\text{C}/\text{min}$ up to 350 $^{\circ}\text{C}$ in a Q500 TA instrument (USA). Moisture content (%) was determined by the stable weight loss (%) at a temperature around 150 $^{\circ}\text{C}$.



S2. Optical microscopy images of the five different grades of Mannitol.