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Development and Evaluation of a Micro-dynamic Method for Characterising Powder Flowability at Low Consolidation Stresses Using Small Sample Volumes

by

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ACADEMIC DISSERTATION

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Abstract

Powder flow behaviour during filling processes in tablet presses remains insufficiently understood and characterised. The challenge lies in reproducing the processing conditions during the separation of the dosage unit or small volumes from the powder mass. Different physical mechanisms govern flowability at this scale, and particle-level flow behaviour dominates over bulk (macroscopic) behaviour. Current knowledge on filling performance largely originates from the analysis of bulk powders and, in practice, is limited to iterative testing of the final product. Building quality into the development process can drastically reduce formulation and scale-up time and costs. The aim of this project was to develop and evaluate a novel flow testing method for the characterisation and rationalisation of material performance in powder filling operations at the earliest stages of drug research and development (R&D).

Miniaturisation of the pharmacopoeial measuring principle of 'powder flow through an orifice' enabled small-scale measurements (< 200 mg) within a machine vision-based testing setup. The relevance, sensitivity and practicality of the system determined the quality of the novel method. Commonly used filling geometries in early formulation development –ranging from gravity feeding of small tablets to multi-paddle forced feeding for standard tablets– were evaluated and systematically compared with state-of-the-art testing methods. Primary particle properties, surface modification techniques and environmental conditions were considered in evaluating their effects on flowability. Understanding the impact of testing conditions and powder characteristics laid the theoretical foundation, and potential applications throughout the drug development process were explored.

Flowability of powder volumes close to the dosage unit (i.e., micro-dynamic flowability) strongly correlated with the filling performance in the R&D press machine settings investigated. Cohesive forces and associated powder agglomeration largely governed flow behaviour of small powder volumes and determined the uniformity of dosage units. Bulk flow analysis hindered accurate measurements in these very low stress environments: frictional contact forces dictated material behaviour and did not match in-process performance. Digital imaging proved highly versatile for visualising and interpreting results. Advanced agglomerate detection captured the mechanisms of flow enhancement and cohesion governing small-scale filling processes and cannot be elucidated from numerical data alone.

This more fundamental (particle-level) understanding of flowability showed remarkable sensitivity for material differentiation compared with measurements at higher consolidation stresses. Micro-dynamic flow studies revealed substantial differences in product attributes and technological processability that were not detected in bulk measurements. The increased sensitivity (and visualisation) to cohesive forces facilitated the achievement of robust target flowability during formulation development and was instrumental in process optimisation and validation strategies later in the scale-up. In addition, integrating small-scale measurements into powder flow analysis addressed the challenge of characterising active pharmaceutical ingredients (APIs) at the pre-formulation stage.

In summary, our findings demonstrate that the miniaturised flow test characterises dynamic flow properties at very low stresses, as observed in R&D tablet presses. This has far-reaching consequences for the manufacture of solid dosage forms such as tablets, which are now restricted to indirect, sample-consuming flow tests and lengthy compression trials. Using less than 200 mg per measurement, micro-dynamic flow studies offer a cost-effective sustainable solution to identify potential manufacturing issues from the beginning of the formulation work.

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Nothing but respect to Finland, the locals, and its forests, where silence teaches the deepest truths, your truths.

'There is no favourable wind for the sailor who doesn't know where to go.'
—Lucius Annaeus Seneca

A mis queridos padres.

List of abbreviations

AG	Agglomeration Ratio
AIF	Angle of Internal Friction
AG	Agglomerate Ratio
AI	Artificial Intelligence
AIF	Angle of Internal Friction
AM	Additive Manufacturing
ANOVA	Analysis of Variance
API	Active Pharmaceutical Ingredient
APAP	Acetaminophen
AOR	Angle of Repose
ASTM	American Society for Testing and Materials
BFE	Basic Flowability Energy
Bo	Granular Bond Number
C	Cohesion
CBD	Conditioned Bulk Density
CBER	Centre for Biologics Evaluation and Research (FDA)
CDER	Centre for Drug Evaluation and Research (FDA)
CI	Carr's Index
CM	Continuous Manufacturing
CSD	Colloidal Silicon Dioxide
CQA	Critical Quality Attribute
CSD	Colloidal Silicon Dioxide
DC	Direct Compression
DEM	Discrete Element Method
DPIs	Dry Powders for Inhalation
Dv10	Volume Diameter 10%
Dv50	Volume Diameter 50%
Dv90	Volume Diameter 90%
ECD	Equivalent circular diameter
EMA	European Medicines Agency
FDA	Food and Drug Administration
FFc	Flow Function Coefficient
FRI	Flow Rate Index
HR	Hausner Ratio
ICH	International Council for Harmonisation
IR	Immediate Release
LOD	Loss on Drying / Limit of Detection

L80M	Coarse Lactose Monohydrate (Sieved)
L200M	Milled Lactose Monohydrate
MCC	Microcrystalline Cellulose
MCS	Major Consolidation Stress
MgSt	Magnesium Stearate
MCS	Major Consolidation Stress
MFI	Micro-dynamic Flowability Index
ML	Machine Learning
MPIF	Metal Powder Industries Federation
NCE	New Chemical Entity
OSD	Oral Solid Dosage Form
PD	Packing Density
Ph. Eur.	European Pharmacopoeia
PSD	Particle Size Distribution
PTDS	Product Temperature During Spraying
RSD	Relative Standard Deviation
R&D	Research and Development
SEM	Scanning Electron Microscopy
SI	Stability Index
StDev	Standard Deviation
USP	United States Pharmacopoeia
UYS	Unconfined Yield Strength
QbD	Quality by Design
QC	Quality Control
vdW	Van der Waals

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List of original publications

This thesis is based on the following publications, which are referred to in the text by their respective roman numerals (**I-IV**).

I. Blanco, D., Antikainen, O., Räikkönen, H., Mah, P. T., Healy, A. M., Juppo, A. M., & Yliruusi, J. (2020). Image-based characterisation of powder flow to predict the success of pharmaceutical minitablet manufacturing. *International Journal of Pharmaceutics*, 581, 119280. https://doi.org/10.1016/j.ijpharm.2020.119280

II. Blanco, D., Antikainen, O., Räikkönen, H., Yliruusi, J., & Juppo, A. M. (2021). Effect of colloidal silicon dioxide and moisture on powder flow properties: Predicting in-process performance using image-based analysis. *International Journal of Pharmaceutics*, 597, 120344. https://doi.org/10.1016/j.ijpharm.2021.120344

III. Blanco, D., Pätzmann, N., & García-Triñanes, P. (2025). Microdynamic flowability for early API characterisation: A case study on Palbociclib. *Pharmaceutical Science Advances, 100, 100069*. https://doi.org/10.1016/j.pscia.2025.100069.

IV. Blanco, D., García-Triñanes, P. & Juppo, A. M. (Submitted). Microdynamic flowability for optimisation and validation strategies during scale-up: A case study on fluidised-bed granulation.

List of additional publications:

Additional publications that are not included in the experimental part of this thesis are listed below.

Blanco, D., Pentikäinen, H., Antikainen, O., & Juppo, A. M. (2023). Behaviour of magnesium stearate at particle–particle interfaces: Microdynamic flowability to monitor distribution in powders. *Powder Technology*, 419, 118337. https://doi.org/10.1016/j.powtec.2023.118337

Blanco Fernández, D. (2024). Insertion, measuring cuvette, device and method for powder characterization (WO 2024/038147 A1). *World Intellectual Property Organization*. https://patents.google.com/patent/WO2024038147A1/en

1 · Introduction

Despite significant advances in powder flow research over the last few decades, the accurate assessment of the flowability of small powder volumes remains a persistent challenge in powder processing industries. Powders do not behave in the same way in bulk volumes as they do when separated from the powder mass [Harnby et al., 1987; Prescott & Barnum, 2000; Schulze, 2008]. Many industries, including pharmaceuticals, chemicals, additive manufacturing (AM) and the nuclear sector, require a deeper understanding and control of flowability in small powder volumes to ensure product consistency and quality, optimise manufacturing processes and minimise waste. Nevertheless, while powder flow analysis has primarily focused on bulk powders, an important aspect –powder flow in small volumes within confined spaces– has received comparatively less attention.

The filling or dispensing of self-metered doses involve the consistent and precise extraction of a small powder volume at an acceptable processing speed into very small containers, such as tablet dies, capsules and other vessels. Regardless of the manufacturing route, successful processing and final product quality depend on filling performance [Natoli et al., 2017; Van Snick et al., 2018]. In pharmaceuticals, such as oral solid dosage forms (OSDs), require consistent filling to ensure the uniformity of dosage units and compliance with stringent acceptance criteria [Ph. Eur. 2.9.40; USP <905>]. To achieve this, upstream processing units, such as powder blending and granulation, are specifically designed to improve powder flowability and ensure efficient filling. Downstream processes, such as tablet compression and encapsulation, fundamentally depend on the success of the filling stage to maintain critical quality attributes (CQAs), including content uniformity, mass variation, disintegration, and dissolution of dosage units.

Despite extensive research on powder filling, no consensus has been reached regarding suitable tests to characterise the flow behaviour inside the tablet press. Flow testing methods are limited by the data relevance to the processing conditions [Søgaard et al., 2014, Stavrou et al., 2020]. Early assessment of filling performance remains inaccessible during formulation development and scale-up. End-product testing remains the quality benchmark, with limited understanding of the process and considerable time as well as resource consumption [FDA/CDER/CBER, 2011; Cholayudth, 2016]. As a result, formulators and manufacturers must rely on iterative testing of the final product and/or flow tests of limited relevance to the actual process to achieve target flowability.

Two aspects of the filling process are highly challenging in powder flow analysis: (i) very low stresses and (ii) high strain rates. Few recently developed techniques can measure flowability in low stress environments, and even fewer do so under dynamic conditions [Ghadiri et al., 2020]. The measuring principle and/or design of available

bulk flow testers hinders measurements at the very low stress range observed in the tablet press [Søgaard et al., 2017; Swize et al., 2019; Stavrou et al., 2020]. During filling operations, particle velocities are high and/or involve very loosely packed or consolidated states; physical contacts are short-lived, and the small contact areas that exist between particles are insufficient to transmit solid pressure, that is, the normal stress within the powder bed from particle weight or applied loads. Under such low stresses, flowability differs significantly from that of a bulk powder bed, where particles remain in continuous contact.

Funnel discharge techniques involve a similar mechanism to the flow of powder into a die cavity and remain the preferred choice in industry for characterising and optimising filling processes [Ph. Eur. 2.9.16; Ph. Eur. 2.9.36; USP <1174>; ASTM B213-17]. However, the bulk powder bed does not replicate the complex flow behaviour of small powder volumes, is impractical for small-scale R&D due to material constraints, and is only suitable for relatively free-flowing powders. The present thesis reports initial work on a novel in-house device based on the miniaturisation of the pharmacopoeial test 'powder flow through an orifice'. The method proved to be highly versatile in addressing the aforementioned limitations by capturing dynamic particle interactions in a small powder volume without introducing additional sources of consolidation stress.

2 · Literature review

This section presents the fundamental concepts and the most relevant descriptors of flow behaviour in bulk solids. It begins with an introduction to the fundamentals of classical mechanics relevant to the applied external forces acting on the novel measuring system. The macroscopic flow response to external forces and the role of microscopic attributes, such as interparticle forces, are then reviewed under the key concepts of bulk friction and cohesion. This section also relates flow behaviour in bulk solids to operating conditions, such as shear strain rate and very low consolidation stresses. Subsequently, the main particle properties and environmental factors affecting bulk friction and cohesion are described. These include surface modification techniques of relevance to this thesis. An overview of the role of powder flowability in drug development is provided. Finally, the state-of-the-art in powder flow analysis is reviewed and evaluated.

2.1 Principles of Classical Mechanics

2.1.1 Kinematics

Kinematics describes the motion of a system (i.e., the velocity and acceleration) without considering the applied forces [Halliday et al., 2023]. In this section, a set of useful equations for kinematic relationships under constant acceleration ($\vec{a} = a = constant$) are presented. A body is in uniformly accelerated rectilinear motion when its trajectory is a straight line, and its acceleration is constant and non-zero. This implies that the velocity increases or decreases its magnitude uniformly. For motions in which acceleration changes drastically, such as accelerating to top speed and then braking to a stop, motion can be considered in separate parts, each having its own constant acceleration. The standard formulas for calculating the final velocity and position of an object experiencing constant acceleration are written as

$$v = v_0 + at \tag{1}$$

$$x = x_0 + v_0 t + \frac{1}{2} a t^2 \tag{2}$$

where v_0 and v are the initial and final velocities of the object, x and x_0 are the initial and final positions of the object, a is the acceleration, and t is the time interval (Δt).

2.1.2 Dynamics

Dynamics involves the study of the forces that cause motion in systems (i.e., how forces affect kinematics) [Halliday et al., 2023]. The relationship between a force and the acceleration it produces is described in the laws of motion stated by Isaac Newton (1642–1727). Newton's second law is closely connected to his first law and is widely used to determine outcomes in situations involving force. It provides the mathematical relationship between force and changes in motion, specifically changes in velocity. Since a change in velocity implies acceleration, Newton's first law says that a net external force acting on a system causes a change in motion; thus, a net external force causes non-zero acceleration. Only external forces affect the motion of a system according to this law and only those that originate outside the system. Internal forces are ignored to formulate Newton's second law and are later discussed as the key concepts of bulk friction and cohesion (*Section 2.2.1 "Bulk friction and cohesion"*).

For the kinematic relationship described above, a reasonable assumption is that acceleration would be directly proportional to and in the same direction as the net external force. Additionally, acceleration is inversely proportional to the mass of the system. This means that the greater the mass (or inertia), the smaller the acceleration produced by a given force. Combining these two proportionalities leads to Newton's second law of motion. In equation form, Newton's second law is

$$\vec{a} = \frac{\vec{F}_{net}}{m} \tag{3}$$

where $\vec{a}$ is the acceleration, $\vec{F}_{net}$ is the net force, and m is the mass. When considering only the magnitudes of force and acceleration, the equation can be expressed in a simpler scalar form as

$$F_{net} = ma \tag{4}$$

In the preceding example, only the net force is shown for simplicity. However, another external force acts on a bulk solid. The particle weight, $\vec{w}$, represents the net gravitational force acting on an object of mass m. Since weight has both magnitude and direction, it can be expressed as a vector, where the direction is downward, aligned with gravity. Consequently, weight is a downward force. In response, the ground applies an upward force on the particle, known as the normal force $\vec{N}$, on the particle. This leads to Newton's third law of motion: whenever one body exerts a force on a second body, the first body experiences a force that is equal in magnitude and opposite in direction. These forces are balanced on a horizontal surface ($\vec{w} = -\vec{N}$), and do not produce vertical acceleration in the measuring system.

2.2 Flow behaviour of bulk solids

The flow behaviour of bulk or particulate solids arises from the combined forces acting on them and their spatial distribution. This includes external forces (particle weight and applied forces) and internal forces (frictional contact and interparticle forces). For simplicity, the classical approach taken in powder technology is to consider the bulk solid as a continuum [Schulze, 2008]. Rather than considering forces acting on individual particles, the forces or stresses acting on boundary areas of a bulk solid system are considered, similar to the treatment in fluid mechanics. In bulk solid flow, where stresses and deformations are usually investigated, understanding the differences between normal force and normal stress is essential. The normal force, $\vec{N}$, is the resultant perpendicular component of an external force acting in arbitrary directions when a bulk solid is in contact with a surface. The load on the bulk solid is described by computing stresses based on the applied forces. Normal stress, σ, defines how a normal force is distributed in terms of force per unit area, A, as ($\sigma = \frac{\vec{N}}{A}$). Thus, a normal stress provides information on how forces are distributed across a cross-sectional area or cutting plane of a bulk solid.

2.2.1 Bulk friction and cohesion

2.2.1.1 The Mohr-Coulomb criterion

Friction or shear is a force that opposes the relative motion between systems in contact. In bulk solids, this resistance arises from the particles interacting with their surroundings. Depending on the contact surfaces and the collective forces acting on the bulk solid, three scenarios can be differentiated: shear stresses (i) for non-cohesive bulk solids (ii) for cohesive bulk solids and (iii) at the wall. The flow behaviour of a *non-cohesive bulk solid* is frictional when the particle weights or applied forces are much greater than interparticle forces, and the particles undergo no or negligible deformation [Schulze, 2008]. The shear force must reach a given threshold to start and maintain flow, also known as the failure criterion, which is proportional to the normal force. Based on the Coulomb law of friction between two solids, Bowden and Tabor (2001) described the friction of particulate solid systems. Considering the area of the shear plane, the correlation between the shear stress, τ, and the normal stress, σ, is given as

$$\tau = \mu\sigma \tag{5}$$

where μ is the apparent coefficient of friction of the material, which depends not only on the friction coefficient between solid particles, but also on their morphology and packing state. Loose and dense packing states differ in the density (or number)

and orientation of the contacts between particles [Santomaso et al., 2003; Langroudi et al., 2010]. In this context, a bulk solid refers to a particulate system consisting of solid particles that occupy only a fraction of the total volume (solid fraction). The remaining space between particles is known as porosity, which arises from the particle´s physical properties and their spatial distribution within the bulk solid. The two parameters are inversely proportional: a higher solid fraction corresponds to a lower porosity, and vice versa. Each of them can be used to describe the packing state, which reflects how densely the particles are arranged.

When two solid objects are in contact and remain stationary relative to each other, the friction between them is referred to as *static friction*. Conversely, when the objects are in contact and move relative to one another, the friction is known as *kinetic friction*. In static situations, the friction at the beginning of flow, μ_s, depends on the duration of the static stage until failure. In dynamic conditions, the dynamic friction coefficient, μ_d, typically has a lower value than μ_s, and it depends on the shear rate (or shear velocity). A more detailed description of the different flow regimes can be found in *Section 2.2.2.1 "Shear strain rate dependency"*. For *cohesive bulk solids*, when attractive interparticle forces are present, these must be overcome to initiate flow. The strength of the bulk solid increases, leading Coulomb to propose the criterion for failure as Equation 6

$$\tau = \mu\sigma + c \tag{6}$$

$$\tau_w = \mu\sigma_w + a_w \tag{7}$$

where the additional term, c, is the cohesion, and has the dimensions of stress (tensile strength, σ_t). The link between cohesion and interparticle forces -*the Rumpf relation*- is described in Equation 8. Similarly, the *failure criterion at a wall* has been described as Equation 7; where τ_w *and* σ_w are the shear and normal stresses exerted on the wall, μ_w, is the wall-bulk solid coefficient of friction, and a_w is the adhesion, analogous to cohesion in bulk solids, which depends on both the wall and particle properties.

The stress distribution in a bulk solid can be determined from the normal stress, σ, and shear stress, τ, acting on all cutting planes and for every orientation or angle, α. When all pairs of values are calculated and plotted in a σ,τ-diagram a circle is formed, also known as the Mohr circle stress theory. For a simple description, the situation of plane deformation in two dimensions is shown in *Figure 1*. The principal (normal) stresses acting in a bulk solid are defined from the intersections of the Mohr circle with the σ-axis, where σ_1 is the larger or major principal stress and σ_2 is the smaller or minor principal stress. Depending on the magnitude of the normal stresses, σ_1 and σ_2, different scenarios can be described and certain parameters relevant to flow behaviour in bulk solids can be outlined. For example, in unconfined conditions, when $\sigma_2 = 0$, the

Mohr circle describes the stresses at the free surface. The major principal stress then represents the unconfined yield strength UYS, or maximum stress before failure. A more detailed explanation of the failure parameters and criteria can be found elsewhere [Schulze, 2008].

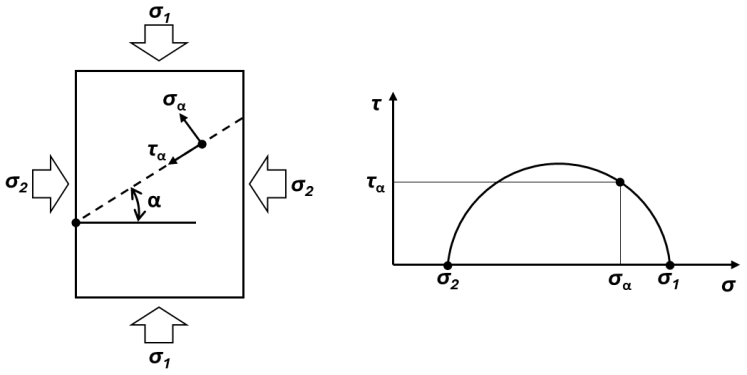


Figure 1. The Mohr circle theory for a plane deformation in two dimensions. *Left*: element submitted to the two principal (normal) stresses, σ_1 and σ_2. Dashed line represents the face inclined by the angle α from the direction where σ_1 is normal. The stress vector on the face α is separated into the tangential and normal components τ and σ. *Right*: stress plane. The shear stress on a face is plotted versus the normal stress for all the cutting planes and yields the Mohr circle. *Adapted from Nedderman (1992)*.

Schulze (2008) observed that for simple practical applications, such as flowability tests, characterising a two-dimensional stress state by two principal stresses is often too challenging; consequently, only the major principal stress is usually described. The greatest of all normal stresses acting in different directions within a bulk solid is responsible for the actual condition of the bulk solid. Thus, the major principal stress corresponds to the consolidation stress during a flow test [Leung et al., 2017]. Throughout this thesis, the term 'consolidation stress' and similar terms are used to refer to the packing state of a powder sample under an applied load. The tapping studies (or compressibility response) are a pertinent example of the impact of applied stress on the packing state and are typically used in powder processing industries to characterise the flow behaviour in bulk solids (*Section 2.5.1.2.1 "Pharmacopoeial tests"*)

In the pharmaceutical industry, the determination of the flow function (or flow function coefficient, FFc) remains the gold standard for powder flow characterisation [Hou & Sun, 2008; Wang, Y. et al., 2016]. The flow function coefficient can be defined as the ratio of the major principal stress to the unconfined yield strength of a pre-consolidated powder bed ($FF_c = \frac{\sigma_1}{\sigma_c}$). Thus, it accounts for the cohesive strength of a bulk solid under a given consolidation stress. Although the flow function is an intrinsic

material property, it does not consider the specific equipment or process and cannot be generalised to all operations or manufacturing scales [Wang et al., 2016; Leung et al., 2017].

2.2.1.2 Interparticle forces

Interparticle forces include the interactions between particles –cohesion– and between the powder and processing equipment –adhesion–. Regardless of the nature of the contact surfaces, there are three main forces in a dry powder system: van der Waals, electrostatic and capillary forces (or liquid bridges). Their magnitude depends on their physical origin. While electrostatic or capillary forces can affect powder flow behaviour, the van der Waal force (vdW) is recognised as the most significant cohesive force for dry and uncharged powders, as well as when dealing with particles of small size [Podczeck et al., 1997; Takeuchi, 2006; Schulze, 2008; Capece et al., 2016]. In this thesis, mechanical interlocking, understood as the entanglement or geometrical interconnection of irregularly shaped particles, is not classified as an interparticle force, but rather as a physical mechanism that restricts particle mobility. While interparticle forces originate from physicochemical interactions, mechanical interlocking results from the morphological characteristics of the particles and their spatial arrangement. Given its distinct underlying mechanism and implications, it is addressed separately in *Section 2.3.1*, which discusses the effect of primary particle properties.

The relative cohesivity of a powder is generally described by the granular bond number (Bo), which is the ratio of interparticle force (adhesive or cohesive) to the particle weight [Castellanos, 2005]. When the vdW force becomes significant and overcomes the particle weight and/or external force, powder cohesion and agglomeration occur, as well as adhesion to the processing equipment. This is the reason why small particles, such as fine dust, adhere to a vertical wall while larger particles, such as salt grains, cannot. A more detailed description of the influence of particle properties on the granular bond number is given in *Section 2.3.1 "Primary particle properties and moisture"*. H. Rumpf (1962) proposed a mathematical model to estimate the impact of interparticle forces on bulk cohesion [Rumpf, 2012]. The tensile strength, σ_t, analogous to bulk cohesion, c, in Equation 6, is estimated as

$$\sigma_t = F/S \tag{8}$$

where F is the force exerted and S is the area across which the material separates during failure, i.e., the contact surface between two opposing particle assemblies. The force exerted is approximated by $F = nfk/2$, where n is the number of particles facing each other on the surface, f is the sum of all forces, and k is the mean number of contacts per particle, also known as the coordination number. Higher packing states

(or consolidation stresses) reduce the area of separation surface, as particles are packed more tightly together, leaving fewer gaps and contact points to break apart, thereby increasing the influence of interparticle forces on the shear stress. Theoretical frameworks and analytical descriptions on vdW forces have been published by Tomaš (2007) and Israelachvili (2011), on electrostatic forces by Peart (2001) and Naik et al. (2016), and on capillary forces by Schubert (1984) and Rabinovich et al. (2005).

Van der Waals (vdW) forces

Attributed to the non-ideal behaviour of gases in 1873 by Van der Waals, these forces were described as permanent or induced dipoles that act over a short range and, unlike the other cohesive forces, are always present. Hamaker (1937) introduced a microscopic approach to describe vdW forces, F_{VW}, by representing the attraction energy between two solid particles. Later, Lifshitz (1956) developed a macroscopic approach to incorporate the influence of surrounding particles, assuming bodies as a continuous medium. For instance, the interaction between a spherical particle and a semi-finite body can be estimated using the following equation [Israelachvili, 2011]

$$F_{vw} = \frac{A_H R}{12 d^2} \tag{9}$$

where A_H is the Hamaker constant, which is a material property and can be calculated based on the surface energy, R is the particle radius, and d is the separation distance between the two bodies. The van der Waals force is proportional to the separation between the centres of mass and is therefore highly dependent on the particle size and, to some extent, on the particle shape and surface roughness. These forces are very large at small separation distances, such as contact surfaces, but they decrease rapidly with increasing separation. Larger and more spherical particles, as well as the presence of asperities on the surface, increase the separation distance [Forsyth et al., 2002; Takeuchi, 2006; Israelachvili, 2011]. In this context, gravitational forces decrease more rapidly with decreasing particle size than vdW forces, as they have been described as proportional to the cube of the particle diameter. A more detailed description of the effect of particle size is given in *Section 2.3.1 "Primary particle properties and moisture"*.

Capillary forces or liquid bridges

Capillary forces arise from the condensation of moisture on the surface of two particles in contact. The magnitude depends on the relative humidity (RH), the separation distance between surfaces and the material properties. The hygroscopicity of a material determines the spatial distribution of moisture in the particle [Juarez-Enriquez et al.,

2017]. Water molecules can either be adsorbed onto the surfaces or absorbed within the particle. When exposed, adsorbed layers can lead to the formation of liquid bridges that strengthen cohesion and lead to clumping and/or agglomeration phenomena [Emery et al., 2009; Sandler et al., 2010; Crouter & Briens, 2014; Opaliński et al, 2021]. Like vdW forces, liquid bridges are also large at small separation distances but decrease slightly with increasing distance. Particle size, shape and surface roughness strongly influence the bridge formation as well as the separation distance [Ata et al., 2002; Forsyth et al., 2002; Butt & Kappl, 2009].

For non-hydrophobic materials and certain levels of moisture (the concept of critical humidity), capillary forces overcome vdW forces and govern powder cohesion [Forsyth et al., 2002; Juarez-Enriquez et al., 2017]. Nevertheless, the effect of moisture on powder flow ultimately depends on the processing conditions. Karde et al. (2017) investigated the effect of moisture and consolidation on corn starch. Shear cell analysis showed that cohesion increases at low stresses, but it decreases at higher stresses. Hydrogen bonds contribute to cohesion at lower packing densities, while frictional contact forces increase at higher packing densities and water acts as lubricating agent and/or glidant. A more detailed description of the concept of critical humidity and the mechanisms that lead to bridge formation can be found elsewhere [Ata et al., 2002; Butt & Kappl, 2009].

Electrostatic forces

Electrostatic forces arise when two bodies with different electrical potentials are in close proximity. The two entities acquire opposite charges due to friction during handling, contact with other surfaces, or changes in temperature or humidity. Depending on the charge distribution, these forces can either attract or repel particles and can influence the degree of dispersion or agglomeration within the powder [Rescaglio et al., 2019]. Electrostatic forces act over a long range (non-contact force), and their magnitude depends on both particle shape and separation distance. In accordance with Coulomb's law, their magnitude decreases with increasing distance, although at a slower rate than van der Waals forces. Compared to vdW forces and liquid bridges, electrostatic forces are significantly weaker at small separation distances. Zhou et al. (2003) and Takeuchi (2006) explored the impact of particle charge on cohesion and concluded that the electrostatic force dominates when the separation distance is sufficiently large to overcome the vdW force. In terms of powder flowability, the electrostatic force can often be neglected as its influence at small separation distances is very limited [Schulze, 2008].

2.2.2 Operating conditions and bulk flow

2.2.2.1 Shear strain rate dependency

Experimental work on Couette-type powder rheometers reported by Lun et al. (1984), Tardos et al. (1998) and Klausner et al. (2000) showed the dependency of the shear stress on the strain rate for several materials, and classified powder flow in bulk solids into four distinct flow regimes (or flow fields), as shown in *Figure 2* and described below. In this context, powder flow is defined as the deformation of a particulate assembly under shear stresses. A powder can experience various rheological states based on particle-particle interactions, depending on the applied stress (and strain) rate. Tardos et al. (2003) established approximate boundaries between the quasi-static and intermediate regimes (γ_o = *0.15 to 0.25*), and between the intermediate and rapid regimes (γ_o = *3*) granular flow regimes, based on the dimensionless strain rate, γ, defined as

$$\gamma^{0} = \gamma \sqrt{\frac{d_p}{g}} \tag{10}$$

where d_p is the particle diameter, and g is the gravitational constant. As the dimensionless shear rate varies, the powder flow falls into different regimes, which influence the stress-strain rate relationship. Vidyapati et al. (2012) conducted discrete element method (DEM) simulations using the Couette device and found good agreement with these boundaries, adding that the number of solid contacts decreases with increasing strain (or flow) rate and increases with solid fraction and interparticle forces. Berger et al. (2016) supported these results using contact numerical simulations to describe the effect of flow rate on bulk cohesion within the dynamic regime. Following the Rumpf relation in Equation 8, higher rates logarithmically decreased the coordination number, thus reducing the influence of interparticle forces on the shear stress. Several researchers have experimentally confirmed a decrease in bulk cohesion with increasing flow rate, solid fractions and interparticle forces [Vivacqua et al., 2019; Shi et al., 2020; Janssen et al., 2021]. More recently, Hare and Ghadiri (2017) proposed another framework for defining the boundaries between flow regimes, based on energy dissipation mechanisms rather than dimensionless strain rate alone, and reported significant differences to the classification by Tardos et al. (2003).



Figure 2. Powder flow regimes as a function of dimensionless shear rate. *Adapted Tardos et al. (2003).*

Static regime – No shear within the powder bed. The powder may deform in the presence of large stresses, where the failure criterion is defined as the onset of this deformation. For instance, powder bridging in a storage hopper, powder agglomeration and powder deposition and accumulation within equipment can be considered static because the powder is often in a settled or compacted state with little to no kinetic energy or motion.

Quasi-static flow regime – Particle motion is very slow, frictional and with very few collisions occurring. This flow regime is extensively studied in solid mechanics, with the main assumption being that the flow is uninterrupted, and the shearing field is continuous. The shear stress is constant and independent of the strain rate, while powder flow behaviour is governed by the magnitude of the applied consolidation stress. Material properties determine the contact areas between constituent particles to transmit solid pressure, that is, the normal stress within the powder bed from particle weight or applied loads. In industry, quasi-static flow conditions can be observed during discharge from bulk storage containers.

Intermediate flow regime – The intermediate regime occurs at strain rates between the quasi-static regime and the rapid granular regime, although boundaries are not yet clearly defined. First proposed by Hibler (1977), this regime is characterised by fluctuations in shear stress (and strain rate) that decrease as the flow slows. The shear strain rate dependency has been described as being significantly higher for confined conditions. Beyond the quasi-static regime, the bulk flow parameters are all sensitive to the strain (or flow rate) and applied consolidation stress. Both collisional and frictional interactions between particles must be considered. The general agreement is that frictional contact forces increase with the flow rate in the intermediate and rapid flow regimes, whilst cohesive forces decrease due to looser packing states (or aerated powder beds). Most industrial processes operate in this regime, with the bottleneck being cohesive powder flow [Tan et al., 2015; Ghadiri et al., 2020]. This includes various operations, such as blending, granulation, fluidisation, dispensing and filling of powders. Throughout this thesis, the term ‘dynamic flow’ and similar terms are used to refer to this regime, as generally acknowledged in powder technology.

Rapid flow regime – At very high strain rates, the flow is characterised by rapid and short-duration collisions between particles rather than continuous friction; hence, particle inertia is influential. This applies, for example, to the flow of cohesionless granular materials in chutes and channels.

2.2.2.2 Flow properties at very low stresses

Powders do not behave in the same way in bulk volumes as they do when they are separated from the powder mass. During processing of small powder volumes, particle velocities are high, the physical contacts are short lived, and the small contact areas

that exist between particles are not sufficient to transmit solid pressure. Flowability under such low stresses cannot be treated as representing that of a contacting powder bed [Harnby et al., 1987; Prescott & Barnum, 2000]. *Figure 3* presents a schematic representation of these mechanisms. Leung et al. (2019) observed a decrease in the consolidation stress by orders of magnitude as soon as a powder discharges from a container. Similarly, Freeman (2005, 2007) reported that approximately 100 times less energy is needed to initiate and maintain flow in aerated bulk solids than when they are consolidated. For gravity-driven powder discharge from bins or hoppers, stresses less than 200 Pa have been described at the outlet, regardless of the equipment size [Gentzler et al., 2015; Leung et al., 2019]. Søgaard et al. (2014) first reported a stress of 200 Pa at the outlet of a pilot-scale 4.75 L rotary press hopper. Zhou, X et al. (2020) estimated the major principal (or consolidation stress) at the outlet of a commercial hopper discharge apparatus to be on the order of 100 Pa. Stresses are assumed to be even lower during the separation of the dosage unit because of the limited powder quantity, small openings and high filling speeds.

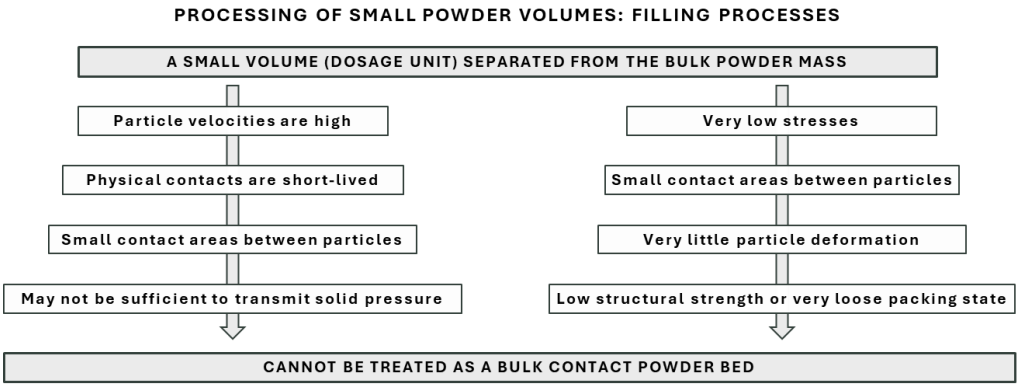


Figure 3. Flow behaviour during the processing of small powder volumes in filling processes. *Left*: According to Harnby et al. (1987) and Prescott & Barnum (2000). *Right*: According to Schulze & Wittmaier (2003), Wu & Cocks (2004), Leung et al. (2017) and Søgaard et al. (2017). The arrowed line illustrates the progression of powder flow under low-stress conditions during filling. In both cases, the processing of small powder volumes results in very low consolidation stresses, limited interparticle friction, and does not correspond to bulk flow behaviour or a contact (bulk) powder bed.

Many processes in powder processing industries involve bulk solid flow under stresses that are significantly less than 100 Pa, such as when filling very small containers (a few cm^3) or the dies of tableting machines [Schulze, 2008]. Under these low stresses, small contact areas exist between the constituent particles and very little particle deformation occurs, leading to low structural strength or very loose packing states [Schulze & Wittmaier, 2003; Wu & Cocks, 2004]. Bulk friction and cohesion have been previously described as being strongly dependent on the applied consolidation stress and thus on the flow behaviour. This has been reported to be

particularly relevant at the very low stresses found in tablet presses, where frictional contacts are limited and the flow behaviour is predominantly governed by cohesive forces [Leung et al., 2017; Søgaard et al., 2017]. Throughout this thesis, the term 'low stress' and similar terms are used to refer to normal stresses under 1 kPa, as generally acknowledged in powder technology.

Understanding the flow properties in the very low stress range (<100 Pa) is highly challenging using the available measurement technologies. The measuring principle or design of most testers hinders measurements in such low stress environments [Søgaard et al., 2017; Swize et al., 2019; Stavrou et al., 2020]. Even when filling powder layers of a few millimetres in height, stresses exceeding 100 Pa can be generated, although this depends on the packing state [Schulze, 2008]. Furthermore, the weight of the components placed on the bulk solid specimen for measurement (e.g., a lid or rotating impeller) can introduce additional stresses that densify the powder bed. The lower stress limit depends on the specific tester [Jager et al., 2015]. A more detailed description of the applied consolidation stress according to the measuring principle is given in *Section 2.5.1 "General classification"*.

Due to the complexity of measuring flow properties at very low stresses, assessments are often conducted at higher stresses and extrapolated to lower stress levels. Linearity is commonly assumed towards zero normal stress, and this is justified by particle interactions, especially in the range of sufficiently high stresses [Tomas, 2003; 2004]. However, this linear assumption is inaccurate at stresses below 500 Pa, as demonstrated by measurements made using a specially designed ring shear tester [Schulze & Wittmaier, 2003; Swize et al., 2019]. At very low stresses, interparticle forces become dominant, disrupting the expected linear relationship between the consolidation stress and flow behaviour [Søgaard et al., 2014; Stavrou et al., 2020; Rhodes et al., 2023]. Instead of a smooth decrease in flow resistance, powders may exhibit abrupt cohesion changes, agglomeration, or even flow disruption due to insufficient external forces to overcome these attractive interactions.

2.3 Factors and conditions influencing flow behaviour.

2.3.1 Primary particle properties and moisture

Particle size, shape, surface roughness and size distribution

Particle size and shape are among the most important determinants of powder flow [Fu et al., 2012; Stavrou et al., 2020]. All the cohesive force types described above are dependent on the separation distance. Smaller particle sizes reduce the area of separation surface or interparticle distance, as shown in Equation 8, and bulk cohesion increases, although this depends on the packing state and surface chemistry. For particle sizes below 100 µm, the vdW force is generally considered to start to overcome the particle weight (see the granular bond number Bo in *Section 2.2.1.2 "Interparticle*

forces"), and is dominant below 30 μm [Castellanos, 2005]. Thus, fine powders reduce the possibility of gravitational flow or gas fluidisation. For particle sizes above 100 μm, gravity and inertia are generally greater than the vdW force and the powders flow well. Similarly, increased surface roughness acts as a spacer and thus reduces the magnitude of cohesive forces.

Size distribution also plays an important role in flowability, and improved performance has been reported for narrower distributions [Hou & Sun, 2008; Yu et al., 2011]. Lumay et al. (2012) observed the same flow behaviour, adding that when the fine fraction (d10) becomes larger in a granule mixture, the flowability improves. The frictional shear stress in the granule mixture is reduced because the fines act as a glidant. This is not typically the case, as the addition of fine particles generally reduces flowability [Kojima & Elliot, 2012]. Particle morphology has been extensively attributed to the magnitude and number of contact points between particles in a bulk solid [Liu et al., 2008]. Particles with greater irregularity, such as platelets, fibres, or needles, encourage mechanical interlocking and frictional contact forces, which minimise particle motion and reduce flowability. The bulk solid properties, such as compressibility (i.e., the ability of a powder to compact under pressure) and permeability (i.e., the ease with which air passes through the powder bed), are also affected. Irregular shapes and increased surface roughness minimise the packing efficiency, which results in a more porous powder bed [Fu et al., 2012]. Particle size distribution (PSD) also influences the packing state, since the displacement of larger particles needs a collective displacement of fine particles.

Moisture

Processing and storage humidity conditions also significantly affect the flowability of powders. Depending on particle surface chemistry and internal structure, water molecules can affect particle interactions by changing physical, mechanical and/or surface properties, thus affecting the bulk flow behaviour, as discussed in *Section 2.2.1.2 "Interparticle forces"*. Variations in the solid-state properties can also be induced by moisture fluctuations. In both cases, these changes affect the frictional contact and interparticle forces and thus the flow behaviour. For powders that are susceptible to electrostatic charging, increased moisture can minimise electrostatic phenomena due to the formation of adsorbed layers on the particle surface [Naik et al., 2016, Rescaglio et al., 2019]. By contrast, excessive drying may result in increased electrostatic charges, causing particles to repel each other and disrupting flow. In most pharmaceutical applications, strict control of relative humidity (RH) and temperature is needed to ensure process efficiency and product quality.

2.3.2 Flow additives

Flow additives and lubricants are commonly used in the pharmaceutical industry to improve the flowability and processability of powders [Shah et al., 2023]. Both glidants and lubricants work by reducing the shear stress between powder particles and/or between the powder and processing equipment. This reduction in shear stress can improve powder flow and enhance tableting properties (i.e., compressibility, compactability and tabletability). Throughout this thesis, compressibility refers to a material's ability to reduce in volume under applied pressure, compactability describes its capacity to form tablets with sufficient mechanical strength as a function of porosity, and tabletability defines its ability to be compressed into tablets of a specified strength under compaction pressure [UPS <1062>]. These materials differ in their mechanism of action, and their use depends on the specific powder properties and processing requirements. In any case, a sufficiently small particle size is a prerequisite for adhesion and modification of the particle surface characteristics of individual particles; therefore, usually only a small amount is needed (typically up to 1% by weight).

Colloidal silicon dioxide

Glidants are commonly used to improve flowability of poorly flowing materials, such as micronised active ingredients, and to reduce agglomeration of fine powders. Colloidal silicon dioxide (CSD) has been used as a pharmaceutical adjuvant since the early days of direct compression tableting to improve flowability [Jones, 1970]. Classified as a nanomaterial with an average particle size around 30 to 40 nm, it is an amorphous solid consisting of highly pure silicon dioxide. As already discussed, shear stresses arise from frictional contact and cohesive forces acting in a bulk solid. Colloidal silicon dioxide counteracts these mechanisms by adhering to the particle surface [Jonat et al., 2004; Majerová et al., 2016; Zhou and Zhu, 2021; Verbeek et al., 2025]. First, small CSD aggregates adhere to the surface of the material, filling the voids and irregularities on the particle surface and thereby reducing mechanical interlocking and frictional contacts. The vdW and electrostatic forces decrease accordingly because the separation distance between individual particles increases. Additionally, the hydrophilic nature of some types of CSD retains moisture, which helps to reduce the formation of liquid bridges between solid particles that hinder powder flow. The type and concentration of CSD depends on the physical properties of the powder, such as composition, particle shape and size, and the processing equipment [Zimmermann et al., 2004].

2.4 Powder flowability in drug development

Drug research and development is a complex process that often takes several years from the discovery phase to commercialisation. After testing and screening a new chemical entity (NCE) through the process of drug discovery and confirmation of its efficacy and safety in clinical trials, the selected drug candidate, commonly known as an active pharmaceutical ingredient (API), needs to be formulated and scaled up for large-scale manufacturing (*Figure 4*). The aim is to develop a robust formulation as quickly as possible to reduce time-to-market and associated costs. Current efforts heavily rely on better understanding, monitoring and control of products and processes towards identifying possible manufacturing bottlenecks early in product development [Mishra et al., 2018]. This is paramount in the evolving pharmaceutical landscape, which is characterised by recent regulatory initiatives, such as Quality by Design (QbD), and the increasing implementation of continuous manufacturing (CM) [International Council for Harmonisation (ICH), 2009; European Medicines Agency (EMA), 2023].

At the beginning of small-scale R&D, generally referred to as the pre-formulation phase prior to clinical trials, the API is extensively characterised to define the most suitable manufacturing route (i.e., the pertinent unit operations) and to support excipient selection [Ahirwar & Shukla, 2023]. This includes various investigations, such as physicochemical analysis, biopharmaceutical profiles, compression trials and flowability assessments. For instance, the poor solubility of new APIs often requires particle size reduction techniques to improve dissolution and bioavailability, which in turn compromises powder flow [Baghel et al., 2016; Szabó et al., 2019]. Other prerequisites, such as production volume, continuous or batch-type production, raw material suppliers, machinery, storage conditions and stability considerations, as well as other downstream processes, such as tablet coating, are anticipated for large-scale manufacturing. The aim of all these considerations is to ensure stable drug quality attributes over the long term [ICH, 2009; FDA/CDER/CBER, 2016]. If the material is scarce, as is often the case in small-scale R&D such as in early API characterisation, powder flow analysis is often not conducted. Most traditional testers in industry require tens of grams for measurement [Chendo et al., 2023]. A more detailed review and discussion of available methods is given in *Section 2.5.1 "General classification"*.

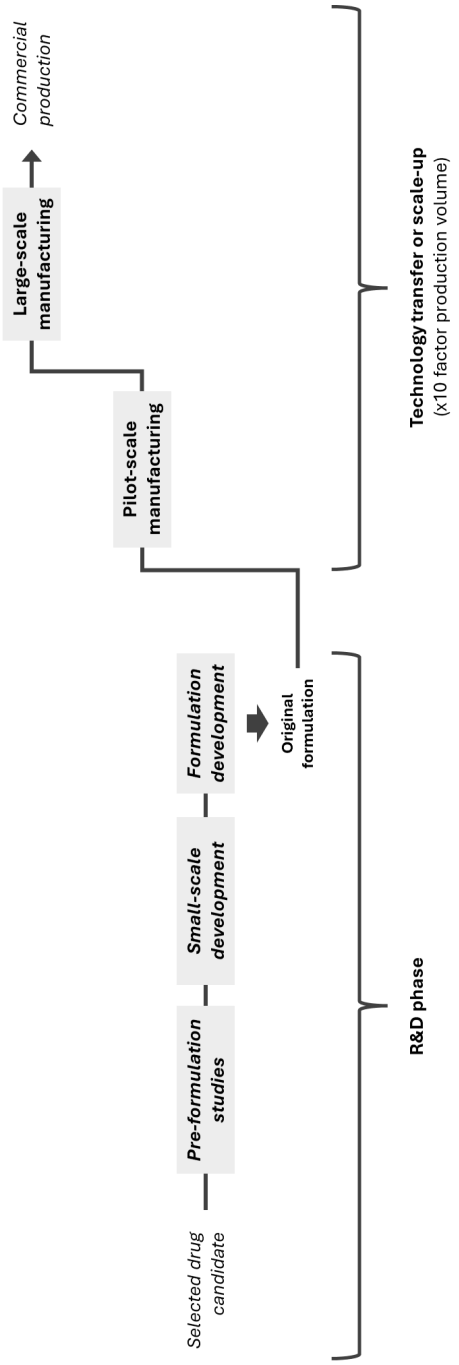


Figure 4. Research, development and scale-up process of solid dosage forms. During the research and formulation development (R&D) phase, and particularly in pre-formulation and small-scale development stages, the amount of material is limited. Throughout scale-up, the original formulation is typically fixed, and optimising manufacturing conditions ensures product consistency.

Eventually, a prototype formulation is developed for testing and, if validated, for scale-up (*Figure 4*). During technology transfer from the lab to commercial production, the original formulation is generally fixed. Successful scale-up relies on adjusting the processing parameters for each unit operation to achieve the same quality as was observed in the R&D phase [Vladisavljević et al., 2013; Jang et al., 2020]. The FDA and EMA guidelines define scale-up and scale-down processes for solid dosage forms as a gradual change in batch size by a factor of at least 10, which implies technology transfer to new equipment that must follow the same operating principles [ICH, 2009]. The objective is clear: to mass-produce a product identical to the original formulation, regardless of the production volume. Quality control (QC) and validation strategies are therefore systematically applied throughout development to meet regulatory standards and ensure the safety and efficacy of the processes and products [FDA/CDER/CBER, 2011; Salade et al., 2022]. Among these strategies, powder flow characterisation plays a crucial role in ensuring consistent material handling, blend uniformity and efficient manufacturing processes.

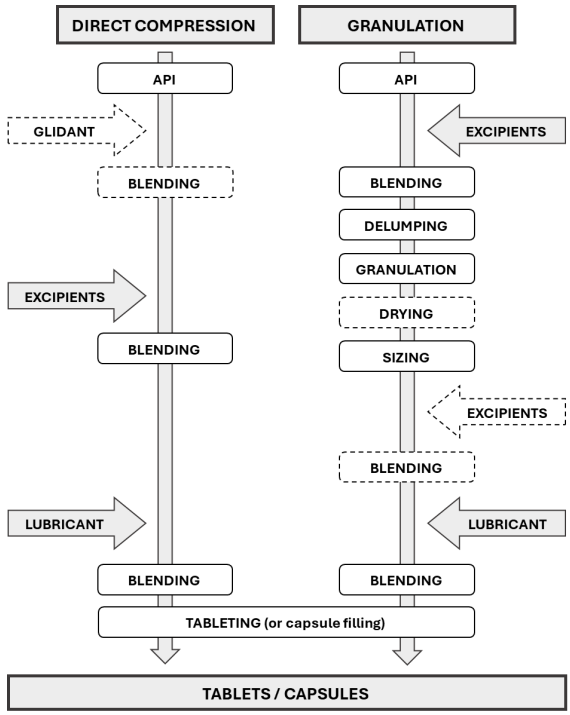


Figure 5. Schematic representation of two generic manufacturing routes for oral solid dosage forms (OSDs) and their associated unit operations. The choice between these routes depends on the API's properties and formulation requirements. The figure illustrates a simplified workflow and does not cover all formulation-specific variations. The final product quality fundamentally depends on blend homogeneity and filling consistency, which directly influences tableting or capsule-filling performance. *Left*: Direct compression (DC), *Right*: Granulation, which enhances powder flow and tabletability, followed by drying (if wet granulation is used).

Ideally, an API should flow well (i.e., has a low tendency to agglomerate) and compact efficiently. However, this does not normally happen, and the API needs to be processed before tableting or encapsulation. For instance, if the API is too cohesive or its compactability is poor, it may be granulated to improve the flow and/or tabletability and handling, as exemplified in *Figure 5*. Conversely, for direct compression (DC), the API and selected excipients must show acceptable processability immediately after blending. At this stage, the main objective is blending homogeneity rather than flowability, since inadequate mixing can lead to content uniformity issues. The use of glidants is often counter-productive, as it may promote segregation, and the requirement for API flowability largely depends on the dose (fraction in the formulation), which in turn determines the particle sizes needed [Abe et al., 2009]. In any case, the final formulation blend is discharged from an intermediate bulk container (IBC) to the press hopper within the feeder and, ultimately, into the die. Consistent and reliable flow during each unit operation is critical to overall manufacturing costs, time-to-market and the final product quality [Prescott and Barnum, 2000; Worku et al., 2017; Hildebrandt et al., 2019]. Consequently, powder flow characterisation throughout the drug development process includes monitoring and controlling the flow properties of the API, excipients (raw materials), intermediate products (e.g., granules or pre-blended glidants), and the final formulation blend.

2.4.1 The importance of effective filling

Many pharmaceuticals are produced in self-metered doses or small powder volumes, such as tablets, capsules, dry powders for inhalation (DPIs) and parenterals for dissolution. While biologic therapies and parenterals have experienced significant advances in recent years, oral solid dosage forms (OSDs) remain at the forefront of the industry and are expected to grow in the coming years [Brown & Wobst, 2021; USP <1151>]. Filling processes are therefore a routine yet decisive aspect of pharmaceutical manufacturing. Although the specific filling procedure depends on the application and the characteristics of the processed material, one constant remains: successful processing hinges on filling performance. Product quality fundamentally depends on filling consistency, as it directly affects dosage uniformity attributes, such as tablet mass variation and drug uniformity content, as well as the subsequent compaction and ejection steps, ultimately affecting overall tablet quality [Natoli et al., 2017; Goh et al., 2018a; Van Snick et al., 2018]. Optimal flow behaviour in filling operations is therefore essential to ensure product consistency and quality, optimise manufacturing processes and minimise waste [Sun, 2010; Leane et al., 2018].

The R&D phase (see *Figure 4* drug development diagram) typically involves the use of compaction simulators, which allow the study of compression behaviour using limited amounts of material (often 100–1,000 times less than required in large-scale

production). From the earliest preformulation steps through formulation development and scale-up, compaction simulators are now preferred over eccentric tablet presses, which require comparable or larger quantities of powder and cannot reproduce production-scale compression dynamics. These instruments, whether hydraulically driven with programmable punch displacement profiles or based on advanced mechanical constructions, can closely mimic the compression kinetics of high-speed rotary tablet presses [Wünsch et al., 2020]. Advanced commercial compaction simulators are highly instrumented, sample-saving devices that not only replicate compression kinetics but, in some cases, integrate pre-compression modules to assess hopper discharge and die filling, partly overcoming the limitations highlighted in USP <1245>. This versatility makes them key tools for bridging the gap between R&D and production-scale manufacturing. However, developing a formulation that can be scaled up to production without any issues remains challenging [Sun, 2010; Wünsch et al., 2020].

The subsequent pilot-scale production phase increases the processed powder volume using model rotary tablet presses (approximately 10 times less than full production). The third phase evaluates the technology transfer to the intended high-speed production presses, ultimately achieving commercial production at the manufacturing site. Standards to generalise and determine critical quality attributes (CQAs) for the compression and ejection steps, as well as final tablet properties, are well-established from the early development stage using compaction simulators and small amounts of material [Ph. Eur. 2.9.40; USP <1245>]. Nevertheless, USP <1245> still recognises that compaction simulators cannot fully assess pre-compression events such as hopper discharge or die filling, or time-dependent effects like powder build-up or segregation. Although effective filling of materials into cavities has been widely studied, no consensus has been reached regarding a suitable test for characterising powder flow during the filling process (*Section 2.2.2.2 "Flow properties at very low stresses"*). Consequently, early assessment of die-filling performance remains inaccessible during pre-formulation and development stages. Iterative end-product testing continues to serve as the benchmark for quality, despite providing limited process insight and requiring substantial investments of time and resources [USP <905>; FDA/CDER/CBER, 2011; Cholayudth, 2016, 2017].

A powder that performs well in the lab can perform poorly in large-scale manufacturing. Feed systems in rotary tablet presses are more sophisticated and involve different and simultaneous filling mechanisms, such as gravity filling, force feeding, or suction filling. Filling performance in rotary presses is affected by many factors, including powder properties, operating parameters, and feeder design frame configuration [Peeters et al., 2015; Goh et al., 2018a]. Compared to gravity filling, the use of suction filling in certain rotary tablet presses has been found to typically improve die filling, particularly for more cohesive powders [Baserinia & Sinka, 2019; Tang et al., 2020]. In contrast, Zheng et al. (2022) observed that poor-flowing powders

demonstrated slightly better flow performance in linear die filling typically found in eccentric tablet presses than in rotary filling systems. These examples demonstrate the complexity of determining die-filling performance across different tablet presses and highlight the necessity of ultimately evaluating material performance in each specific type of equipment. Detailed explanations of these mechanisms and tooling kinematics can be found elsewhere [Wu et al., 2004; Goh et al., 2018; Grymonpré et al., 2018; Zakhvatayeva et al., 2018; Baserinia & Sinka, 2019; Dühlmeyer et al., 2019; Goh et al., 2019; Puckhaber et al., 2020; Zheng et al., 2022].

Flow issues encountered during tablet press scale-up can be addressed by redesigning equipment to match filling-machine geometry with the demands of specific formulations. This approach may involve modifications to components such as the hopper, feed frame, die cavity, or paddle configuration, thereby accommodating variations in powder flowability. However, due to the high costs associated with equipment redesign, flow problems are frequently managed by slowing down the manufacturing speed or adjusting press machine operating parameters [Mendez et al., 2010; Sun, 2010; Goh et al., 2018a]. Die-filling performance of cohesive powders typically improves at lower turret speeds or increased paddle speeds [Zakhvatayeva et al., 2019a; Tang et al., 2020]. To prevent manufacturing problems, the original formulation must have adequate flow properties to ensure consistent performance across different processing equipment and acceptable production speeds.

2.5 Flow characterisation techniques

Prescott and Barnum (2000) gave a simple but accurate definition of powder flowability as 'the ability of a powder to flow in desired manner in a specific piece of equipment'. The diverse range of unit operations subjects powders to different strain rates and stresses, as discussed in *Section 2.2.2 "Operating conditions and bulk flow"*, ranging from the static conditions and high stresses observed in silos to the dynamic conditions and very low stresses present in the die-filling process. For each application, a unique set of properties dictates performance. Equally, different test methods yield different results since different physical mechanisms are measured in each test [Shah et al., 2008; Stavrou et al., 2020]. A testing strategy using a combination of techniques is usually necessary to understand and control powder flowability through the drug development process. For each application, the methods that most closely reproduce the processing conditions to which the powder is subjected may be selected [Krantz et al., 2009; Wu et al., 2012; Leturia et al., 2014; Goh et al., 2018b]. Although powders with good flowability are generally considered to maximise filling performance and allow for higher processing speeds, it remains unclear which specific flowability parameters are most relevant and how they correlate with critical aspects of filling processes and product performance.

2.5.1 General classification

Assessment of the flow testers focuses on the test principle and the physical processes in the bulk solid. Two aspects of powder flow characterisation that are relevant to the filling of self-metered doses remain highly challenging to available flow measurement technologies: (i) very low stresses and (ii) dynamic conditions or high strain rates. According to these criteria, the most applied methods in the literature are listed for review, divided into dynamic and static tests, and the operating stress range is reported. The influence of the measuring principle on the consolidation stress is then evaluated (*Figure 6*). Finally, the methods (or measuring principles) considered relevant to this thesis are reviewed in more detail.

Static tests

Characterisation of the incipient flow in a wide range of stress conditions within the quasi-static flow regime is well established. Incipient failure properties describe the transitioning flow behaviour from static to dynamic friction and are quantified as a function of an applied load (compressive forces and/or shearing) to a pre-consolidated powder bed and the consolidation time (caking). Certain levels of cohesion are needed to obtain meaningful results, and reduced sensitivity has been reported when cohesion decreases, although not significant for free-flowing powders [Shah et al., 2008; Saw et al., 2015; Tay et al., 2016]. Similarly, improved characterisation with dynamic testing is reported for non-cohesive powders, and sensitivity decreases with increasing cohesion. All these quasi-static test methods generate different quantitative values for the bulk parameters, depending on the consolidation stress acting on the powder bed [Koynov et al., 2015; El-Balawi et al., 2023].

Examples of these instruments in descending stress order are as follows: The unconfined compression tester [Parrella et al., 2008] requires a minimum consolidation stress for the failure test of the order of 10 kPa and a very cohesive bulk solid. The consolidation stress increases for less cohesive powders. In the moderate-to-high stress range, the industry-standard Jenike-type translational and Peschel-type rotational shear testers, such as the rotational shear cell in FT4 Powder Rheometer of Freeman Technology [Freeman, 2007], are limited to normal stresses above 1 kPa to achieve reliable results [Søgaard et al., 2014; Ghadiri et al., 2020]. As discussed in *Section 2.2.2.2 ("Flow properties at very low stresses")*, the results cannot be extrapolated to low stresses. Measuring flow properties at lower stress conditions has often been attempted. The Schulze-type annular shear tester model RST-XS.s [Schulze, 2008], such as the Brookfield powder flow tester [Søgaard et al., 2014], was able to decrease the major principal stress to approximately 500 Pa for reliable measurements, and this was further decreased to 250 Pa [Søgaard et al., 2014; El-Balawi et al., 2023] by introducing a mechanism allowing the lid of the cell to be lifted from the powder bed and then by reducing the weight of the lid, thereby decreasing the

consolidation stress. Low stresses have also been achieved by manipulating the pressure drop across the bed in the fluidised state and by calculating the tensile stress at break when compressed (e.g., the Sevilla powder tester [Castellanos et al., 2004] and the raining bed method [Girimonte et al., 2018]). Both techniques achieve a reproducible initial packing state of the bed, and the tensile strength can be determined at low levels of stress ($\lesssim$ 1 kPa). The ball indentation method [Hassanpour & Ghadiri, 2007] reported stresses of approximately 1 kPa by measuring the hardness of a pre-consolidated powder bed. The SSSpinTester by Material Flow Solutions Inc. [Johanson, 2012; 2019] handled measurements at stresses as low as 50 Pa (50 to 500 Pa) using very small amounts of powder (0.5 grams).

For dynamic applications, none of these quasi-static test methods is predictive because they do not characterise the bulk parameters at higher strain rates [Lumay et al., 2012; Wu et al., 2012; Baserinia et al., 2016; García-Triñanes et al., 2019; Shi et al., 2020]. For instance, a powder that flows well under static conditions may perform poorly in the dynamic regime. Apart from the rotational shear cell in the FT4 powder rheometer, which is widely used in powder processing industries for comparative testing [Hou H et al., 2008; Jager et al., 2015; ASTM D7891-24], and the SSSpinTester, which operates at very low stress environments using very small amounts of sample (0.02 to 1.00 grams, depending on density of sample material), static methods are not considered relevant to this thesis and will not be discussed further.

Dynamic tests

Characterisation of bulk flow properties in a wide range of stress conditions within the dynamic regime is limited. Dynamic flow testers have been conveniently classified by Ghadiri et al. (2020) into two categories: (i) those which address powder rheometry by measuring the powder resistance to shearing of a rotating impeller or texturised surface, and (ii) other dynamic flow testers in which the flow behaviour and characteristics are indirectly inferred. In this context, “indirect” or “qualitative” methods are defined as those that do not directly quantify the powder’s mechanical response to an applied force (e.g., torque or normal load) but instead deduce flow behaviour from secondary observations such as particle motion, discharge time, or changes in bed geometry. Found in the first category are the Couette-type device [reviewed by Langroudi et al., 2010] and rotating-blade rheometers, such as dynamic tests in FT4 Powder Rheometer of Freeman Technology [Freeman, 2007] and the powder cell of the Anton Paar Modular Compact Rheometer [reviewed by Salehi et al., 2018]. Avalanche techniques, such as dynamic angle of repose in GranuDrum of GranuTools [reviewed by Shi et al., 2020] and static angle of repose in pharmacopoeias [Ph. Eur. 2.9.36, USP <1174>], hopper discharge methodologies [Ph. Eur. 2.9.16, Ph. Eur. 2.9.36, USP <1174>] such as Flodex™ apparatus of Hanson Research Co. [reviewed by Zhou, X. et al., 2020], and the ball indentation method at high strain rates

[Hassanpour & Ghadiri, 2007], are placed in the second category. Beyond the quasi-static flow regime, the bulk flow parameters are all sensitive to the strain (or flow) rate and the consolidation stress during measurement, as discussed in *Section 2.2.2.1 ("Shear strain rate dependency")*.

The Couette device has been widely used experimentally to find constitutive equations that span shear strain rates in the intermediate regime. However, intrinsic limitations in the measuring principle, such as wall slip, the presence of secondary flows and lack of commercial availability, hinder its applicability [Ghadiri et al., 2020]. Therefore, the Couette device is not considered relevant to this thesis and will not be discussed further. Rotating-blade powder rheometers have been widely investigated during the last decades, but the measured stress range remains unclear [Li, M. et al., 2018; Vivacqua et al., 2019]. Since the depth of the powder bed and the weight of components placed on the bulk solid specimen for measurement have been recognised as sources of increased consolidation stress (*Section 2.5.1 "General classification"*), a reasonable expectation is that very low stresses cannot be achieved. Recent research on the commercial avalanche drum estimated the operating stress to be about 400 Pa [Shi et al., 2020]. Another recent investigation on the commercial hopper discharge method estimated a main principal stress at the outlet on the order of 100 Pa [Zhou, X. et al., 2020]. A more detailed discussion on gravitational discharge and associated stresses can be found in *Section 2.2.2.2 ("Flow properties at very low stresses")*. Stresses around 1 kPa have been reported with the ball indentation method at high strain rates by measuring the hardness of a powder bed [Zafar et al., 2020]. Since the powder bed is consolidated under an applied load prior to measurement and the measuring principle involves external stresses during the measurement, very low stresses would not be expected to be achieved using this method. Although this test method can be used to rank cohesive powders using relatively small amounts of sample, the relevance of the measuring principle to the filling of self-metered doses is considered very limited and will not be discussed further in this thesis.

Consolidation stress and measuring principle

The major principal (or consolidation) stress depends on the applied normal force and its distribution per unit area. In quasi-static conditions, where no or negligible kinetics are present in the system, the applied force depends on the weight of the components placed on the bulk solid and the area of the shear plane, which defines the lower stress limit (*Figure 6*). Under dynamic conditions, the magnitude of the normal force also increases with the acceleration and mass of the particulate solid. A more detailed explanation of these measuring principles is given below.

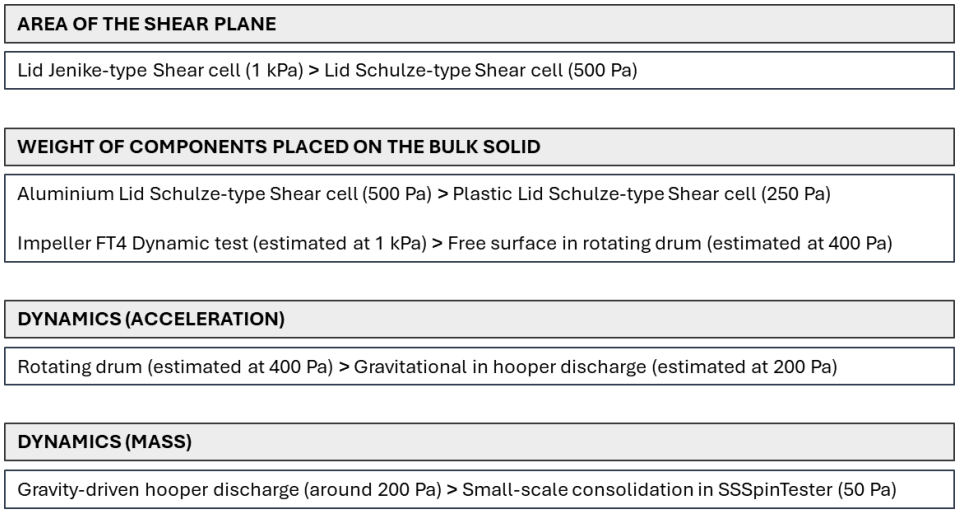


Figure 6. Consolidation stress and measuring principle, including the lower stress limit reported in the literature.

2.5.1.1 Static methods

Shear cell analysis

Shear cell methodology was first developed by Andrew Jenike in the 1960s for storage hoppers and silo designs on a more fundamental basis [Jenike, 1964, 1967; Schulze, 2008]. Over the years, shear cell analysis has been described as the gold standard for powder flow analysis in powder processing industries, with issued pharmacopoeial [Ph. Eur. 2.9.36, Ph. Eur. 2.9.49, USP <1063>, USP <1174>] and ASTM standards [ASTM D6773-08, ASTM D6128-16, ASTM D7891-24]. The test principle involves measuring the forces required to shear one consolidated powder plane relative to another in a moderate-to-high stress environment and very low (shear) strain rates. Derived data, such as the unconfined yield strength, UYS (kPa), major consolidation stress, MCS (kPa), cohesion, C (kPa), flow function coefficient, FFc, and angle of internal friction, AIF (°), quantify the flow behaviour in bulk solids. Other tests, such as wall friction, time consolidation, attrition and compressibility, can be also conducted in the same setup. Through the years, the method has been automated, ensuring a more precise control of the experimental environment. Accordingly, the impact of processing variables, such as consolidation load and time, on flow properties can be determined and must be well defined for cross-comparison.

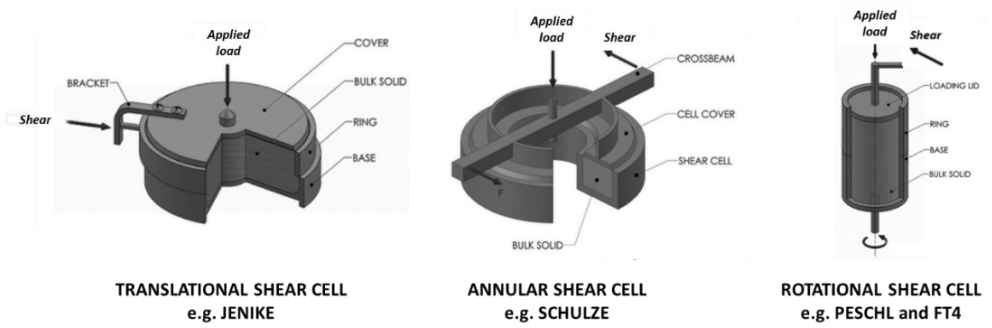


Figure 7. Descriptive diagram of most common variations of shear cell components and design [USP <1063>]. *Left:* Jenike-type translational shear cell. *Centre:* Schulze-type annular shear cell. *Right:* Peschl-type rotational shear cell. *Adapted from USP <1063>.*

Many variations of the shear cell are described in the pharmacopoeia [USP <1063>], although the most widely used shear tester is currently the Schulze-type annular shear cell (*Figure 7*). Compared to the Jenike and Peschl-type shear testers, the annular shear cell is more accurate and more repeatable [Bell, 2001; Schulze, 2008]. Shear properties of bulk solids are often underestimated with torsional shear testers such as the FT4 powder rheometer [Schwedes, 2003; Leonard & Abatzoglou, 2010; Søgaard et al., 2014; Ghadiri et al., 2020]. However, the FT4 provides fully automated measurements in the static regime as well as under a wide range of processing conditions (*Section 2.5.1.2.3 "Powder rheometry"*), and good correlation with the annular shear cell has been reported for certain materials [Freeman, 2007; Koynov et al., 2015]. The standard test method for shear testing of powders using the FT4 powder rheometer shear cell has been described in industrial standard ASTM D7891-24. A detailed description of the shear test can be found elsewhere [Freeman, 2007]. Cohesion (kPa), flow function coefficient FFc (-) and angle of internal friction AIF (°) are reported as the most useful parameters for material comparison purposes. In general, better flowing powders yield lower shear values of these metrics, except for FFc, where a higher value better describes the material behaviour from static to dynamic friction. A 10 mL powder sample has been reported as sufficient for FT4 shear cell measurements. The relationship between quasi-static shear testing and dynamic applications has been discussed in detail in *Section 2.5.1 ("General classification")*. However, since material behaviour under quasi-static conditions is not the primary focus of this thesis, further details on this topic can be found elsewhere [Schulze, 2008].

SSSpinTester

The SSSpinTester was recently developed to characterise fine cohesive powders when only a limited sample amount is available as occurs, for example, in early API

characterisation [Johanson, 2012, 2019]. The novel involves pre-consolidation of a small powder sample in a cell, which is then spun. As centrifugal force increases, the force required to break the cake (failure criterion) is measured. The powder flows out, and a laser detects the free path; therefore, the flow function coefficient is calculated and sorted into different categories (qualitative method). Major principal stresses as low as 50 Pa (50 to 500 Pa) have been reported. The measurement cell volume is only 0.38 cm^3 per run (0.02 to 1.00 grams), depending on density of sample material) and the analysis can be conducted in less than 5 minutes. Notably, most bulk static techniques require significant extrapolation to lower stresses, as discussed in *Section 2.2.2.2 ("Flow properties at very low stresses")*, whereas this small-scale technique directly measures failure at very low stresses. However, while a very low stress environment may simulate filling processes, no studies have been conducted on these operations, and no correlations have been reported for dynamic applications. The test results are highly dependent on the method used; therefore, sample preparation, consolidation stress and cell geometry must be well-defined for cross-comparison. Difficulties in reaching sufficient weight for reproducible consolidation have been observed and as in conventional shear cell analysis, a certain cohesiveness is required to consolidate the powder sample. Further research is needed to fully understand the capabilities and limitations of this promising instrument.

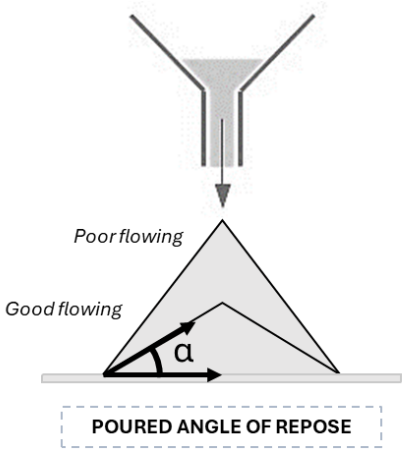
2.5.1.2 Dynamic methods

2.5.1.2.1 Pharmacopoeial tests

Angle of repose

The poured angle of repose (AOR) is a simple, fast and widespread testing method for characterising the flow properties of powders across powder processing industries [Ph. Eur. 2.9.16; Ph. Eur. 2.9.36, USP <1174>, ASTM D6393/D6393M-21]. The measuring principle is simple and well understood and involves testing a free surface under static or quasi-static avalanche conditions. This gives the constant, three-dimensional angle (relative to the horizontal plane and the slope) measured from the cone-like pile when a powder settles after flowing from a funnel, as shown in *Figure 8*. The angle, α, is calculated in static conditions (after flowing), and defines the resistance to movement between particles in a low gravity-driven stress environment. Powder flowability is classified according to this angle and a general scale of flowability is described in the pharmacopoeia. Better flowing properties exhibit lower angles of repose, while more cohesive materials have higher values. This parameter can be useful when considering the storage of powders, especially in heap form, and for predicting the constrained flow behaviour of a powder [Seville et al., 2000; Prescott & Barnum, 2000]. The measuring principle involves relatively slow frictional particle movement on the pile surface and may not be applied to characterise the complex dynamic conditions in the filling

operation [Carson, 1975; Yaginuma et al., 2007; Lumay et al., 2012]. Some researchers have reported positive correlations with the filling performance [Yaginuma et al., 2007; Goh et al., 2018b], while other researchers observed no correlations for either small-scale or large-scale tablet manufacturing [Zettler et al., 2016].



ANGLE (α)	FLOW CLASSIFICATION
<25	Excellent
25-30	Good
30-40	Moderate
>40	Poor

$$\alpha = tan^{-1}\left(\frac{2*heigh}{D_a - d}\right)$$

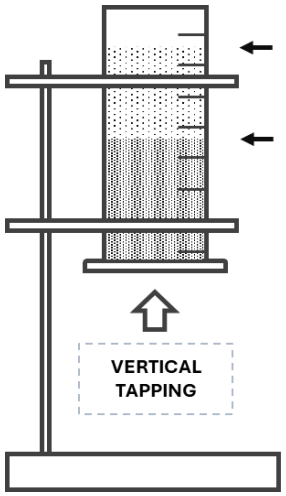
Figure 8. Ph. Eur. angle of repose measurement and flow classification according to the measured static angle (α), where *h* and D_a are the height and diameter of the conical pile, and *d* is the orifice diameter of the funnel. Lower angles of repose indicate better flowing properties, while higher angles suggest increased cohesion and poorer flowability.

The test results are reportedly very dependent upon the method used; the height of the funnel relative to the base and the base diameter must be well defined as the protocols are not standardised. Experimental difficulties arise from the segregation of the material and consolidation or aeration of the powder as the cone is formed, especially for more cohesive powders [Emery et al., 2009; Krantz et al., 2009; Boschini et al., 2015]. Multiple angles may form from a single pile, leading to poor repeatability and reproducibility, and the lack of precision and low sensitivity are generally acknowledged. Despite its difficulties and limited relevance, the method continues to be used in the pharmaceutical literature for comparison between batches and to predict manufacturing problems [Léonard et al., 2017; Salústio et al., 2021; Chendo et al., 2023]. Advantageously, the method is quick, intuitive and easy to use. Geldart et al. (2006) investigated the effect of sample size on the measured parameters and concluded that 100 grams was the minimum amount for reliable measurements.

Tapping studies: Compressibility Index and Hausner Ratio

Although density is simply defined as the ratio of mass to volume, other factors influence the powder density (or packing state) in bulk solids, and a defined mass of powder may occupy different volumes depending on the air entrained in the powder

bed (i.e., the solid fraction to porosity ratio). Compressibility is a measure of how the packing state changes as a function of applied normal (or consolidation) stress. For non-cohesive bulk solids, these changes are minimised as the entrained air can be easily released, whilst for more cohesive bulk solids, the loose packing state at low consolidation stresses shows significant differences in density when compared to higher stresses. Packing densities and derived flow indexes (Carr´s Index, *CI*, and Hausner Ratio, *HR*) are determined by applying unidirectional vertical tapping to consolidate a powder into a more densely packed state [Ph. Eur. 2.9.34, Ph. Eur. 2.9.36, USP <1174>, ASTM D6393/D6393M-21]. The untapped bulk density (also referred to as "apparent bulk density" in Ph. Eur. 2.9.36), ρ_b, is calculated from the initial volume, V_o, for a constant mass of powder (typically 100 grams) and is compared to the density after tapping or tapped bulk density, ρ_t, calculated from the final volume, V_f. The rate of consolidation can also be measured by systematically controlling the tapped volume. A higher change in density is associated with a more cohesive powder as it is poorly packed when unconsolidated. A schematic of the measurement setup in the pharmacopoeias and the constitutive equations of the flow parameters are shown in *Figure 9*.



CALCULATED FLOW INDEXES

$$\text{HR}\,[-] = \frac{\rho_t}{\rho_b}$$

$$CI\,[\%] = 100 * \frac{\rho_t - \rho_b}{\rho_t}$$

CI, %	HR	FLOW CLASSIFICATION
1-10	1.00-1.11	Excellent
11-15	1.12-1.18	Good
16-20	1.19-1.25	Fair
21-25	1.26-1.34	Passable
26-31	1.35-1.45	Poor
32-37	1.46-1.59	Very poor
>38	>1.60	Very very poor

Figure 9. Schematic measurement setup for tapping studies, constitutive equations of the flow indexes (CI and HR) and general flow classification according to Ph. Eur. 2.9.36. The bulk density (ρ_b) is determined from the initial volume (V_0) of a defined powder mass, while the tapped density (ρ_t) is measured after consolidation by tapping, reducing the final volume (V_f). The Compressibility Index (CI) and Hausner Ratio (HR) quantify the degree of powder densification, with higher values generally indicating greater cohesiveness and poorer flow properties.

These indexes have been proposed as an indirect measure of size and shape, surface area, moisture content, and cohesiveness of materials because all can influence the flow properties measured by tapping [Yaginuma et al., 2007; Fu et al., 2012; Lumay

et al., 2012; Tay et al., 2017; Goh et al., 2018b]. These studies concluded that compressibility indexes from tapping studies are primarily influenced by particle size, while higher stresses, such as in the powder rheometer, mostly depended on the particle shape. Smaller particle sizes, increasing amounts of fines and more irregular particles increased the compressibility indexes, indicating a more cohesive material. Significant correlations have been found between the static angle of repose (AOR) and the compressibility indexes for differences in particle size, shape, number of fines and moisture content. Both tests are generally considered quasi-static, as the measuring principle involves relatively slow frictional motion, with few collisions occurring, and may not be applied to characterise filling operations. However, several researchers have reported positive correlations between compressibility indexes and filling performance in the tablet press, mainly due to the detection of particle size variations [Yaginuma et al., 2007; Freeman & Fu, 2008; Ilić et al., 2009; Sun, 2010]. Test results are reported to depend very strongly upon the method used, the diameter and size of the cylinder, the number of times the powder is tapped to achieve the tapped density and the mass of material used; therefore, all these variables must be well defined. Difficulties associated with monitoring the changing volumes have also been discussed. Although the test is relatively automated, multiple initial packing states (or initial volumes V_0) may form depending on the operator, leading to poor repeatability and reproducibility.

Flow through an orifice

Powder flow through an orifice or hopper discharge remains the first choice in industry for characterising and optimising die-filling processes, as it involves a similar mechanism to that of the flow of powder into a die cavity [Ph. Eur. 2.9.16; Ph. Eur. 2.9.36; USP <1174>; ASTM B213-17; MPIF 03]. The measuring principle involves the continuous or discrete measurement of the mass/volume per time flowing from an orifice of closely defined dimensions on a low gravity-driven stress environment, typically a funnel or hopper, as shown in *Figure 10*. Powder flow rate through an orifice has many of the same characteristics of static angle of repose but has been proposed as a better measure of powder flowability in the dynamic regime. Either the mass flow rate or volume flow rate can be determined using a weight balance. Since die filling is volumetric, determining the volume flow rate may be preferable. A higher flow rate is an indicator of better flowability. Alternatively, comparative tests are often conducted by measuring the minimum/critical orifice diameter that allows flow (i.e., whether powder flows through or forms an arch for an individual orifice) [Taylor et al., 2000; Wu, C. Y., et al., 2012; Zhou, X. et al., 2020]. The powder is discharged from a funnel into a vessel with a specific orifice diameter. The orifice is then opened to determine if the powder flows, until the minimum orifice diameter is reached. A more detailed

discussion of stresses in hopper discharge is given in *Section 2.2.2.2 ("Flow properties at very low stresses")*.

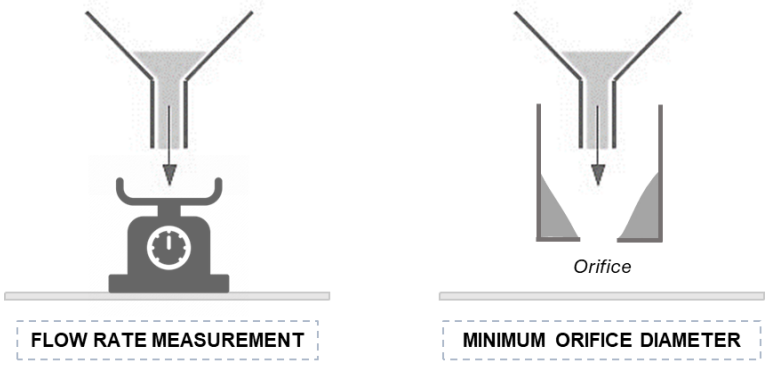


Figure 10. Flow through an orifice. *Left:* Measurement of the flow rate using a balance, where the mass per unit time is recorded as powder discharges from a funnel. *Right:* Determination of the minimal orifice diameter that allows flow by systematically reducing the orifice size until the powder ceases to flow. The flow rate method provides a dynamic measure of powder flowability, while the critical orifice diameter method identifies the flowability threshold based on arching tendencies.

The test results are reported to depend strongly upon the method used; therefore, the diameter and shape of the orifice, the type of the container material and the diameter and height of the powder bed must be well defined. No general scale is available, and data are not standardised for cross comparison. Wu and Cocks (2004) determined that the lack of monitoring of consolidation stress hinders its applicability to simulate the effect of filling speed in the tablet press. Schulze (2008) observed that both the filling method and the discharge pattern affect the measurement. Kulkarni et al. (2010) reported that both in AOR and flow rate measurements results are significantly influenced by how the sample is loaded by the operator (i.e., the initial packing state). Wu et al. (2012) investigated the correlation of the pharmacopoeia flow tests and concluded that hopper discharge methods do not mimic filling performance. They associated this with the air pressure effects and enduring contact and shearing during die filling, which were not properly characterised according to the size differences between two spherical cellulose grades. Huang et al. (2015) reported significant differences in flow properties due to dry particle coating measured using the critical orifice methodology, although more cohesive powders were poorly differentiated. Zetter et al. (2016) observed no correlations with filling performance in small and large-scale tablet manufacturing for common pharmaceutical excipients either in flow rate or critical diameter flow measurements. Better qualitative results were reported for flow rate measurements upon increasing API loading blends. Schiano et al. (2018) found a strong correlation between the flow rate and the critical filling speed in a model die-filling system according to particle size variations. Other researchers have also reported that the critical orifice diameter correlates with particle

size variations, although it becomes insensitive when the particle size is below 120 μm [Zakhvatayeva et al., 2018]. Xue et al. (2019) confirmed numerically and experimentally the dependency of the minimal orifice diameter on the particle size for spherical glass particles. Zhou, X. et al. (2020) estimated the level of stress in a commercial hopper discharge test to be around 100 Pa and proposed a flow index. However, significant correlations were observed with the linear extrapolation of flow function coefficients FFc in a Schulze-type shear cell operating at 1 kPa; therefore, the results may be overestimated.

The gravity-driven powder discharge implies that flow rate can be only measured for relatively free-flowing powders. More cohesive powders agglomerate within the funnel (arching tendency). For more cohesive powders, wider openings and steeper funnel surfaces are typically used [Marchetti et al., 2021], although very cohesive powders cannot be analysed [Muñiz-Lerma et al., 2018; Marnani et al., 2019]. The use of alternative apparatuses, such as stirrers or fluidisation systems, and discharging techniques have been widely reported [Wu & Cocks, 2004; Yang & Evans, 2005; Ruppel et al., 2009; Seppälä et al., 2010]. These systems use external forces to break the agglomerates, but poor reproducibility has been recognised due to irregular flow patterns and inconsistent flow discharge. Despite its difficulties, the method is simple, easy to use and relatively relevant to dispensing and filling processes; thus, it is recommended for comparative purposes in pharmacopoeial and industrial standards. A 50 g sample has been reported reasonable for measurement.

2.5.1.2.2 Avalanche testing in rotary drum

Avalanche testing in rotating drums has been used since at least the 1950s to study the flow behaviour of powders and granular materials. However, its commercial implementation for powder characterisation under low-stress, dynamic conditions became more extended in the 1990s with the introduction of optical evaluation systems [Kaye et al., 1995; Lee et a., 2000: Wojtkowski et al., 2013]. The measuring principle involves testing a free surface under dynamic avalanche conditions. No additional stresses are introduced in the measurement, and low stress levels may be assumed [Lumay et al., 2012; Yang et al., 2017]. Indeed, the avalanche behaviour is similar to many industrial processes, such as mixers and granulators. A controlled stress – typically a vibrational frequency or rotation speed– is applied to a powder sample introduced in a rotating cylindrical blender with horizontal axis to induce an avalanche flow, as shown in *Figure 11*. Bulk flow properties are determined from the random rearrangement of the avalanche-induced broken frictional contact and interparticle forces from a previous avalanche event. As the drum rotates, the time between successive powder avalanches (cascading regime) is recorded at different rotating speeds by means of real-time image analysis, yielding an avalanche frequency distribution. Derived data, such as the mean avalanche time AT (s), avalanche angle

AA (°), avalanche energy AE (mJ/kg) and coefficient of variation, quantify the bulk flow properties. A 50 ml sample size has been reported as sufficient for reliable measurement.

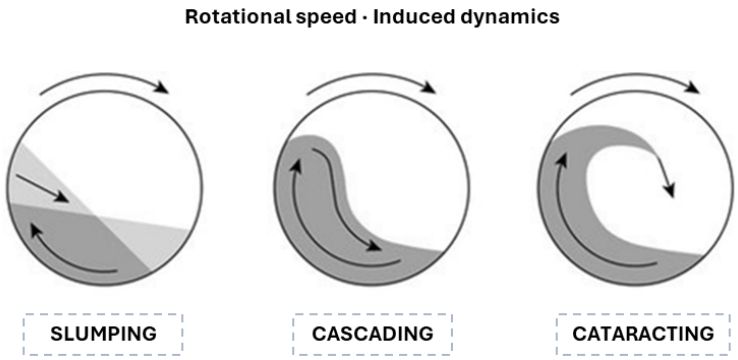


Figure 11. Main categories of avalanche behaviour observed in rotating drum avalanche testing. *Left*: Slumping, where the powder mass moves as a whole with minimal internal shearing. *Centre*: Cascading, a characteristic rolling motion with intermittent avalanches that defines the mean avalanche time (AT). *Right*: Cataracting, where particles detach from the surface and travel in a parabolic trajectory before landing. These behaviours provide insight into powder cohesion, flowability and interparticle interactions under low-stress dynamic conditions.

The test results are reportedly very dependent upon the method used, and the drum diameter, fill volume and rotating speed must be well defined for cross-comparisons. Different categories of avalanche behaviour, such as slumping, cascading or cataracting, can be clearly distinguished for non-cohesive powders [Hancock et al., 2004; Morrison et al., 2016; Trperkova et al., 2020]. The effect of shear strain rate can be determined at different rotational speeds [Janssen et al., 2021]. Although process-relevant measurements can be obtained for non-cohesive granular materials, rotational-induced segregation has been reported, leading occasionally to inconsistencies between measurements. Positive correlations have been reported between the dynamic and static angles of repose for non-cohesive materials [Lavoie et al., 2002; Yaginuma et al., 2007; Krantz et al., 2009; Nalluri & Kuentz, 2010; Lumay et al., 2012; Tay et al., 2017]. For cohesive powders, avalanching tests have been proposed as useful for assessing flow properties that were otherwise difficult or not measurable using other dynamic methods, such as hopper discharge techniques and dynamic testing in the FT4 powder rheometer [Tay et al., 2017; Hurychová et al., 2018]. Poor flow properties were associated with a more rugged contour line in the bulk solid. Difficulties in determining the bulk flow parameters due to powder agglomeration have been observed, due to the irregular avalanche surface and intermittent cascading regime [Lumay et al., 2012, 2016; Shi et al., 2020]. Adhesion to the drum walls also influenced the consistency of the measurements, leading to poor differentiation. Trperkova et al. (2020) compared the avalanche behaviour for a wide range of

materials to traditional tests. The lowest cohesion and highest flow function FFc measured by the rotary drum and shear cell (i.e., for round smooth particles as the best flowing material) translated to poor flow behaviour in the pharmacopoeial funnel test. A reasonable conclusion is that higher stresses in both the shear cell and avalanche techniques overcame the cohesive forces governing the flow behaviour at very low stresses. Shi et al (2020) estimated the lowest operating stress at around 400 Pa. However, it should be noted that this study investigated limestone particles, which typically exhibit a higher bulk density than pharmaceutical powders. Therefore, the operating stress should be interpreted with caution for more cohesive powders. Furthermore, the reported correlation between the internal angle of friction (AIF) measured in a Schulze-type ring shear cell and the flowing angle in the rotating drum was based on an extrapolation of the avalanche angle to zero rotation speed, rather than a direct comparison of operational conditions. Quantitative stress values reported in rotating drum studies vary widely depending on factors such as particle density and shape, drum size and rotation speed. Reported estimates for shear or normal stresses in the flowing layer range from tens to several hundreds of pascals, depending on the system [Bonamy et al., 2002; Renouf et al., 2005; Wang et al., 2024].

2.5.1.2.3 Powder rheometry

Automated dynamic powder testing was developed in the 1990s to address the analytical gap of accurate measurement of bulk powder flow properties under dynamic conditions. Powder rheometers have become increasingly popular in the past decade for use in multi-faceted powder flow testing methodologies. Modern rheometers offer multiple measuring techniques in the same setup, complementing dynamic testing with bulk properties data (bulk density, compressibility, and permeability) and shear cell analysis. The measured bulk properties have been recognised as helpful to interpret the measured flow behaviour [Freeman, 2007; Leturia et al., 2014; Nagashima & Ishikura, 2015]. Thanks to their versatility, ranging from consolidated to aerated or fluidised states, and degree of automation, powder rheometers are currently the state-of-the-art instruments for the analysis of flow behaviour in bulk solids.

Dynamic tests evaluate the torque resistance forces (axial and rotational) acting on an impeller (typically a helical two-blade stirrer) while traversing a pre-consolidated powder bed. A pre-test conditioning ensures a reproducible initial packing state for a confined fixed volume (i.e., a loosely packed bed), removing the packing history and thus improving reproducibility. In the FT4 powder rheometer, depending on the direction and speed of movement, several flow patterns and rates can be achieved [Freeman & Fu, 2008]. The basic flow energy BFE (J), also referred to as forced flow, is calculated from the confined flow pattern of the downward clockwise motion of the blade compressing the powder (i.e., in a higher stress environment) while the unconfined flow pattern upwards allows the powder to expand and yields the specific

energy SE (J) in a lower stress environment, also referred to as gravity flow (see *Figure 12*). For both tests, a greater value of flow energy is generally an indicator of reduced flowability [Kinnunen et al., 2014; Worku et al., 2017; Jüptner & Scherließ, 2019]. Derived parameters, including the flow rate index (FRI) and stability index (SI), characterise the sensitivity of the powder to changes in flow rate and the energy gradient between cycles, respectively. In this context, cohesive powders are more sensitive than non-cohesive or granular materials to changes in the flow rate and energy gradient; therefore, lower values indicate better flow performance. A 25 ml powder sample has been reported reasonable for dynamic tests.

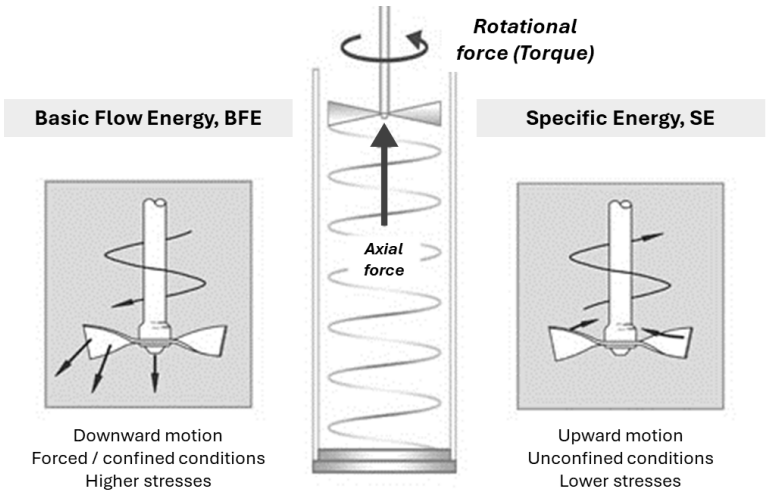


Figure 12. Dynamic testing in a powder rheometer. *Left*: Basic Flow Energy (BFE) measurement, where the downward, clockwise motion of the impeller compresses the powder bed under a higher stress environment (forced flow). *Right*: Specific Energy (SE) measurement, where the impeller moves upwards, allowing the powder to expand under a lower stress environment. The measured torque resistance forces provide flow energy values that indicate powder flowability, with higher values generally corresponding to reduced flow performance.

Dynamic testing in a powder rheometer can differentiate flow properties that otherwise exhibit similar behaviour under shear testing [Freeman, 2007; Zhou, Q. et al., 2010]. Freeman (2007) reported a significant correlation of the measured SE data with the cohesion parameter in the FT4 rotational shear cell, while BFE measurements were more sensitive to noncohesive powders and did not correlate with measured shear data. Freeman and Fu (2008) later described BFE as highly sensitive for differentiating small changes in flow properties. The FT4 dynamic tests have been correlated with other conventional tests, such as static angle of repose and compressibility, although the FT4 demonstrated improved sensitivity to material properties [Zhou et al., 2010; Leturia et al., 2014]. Over the years, numerous researchers have experimentally and numerically examined the mechanics of powder flow induced by the impeller. From

these studies, dynamic tests can be concluded to be more sensitive to frictional contact forces, such as those used for the differentiation of non-cohesive powders or the effect of particle shape. Difficulties in differentiation arise with increasing cohesion in response to decreasing particle size, very low stress environments or the presence of fines in the mixture.

Regarding the effect of particle size and shape, Bharadwaj et al. (2010) simulated the flow of non-cohesive materials using the discrete element method (DEM) and reported similar results to those of Freeman (2007). Particle size and size distribution had less effect on the mixing torque and force, whereas the particle shape was determined to be a major factor influencing dynamic flow measurements. Fu et al. (2012) analysed experimentally the effect of particle size and shape in three grades of lactose. Both particle shape and particle size had an effect on the measured flow energy, although particle shape was notably more influential. In this context, significantly higher flow energy values have been observed for irregular particles than for spheres, due to increased frictional contacts and facilitated mechanical interlocking [Nan et al., 2017; Vivacqua et al., 2019]. Higher SE values have been correlated to smaller particle sizes, whereas BFE remained insensitive [Tay et al., 2017; Van Snick et al., 2018; Zakhvatayeva et al., 2018]. Recently, López et al. (2019) examined the effect of particle shape on flow behaviour in screw feeders and FT4. A close relationship was found between the flow regimes in both devices at similar shear rates. Dynamic tests proved to subject powders to processing conditions similar to those found in screw feeders. Notably, powder flow in industrial operations is not necessarily actuated by a rotating impeller; therefore, its presence cannot be ignored [Ghadiri et al., 2020].

In terms of bulk friction and cohesion, Freeman and Fu (2008) described the mechanisms involved in the SE unconfined measurement and claimed that gravity dominates in this test. Thus, cohesion or particle-scale vdW forces may be the most influential property. Hare et al. (2015, 2017) examined the flow of cohesive powders using DEM and highlighted the influence of the coefficient of friction between particles in the measured flow energy. This work concluded that the resistance to flow was predominantly rotational. Wilkinson et al. (2017) confirmed these previous results and concluded that although frictional contacts play a major role in the determination of the BFE and SE, the cohesiveness of the powder also influences the flow energy. These results agree with the observed effect of particle size and shape on flow energy values. Pantaleev et al. (2017) optimised the model parameters in DEM simulations and observed that the BFE increased significantly when the moisture content was high (i.e., strong cohesive capillary forces). However, the difference in flow energy was not significant for the medium moisture content. Recently, Li et al (2018) examined cohesive powders using dynamic tests and reported difficulties to distinguish between similar materials. The lower sensitivity was linked to particle agglomeration behind the blade causing torque oscillations.

Concerning the effect of shear strain rate, the functional dependence of bulk cohesion on the shear strain rate has been analysed by various researchers [Luding, 2008; Berger et al., 2015; Vivacqua et al., 2019]. Following Coulomb´s law in Equation 6, numerical simulations showed that increasing the blade speed logarithmically decreases the influence of interparticle cohesive forces on the blade (i.e., the measured flow energy at higher strain rates was increasingly governed by frictional contact forces). This effect was attributed to the reduction in the coordination number. Nan & Wu (2020) confirmed the observations reported by Tardos et al. (2003), adding that the measured flow energy in dynamic tests increases with increasing strain rate.

With respect to filling of self-metered doses, several researchers have investigated the effects of material properties in the filling performance using FT4. SE data has been reported particularly relevant to predict powder flow properties in low stress applications, such as die and capsule filling [Freeman & Fu, 2008; Freeman et al., 2011; Osorio & Muzzio, 2013; Van Snick et al., 2018; Zakhvatayeva et al., 2018], although SE data alone do not correlate to filling performance. Freeman and Fu (2008) examined the effect of particle size in the flow energy on two model glass spherical beads and results were compared with the filling performance in a model die-filling rig. While larger particles (Dv_{50} > 100 μm) performed better in the die, the measured flow energy (BFE and SE data) showed significantly better flow properties for the smaller particles (Dv_{50} < 100 μm). Frictional contacts governed the flow behaviour and did not match in-process performance. Negative correlations with rotational rheometers were also recently reported using two different hopper discharge techniques, where cohesive forces govern the flow behaviour [Marchetti & Hulme-Smith, 2021]. Very low stresses such as those observed in gravitational hopper discharge, cannot be achieved. From these investigations it was concluded that for gravity filling processes powders having lower values of flow energy, FRI and compressibility may perform better.

2.5.2 Evaluation criteria

Several techniques are available to characterise the flow behaviour in bulk solids, each with its own advantages and limitations. In any case, there is a major requirement: the tested data must be relevant, correlating to some aspect of the process or product performance. The measuring principle determines the extent to which the processing conditions are reproduced [Swize et al., 2019; Stravrou et al., 2020]. Another important consideration is sensitivity: the tested data should differentiate subtle changes in material properties [Freeman & Fu, 2008; Schulze, 2008; Tay et al., 2017]. For instance, in formulation development, greater sensitivity facilitates the formulator to achieve a robust target flowability. In quality control (QC), improved detection of small variations in flow properties is essential for problem solving applications (troubleshooting). Sensitivity is highly dependent on the reproducibility and repeatability of the test. The degree of automation plays a crucial role here, as it

prevents operator-induced measurement errors. In this context, a well-defined setup and methodology ensure a reproducible degree of packing (and consolidation stress) between measurements and thus have a considerable impact on reproducibility and sensitivity. Standardised test protocols also enhance the quality of the data for cross-comparison. Leturia et al. (2014) reviewed the significance of sample conditioning before measurements to eliminate any packing history in the bulk solid and thus improve reproducibility.

Although relevance and sensitivity measure the quality of a technique, its practicability cannot be neglected. Some qualitative techniques have proven particularly useful for QC, as they are quick, easy to use and can be performed on site to sort and compare materials, while others are quantitative, providing control of the consolidation stress and thus being informative in the design of manufacturing processes [Wu et al., 2012; Leturia et al., 2014]. To date, the use of shear cell analysis has only been demonstrated for silo and hopper process design, while other available techniques are used for comparison of materials under different processing conditions. Here, some criteria for a test apparatus to assess the filling of self-metered doses in the tablet press are proposed (Table I). Additionally, beneficial characteristics for a flow tester applied during early formulation development and for QC purposes are included.

Table I. Classification of the reviewed flow testers according to the following evaluation criteria.

1. Operates in the dynamic regime at high strain rates – relevant to the filling processes
2. Achieves very low consolidation stress (<100 Pa) – relevant to the filling processes
3. *Enables shear strain rate analysis* – relevant to the maximum filling speed
4. *Ensure a high level of automation* – minimises dependency on the operator and the method used
5. *Provides standardised sample conditioning* – eliminates packing history and ensures reproducible packing
6. Offers a high level of sensitivity – improves material comparison
7. *Require low sample consumption* (< 10 ml) – applicable early in small-scale R&D
8. *Deliver quick measurements* (< 5 min) – suitable for QC purposes
9. Generate intuitive results – no expertise needed
10. Ensure easy to use – no expertise needed

"Unclear" indicates that the criterion has not been conclusively verified, or its fulfilment depends on specific conditions. "Varies" suggests that the applicability of the criterion depends on material properties, test settings, or specific experimental conditions.

Evaluation criteria	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Shear cell tests	No	No	No	Yes	Yes	Varies	No	No	No	No
SSSpinTester	No	Yes	No	Yes	Yes	Varies	Yes	Yes	Yes	Yes
Dynamic rheometer	Unclear	No	Yes	Yes	Yes	Varies	No	No	No	Yes
Avalanche testing	Unclear	No	Yes	Yes	No	Varies	No	No	Yes	Yes
Angle of repose	No	No	No	No	No	No	No	Yes	Yes	Yes
Flow through an orifice	No	No	No	No	No	No	No	Yes	Yes	Yes
Tapping studies	No	No	No	No	No	No	No	No	Yes	Yes

Observation remarks

- High strain rates (criterion no. 1) observed during filling processes may not be achieved in bulk dynamic tests (classified as unclear in *Table I*). The shear stress increases with the strain (or flow rate) for a bulk contact solid bed, while the influence of cohesive forces logarithmically decreases (*Section 2.5.1.2.3 "Powder rheometry"*). For instance, no correlations have been found for high strain rate applications using powder rheometers, such as AM and filling processes, where cohesive forces govern powder flow behaviour.
- Very low stresses (criterion no. 2) assumed during filling operations may not be accurately determined from bulk powder analysis in either the static or dynamic regime. The weight of the powder bed may be an additional source of consolidation stress, increasing particle contact areas and preventing the very loose packing states observed during filling processes (*Figure 3*). Stresses below 100 Pa have only been reported for the SSSpinTester, where rotation-induced dynamics act on a very small amount of powder.
- Dynamic tests exhibit higher sensitivity to non-cohesive materials (criterion no. 6), as fine cohesive powders form clusters that impair dynamic flow measurements. Cohesive materials are best differentiated in the static regime, where higher consolidation stresses neglect the spatial (cohesive) distribution of the powder observed at lower stresses.

3 · Aims of the study

The goal of this thesis was to advance the understanding and control of powder flow behaviour in small volumes and its differences from bulk solid systems, with a particular focus on tablet manufacturing. Accordingly, the aim was to develop and evaluate a novel test method to characterise and rationalise die-filling processes. *The numbers in parentheses (I–IV) correspond to the List of Publications.*

More specifically, the objectives of this thesis were to:

1. Design and validate a robust and reproducible method for powder flow analysis relevant to die-filling processes (**I**)

2. Verify the accuracy, reliability and consistency of the method by linking material performance to manufacturing properties in small-scale R&D tablet presses (**I, II**)

3. Assess the quality of the method by benchmarking it against state-of-the-art flow characterisation techniques and evaluating its sensitivity to subtle changes in material characteristics (**I, II**)

4. Investigate additional applications throughout the drug development process (**III, IV**)

4 · Experimental

4.1 Materials

4.1.1 Model compounds

A broad class of materials with different particle physical properties, ranging from cohesive to free-flowing powders, were investigated. These included a total of 12 active ingredients (APIs) and excipients (*Table II*).

Table II: Model compounds investigated. The roman numerals indicate in which publication each compound was used.

Type	Grade	Abbreviation	Functionality	Supplier
Microcrystalline cellulose MCC (I)	Avicel® PH-200	PH200	Filler-binder, Flow aid, Binder. DC grade	JRS Pharma, Rosenberg, Germany
Microcrystalline cellulose MCC (I)	Avicel® PH-102	PH102	Filler-binder, Flow aid, Binder. DC grade	FMC BioPolymer, Ireland
Microcrystalline cellulose MCC (I)	Vivapur® 101	PH101	Binder, Flow aid, Diluent	JRS Pharma, Rosenberg, Germany
Lactose monohydrate (sieved) (I)	Pharmatose® 80 M	L80M	Filler-binder, Diluent, Flow aid, Binder	DmVFonterra Excipients, Veghel, NL
Lactose monohydrate (milled) (I, II)	Pharmatose® 200 M	L200M	Filler-binder, Diluent, Thinner, Binder	DmVFonterra Excipients, Veghel, NL
Native potato starch (I)	Fine grade	Starch	Filler-binder, Disintegrant, Binder	Chemical GmbH, Espoo, Finland
Vortioxetine (IV)	Ph. Eur. grade	-	API	Zentiva k.s., Prague, Czech Republic
Palbociclib (III)	Ph. Eur. grade	-	API	MSN Inc., New Jersey, USA
Caffeine (I)	Ph. Eur. grade	-	API	ORIOLA, Espoo, Finland
Acetaminophen (I)	Ph. Eur. grade	APAP	API	ORIOLA, Espoo, Finland
Colloidal silicon dioxide (II)	Aerosil® 300	CSD	Glidant	Evonik Industries, Essen, Germany
Magnesium stearate (II)	Ph. Eur. grade	MgSt	Lubricant	Orion Pharma, Espoo, Finland

4.1.2 Sample conditioning

Pre-test conditioning significantly improves analytical reproducibility by producing a homogeneous, loosely packed powder bed. Prior to analysis, all powders were manually sieved through a 710 μm sieve to remove possible lumps resulting from consolidation during storage ‘caking’, releasing air from an overly aerated sample or introducing it into a compacted one, thus eliminating powder processing history. This also standardised the size of lubricant aggregates, which is known to determine MgSt

surface distribution. Most experiments were conducted in a humidity-controlled environment, at 30–35% RH (Testo 440 kit, resolution 0.1% RH, West Chester, PA, USA). During handling and storage, powders can easily absorb moisture from the air, as the ambient RH is generally higher than the equilibrium RH of most dry commercial powders. Thus, samples were conditioned for 5 days in a controlled environment.

When required (II), powder samples were weighed individually and stored separately in anti-static polystyrene weighing dishes for 5 days in four different desiccators with adjusted humidity, at 25 °C (23% RH: CH_3CO_2K; 33% RH: $MgCl_2$ $6H_2O$; 43% RH: K_2CO_3; 53% RH: $Mg[NO_3]_2$). This single-sample preparation process minimised moisture exchange during the analysis. Surface water activity, or the vapor pressure of water, was determined using an AquaLab Model Series 3TE (Decagon Devices, Inc., Washington, USA). Loss on drying (LOD) was measured thermogravimetrically using a Moisture Analyzer (MA100, Sartorius AG, Göttingen, Germany) and the temperature specifications detailed in the pharmacopoeia [Ph. Eur. 2.9.39]. All measurements were performed in triplicate ($n=3$) unless otherwise specified.

4.2 Methods

4.2.1 Material characterisation

Particle size and size distribution (PSD) were determined by laser diffractometry using both dry and wet methods (I, III). All measurements were carried out in triplicate and average values were calculated. Particle morphology and surface microstructure were examined using scanning electron microscopy (SEM; Quanta FEG250 SEM, ThermoFisher, Oregon, USA; equipped with a large field low vacuum detector [LFD]). Powder samples were sputtered with gold or titanium prior to the examination. SEM measurements were performed at 15 kV with a beam current of 2×10^{-10} A and the distance to the sample was set at 15 mm to achieve good image quality (I, III).

For dry laser scattering diffractometry (I), measurements were performed using the Malvern Mastersizer 3000 (Malvern Instruments Co. Ltd., Worcestershire, UK). Dry powder samples were prepared to generate single particle measurements using the Aero S dry powder disperser equipped with a microvolume sample tray (2 to 10 grams), applying pressurised air at 3 bar and a vibration feed rate of 50%. The dispersed particles move through the measurement zone, where a laser beam was directed. The particles scattered the light, producing a diffraction pattern collected by detectors at various angles. MS3000 software (v3.5) was used to generate the PSD data.

For wet dispersion measurements (III), a Mastersizer 2000 with Hydro 2000S (Malvern Instruments Co. Ltd., Solihull, UK) was used. Given the high toxicity of Palbociclib in dry conditions and the substantial sample requirement (over 2 grams),

the wet dispersion method was chosen. The drug powder (200 mg) was added to 50 mL of water and 0.05 mL of Tween 80. To prepare a dispersion, the sample was stirred and mixed for 10 minutes (±30 seconds) and then immediately placed in the diffractometer until a stable obscuration between 10% and 20% was achieved. The refractive index for the dispersion medium (water) was set to 1.33, and the value for the particle was selected based on published refractive indices of the respective compound. The stirring speed was set to 2100 rpm, and the measurement duration was 30 seconds.

4.2.2 Formulation development

Mixtures were prepared using a laboratory-scale 3D shaker mixer (Turbula T2C, W.A. Bachofen, Switzerland). 2L glass container with a 50% filling ratio (2L container, batch size ± 500 g) and medium rotation speed (34 rpm) were the standard processing parameters (II). Pre-blending of the formulation constituents was performed for 20 minutes to ensure a homogeneous distribution of the model components in the mixture. After pre-blending, magnesium stearate was added and blended for an additional 5 minutes to ensure uniform distribution.

Milling (III) was conducted using a vibrational ball mill (MM 200, Retsch, Haan, Germany). 250 mg (± 0.1 mg) of the model drug and three 9 mm stainless steel balls were placed in a 25 mL stainless steel milling jar. The milling process took 15 min at a frequency of 15 Hz. Granules (IV) were prepared using pilot-scale fluidised-bed granulators (Glatt WSG CD 15, Glatt Ingenieurtechnik GmbH, Germany and Niro-aeromatic T-5, GEA Group, Germany). Granulation was performed using a top-spray process with aqueous binder solutions. The spraying parameters were already optimized to ensure uniform granule formation while maintaining batch-to-batch consistency, reproducing real-world manufacturing conditions (*Table III*). During granulation, product temperature (PTDS) was closely monitored, and loss on drying (c-LOD) was determined post-processing to ensure optimal moisture content, a critical factor for maintaining granule stability and downstream processability.

Table III. Comparison of processing conditions for the two granule batches prepared using different pilot-scale fluidised-bed granulators.

Coding	Equipment	Nozzle size (mm)	Spraying pressure (bar)	PTDS (ºC)	c-LOD (%)	Size (kg)
Sample A	Glatt WSG CD	1.2	2.0	23.0	1.3	15
Sample B	Niro-aeromatic	1.8	4.5	21.5	1.7	120

4.2.3 Flow testing methods

4.2.3.1 Bulk flow techniques

Pharmacopoeial tests

Flow through an orifice and tapping studies were conducted according to pharmacopoeial guideline (Ph. Eur. 2.9.36). Bulk and tapped densities were calculated using the procedure 'Measurement in a graduated cylinder' and Erweka SVM equipment (Erweka Apparatebau GmbH, Germany). Haussner Ratio (HR) and Carr Indexes (CI) derived from the tapping studies, as described in *Section 2.5.1.2.1 ("Pharmacopoeial methods")*. Powder flow rate through an orifice was determined for 50 grams of powder in a pharmacopoeial standardised funnel (Ø = 9 mm), as described in *Section 2.5.1.2.1 ("Pharmacopoeial methods")*.

Powder rheometry

Dynamic and failure tests were conducted in a FT4 powder rheometer (Freeman Technology, Worcestershire, UK). The device was calibrated prior to analysis in terms of height, force and torque, and all the analysis protocols were integrated with conditioning and test cycles. A more detailed description of the powder rheometer is given in *Section 2.5.1.2.3 ("Powder rheometry")*.

Flow energy measurements or dynamic tests were conducted in a 25 mm X 25 mL splitting cylindrical vessel. Conditioning and test cycles were performed using a precision impeller blade with a helix angle of −5° and 23.5 mm in diameter. Conditioned bulk density CBD, specific energy SE (mJ/g), basic flowability energy BFE (mJ), stability index SI (-) and flow rate index FRI (-) data were generated. Flow energies (BFE and SE) and derived parameters (FRI and SI) were measured using a blade tip speed of 100 mm/s for the former and 100, 70, 40 and 10 mm/s for the latter.

Failure measurements or static tests in shear cell were performed in a 25 mm X 10 mL splitting cylindrical vessel. Powder samples were conditioned using conditioning wire and pre-consolidated at 9 kPa using a vented piston. Shear analysis was conducted using a 24 mm shear cell head accessory [Freeman, 2007]. Cohesion (kPa), flow function FFc (-), unconfined yield strength (UYS) and angles of internal friction AIF (°) data were generated.

4.2.3.2 Novel measuring system

The measuring principle determines the extent to which the processing conditions are reproduced. General guidelines were followed to standardise the measurements [Schulze, 2008; Ph. Eur. 2.9.16, Ph. Eur. 2.9.36; USP <1174>], with an emphasis on die-filling processes (*Figure 13*).

RELEVANCE TO THE FILLING PROCESS	IMPORTANT CONSIDERATIONS
SIMILAR MECHANISM TO THE FLOW OF POWDER THROUGH A DIE CAVITY	**FLOW DETERMINED BY THE MOVEMENT OF POWDER-ON-POWDER**
Hooper discharge techniques or funnel-based design	Flat-face or truncated funnel to minimize powder-wall friction
	Option to vary the funnel aperture and provide maximum flexibility
VERY LOW STRESS ENVIRONMENT AND DYNAMIC CONDITIONS	Steep funnel to promote mass flow, preventing blockages and irregular flow patterns
Measurement of very small amounts of powder sample in motion	
No additional external sources of consolidation stress	**WELL-DEFINED TEST PROTOCOLS AND HIGH LEVEL OF AUTOMATION**
	Standardize sample conditioning procedure
HIGH STRAIN RATES IN A FUNNEL-BASED GEOMETRY	Controlled consolidation stress
Controlled applied stress to discharge the sample, i.e., other than gravity	Machine vision-based testing setup

Figure 13. General considerations and development criteria.

Measuring principle

Miniaturised powder flow through an orifice involves small scale testing of powder flowability in a horizontally positioned funnel-based geometry. It is the discrete measurement of the shear stress acting on a powder specimen as it flows from an orifice. A precisely controlled stress (linear motion) is applied to discharge the powder sample, replacing gravity in conventional hopper discharge techniques. No additional stresses are introduced into the measurement. The flow behaviour is inferred from observable changes in the system via image analysis (semiquantitative technique). A pre-test conditioning process ensures a reproducible initial packing state for a fixed powder volume.

Uniformly accelerated rectilinear motion induces the dynamics in the measuring system, as discussed in *Section 2.1 ("Principles of Classic Mechanics")*. The motion is considered in two separate parts (*Figure 14*), which presents model-based kinetic profiles for displacement, velocity and acceleration. During displacement, the system accelerates to a defined top speed (acceleration phase) and then brakes to a stop (deceleration phase). Each phase has its own constant acceleration, being significantly higher during the deceleration phase. If one neglects the gravitational force acting on the solid specimen and assumes that no friction occurs between the powder and the horizontal plane surface during motion (vertical stress), then the flow behaviour is the result of frictional and collisional interactions between particles. The net force (or breaking force) at the beginning of deceleration is the only external force affecting the motion of the particulate solid. Depending on the magnitude of the acceleration, different flow patterns and rates can be achieved. The so-called micro-dynamic flow properties characterise the internal forces counteracting the induced dynamics, according to material properties.

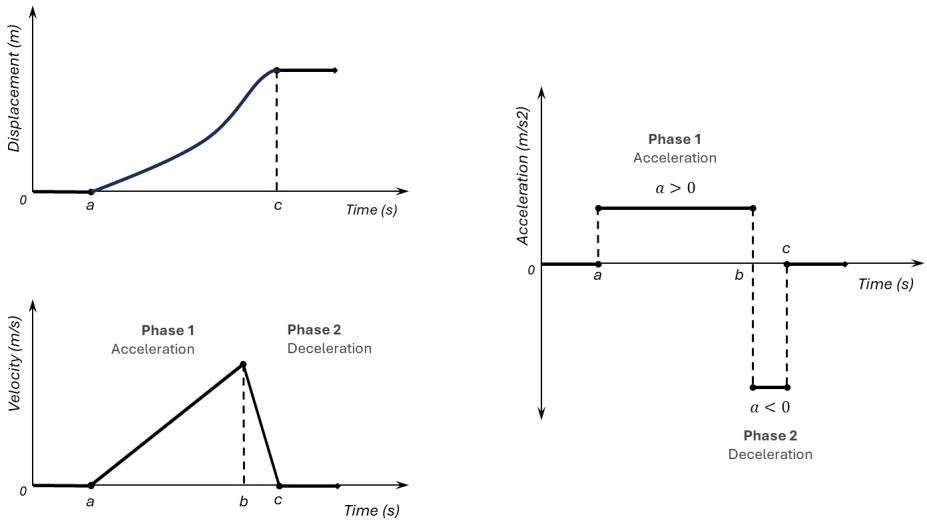


Figure 14. Kinetic (model) profiles in the measuring system for displacement (m), velocity (m/s) and acceleration (m/s^2), where *a, b* and *c* represent changes in velocity. Initial and final positions, *a* and *c*, respectively. Acceleration and deceleration stages are differentiated.

Testing setup

The machine vision-based testing setup consists of a sample cuvette mounted on a linear actuator, where the cuvette is illuminated from below and monitored from above (*Figure 15*). The cuvette comprises two horizontally positioned chambers separated by an orifice. The powder sample (0.2 cm^3) is placed in the left chamber (a) and the cuvette is subjected to a specific acceleration profile as it moves to the right, as described in *Figure 14* and *Figure 15*. Deceleration-induced dynamics discharge the sample through the funnel into the opposite imaging chamber (c), where a pivot (b) disturbs the powder flow stream. The resistance of the powder to such displacement yields unique flow patterns, depending on material properties. Advantageously, the horizontal positioned measurement setup enables cutting-edge imaging of powder flow properties. Test results are very dependent on the testing setup: the funnel geometry and the motion profile must be well defined for cross-comparison.

Additional frictional and collisional interactions between particles were a prerequisite for the analysis of very small amounts of powder in dynamic conditions. Otherwise, material properties were poorly differentiated. Interparticle cohesive forces govern flow behaviour at such low stress environments, easily counteracting particle motion. Powder-pivot collisions induced changes in particle trajectories, velocities and orientations, thereby redistributing internal forces acting in the particulate system. Particle velocities remain high until the impact, when the controlled flow rate from the funnel undergoes certain aeration. Force redistribution reduces physical contacts

between particles, thus minimising cohesive forces and powder agglomeration. The powder flow pattern arises from the 'separated' mass at high strain rates.

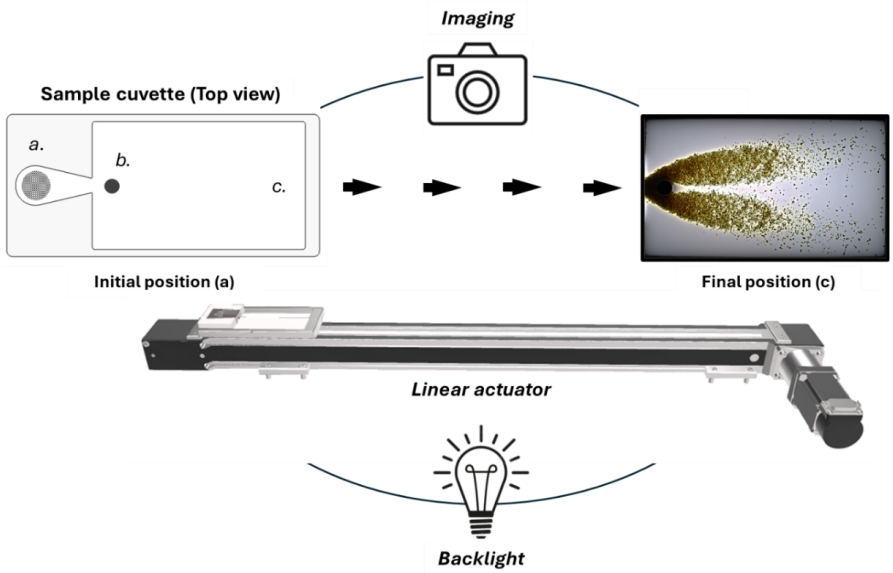


Figure 15. Schematic representation of the testing setup for powder flow analysis. The sample cuvette is mounted on a linear actuator, illuminated from below, and monitored from above. The cuvette is shown at its initial (a) and final (c) positions after the deceleration stage, when the powder flow pattern is created. The measuring cuvette consists of three main components: (a) a funnel part that holds the powder sample, (b) a pivot, and c) an analytical chamber. The black arrows indicate the cuvette's motion along the linear actuator. *Adapted from Blanco, D., et al. (2020).*

Initially, a prototype was designed and developed to test the hypothesis **(I, II).** This included a controlled humidity cabinet to simulate various manufacturing scenarios. Volumetric sampling was selected for the analysis, as die filling is a volumetric process and is preferable when assessing the flow through an orifice [Ph. Eur. 2.9.36; USP <1174>]. A volume of 0.20 cm^3 was set as the standard to prevent complete discharge from the analytical chamber, ensuring a powder-on-powder flow pattern, as recommended in previous chapters of the pharmacopoeia and described by Schulze (2008). Bulk density, ρ_b, calculated from tapping studies, was used to determine the sample weight, as described in Blanco, D., et al. (2020). Image processing defined the flowability as a single value, micro-dynamic flow index MFI (%), calculated from the area fraction or percentage of pixels occupied by the powder after flowing through the orifice (*Figure 16*). Higher MFI values indicate better flow properties as lower shear stresses counteract the applied dynamics (i.e., lower cohesion within the powder mass). Other relevant flow descriptors, such as agglomeration or dispersion, and the presence of processing-related foreign bodies, were qualitative for this prototype.

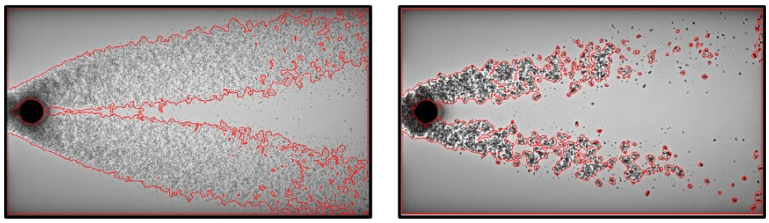


Figure 16. Example of micro-dynamic flow index (MFI) calculation for a free-flowing sample (left) and a more cohesive sample (right). MFI is determined from the area fraction or percentage of pixels occupied by the powder after flowing through the orifice. Higher MFI values (left) indicate better flow properties with lower cohesion, while lower MFI values (right) correspond to more cohesive powders.

The testing setup was then optimised (*Figure 17*), including precise motion control, high-resolution digital imaging and interchangeable funnel geometries for maximum flexibility (**III, IV**). This allowed an analysis of both coarser materials and more cohesive powders. The shear stress (or flow rate) in the measurement system resulted from the combined effects of funnel geometry and motion profile. For cohesive (or fine) powders (Dv_{50} < 100 µm), where attractive forces exist between particles, these must be overcome to initiate flow. Higher breaking forces and wider funnel orifices facilitated the flowability of more cohesive powders. For non-cohesive (or coarse) powders (Dv_{50} > 100 µm), where the particle weight overcomes attractive forces, particles begin to behave as individual units. This frictional shear stress was determined by increasing the strength (and number) of interparticle contacts. Higher breaking forces and/or narrower funnel orifices promoted frictional and collisional interactions. Therefore, by controlling the flow rate, larger areas of powder flow patterns were generated depending on material properties, significantly increasing the sensitivity of the test method. The dome-shaped portion in the new testing setup showed an improved reproducibility between measurements, suggesting a more structured arrangement of the powder sample during the acceleration stage.

High-resolution imaging allowed for improved characterisation of the observed flow behaviour. MIPAR software (MIPAR Image Analysis, LLC, Worthington, OH, USA) was used for image processing and particle characterisation to ensure accurate segmentation and data extraction. For cohesive materials, the agglomeration ratio, AG (dimensionless, from 0 to 1), described the cohesive forces acting in the particulate solid and was quantitatively determined from the area fraction or percentage of darker pixels within the powder flow pattern. For non-cohesive materials, the agglomerate fraction described darker coarse particles, which contrasted with the lighter fine fraction.

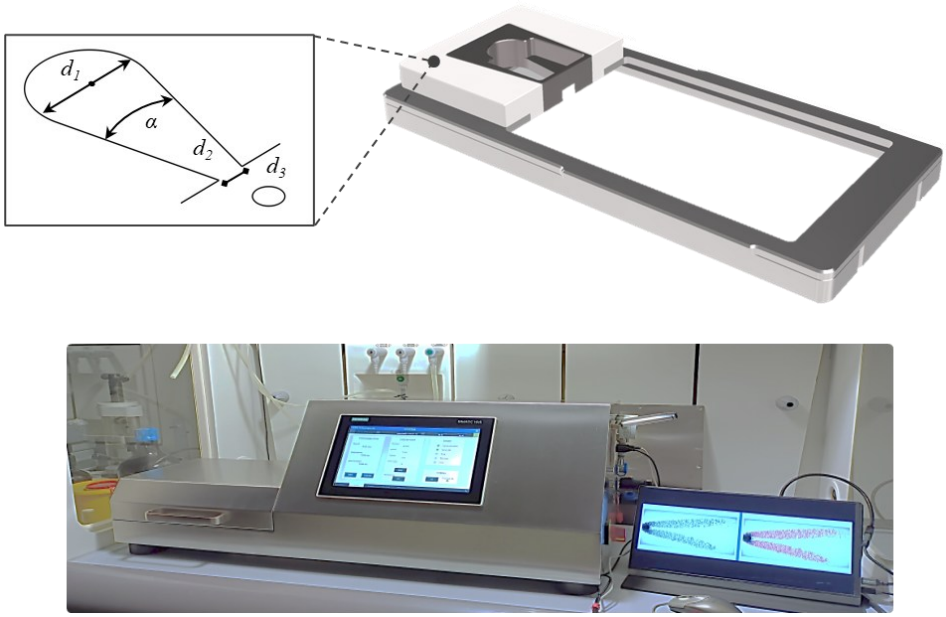


Figure 17. Detailed diagram of the funnel part in the sample cuvette and image of the optimised measuring system (Prototype v.4), where d_1 is the diameter of the dome-shaped portion, α is the angle of incidence, d_2 is the diameter of the orifice and d_3 is the diameter of the pivot. Specific dimensions for these parameters can be found in Blanco Fernández (2024). *Adapted from Blanco, D., et al. (2023).*

An example of agglomeration phenomena due to cohesion is shown in *Figure 18*. To achieve this, histogram analysis and Otsu's method were applied to automatically isolate the darkest regions via thresholding [Sezgin & Sankur, 2004]. In practical terms, this approach divides the grayscale image into two major classes (cohesive agglomerates and individual particles) without requiring any manual input. Although Otsu's method is effective when the image histogram exhibits relatively bimodal distribution (e.g., distinctly darker cohesive lumps vs. brighter, smaller particles after milling), further refinement may be needed in cases where single, dense particles have similar grayscale values to those of agglomerates.

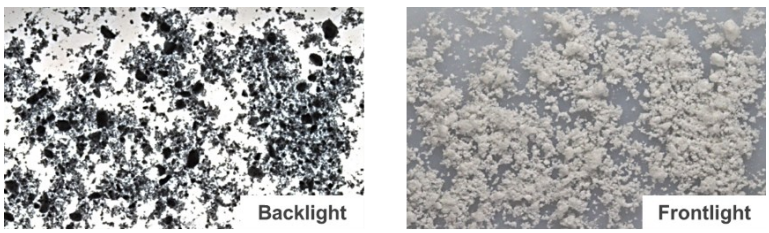


Figure 18. Agglomeration phenomena under different lighting conditions using the method. *Left*: Back lighting. *Right*: Front lighting. *Adapted from Blanco, D., et al. (2025)*.

In the early stages of R&D such as during early API characterisation when available material is limited, bulk density cannot be determined using conventional methods. A miniaturised sampling apparatus was designed which, after applying a controlled consolidation stress (5 seconds of mechanical vibration), doses the standard volume (0.20 cm^3). The packing density PD (g/cm^3) was calculated from the weight of the consolidated volume. This is a measure of the packing properties of a material and can be used for comparative purposes.

Sample conditioning: Initial packing state and pre-consolidation

A well-defined methodology was a prerequisite for consistent and reproducible deposition of the powder sample into the cuvette. Sieving and gravity feeding were combined to remove the packing story and to minimise the stress applied to the sample prior to measurement. This two-step procedure ensured (i) a loosely packed initial state and (ii) minimal operator intervention. Sample feeding was performed by means of a plug-in accessory to the cuvette already placed in its final position for analysis, as shown in *Figure 19*. First, the operator weighs the sample (0.20 cm^3), which is sieved and deposited in the funnel (closed orifice). The funnel orifice is then opened, and the sample is discharged by gravity into the centre of the analytical chamber of the cuvette. A wide opening and a polished, steep funnel surface facilitated the discharge of the small sample amounts, even of very cohesive materials.

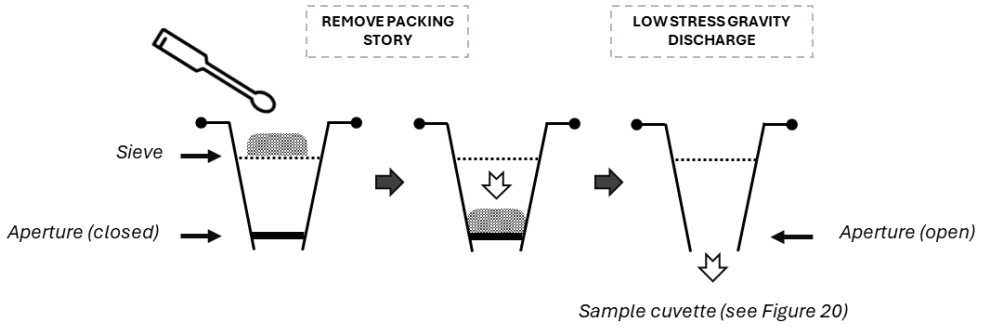


Figure 19. Schematic view of the feeding apparatus and loading procedure in the sample cuvette. *Left*: Sample loaded. *Centre*: Sample sieved and deposited into the funnel with the aperture closed. *Right*: Sample discharged into the cuvette when the aperture is opened.

After loading the sample into the cuvette, the initial acceleration stage pre-consolidates the sample, as shown in *Figure 20*. As an inherent aspect of the measurement principle and its motion, this pre-consolidation phase is highly dependent on the acceleration phase (or measuring conditions) applied during testing. A more detailed description of the acceleration phase is given in *Figure 14*. The pre-consolidation step further standardises the loosely packed initial state for the fixed

volume. Samples are subjected to the same acceleration profile for cross-comparison. Considering the area of the consolidation plane, the net force (or normal force) in the acceleration phase is proportional to the pre-consolidation stress. Since the weight of sample is very low, the expectation of very low consolidation stresses is reasonable. Advantageously, the direction of the applied load or orientation of the major principal stress is linear for both the pre-consolidation and subsequent discharging [Schulze, 2008].

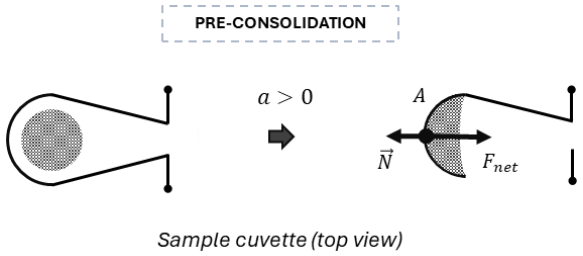


Figure 20. Schematic view of the pre-consolidation step in the sample cuvette after loading the sample. *Left*: Sample discharge into the funnel part of the cuvette. *Right*: Pre-consolidation stress in the powder sample, where $\vec{N}$ is the normal force calculated from the applied net force, F_{net}, and A is the area of the consolidation plane. The pre-consolidation step depends on the acceleration phase (or measuring conditions) applied during testing and standardises the initial packing state.

4.2.4 Lab scale compression studies

Powder compression studies were conducted using an eccentric tablet press (**I**, Type F3, Manesty Machines LTD, Liverpool) equipped with a gravity feeder and a concave single-punch (Ø = 5 mm, 60 tablets min^{-1}) and an eccentric tablet press (**II**, EKo, Korsch, Berlin, Germany) equipped with a force feeder (multiple paddles) and a flat single-punch (Ø = 9 mm, 60 tablets min^{-1}). The equipment selection depended on the specific properties of the powder and the desired outcome. In all cases, powder was loaded into the hopper to approximately 3 cm from its top. Between batches, the equipment was cleaned, and the feeder-loading process was repeated. Over the production time, the powder bed consolidates at the hopper due to mechanical tapping, affecting the tablet physical properties and filling performance. From each batch, initial tablets were removed from the analysis.

4.2.5 Tablet characterisation and data analysis

Die-filling performance was assessed by two methods: first, from the tablet mass variation (**I**) and second, from the die-filling ratio (**II**), as a reliable descriptor of powder flow properties inside the tablet press. All measurements were conducted in

triplicate. Mass variation was determined according to pharmacopoeial guidelines [Ph. Eur. 2.9.40, USP <905>], which specify weighing 10 dosage units. However, in this study, 50 dosage units were weighed to allow for a more detailed statistical evaluation, as moderately/poor-flowing materials were analysed. Mean, standard deviation and relative standard deviation (RSD) were calculated based on this expanded sample size. Die-filling ratio was determined by comparing the experimental tablet weight to ideal/theoretical weight (optimal die filling) for 100 dosage units, calculated from bulk density data, ρb, from the tapping studies, and the effective die fill volume in the tablet press [Mills and Sinka, 2013]. MatLab (v.2018b, Mathworks Inc., Natick, Massachusetts) analysis software was used to model the data and build suitable interpolation and smoothing algorithms. Multiple comparison test (Tukey's Honest Significant Difference) explored the differences between data sets (**II**). One-way analysis of variance (ANOVA) analysed the differences within a data set (**I, II**).

5 · Results and discussion

5.1 Operational range in early-stage R&D tablet presses (I, II)

This section examined the operational fundamentals governing micro-dynamic flowability and their relevance to filling processes in small-scale R&D tablet presses. First, the effect of consolidation stress among dynamic flow testers was investigated and systematically compared to the operating conditions in the tablet press (*Section 5.1.1 "Consolidation stress and flow properties"*). Next, the miniaturised funnel test was applied to understand and characterise the mechanisms of flow enhancement and cohesion in another filling geometry (*Section 5.1.2 "On the mechanisms of flow enhancement and cohesion"*). Subsequently, failure measurements or static shear cell tests were included for comparison, aiming to further understand the differences in flowability across flow regimes and to assess their sensitivity to particle characteristics and material differentiation (*Section 5.1.3 "From static to dynamic conditions"*). Commercial raw materials typically used in OSDs manufacturing, including APIs and excipients, were studied to assess the influence of primary particle properties on the observed flow behaviour. Laser diffractometry and SEM were used as supporting techniques, and mass variation-based assessment of die-filling performance served as a direct descriptor of flow behaviour inside the tablet presses.

5.1.1 Consolidation stress and flow properties

Small tablets (Ø = 5mm) and gravity feeding constituted a basic filling geometry operating in a very low stress range with high flow requirements. Initially, coarse-grade MCC PH200 (microcrystalline cellulose with larger particle size, typically ~180–200 μm), medium-grade MCC PH102 (microcrystalline cellulose with intermediate particle size, ~90–110 μm), fine-grade MCC PH101 (microcrystalline cellulose with small particle size, ~50 μm), lactose L200M and starch were selected as model compounds due to their clear differences on particle size distributions (*Section 5.1.1.1 "Relevance to filling performance"*). The remaining materials, known for their poor compactability, were excluded from this initial section as they could not be processed in the tablet press nor assessed for mass variation. The level of consolidation stress during the filling process was investigated and systematically compared to dynamic flow tests and Ph. Eur. Tapping studies, including dynamic tests using in powder rheometer, the Ph. Eur. Funnel test and the miniaturised funnel test. Static shear cell analysis is not predictive for dynamic flow applications [Shi et al., 2020; Zafar et al. 2021], as evidenced in *Section 5.1.3 ("From static to dynamic conditions")*, and was intentionally excluded. To deepen the understanding of consolidation stress effects on dynamic flow properties and their relevance to the actual flow behaviour in the tablet

press, additional materials (listed in *Table IV*), were included in a subsequent analysis (*Section 5.1.1.2 "Effect of bulk friction and cohesion"*).

The selected materials exhibited significant differences in PSD and morphology (*Table IV* and *Figure 21*), ranging from free flowing to highly cohesive powders. MCC grades (PH200 and PH102) and fine-grade PH101 appeared as elongated, fibrous, irregular particles with clear differences in PSDs. Lactose grades (sieved L80M and milled L200M) showed as tomahawk-like shape with significant different PSDs resulting from their respective manufacturing process. Starch particles were small, spherical-shape, and exhibited a narrow PSD. Caffeine crystals presented as silky, needle-shape particles, forming fleecy masses due to cohesion. Acetaminophen (APAP) appeared as small, elongated, irregular plates. Medium-grade MCC PH102 was considered at the boundary between acceptable and poor flowing performance for high-speed machinery, as generally acknowledged in powder technology [Sun, 2010; Van Snick et al., 2018].

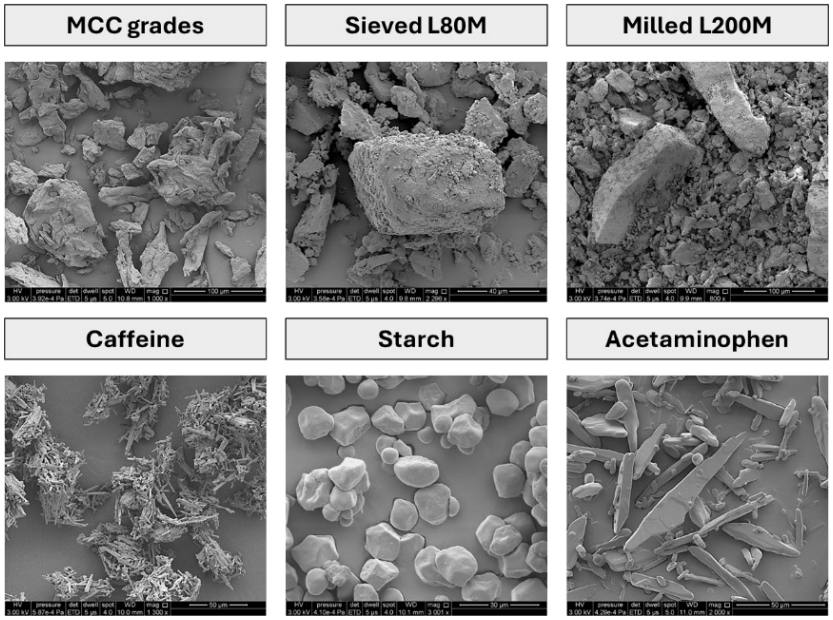


Figure 21. SEM micrographs for cellulose (MCC PH102), lactose grades (sieved L80M and milled L200M), caffeine, starch and acetaminophen (APAP), showing significant differences in particle morphologies. *Adapted from Blanco, D., et al. (2020).*

Table IV. Laser diffractometry data for the selected materials (*n=3*), showing clear differences on particle size distribution (PSD).

	PH200	PH102	PH101	L80M
Dv_{10} (μm)	40.83±0.38	23.40±0.10	21.47±0.15	39.80±2.03
Dv_{50} (μm)	189.33±1.15	102.67±0.58	63.20±0.17	212.67±2.08
Dv_{90} (μm)	427.67±2.08	259.33±0.58	142.33±0.58	389.67±2.08
Span	2.04±0.01	2.26±0.01	1.91±0.01	1.65±0.01
Uniformity	0.64±0.01	0.710±0.00	0.59±0.00	0.48±0.01
SSA, m^2/kg	64.70±0.50	146.00±4.80	104.10±10.50	111.50±0.50
	L200M	**Caffeine**	**Starch**	**APAP**
Dv_{10} (μm)	6.21±0.36	4.73±0.09	9.72±0.07	4.01±0.01
Dv_{50} (μm)	40.10±0.95	40.97±0.75	20.80±0.20	20.73±0.23
Dv_{90} (μm)	131.33±2.52	201.33±8.50	55.87±0.31	141.67±10.21
Span	3.12±0.03	4.80±0.12	3.22±1.75	6.62±0.46
Uniformity	1.10±0.03	1.68±0.09	0.70±0.00	4.58±0.63
SSA, m^2/kg	431.10±25.20	520.10±6.80	609.20±43.10	622.90±1.70

According to the measured physical particle properties (*Table IV* and *Figure 21*), PH101, caffeine, starch, L200M and acetaminophen are likely to exhibit cohesive behaviour (Dv_{50} < 100 μm), whereas PH200, L80M and PH102 are expected to show good flowability. Among the MCC grades, coarse PH200 is expected to flow better than PH102, followed by fine-grade PH101. A similar trend can be anticipated between sieved L80M and milled L200M; however, morphological differences arising from processing and a significant presence of fines or debris in the milled grade should be considered. Morphologically, the irregular shapes of caffeine and APAP particles may promote physical contacts, unlike the low-friction sphericity of starch. Nevertheless, powder flow behaviour cannot be accurately predicted solely based on particle physical measurements, as reviewed in *Section 2.5.1 ("General classification")*. The operating and/or testing conditions largely govern the flow behaviour, as evidenced across measurement methods (*Table V and VI*).

Table V. Shear cell measurements and tapping studies (*n=3*).

	Shear cell measurements (FT4 Powder rheometer)				*Tapping studies*	
Material	**Cohesion, kPa**	**UYS, kPa**	**FFc**	**AIF, °**	**CI, %**	**Flow classification**
PH200	0.75±0.12	2.7±0.42	6.58±0.96	32.02±0.79	27±1	Poor
PH102	0.45±0.10	1.54±0.32	10.19±1.71	29.86±2.14	33±1	Very poor
PH101	0.88±0.18	3.32±0.83	5.52±0.98	33.55±3.28	39±1	Extremely poor
L80M	0.80±0.24	2.63±0.72	6.18±1.44	32.53±1.88	22±1	Passable
L200M	1.64±0.25	5.94±0.86	2.83±0.32	32.15±0.53	40±1	Extremely poor
Caffeine	1.79±0.08	6.4±0.29	2.61±0.11	31.47±1.93	37±1	Very poor
Starch	0.64±0.12	1.97±0.33	7.05±1.13	24.37±1.89	32±1	Very poor
APAP	2.09±0.07	7.41±0.23	2.34±0.04	31.21±2.14	44±1	Extremely poor

Table VI. Dynamic flow measurement datasets across investigated tests (*n=3*). Filling performance as reference. "N/A" (not applicable) indicates that the material could not be processed in the tableting machine. "No Flow" indicates poor flowing properties, preventing measurement in the respective test.

	Filling performance	*Dynamic test · Powder rheometer*			
Material	**Mass variation (RSD)**	**BFE, mJ**	**SE, mJ/g**	**SI**	**FRI**
PH200	0.75±0.16	243.83±87.17	5.38±0.25	1.14±0.21	1.27±0.10
PH102	3.49±1.03	272.06±37.41	6.08±0.66	1.05±0.06	1.42±0.06
PH101	7.01±1.57	290.08±37.10	7.98±0.95	0.97±0.08	1.57±0.21
L80M	N/A	495.40±6.85	5.70±0.16	1.05±0.07	1.11±0.02
L200M	No Flow	124.67±4.13	6.02±0.24	0.96±0.05	1.85±0.15
Caffeine	N/A	229.53±51.13	9.16±1.01	0.72±0.21	1.57±0.33
Starch	No Flow	81.28±1.78	5.28±0.43	1.16±0.03	1.57±0.09
APAP	N/A	112.8±18.19	14.46±0.80	0.95±0.08	1.14±0.21

	Filling performance	*Ph. Eur. Funnel*	*Miniaturised funnel*
Material	**Mass variation (RSD)**	**Flow rate, g/s**	**MFI, %**
PH200	0.75±0.16	9.80±0.70	48.59±3.22
PH102	3.49±1.03	6.40±0.60	26.75±2.76
PH101	7.01±1.57	No Flow	11.36±1.70
L80M	N/A	10.40±0.70	45.17±4.34
L200M	No Flow	No Flow	1.89±0.82
Caffeine	N/A	No Flow	14.83±1.42
Starch	No Flow	No Flow	4.94±1.02
APAP	N/A	No Flow	1.35±0.46

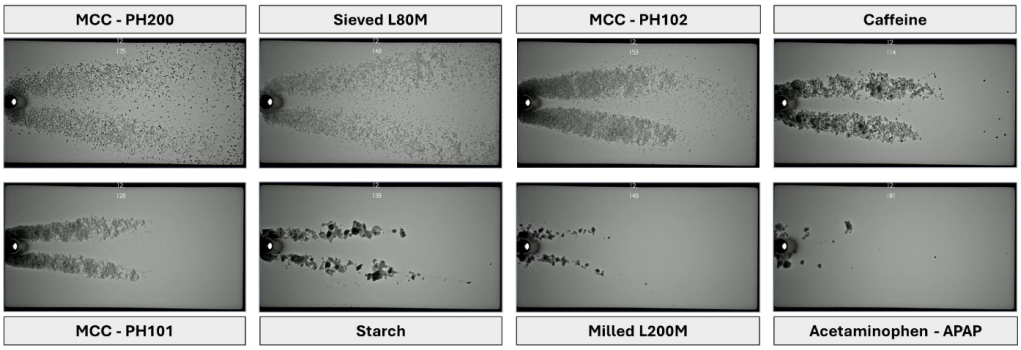


Figure 22. Micro-dynamic flow patterns in descending order of flow performance (FI). Agglomeration, dispersion and texture as direct (qualitative) descriptors of cohesive forces acting in the powder specimen. *Adapted from Blanco, D., et al. (2020).*

5.1.1.1 Relevance to filling performance

In the tablet press, clear differences in flow properties among MCC grades were observed, while the fine lactose L200M and starch were cohesive and did not flow into the die. Both relative standard deviation (RSD) and batch-to-batch variability (StDev) increased as particle size decreased (*Figure 23*), indicating reduced mass uniformity in dosage units. Particle-scale vdW attractive forces primarily governed powder flow

under gravity-driven filling conditions. These findings align with prior research, highlighting the strong dependence of bulk friction and cohesion on applied consolidation stress, particularly at the very low stress levels encountered in tablet presses [Leung et al., 2017; Søgaard et al., 2017]. Under such conditions, where frictional contacts are limited, flow behaviour is predominantly governed by cohesive forces. Other dynamic tests introduced additional sources of consolidation stress, thus influencing frictional contact forces. The measuring principle or design of most testers prevents accurate measurement at such low stress levels [Søgaard et al., 2017; Swize et al., 2019; Stravrou et al., 2020].

In the Ph. Eur. Funnel, very low consolidation stresses (~ 200 Pa) have been reported [Gentzler et al., 2015; Leung et al., 2019; Zhou, X. et al., 2020]. Consistent with these findings, relatively free-flowing MCC grades (coarse and medium) were clearly differentiated and partially correlated with the filling performance (*Figure 23*). In contrast, cohesive powders (Dv_{50} < 100 µm) overcame the applied stress (or gravitational effects), resulting in agglomeration and blocking the funnel, even with large openings (arching tendency), thus hindering reliable flow-rate measurement [Huang et al., 2015; Muñiz-Lerma et al., 2018; Marnani et al., 2019; Marchetti et al., 2021]. This contrasted with the fine-grade MCC, which could flow into the die despite similar applied stress and higher flow requirements due to the smaller opening cross-section (5 mm vs. 9 mm). Wu et al. (2012) similarly reported limitations in pharmacopoeial methods (Ph. Eur. Funnel and tapping studies) in replicating filling performance, primarily due to differences in air pressure effects, and limited physical contact, and reduced shearing during die filling. This limitation was further evidenced by fine spherical starch particles, which were classified as equally free-flowing as medium-grade MCC PH102 in tapping studies (*Figure 23*). Other researchers reported that the critical orifice diameter correlates with particle size variations, although it becomes insensitive when the particle size is below 120 µm [Zakhvatayeva et al., 2018]. Consequently, the improved flowability observed during die filling for fine-grade MCC PH101 was attributed to feeder-induced vibrations aiding powder discharge and/or lower consolidation stresses inherent to smaller powder volumes during filling, and was further investigated using the miniaturised funnel test as follows.

In the miniaturised funnel-based system, differences in particle size closely correlated with the observed behaviour in the press. Although frictional contacts contributed to the overall flow behaviour, micro-dynamic flowability was predominantly governed by cohesive forces. Notably, the spherical starch particles exhibited improved flowability despite their smaller size relative to lactose L200M. For the tested materials (*Table VI*), a high correlation (r = 0.96) was observed between the Ph. Eur. Funnel and micro-dynamic tests. Remarkably, the miniaturised setup enabled the analysis of more cohesive powders in a funnel-based geometry, as the lower powder volumes were more loosely packed and thus required less force to initiate flow (or to overcome cohesion). By contrast, bulk powder volumes facilitated greater

consolidation under load (i.e., forming a denser packing state where particles remain in continuous contact), thereby strengthening both bulk cohesion and friction. Such friction arises from gravitational forces applied by the weight of the powder bed, aligning with findings from the Ph. Eur. Funnel and tapping studies (*Figure 23*).

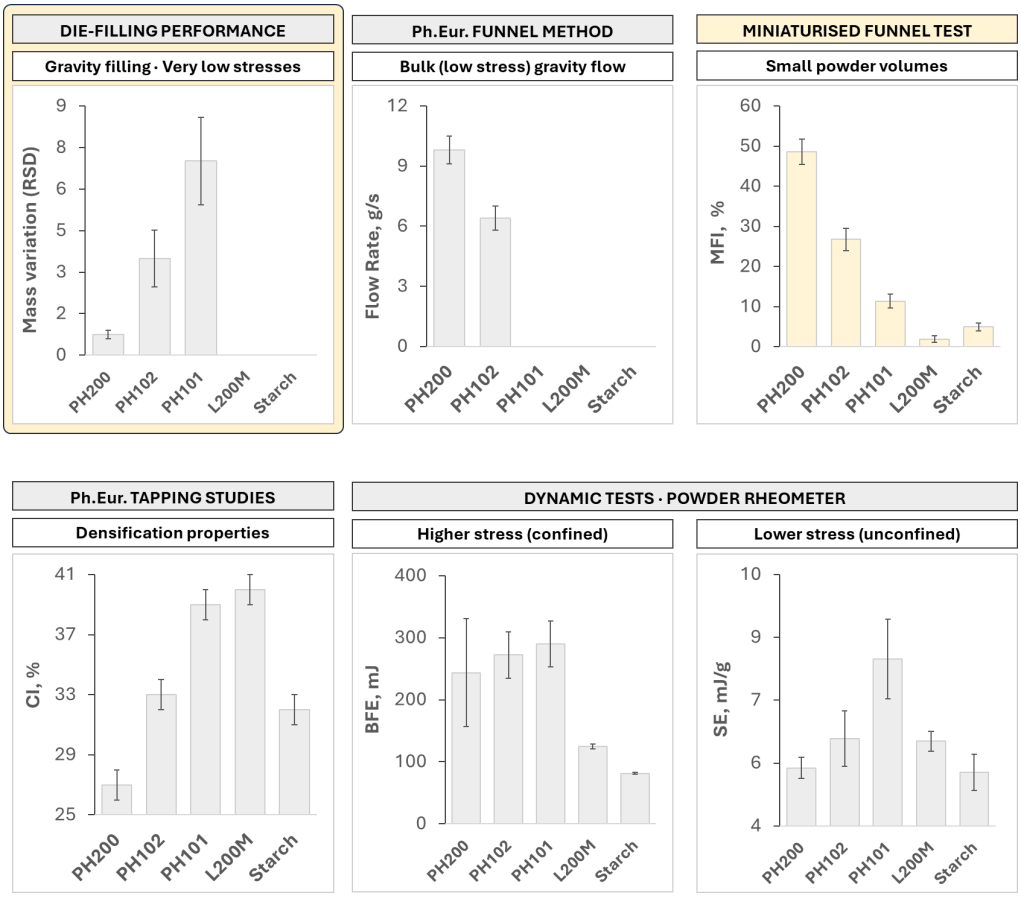


Figure 23. Effect of consolidation stress on filling performance, dynamic flow properties and tapping studies for the analysed materials, ordered by decreasing particle size (*n=3*). Particle sizes (Dv_{50}): PH200 (190 µm), PH102 (102 µm), PH101 (63 µm), L200M (40 µm) and starch (21 µm). Poor flowing materials in the tablet press (L200M and starch) were classified as good flowing in the powder rheometer, while funnel-based methods correlated with filling performance. Tapping studies classified all materials with exception to starch, which showed good packing properties, as observed in the tablet press. Significant differences are indicated by standard deviation (StDev) bars. *Adapted from Blanco, D., et al. (2020).*

Consequently, in the miniaturised system, the consolidation stresses were significantly lower (≪ 200 Pa) than those observed in the Ph. Eur. Funnel, which is consistent with the improved filling performance of fine-grade MCC PH101 in the tablet press. A detailed discussion of flow properties at very low stresses and the

differences between bulk and small powder volumes is provided in *Section 5.4.1 ("Flow properties at very low stresses")*. Finally, the image-based flow characterisation readily captured powder agglomeration as a direct (qualitative) descriptor of cohesive forces acting within the powder specimen (*Figure 22*), an aspect investigated further in *Section 5.1.2* (*"On the mechanisms of flow enhancement and cohesion"*).

In powder rheometry, the dynamic flow properties exhibited significant variations depending on the applied stress (i.e., compressive forces and shear strain effects), yet these variations did not directly correlate with in-process performance (*Figure 23*). Shear strain rate dependency within the dynamic regime has been reported to increase substantially under confined conditions [Luding, 2008; Berger et al., 2015; Vivacqua et al., 2019]. During helix penetration (confined BFE measurements), the higher applied stresses largely overcame interparticle cohesive forces, and the flow behaviour is predominantly frictional. In contrast, during helix extraction (unconfined SE measurements), the lower applied stresses only partially counteracted cohesive forces, resulting in a flow regime that was less frictional and more cohesive. Consequently, SE measurements detected MCC particle size variations, whereas BFE measurements did not (*Figure 23*). BFE measurements were more sensitive to differences in frictional contacts, including the number of fines and particle morphology (e.g., L200M vs. starch), as discussed in detail in *Section 5.1.1.2* (*"Effect of bulk friction and cohesion"*).

These findings align with previous research on powder rheometry and filling performance. Higher SE values (i.e., more cohesive behaviour) have been associated with smaller particle sizes, whereas BFE measurements remain largely insensitive to such variations [Tay et al., 2017; Van Snick et al., 2018; Zakhvatayeva et al., 2018]. Consequently, SE measurements have often been reported as particularly relevant for predicting powder flow properties in low-stress applications, such as die and capsule filling. However, SE data alone do not directly correlate with filling performance [Freeman & Fu, 2008; Freeman et al., 2011; Osorio & Muzzio, 2013; Snick et al., 2018]. Unlike in previous studies, our results indicated that although frictional contacts decreased during SE measurements, thereby differentiating size-dependent cohesive forces between the MCC grades, they largely governed the observed flow behaviour. For instance, fine materials (L200M and starch) exhibited the opposite trend: significantly lower SE values, indicating much less cohesive behaviour, even lower than that of the coarse-grade MCC PH200 (a free-flowing material). Although SE unconfined measurements are often attributed to gravitational effects, cohesion or particle-scale vdW forces governing the filling process did not appear to be the most influential property in our study. In both cases, flow energy values indicated enhanced flowability for the fine cohesive materials (L200M and starch), particularly for frictionless, spherical starch particles. Overall, flow behaviour in dynamic tests was predominantly governed by frictional contacts, though size-dependent cohesive forces were influential under lower stress (SE) conditions, as evidenced by the differences

among MCC grades (*Figure 23*). Accordingly, the tested materials were classified as moderately cohesive [5 < SE < 10], while starch was classified as a good-flowing material [SE < 5].

To summarise, our findings highlight the strong dependence of powder flow behaviour on stress level. Higher stresses were increasingly affected by frictional contacts and less by size-dependent cohesive forces (BFE > SE > Ph. Eur. Funnel test > Miniaturised funnel test). Notably, the high stresses during helix penetration (BFE) were more sensitive to differences in particle morphology and/or frictional contacts, while the lower stresses during helix extraction (SE) were slightly less sensitive to frictional contacts and instead more sensitive to particle size. Similarly, in the miniaturised system, very low stresses were primarily governed by size-dependent cohesive forces, although material differentiation based on frictional contacts for fine cohesive materials (i.e., starch vs. L200M) was similar to that observed in both BFE and SE measurements. Under higher stress conditions, however, fine cohesive materials were overestimated at higher stresses and did not correlate with filling performance. To rationalise these results, the effect of consolidation stress was evaluated for other sample characteristics in the following section (*"Effect of bulk friction and cohesion"*).

Observation remarks

- The applied (consolidation) stress determined the physical mechanisms governing flowability.
- Bulk flow tests hindered measurements in very low stress range observed in the tablet press.
- Micro-dynamic flow properties strongly correlated with the filling performance in a gravity feeder.

5.1.1.2 Effect of bulk friction and cohesion

For the tested materials, the Ph. Eur. Funnel yielded another relevant outcome (*Table VI*); therefore, the effect of consolidation stress was compared across the lactose grades (*Figure 24*). Higher stress conditions (BFE) showed significant differences in material properties that were not detected at lower stresses (SE). Considering the large differences in particle size between lactose grades, the fine fraction in milled L200M had a major impact on the measured energy values. At lower stresses (SE), differences in particle size were expected, aligning with previous findings (*Figure 23*). However, both lactose grades described similar flow behaviour and were not differentiated from MCC PH102 (used as a reference); differences in particle size appeared to be compensated by the fine fraction acting as a glidant. Consequently, frictional forces emerged as the major influence this time, leading both lactose grades to be classified as moderately cohesive [5 < SE < 10]. At higher stresses (BFE), coarse L80M exhibited

poor flow characteristics, likely due to frictional contacts among its irregular particles and mechanical interlocking, whereas milled L200M showed significantly better flow properties.

Several studies have provided empirical and theoretical explanations for these findings [Freeman, 2007; Bharadwaj et al., 2010; and Hare et al., 2015, 2017]. Although particle size and size distribution do influence flow behaviour, particle shape (or frictional contacts) often plays a more decisive role in dynamic flow measurements. For instance, Fu et al. (2012) experimentally investigated three lactose grades and concluded that while both particle size and shape influence flow energy, particle shape tends to have a more pronounce effect. In short, frictional contacts governed the observed flow behaviour in powder rheometry, with mechanical interlocking leading to high stress in coarse L80M, whereas milled L200M experienced reduced interlocking and frictional contacts. Moreover, these results from the funnel-based techniques support earlier analyses in classifying the materials according to cohesive forces operating under very low stress conditions. In this context, negative correlations between rotational rheometers and funnel-based methods have been reported by Marchetti & Hulme-Smith (2021). Very low stresses characteristic of gravitational hopper discharge cannot be reproduced in powder rheometers, thus highlighting the limitations of high-stress rotational measurements for predicting material behaviour during filling processes.

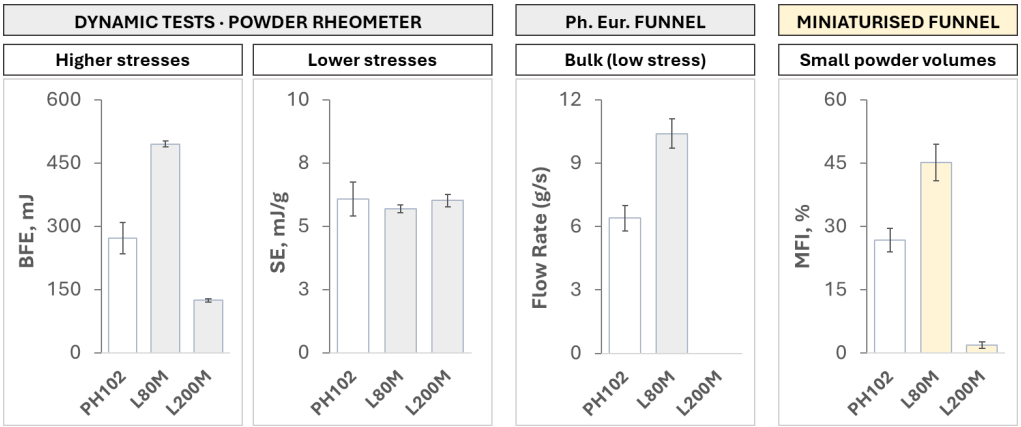


Figure 24. Effect of consolidation stress on dynamic flow properties for lactose grades (n=3). Particle sizes (Dv_{50}): Sieved L80M (212 µm) and milled L200M (40 µm). Coarse L80M, typically used as a flow aid, was classified as poor flowing in the powder rheometer, while fine L200M, which did not flow in the tablet press, was classified as good flowing material. Funnel-based methods classified both materials according to the expected filling performance. Significant differences are indicated by standard deviation (StDev) bars. PH102 (102 µm) is used as a reference. *Adapted from Blanco, D., et al. (2020).*

To further rationalise these findings, all selected fine materials were compared (*Figure 25*). In powder rheometer, higher and lower stresses (BFE and SE data) described a similar trend. In both cases, more irregular particle morphologies (e.g., caffeine and acetaminophen (APAP)) increased the flow energy values compared to more regular morphologies (e.g., L200M and starch). This limited sensitivity in differentiating similarly cohesive materials has been attributed to particle agglomeration behind the blade, causing torque oscillations and increasing the influence of frictional contacts [Hare et al., 2015, 2017; Li et al., 2018].

Highly frictional (BFE) values described fine cohesive powders as good flowing. In contrast, SE described poorer flowing properties for the more irregular morphologies, and the impact of particle size was determined from the relative position of the reference compound MCC PH102. Apart from APAP, the materials were classified as moderately cohesive [5 < SE < 10], while starch was classified as good flowing [SE < 5]. Although particle size influenced flow behaviour at lower stresses (SE), particle shape remained the major determinant of the measured flow energy [Wilkinson et al. 2017]. Indeed, significantly higher flow energy values have been reported for irregular particles than for spherical ones, due to increased frictional contacts and facilitated mechanical interlocking [Nan et al., 2017; Vivacqua et al., 2019]. This pattern was evidenced in *Figure 23* and *Figure 25*, where the spherical starch particles demonstrated better flow properties compared to the MCC grades, regardless of particle size.

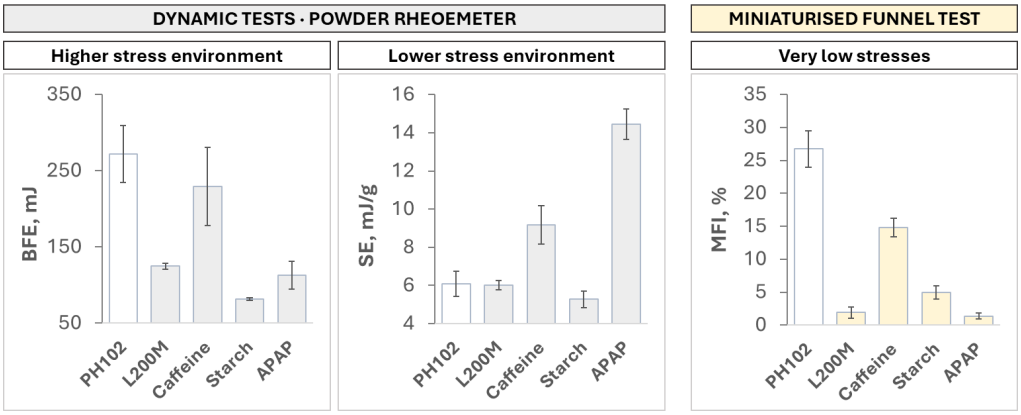


Figure 25. Effect of consolidation stress on dynamic flow properties for fine cohesive materials (*n=3*). Particle sizes (Dv_{50}): L200M and caffeine (40 µm), starch and acetaminophen (20 µm). Higher stresses (BFE values) in the powder rheometer classified all fine cohesive materials as good flowing, while lower stresses (SE values) showed different flow behaviour according to material properties. Micro-dynamic flow measurements classified all materials as moderately or poor flowing. Significant differences are indicated by standard deviation (StDev) bars. PH102 (102 µm) is used as a reference. *Adapted from Blanco, D., et al. (2020).*

Under very low stress conditions (MFI data), size-dependent cohesive forces predominantly governed flow behaviour, although frictional contacts were still relevant. Accordingly, spherical starch particles and caffeine showed improved flowability. In this context, SE and MFI data showed a similar trend for PH102, caffeine and APAP. For caffeine, fleecy masses composed of small particles reduced friction under SE, while their formation was diminished in the very low stress environment. This phenomenon was evident in the observed agglomerates and "fluffy" texture of the powder flow pattern (*Figure 22*). Although the miniaturised system overcame the limitations of the Ph. Eur. Funnel for these fine powders, very cohesive materials did not flow or performed poorly in the novel measuring system.

Observation remarks

- Powder rheometry was largely driven by frictional contacts, with limited correlation to filling performance.
- Particle size and shape both affected flow energy values; however, shape and the fine fraction had a greater impact.
- Micro-dynamic flowability was primarily governed by cohesive forces, though frictional contacts also played a role.

5.1.2 On the mechanisms of flow enhancement and cohesion (II)

Micro-dynamic flow studies demonstrated considerable versatility in detecting, characterising, and quantifying cohesive forces and associated agglomeration phenomena that govern die-filling processes (*Figure 22*). This section explores the underlying mechanisms by which a dry nanocoating pre-blending step enhances the flowability of cohesive materials. The measured flow properties facilitated precise determination of optimal glidant concentrations, and results were subsequently validated against filling performance in a tablet press. Colloidal silicon dioxide (CSD) was gradually added to milled lactose L200M as a model cohesive compound (*Table VII*). Subtle changes in powder characteristics were evaluated from small increments on CSD (0.025% w/w) for a controlled blending time of 10 minutes. Powder densification effects due to glidant addition were assessed via tapping studies, given their relevance to the filling process (*Section 5.1.1 "Consolidation stress and flow properties"*). As previously discussed, cohesive lactose powders are not able to flow through conventional pharmacopoeial funnels and were not included. Standard tablets (Ø = 9 mm) and a multi-paddle force feeder constituted the selected filling geometry. The die-filling ratio was employed as a direct quantitative measure of the flow performance inside the tablet press. Additionally, the influence of moisture content, including the contribution of capillary forces, on cohesion-related flow behaviour under very low stress conditions was evaluated (results not included, **II**).

Table VII. Filling performance, tapping studies and micro-dynamic flow data for increasing amounts of CSD (fixed blending time = 10 min). For three CSD concentrations, filling performance and tapping studies were not conducted due to insufficient sensitivity of these methods to detect significant differences. Accordingly, the 0.025% variation was only evaluated using the miniaturised funnel test (N/A).

	Filling performance	*Micro-dynamic test*	*Ph. Eur. Tapping studies*	
CSD (% w/w)	**Filling Ratio (%)**	**MFI, %**	**CI, %**	**Flow Classification**
0.0	80.91±6.16	1.1±0.3	40±1	Very poor
0.05	87.51±1.96	4.0±0.9	36±1	Very poor
0.075	N/A	7.8±0.8	N/A	N/A
0.100	89.11±2.23	10.3±1.2	35±1	Very poor
0.125	N/A	10.2±1.0	N/A	N/A
0.150	87.49±3.55	12.8±1.2	33±1	Poor
0.175	N/A	12.7±1.3	N/A	N/A
0.20	87.47±1.87	10.3±0.7	32±1	Poor
0.25	N/A	10.9±1.1	N/A	N/A
0.50	88.17±1.54	9.2±1.0	32±1	Poor
1.0	88.19±1.34	8.4±1.1	27±1	Poor
2.0	86.72±1.70	8.6±1.1	33±1	Poor

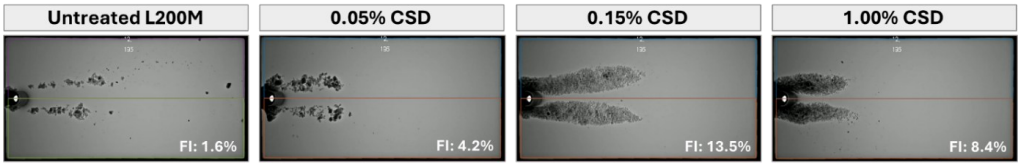


Figure 26. Micro-dynamic flow patterns for increasing amounts of CSD. Agglomeration as a direct (qualitative) descriptor of the effect of glidant addition on cohesive forces acting in the particulate solid. *Adapted from Blanco, D., et al. (2021)*.

Optimal flow performance correlated strongly with optimal filling performance (*Figure 27*). The cohesive mechanisms described by the miniaturised funnel test governed powder flowability during the filling process. Notably, untreated, milled L200M, previously not flowing under gravity conditions (*Figure 23*), also exhibited limited flow performance under forced-feed conditions (*Table VII*). The consistency of results between various geometries and the miniaturised system indicated that very low stresses dictated flow behaviour in conventional eccentric tablet presses during early-stage R&D. Importantly, these flow characteristics depended critically on powder agglomeration, as confirmed by image analysis (*Figure 26*).

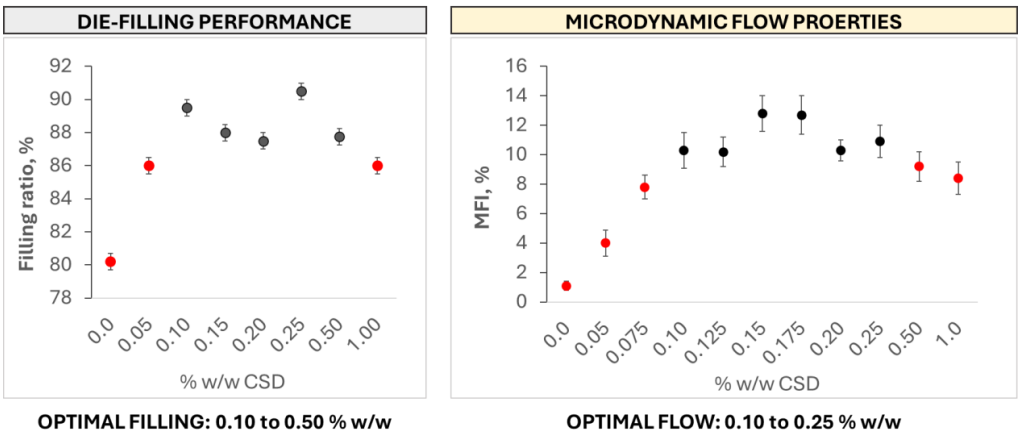


Figure 27. Micro-dynamic flow and filling ratio for increasing amounts of CSD. Suboptimal CSD concentrations coloured in red ($p < 0.05$). Optimal filling performance strongly correlated with optimal flow performance in the miniaturised funnel test. Sensitivity thresholds: 0.050% w/w CSD for filling performance and 0.025% w/w CSD for flow performance. *Adapted from Blanco, D., et al. (2021)*.

Micro-dynamic flow studies captured subtle yet significant differences in powder flow, accurately detecting particle-particle interactions and facilitating optimal glidant determination (*Figure 26*). While previous studies have investigated the effects of CSD on tablet properties or utilised optical testing methods, and despite a well-established understanding of the underlying mechanisms for improving filling performance, empirical determinations of flowability remain infrequent [Jonat et al., 2004; Majerová et al., 2016; Lumay et al., 2019; Escotet-Espinoza et al., 2021; Kunnath et al., 2023; Verbeek et al., 2025]. Currently, optimal glidant concentration is largely determined through iterative testing of the final product (i.e., filling performance assessments) and/or indirect measurements of particle characteristics supported by predictive models. Traditional methods, including powder rheometry, shear cell measurements, and Ph. Eur. angle of repose tests, can detect significant modifications in particle characteristics but often lack the sensitivity to detect small additions of silica (< 0.5 % w/w). Similarly, compressibility data from tapping studies exhibited moderate sensitivity to cohesion phenomena but failed to fully distinguish the underlying mechanisms of flow enhancement and demonstrated limited sensitivity to subtle particle modifications (*Table VII*).

Surface modification by CSD effectively prevented particle agglomeration, significantly improving flow properties compared to the pure excipient (*Figure 26*). Initially, small CSD aggregates adhered to lactose particle surfaces, reducing mechanical interlocking and friction by filling voids and surface irregularities. This enhanced sphericity also minimised cohesion, as attractive vdW forces decreased due to increased interparticle distances. Once the maximum efficiency of anti-cohesive mechanisms was achieved, characterised by homogeneous distribution and low

agglomerate population, the flow pattern was optimised, as exemplified at 0.15% CSD. Further CSD addition negatively impacts powder flow [Chen et al., 2008; Majerová et al., 2016; Zhou & Zhu, 2021; Verbeek et al., 2025]. Excessive CSD amounts aggregated, increasing cohesiveness and reducing flowability, as observed at 1.0% CSD. Correspondingly, tapping studies initially indicated improved flowability (reduced CI values), followed by subsequent increases in CI at higher CSD concentrations. However, powder densification remained unaffected by additional CSD addition, suggesting that beyond a certain threshold, further CSD compromises flow without significantly influencing bulk powder compaction (*Table VII*).

Finally, the effect of moisture content or relative humidity (RH) revealed that capillary forces have a strong influence on flow behaviour, particularly in small powder volumes or under very low stress conditions. These effects were accurately characterised using the miniaturised funnel test (results not shown; **II**). Increased moisture strengthened interparticle cohesion, leading to clumping and/or agglomeration phenomena, as previously reported in the literature [Emery et al., 2009; Sandler et al., 2010; Crouter & Briens, 2014; Opaliński et al., 2021]. While bulk flow measurements in powder rheometry have also shown that moisture can influence flow energy values (BFE and SE data), these methods are relatively insensitive to subtle changes in moisture content [Pantaleev et al., 2017].

In summary, this section highlighted the role of cohesive forces, such as vdW and capillary interactions, in governing powder flow under low stress conditions and/or in small powder volumes, as observed in the tablet press and effectively measured by the miniaturised funnel test.

Observation remarks

- Digital imaging enabled the detection and quantification of powder agglomeration, serving as main descriptor of cohesive behaviour.
- The increased sensitivity of the miniaturised funnel test to cohesive forces allowed empirical determination of the optimum amount of glidant.
- Micro-dynamic flow properties strongly correlated with the filling performance in a forced feeder.
- Particle properties, such as agglomerate size distribution, surface texture and interparticle contact area, changed progressively with increasing CSD concentration, directly influencing measured flowability.

5.1.3 From static to dynamic conditions

How do particle properties behave across the full range of shear strain rates? How do flow regimes influence material differentiation? Quasi-static tests using a rotational shear cell were included for comparison. All selected materials were screened based on

their measured flow properties. Statistical analysis classified the materials into groups ranging from low to high powder cohesion (*Figure 28)*. Additionally, the testing parameters are summarised in *Table VIII*. To account for the influence of testing conditions on measured flow properties, these are also detailed in *Table IX*. A correlation matrix between particle physical properties and flow data is presented in *Table X*.

Table VIII. Summary of processing (or testing) conditions and flow measurement techniques, including the flow regime, consolidation stress according to the literature and its origin for each technique.

Method	Flow regime	Consolidation stress	Consolidation stress – Origin	
Shear Cell	Quasi-static	Very High (> 2 kPa)	Shear head accessory	Bulk mass
Powder Rheometer	Dynamic	Higher (Unknown) Lower (Unknown)	Impeller · Penetration Impeller · Extraction	Bulk mass
Ph. Eur. Funnel	Dynamic	Low (100 to 200 Pa)	Gravitational force	Bulk mass
Ph. Eur. Tapping	Quasi-static	Low (Unknown)	Tapping forces	Bulk mass
Micro-dynamic test	Dynamic	Very Low (Unknown)	Linear dynamics	Small volume

Table IX. Summary of testing parameters, including the sample amount and analysis duration for each measurement technique.

Method	Test	Sample amount, grams (*n=1*)	Testing time, min (*n=3*)
Shear Cell	UYS, FFc and Cohesion	20 (10 ml)	40
Powder Rheometer	SE, BFE, FRI, SI	45 (25 ml)	60
Ph. Eur. Funnel	Flow rate	100	10
Ph. Eur. Tapping	CI Index	100	20 - 30
Micro-dynamic test	MFI, AG	< 0.2 (0.2 cm^3)	10

Quasi-static regime: Shear cell tests

In the quasi-static regime, at high consolidation stresses (>2 kPa), material properties dictated the contact areas between constituent particles, influencing the transmission of solid pressure. A strong correlation was found between FFc and Cohesion, as well as between FFc and UYS (*Table X*). AIF did not provide additional differentiation and was therefore excluded from the analysis. Smaller particle sizes (Dv_{50} < 100 µm) and more irregular morphologies (e.g., APAP vs. starch) increased both the number and magnitude of contact points under the applied load, leading to higher shear stresses (i.e., poorer flow behaviour). As a result, both lactose (coarse L80M and milled L200M) and MCC grades (PH200, PH102 and PH101) exhibited significant differences due to particle size and shape variations, although these differences did not correlate with the observed filling performance (*Figure 23*). Shear cell measurements assess powder flow under conditions that may not accurately represent the very low stress environments encountered in die-filling processes or small-scale applications [García-Triñanes et al., 2019; Shi et al. 2020; Zafar et al. 2021].

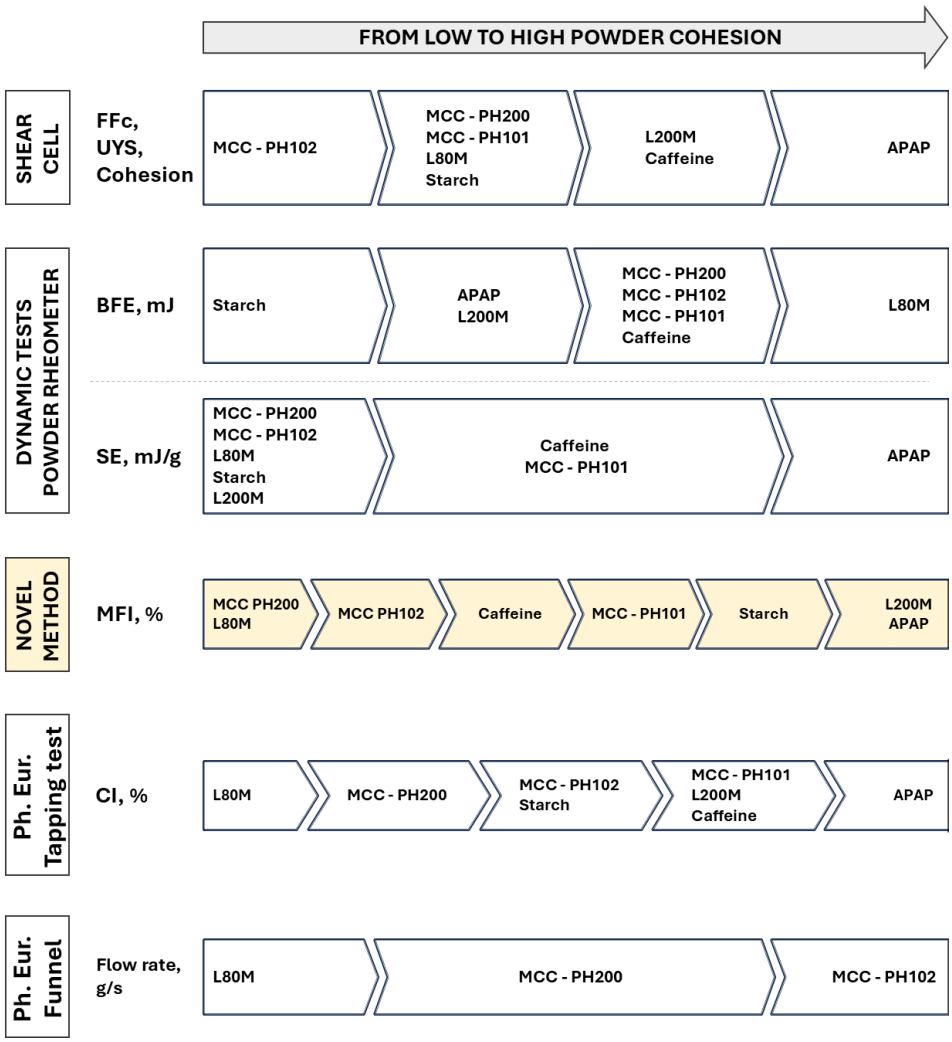


Figure 28. Effect of flow regime and consolidation stress on material behaviour. *From top to bottom*: Static flow regime (shear cell measurements), dynamic tests in powder rheometer, micro-dynamic flow properties, tapping studies and flow through an orifice (Ph. Eur. Funnel). *From left to right*: Results within each variable dataset classified in groups ($p<0.05$) and shown from low to high cohesion. *Part of the figure adapted from Blanco, D., et al. (2020), and part from unpublished data.*

Additionally, while shear cell tests provide valuable insights into powder flow behaviour under static conditions, they cannot be considered predictive for dynamic applications since they do not characterise flow parameters at higher strain rates [Lumay et al., 2012; Wu et al., 2012; Baserinia et al., 2016; Shi et al., 2020]. For example, a powder that exhibited good flowability in the quasi-static regime performed poorly under dynamic conditions (*Figure 28*). This highlighted the importance of selecting appropriate flow test methods based on processing requirements. For each

application, testing methods should be chosen based on their ability to replicate the actual processing conditions to which the powder is subjected [Krantz et al., 2009; Wu et al., 2012; Leturia et al., 2014; Goh et al., 2017].

Among MCC grades, the lowest shear stress was observed for the medium-grade PH102, while both larger and smaller particle sizes resulted in an increase in the magnitude and number of contacts points. However, good flowing powders, such as coarse L80M and MCC grades PH200 and, to a certain extent, PH101, were not differentiated. This suggests that a certain level of cohesion is necessary to obtain meaningful results, as previous studies have reported reduced sensitivity when cohesion decreases [Shah et al., 2008; Saw et al., 2015; Tay et al., 2016].

Dynamic regime: Powder rheometry

In powder rheometer, very different flow behaviours were observed and discussed in detail in *Section 5.1.1* (*"Consolidation stress and flow properties"*), according to the applied consolidation stress. The impeller dynamics described concurrent physical mechanisms that were acting on the bulk solid, which determined the measured energy values. This complexity has hindered numerical models from estimating the consolidation stress in rotational rheometers [Wu, 2013; Li et al., 2018]. Flow energy measurements in the powder rheometer were largely governed by frictional contact forces, and results were very dependent on particle shape and the number of fines (*Figures 24*), while size-dependent cohesive forces slightly influenced the lower stress (SE) environment. Most materials were classified as moderately cohesive [5 < SE < 10], and acetaminophen as cohesive [SE > 10]. PH200, caffeine and starch were classified as physically unstable [SI > 1.1] or [SI < 0.9]. All the other materials were stable [0.9 < SI < 1.1] and responded well to different flow rates [1.5 < FRI < 3.0].

As expected, quasi-static flow measurements were more sensitive to cohesive forces than dynamic tests in powder rheometry. A strong correlation was found between SE data and Cohesion and UYS values from rotational shear cell (r = 0.77; *Table X*). In both shear cell and SE tests, flow behaviour was governed by frictional contacts and cohesive forces, with fine cohesive powders (L200M, starch, caffeine and APAP) being better differentiated under quasi-static conditions (*Figure 28*). These findings align with previous studies [Freeman, 2007; Zhou et al., 2010], which also reported that BFE measurements provide better differentiation for materials that exhibit similar behaviours in shear cell testing, (e.g., starch vs. L80M). Notably, the observed correlation trend between PSD and cohesion, SE and UYS data (*Table X*), supports that the cohesive fraction (Dv_{10}) had a greater influence on flow behaviour than coarser fractions (Dv_{50} and Dv_{90}). While highly frictional BFE measurements were more sensitive to differences in particle shape, they were less effective in differentiating cohesive powders and did not correlate with measured shear data [Freeman & Fu, 2008]. Interestingly, our results contradict previous claims that BFE measurements

are highly sensitive to small changes in flow properties, indicating that further investigation is needed.

Dynamic powder rheometry is particularly effective for differentiating non-cohesive powders (e.g., L80M vs. MCC PH200) and assessing the effect of particle shape [Shah et al., 2008; Saw et al., 2015; Tay et al., 2016], as discussed in *Section 5.2.1.2.3* (*"Powder rheometry"*). However, difficulties arise when cohesion increases, particularly in low-stress environments (*Figure 23*) or when fine particles are present in the mixture (*Figure 24*). Under quasi-static conditions, shear stress increased due to higher particle contacts under compressive forces, whereas in dynamic tests, the fine fraction in L200M exhibited a glidant effect, facilitating particle motion rather than increasing cohesion. Similarly, starch displayed greater cohesion in shear cell testing than in powder rheometry (*Figure 28*), suggesting a stress-dependent transition in flow behaviour. The influence of fine fractions in dynamic powder rheometry was further confirmed under real manufacturing conditions (*Section 5.3.2 "Process optimisation and validation during scale-up*").

Contrary to literature findings, cohesive powders were not more sensitive than granular materials to changes in flow rate and energy gradients (SI and FRI), where lower values indicated better flow performance [Davis et al., 2018]. This was evident in the case of coarse-grade MCC PH200, which was classified as physically unstable as caffeine or starch (*Table VIII*). Furthermore, FT4 dynamic tests have been correlated with other conventional powder flow assessments, with SE reported to exhibit greater sensitivity to material characteristics than tapping studies [Zhou et al., 2010; Leturia et al., 2014]. However, this contradicts the results observed in this study, where compressibility measurements (CI data) demonstrated greater sensitivity than SE data.

Micro-dynamic regime: Novel method

Micro-dynamic flow properties largely correlated to PSD data (*Table X*). Size-dependent cohesive vdW forces governed the flow behaviour, while particle shape or frictional contacts had a minor influence in this dynamic regime for the tested materials and testing conditions (*Figure 28*). Good flowing materials, such as L80M and MCC PH200, did not show significant differences in this study but were later differentiated by adjusting frictional shear within the funnel in the optimised testing setup [Blanco D, et al., 2023]. Frictional contacts became dominant at these higher flow rates in the miniaturised funnel test, and further research is needed to rationalise this behaviour. In any case, very poor flowing powders readily agglomerated at very low stress levels and were not differentiated using this method. The flowability of cohesive powders was investigated in more detail using micronised APIs in *Section 5.3.1* (*"Pre-formulation studies"*).

Notably, micro-dynamic flow studies exhibited a strong correlation with PSD data ($r \geq 0.94$; *Table X*), whereas highly frictional BFE measurements exhibited a weaker but still significant correlation ($r \geq 0.72$). Size-dependent cohesive forces governed the micro-dynamic flow data, and a reduction in particle size generally decreased the mechanical interlocking during helix penetration. Furthermore, tapping studies (CI, %) and micro-dynamic flow data (MFI, %) showed a high correlation ($r = 0.87$) for the tested materials in *Section 5.1.1* (*"Consolidation stress and flow properties"*). Low stresses during tapping studies can be assumed; thus, size-dependent cohesive forces had a major impact on the measured compressibility index CI, as evidenced by the strong correlation with PSD data ($r \geq 0.74$; *Table X*). In this context, it is worth noticing that, while CI exhibited significant correlations with other cohesion-related parameters, such as Cohesion and UYS in shear cell measurements ($r = 0.70$ and 0.72, respectively) and SE measurements in powder rheometer under lower consolidation stresses ($r = 0.70$), the micro-dynamic flow data (MFI) did not exhibit such correlations. Similarly, SE measurements correlated well with Cohesion and UYS data ($r = 0.77$). Different physical mechanisms may be therefore governing powder flow behaviour of tapping studies and the miniaturised test (or small powder volumes).

The MFI/CI correlation was further explored in *Section 5.1.2* (*"On the mechanisms of flow enhancement and cohesion"*), where micro-dynamic flowability was also influenced by particle roughness and moisture. In these cases, tapping studies did not correlate with micro-dynamic flow data or die-filling performance. Overall, micro-dynamic flow studies were primarily governed by interparticle cohesive forces, including vdW forces (i.e., particle size, size distribution and surface roughness) and capillary forces. This flow behaviour was observed in both R&D tablet presses, and flow properties at the very low stress range are discussed in detail in *Section 5.4.1* (*"Flow properties at very low stresses"*). Additionally, micro-dynamic flow studies were distinguished by the small sample amounts and short analysis time (*Table IX*).

Ph. Eur. Tapping studies

Tapping studies (CI) indicated poor densification (or flow) properties for all the tested compounds in both tablet presses. In general, materials densified according to PSD data, consistent with previous findings that particle size primarily influences tapping studies [Yaginuma et al., 2007; Fu et al., 2012; Lumay et al., 2012; Hlosta et al., 2016; Tay et al., 2017; Goh et al., 2018]. However, spherical starch particle shape exhibited improved packing efficiency and was classified as good flowing as medium-grade MCC PH102. Similar results were observed with CSD addition, where powders showed increased densification at higher silica content, as particle sphericity and cohesion decreased.

Compressibility tests or tapping studies are generally considered quasi-static because the measuring principle involves relatively slow frictional motion with few

collisions. However, due to their ability to detect particle size variations [Yaginuma et al., 2007; Freeman & Fu, 2008; Ilic et al., 2009; Sun, 2010], tapping studies have occasionally been reported to correlate with filling performance, as partially observed in the first tablet press investigated (*Section 5.1.1 "Consolidation stress and flow properties"*). Despite this, tapping studies were not sensitive to subtle variations in material characteristics due to the addition of CSD and did not correlate with filling performance in the second tablet press investigated (*Section 5.1.2 "On the mechanisms of flow enhancement and cohesion"*).

Although typically considered a quasi-static test method, the consolidation stress applied during tapping studies is relatively low compared to other measuring principles. Additionally, the timing of consolidation measurements in tapping tests may not be strictly quasi-static. Notably, its relevance to the die-filling process was higher than that of any other bulk test method, including the Ph. Eur. Funnel test, which was limited to good flowing materials. This relevance has been certainly attributed to its sensitivity to particle size variations [Yaginuma et al., 2007; Freeman & Fu, 2008; Ilić et al., 2009; Sun, 2010]. Moreover, the higher sensitivity of compressibility studies was also indirectly reflected in the compacted bulk density (CBD) and packing density (PD) values, as discussed in Section 5.2.2 "Process optimisation and validation during scale-up", where these metrics captured formulation-dependent differences. In contrast, powder rheometer measurements proved largely insensitive to such variations.

Table X. Pearson´s correlation matrix. *From top to bottom*: PSD data (Dv_{10}, Dv_{50} and Dv_{90}), shear cell measurements (Cohesion, FFc and UYS), dynamic tests in powder rheometer (BFE, SE, SI, FRI and CBD), miniaturised funnel test (MFI) and tapping studies (CI). *Note*: Significant correlations (|r| ≥ 0.70) highlighted.

	Cohesion, kPa	FFc	UYS	BFE, mJ	SE, mJ/g	FRI	SI	CBD, g/ml	MFI, %	CI, %
Dv_{10}	-0.68	0.58	-0.67	0.76	-0.53	-0.41	0.55	0.32	0.94	-0.84
Dv_{50}	-0.48	0.40	-0.47	0.81	-0.48	-0.46	0.40	0.46	0.96	-0.82
Dv_{90}	-0.35	0.32	-0.34	0.72	-0.32	-0.50	0.22	0.32	0.97	-0.74
Cohesion, kPa		-0.93	1.00	-0.40	0.77	-0.02	-0.72	-0.22	-0.55	0.70
FFc			-0.94	0.32	-0.61	-0.08	0.66	0.07	0.49	-0.57
UYS				-0.40	0.77	0.01	-0.73	-0.25	-0.55	0.72
BFE, mJ					-0.29	-0.37	0.02	0.57	0.75	-0.67
SE, mJ/g						-0.43	-0.52	-0.57	-0.47	0.70
FRI							-0.25	0.13	-0.45	0.30
SI								0.00	0.36	-0.53
CBD, g/ml									0.39	-0.66
FI, %										-0.87
CI, %										

Observation remarks

- Shear cell measurements did not correlate with the filling performance.
- Micro-dynamic flow measurements showed remarkable sensitivity for material differentiation according to cohesive forces.
- Tapping studies correlated well with bulk cohesion parameters, whereas MFI did not, indicating that they capture different flow mechanisms.
- Micro-dynamic flow studies did not differentiate very cohesive powders.
- Static flow measurements were more effective for differentiating very cohesive powders.
- Dynamic tests with powder rheometer were more effective for differentiating non-cohesive powders.

5.2 Other applications in drug development

Powder flow behaviour plays a crucial role in pharmaceutical development, influencing processes such as die-filling, blending and granulation. This section explores key applications of micro-dynamic flow studies in drug development, with a focus on early API characterization and process optimization. By integrating advanced techniques, formulators and manufacturers can better predict flow-related challenges and optimise manufacturing processes, particularly for poorly flowing drug candidates.

Standard MCC grades (PH200, PH102 and PH101) were selected as reference materials to rank the flow behaviour in the investigated applications. These MCC grades span a spectrum of flow properties typically encountered in die-filling processes during pharmaceutical manufacturing. Their inclusion provided a comprehensive framework for benchmarking and validation, as traditional bulk flow measuring techniques could not be applied in certain scenarios (*Table XI*). It is worth noting that these studies were performed using the optimised testing setup, and therefore the measurement parameters differ from those used in previous studies, as detailed in *Section 4.2.3.2 ("Novel measuring system")*.

Table XI. Micro-dynamic flow properties with model materials representing the boundaries for classification. The micro-dynamic flow index (MFI, %) is used to classify flowability, with higher values indicating better flow. Boundary materials are provided as references, where MCC PH-200 represents the best flow behaviour and MCC PH-101 the poorest. Intermediate flow categories are defined based on MFI ranges between these materials.

MFI, %	Flow Classification	Boundary Material
> 50	Excellent	≫ MCC PH-200
30 - 50	Good	MCC PH-200 ≳ MFI ≳ MCC PH-102
10 - 30	Acceptable	MCC PH-102 ≳ MFI ≳ MCC PH-101
< 10	Poor	≪ MCC PH-101

5.2.1 Pre-formulation studies (III)

Poorly soluble drug candidates often require particle size reduction techniques to enhance dissolution and bioavailability. Micronisation and milling techniques are routine protocols in pharmaceutical development. Traditional mechanical milling was applied to a BCS Class II (poor water-soluble) API, Palbociclib, at a small laboratory scale (300 mg milling batch size). As a cornerstone therapy for advanced or metastatic breast cancer, its high cost and limited availability during early-stage development further highlight the importance of emerging powder flow analytical techniques that minimise sample consumption. Untreated API was used as reference to evaluate the effect of milling on flow and dissolution properties.

Untreated Palbociclib showed as tomahawk-like particles. After milling, the API appeared as small spherical-shaped particles with a narrower PSD (*Figure 29* and *Table XII*). These observations confirm that milling significantly alters the particle size and morphology, which is expected to impact flow properties.

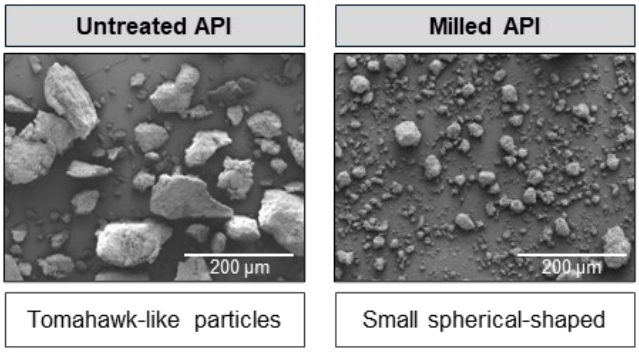


Figure 29. SEM micrographs and average particle size (200x magnification). *Left:* Before milling; *Right*: After milling, illustrating the morphological and size transformation of API particles due to micronisation. *Adapted from Blanco, D., et al. (2025)*.

Table XII. Laser diffractometer (PSD) data before and after milling (*n=3*), highlighting the reduction in particle size and the corresponding span values after milling.

	Before milling	*After milling*
Dv_{10} (µm)	21.86±7.43	2.07±0.11
Dv_{50} (µm)	148.50±16.26	38.74±0.71
Dv_{90} (µm)	556.65±49.56	129.28±7.92
Span	3.60	3.28

Micro-dynamic flow studies described the effects on flowability of particle size reduction at a small laboratory scale (*Figure 30* and *Table XIII*). A fixed flow (or shear) rate was used for cross-comparison, and the same magnification was applied for imaging consistency. Dissolution profiles showed significant improvements after

micronisation and increased specific surface area (results not included). For a detailed analysis of the effects of milling on dissolution profiles and material properties across various APIs, refer to [Pätzmann, N. et al. 2024]. From a flowability perspective, a narrower PSD and a smaller average particle size had an impact on flowability (*Figure 30*). The particle rounding resulting from milling appeared to balance such micronisation and the sample exhibited moderately lower, rather than very poor, flow performance, consistent with previous studies on spherical starch particles (*Section 5.1.1 "Consolidation stress and flow properties"*). Digital imaging was highly effective in visualising and interpreting these results. Image analysis detected agglomeration phenomena in the milled sample, driven by cohesive forces, such as van der Waals forces associated with particle size reduction, which hindered flowability. These findings highlight the challenges of maintaining technological processability after micronisation.

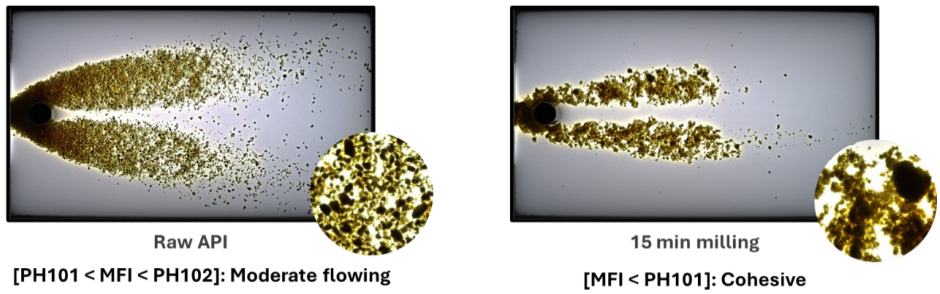


Figure 30. Micro-dynamic flow patterns. *Left*: Before milling; *Right*: After milling, visually depicting the increased cohesion (or agglomeration) in the milled sample. *Blanco, D., et al. (2025)*.

Table XIII. Micro-dynamic flow dataset: Micro-dynamic flow index (MFI), agglomeration ratio (AG) and packing density (PD), showing a substantial decrease in MFI and an increase in AG post-milling (*n=3*).

	Before milling			*After Milling*		
	MFI, %	**AG**	**PD, g/cm³**	**MFI, %**	**AG**	**PD, g/cm³**
Palbociclib	28.35±0.87	0.05±0.01	0.86±0.02	15.52±1.88	0.42±0.03	0.98±0.03

Recent advancements, such as small-sample predictive models and instruments like the SSSpinTester [Johanson, K. 2019; Deng, T. et al. 2022], have enabled the characterisation of fine cohesive powders using small sample amounts. These approaches have shown good agreement with traditional shear cell testers, with reported deviations of less than 22% for cohesive materials. However, it is important to remember that such predictive models are typically validated against bulk flow measurements, which assess powder behaviour under conditions that may not represent the very low stress environments encountered during filling processes in R&D tablet presses. For dynamic applications, quasi-static test methods such as shear

cell analysis are not predictive, as they do not characterise the flow parameters at higher strain rates [García-Triñanes, P. et al. 2019; Shi et al. 2020; Zafar et al. 2021]. Consequently, although small-sample predictive models provide useful insights, their applicability to low stress conditions and/or small powder volumes remains limited and requires further validation. Future research should focus on evaluating the accuracy of these methods under such specific conditions to determine their suitability as reliable alternatives to empirical testers in early-stage drug development.

Observation remarks

- Powder flow measurements were integrated into the earliest stages of drug development.
- Flow differences due to particle size reduction were detected using small sample volumes.
- Pre-formulation flow data relevant to R&D tablet presses were generated.

5.2.2 Process optimisation and validation during scale-up (IV)

This section explores micro-dynamic flowability as an innovative approach for optimising and validating scale-up in solid dosage form manufacturing. Integrating this method into technology transfer strategies enhances process understanding, minimises batch-to-batch variations and facilitates robust manufacturing. Two granule batches were analysed, prepared using different pilot-scale fluidised-bed granulators (Glatt WSG CD 15 and Niro-aeromatic T-5), under optimised and representative manufacturing conditions (*Table XIV*). Flowability and agglomeration characteristics were assessed using conventional powder rheometry, pharmacopoeial funnel testing and micro-dynamic flow studies.

Our findings showed that micro-dynamic flow studies provided enhanced sensitivity to material differences related to cohesion. While rheometer-based assessments showed similar flow behaviour for both batches at higher stress levels (*Table XIV*), funnel-based tests identified significant differences in flow performance. Sample A, produced in the Glatt system, exhibited good flow through the Ph. Eur. Funnel (9.80 ± 0.70 g/s) and high micro-dynamic flow index (MFI = 36.17%), whereas Sample B, produced in the Niro-aeromatic granulator, did not flow through the funnel and showed significantly lower MFI (6.91%). These results indicated stronger cohesive interactions in Sample B. Notably, the miniaturised test largely overcame the previously discussed limitations of the Ph. Eur. Funnel for cohesive powders, enabling consistent measurements using less than 200 mg of powder sample.

In the powder rheometer, measurements under higher stress or confined conditions (BFE data) showed no significant differences between batches. At lower stress levels (SE data), both batches were characterised as easy flowing powders (SE <

5). Both remained physically stable (0.9 < SI < 1.1) and the flow rate sensitivity in Sample A (FRI < 1.0) indicated flow behaviour typically associated with powders containing flow enhancers [Freeman & Fu, 2008]. Sample B described better packing properties (higher CBD value).

Table XIV. Dynamic test powder rheometer, pharmacopoeial funnel and micro-dynamic flow data (*n=3*). AG values were calculated from Sample A in *Figure 30* and Sample B in *Figure 31*, as Sample B was too cohesive to quantify agglomeration within the powder flow pattern.

	Dynamic test – Powder rheometer				
Material	**BFE, mJ**	**SE, mJ/g**	**SI**	**FRI**	**CBD, g/ml**
Sample A	79.78±2.17	2.82±0.08	0.94±0.05	0.91±0.02	0.45±0.01
Sample B	81.92±3.36	3.28±0.08	0.95±0.05	1.42±0.04	0.53±0.00

	Ph. Eur. Funnel	*Micro-dynamic test*		
Material	**Flow rate, g/s**	**MFI, %**	**AG**	**PD, g/cm^3**
Sample A	9.80±0.70	36.17±0.98	0.03±0.01	0.91±0.01
Sample B	No Flow	6.91±0.97	0.24±0.01	1.01±0.03

In the pharmacopoeial funnel test, Sample A demonstrated good flowing properties, while Sample B did not flow. Similar trends were observed in micro-dynamic flow studies, which largely overcame the limitation of conventional funnel methods for cohesive powders (*Table XIV* and *Figure 31*). First, a fixed flow rate (or applied dynamics) was used for cross comparison (*Figure 30*), with the same magnification applied for both samples. Higher MFI and lower AG values indicated better flowing properties for Sample A. Sample B exhibited better packing properties (higher PD value), as observed in the powder rheometer. MCC grades (PH200, PH102 and PH101) were used as references to classify the flow behaviour of both batches, as shown in *Figure 30*. Then the flow rate was adjusted for Sample B according to material´s cohesion (*Figure 31*), further highlighting interparticle cohesive forces (or agglomeration effects) and dispersibility in the powder specimen.

Micro-dynamic flow studies enabled simultaneous assessment of flow behaviour and powder agglomeration. AG values were significantly higher in Sample B (0.24 ± 0.01) than in Sample A (0.03 ± 0.01), confirming increased particle clustering and cohesion. These effects were visually confirmed in the flow patterns (*Figure 30*), with Sample B forming larger agglomerates. A zoom-in analysis described Sample A as composed of regular spherical-shaped granules, whiles Sample B showed larger clusters and a higher fine fraction. Powder agglomeration dictated the flow behaviour for Sample B, further supporting the limitations of bulk flow assessments in detecting differences in material performance at very low stress conditions. Moreover, the technique required no specialised expertise, offering fast (≤ 5 min), reproducible and quantitative data.

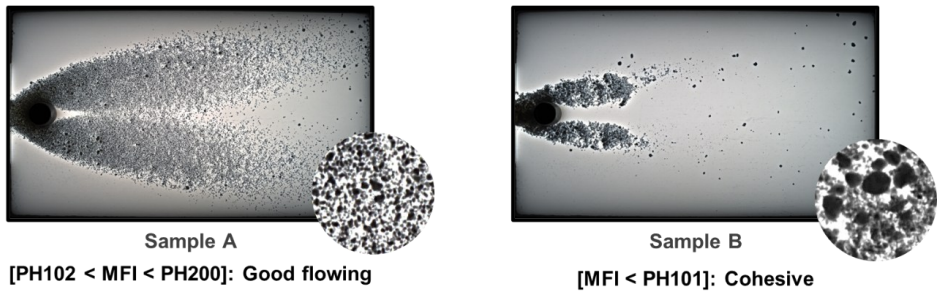


Figure 31. Micro-dynamic flow patterns of both granule batches at a fixed flow rate, visually depicting the increased cohesion (and agglomeration) in Sample B. MCC grades (PH200, PH102, and PH101) were used as references. Same magnification was applied for both samples. *Adapted from Blanco D, et al. (IV)*.

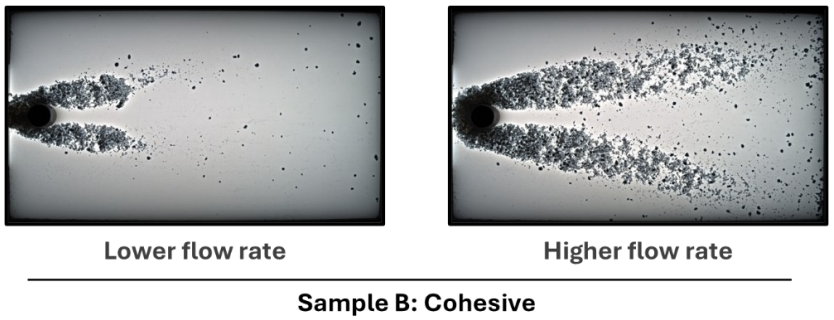


Figure 31. Micro-dynamic flow patterns of cohesive Sample B under varying flow rates (or applied dynamics), highlighting the impact of cohesive forces on flow performance. *Adapted from Blanco D, et al. (IV)*.

Particle size distribution (PSD) analysis further supported these findings. High-resolution imaging enabled simultaneous granule characterisation and flow analysis within a single setup. While the analysis of the good-flowing Sample A was straightforward, the cohesive nature of Sample B required manual dispersion using a spatula (sample size ±10 mg), as segmentation of smaller particles was more challenging due to clustering. Digital imaging revealed significant differences between the two batches. Sample A exhibited a larger mean particle size (Dv_{50} = 117.4 µm) and lower fines content, whereas Sample B presented a smaller average size (Dv_{50} = 96.8 µm) and a broader PSD (Table XV, *Figure 32*). The higher fines content in Sample B was therefore considered a major contributor to the observed agglomeration and flow variability. *Figure 32* presents the PSD histograms, with Sample B showing a significantly higher fraction of fines, supporting the agglomeration phenomenon visually observed in *Figure 30* and quantitatively captured by the AG values in *Table XIV*.

These results explain the different flow performance observed under varying consolidation stresses. Such differences were attributed to variations in processing parameters between batches, with the fine fraction playing a major role in the measured energy values (BFE and SE). At lower stresses in funnel-based tests, the increased fines content in Sample B promoted powder agglomeration and higher cohesion. Conversely, under the higher stress conditions of powder rheometry, the fines acted as a glidant agent, leading to a flow classification similar to that of Sample A. Similar results were observed in previous research on lactose grades *(Section 5.1.1.2 "Effect of bulk friction and cohesion")*. These observations align with the assumption that flow behaviour in powder rheometer is governed by frictional contacts rather than cohesive forces. The large number of particles analysed per repetition (>12,000) and the low variability between measurements (standard deviations shown in *Table XV*) suggest that the measured PSDs were representative of the bulk solid.

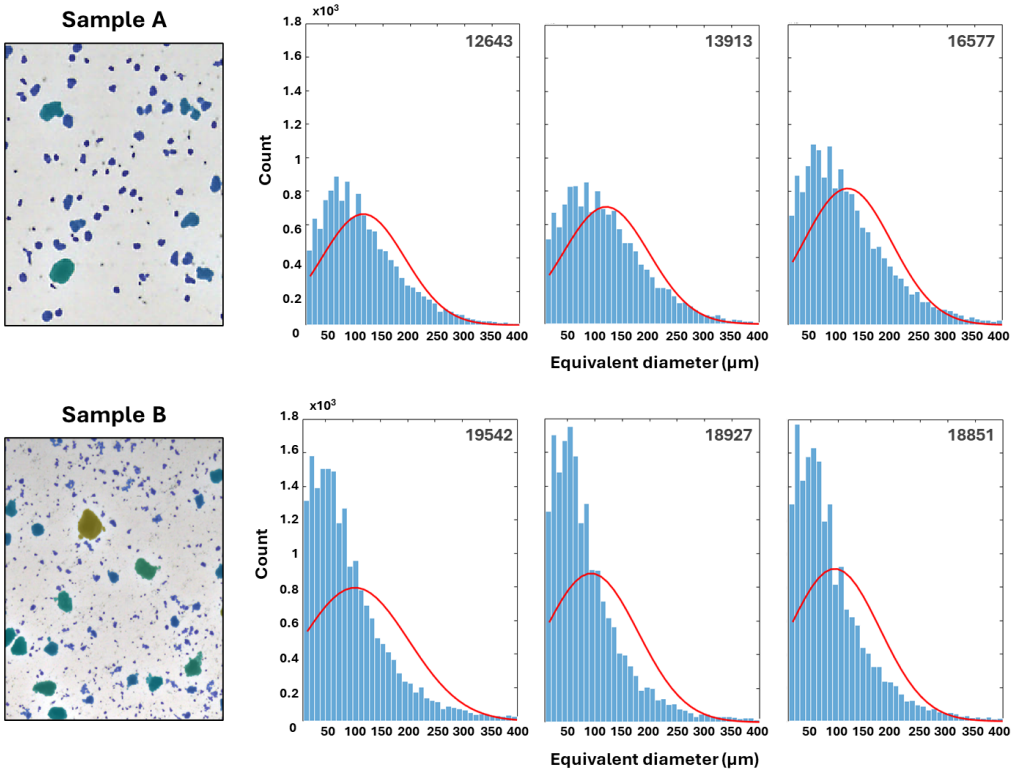


Figure 32. Image-based particle size distribution (PSD) data from micro-dynamic flow studies. *Top*: Sample A (good flowing). *Bottom*: Sample B (cohesive). PSD histograms highlight a significantly higher number of fines in Sample B. The number of particles analysed in each image is provided. Limit of detection (LOD) = 9.2 µm. *Adapted from Blanco D, et al. (IV)*.

Table XV. Image-based particle size distribution (PSD) metrics, showing a lower average particle size for Sample B (*n=3*). Particle size expressed as equivalent circular diameter (ECD, µm).

		Particle size - Equivalent diameter (µm)				
		Rep 1	**Rep 2**	**Rep 3**	**Average**	**StDev**
Sample A	Mean	114.1	120.7	117.4	117.4	3.3
	Min	16.7	16.7	16.7		
	Max	933.3	985.4	771.8		
Sample B	Mean	104.0	93.2	93.4	96.8	6.2
	Min	16.7	16.7	16.7		
	Max	1157.8	1182.4	1174.5		

Overall, the results highlighted the importance of advanced, stress-specific powder characterisation to detect material differences affecting technical processability. Differences in agglomeration and fines content undetected in bulk powder rheometry determined flow performance at lower stresses across granulation scales. Thus, integrating micro-dynamic flow studies into scale-up processes can facilitate robust technology transfer, supporting QbD principles and ensuring regulatory compliance.

Observation remarks

- The miniaturised system showed strong correlation with Ph. Eur. Funnel, largely overcoming its limitation for more cohesive powders.
- Image analysis enabled the correlation between particle characteristics and flow properties within a single testing setup.
- Micro-dynamic flow studies effectively addressed common scale-up and technology transfer challenges.

5.3 General discussion

This section begins by outlining the theoretical foundations of the miniaturised funnel test, with a focus on insights gained through systematic research of the flow behaviour in small powder volumes and their differences from bulk solids. Mechanistic explanations are provided regarding the dependence of flow properties on shear strain rate under dynamic conditions. Finally, the practical implications of innovative approaches, such as machine vision and small-scale flow measurements, are explored, highlighting their potential contributions to drug development and manufacturing.

5.3.1 Flow properties at very low stresses

The lower stress limit depended on the specific tester and the influence of frictional contact forces, listed in decreasing order: BFE > SE > Funnel-based tests. At lower

stresses, flow behaviour was increasingly governed by cohesive forces, as observed during both the filling process and funnel-based testing. This aligns with prior research demonstrating a strong dependency of bulk friction and cohesion on the applied consolidation stress, particularly at the very low stress levels encountered in tablet presses [Leung et al., 2017; Søgaard et al., 2017]. Under such conditions, where frictional contacts are limited, cohesive forces predominantly govern flow behaviour.

The miniaturised measuring principle closely reproduced the processing conditions of both filling geometries (*Section 5.1.1 "Consolidation stress and flow properties"* and *5.1.2 "On the mechanisms of flow enhancement and cohesion"*). A high correlation with the Ph. Eur. Funnel was consistently observed, effectively overcoming limitations in analysing more cohesive powders (*Figure 31*). Bulk consolidation was significantly reduced by using sub-dosage sample amounts (< 200 mg). The results empirically supported the assumption that flowability under such low-stress conditions does not represent that of a bulk powder bed, where particles are in continuous contact [Harnby et al., 1987; Prescott & Barnum, 2000; Schulze & Wittmaier, 2003; Wu & Cocks, 2004]. This highlights the often overlooked but fundamental role of cohesive forces at very low consolidation stresses.

Bulk powder flow measurements, influenced by the weight of the powder bed itself, did not accurately replicate the behaviour of small powder volumes, as observed in Ph. Eur. tapping or funnel tests. This difference became more pronounced under higher stress conditions in the powder rheometer, where results deviated further from actual filling performance. Current techniques are constrained by the limited relevance of their data to real processing conditions [Søgaard et al., 2014]. Accordingly, the lower stresses observed in the pharmacopoeial funnel discharge explain why it remains the first choice in industry for characterising and optimising filling processes. It is considered to simulate the mechanism of powder flow through a die cavity [Ph. Eur. 2.9.16, Ph. Eur. 2.9.36, USP <1174>].

Bulk versus small powder volumes: Stress and flowability differences

The improved flow performance of cohesive materials in both tablet presses and the miniaturised system suggests a looser packing state (i.e., lower consolidation stress) for small powder volumes, as discussed in *Section 5.1.1 ("Consolidation stress and flow properties")*. These findings support Schulze´s (2008) estimate of significantly lower stresses (< 100 Pa) during the processing of small powder volumes, as well as DEM-calculated stresses (~ 200 Pa) at the funnel outlet [Gentzler et al., 2015; Leung et al., 2019; Zhou, X. et al., 2020]. Similarly, Leung et al. (2019) reported a drastic drop in consolidation stress immediately after powder discharge. These results are also consistent with calculated outlet stresses (200 Pa) in a pilot-scale rotary press [Søgaard et al., 2014]. Considering the complexity of rotary filling dynamics, one can reasonably assume higher stresses (and frictional contacts) compared to eccentric tablet presses.

This may explain the enhanced flow of cohesive powders in rotary presses, due to a reduced impact of cohesive forces. For example, untreated, milled L200M that did not flow by gravity demonstrated improved flowability when force-fed with a multi-paddle system. However, further research is needed to rationalise stress differences across filling geometries. Generalising results and comparing geometries remains challenging, as material performance strongly depends on the specific equipment.

As reviewed in *Section 2.5.1 ("General classification")*, the magnitude of the normal force increases with the powder mass under dynamic conditions, influencing both consolidation stress and packing state during flow measurement. The lower stress limit is tester-dependent [Jager et al., 2015]. This agrees with very low consolidation stresses (~ 50 Pa) reported in the SSSpinTester [Johanson, 2019], compared to the 100-200 Pa observed at funnel openings. The bulk contact powder bed in pharmacopoeial funnels did not reproduce the complex flow behaviour of small volumes in this study. During the separation of the dosage unit in filling processes, stresses are even lower due to the limited powder quantity, small orifices, and faster filling or discharge speeds. Therefore, very low stresses, below 100 Pa can be reasonably assumed. As only the SSSpinTester has been used for small-scale flow studies at these stress levels, numerical modelling is needed to estimate the operating stress range in the miniaturised funnel test. Further research is needed to compare the effect of consolidation stress between different flow measurement techniques and particle characteristics. There is a significant gap in knowledge on this topic.

Since measuring powder flow under very low stresses is experimentally challenging, assessments are often conducted at higher stresses and extrapolated downward. However, as discussed in *Section 2.2.2.2 ("Flow properties at very low stresses")*, both bulk friction and cohesion are stress-dependent, making such extrapolations unreliable. In the very low stress regime relevant to rotary tablet presses, where particle contacts are limited, flow behaviour is dominated by cohesion rather than frictional interactions [Leung et al., 2017; Søgaard et al., 2017]. This was supported by micro-dynamic flow studies, which showed that the effects of cohesion on powder flowability cannot be determined at higher stress levels. Flow behaviour changes nonlinearly with consolidation stress [Søgaard et al., 2014; Stavrou et al., 2020; Rhodes et al., 2023]. Therefore, direct assessment under very low stress conditions is essential for accurately characterising powder behaviour in these applications.

Strain rate dependency in low stress applications

As previously discussed, two key challenges in powder flow analysis during the separation of the dosage unit during filling processes are: (i) very low stresses and (ii) high strain rates. Few modern techniques can measure flowability in low-stress environments, and fewer still do so under dynamic conditions [Ghadiri et al., 2020].

In this study, the most relevant dynamic techniques were the powder rheometer and the pharmacopoeial funnel. However, neither appears to fully replicate these criteria. The bulk contact powder bed hinders measurements at very low stresses, while high strain rates are not achieved using funnel discharge techniques and may not be fully represented in powder rheometry.

Observation remarks

- In small-scale R&D tablet presses, stresses significantly lower than 100 Pa can be expected.
- Bulk flow tests hinder measurements at the very low stress range and/or high strain rates.

5.3.2 Relevance, limitations and perspectives

Relevance

Most pharmaceuticals are produced in self-metered doses or small powder volumes. For instance, immediate-release (IR) oral products comprise 82.5% solid dosage forms, with tablets and capsules accounting for 64.5% and 22.7% of these products, respectively [Kotsybar et al., 2023]. Solid dosage forms, such as tablets, capsules, dry powders for inhalation (DPIs) and parenterals for dissolution, require highly precise filling to ensure uniformity of the final dosage units and compliance with stringent regulatory criteria [USP <905>; USP <1151>]. Micro-dynamic flow studies have demonstrated strong relevance, sensitivity and practicality for characterising flow properties in these small-scale operations, which typically operate under very low stresses and high strain rates. Understanding and controlling potential manufacturing bottlenecks earlier in product development can drastically reduce the need for extensive testing of the final product, time-to-market and associated costs [ICH, 2009]. In this thesis, early assessment of filling performance in small-scale R&D tablet presses was investigated and successfully achieved.

Flow data relevant to the filling performance in early-stage R&D tablet presses can now be generated throughout the drug development process (*Figure 33*). First, small-scale measurements integrated powder flow analysis into the pre-formulation stages and can be used for early API characterisation of a selected drug candidate to define the most suitable manufacturing route and support excipient selection. Next, machine vision–based flow studies at the very low stress range facilitated small-scale development of the original formulation, without relying exclusively on final product testing. Finally, fast and reproducible flow measurements can be conducted at-line during technology transfer or scale-up, for process optimisation, validation, or QC, thereby reducing batch-to-batch variability.

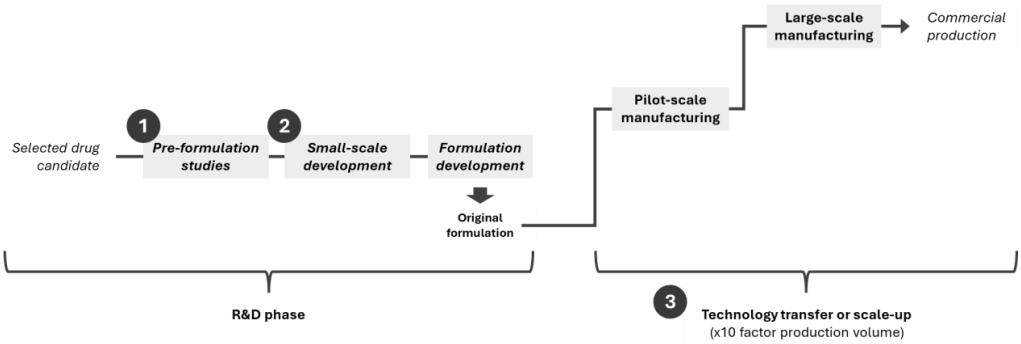


Figure 33. Demonstrated applicability of micro-dynamic flow studies in the formulation and manufacturing process of solid dosage forms. *From left to right*: Early API characterisation (pre-formulation studies), early formulation development, and scale-up (technology transfer on the original formulation).

Although relevance and sensitivity measure the quality or scientific value of a technique, its practicality is equally important. The advanced digital imaging in the novel measuring system enabled detection of powder agglomeration as a direct descriptor of cohesive forces acting on the solid specimen. This is particularly valuable in the very low stress regime typical of tablet presses, where tablet mass variability (i.e., filling performance) can be significantly influenced by poor flowability or agglomeration. Agglomerate detection proved useful in early API characterisation (*Section 5.3.1 "Pre-formulation studies"*), facilitated achieving a robust target flowability during small-scale formulation development (*Section 5.1.2 "On the mechanisms of flow enhancement and cohesion"*) and was decisive for process validation and quality control (QC) purposes during scale-up (*Section 5.3.2 "Process optimisation and validation during scale-up"*). The methodology and testing protocols, including pre-test sample conditioning (*Section 4.2.3.2 "Novel measuring system"*), were validated based on the high repeatability observed in a limited number of repetitions ($n=3$).

The machine vision–based testing setup demonstrated several advantages. Fast, non-invasive, and highly intuitive measurements were generated with minimal operator intervention. Static image analysis was integrated into powder flow analysis. Flow descriptors and powder and/or particle characteristics could be retrieved on a single analytical platform. However, further research is needed to optimise the image processing and testing setup for specific purposes and to determine the boundaries of particle characterisation and/or supporting techniques, such as spectroscopy or microscopy. The possibilities in this regard are vast. Another key advantage of this approach is its miniaturised, enclosed system, which enables powder flow measurements with minimal sample consumption (≤200 mg). This not only facilitates a safer handling of toxic compounds but also ensures feasibility when materials are scarce or expensive. Additionally, its non-invasive nature, operating at very low

stresses via image analysis, preserves the physical and chemical integrity of the samples, allowing for their reuse in further analyses.

Limitations

Despite its advantages, the miniaturised funnel test presents limitations when assessing highly cohesive APIs, particularly those with very small particle sizes that do not flow well under very low consolidation stresses. Micro-dynamic flow properties are relevant for filling performance in early-stage R&D tablet presses, where cohesive forces and agglomeration largely govern flow behaviour. Increased cohesion often leads to higher tablet mass variability, interrupted die filling, and lower repeatability in the miniaturised system. Notably, most newly developed APIs are extremely cohesive and adhesive, typically exhibiting a Dv_{50} below 100 µm, broad PSDs, and a strong tendency to agglomerate. These characteristics make accurate filling a challenge and often require pre-processing steps to ensure downstream manufacturability [Seville et al., 2000, Majerová et al., 2016, Chen et al., 2019]. Nevertheless, the miniaturised funnel test can be effectively applied to assess these effects at a small laboratory scale, offering valuable insights into early powder behaviour. Conversely, coarse powders or granules above a certain size may also be difficult to evaluate using the miniaturised funnel test. For non-cohesive (or coarse) materials (Dv_{50} > 200 µm), where gravitational forces (or particle weight) dominate over interparticle attractive forces, particles tend to behave as individual units. This may reduce the method's sensitivity to relevant flow characteristics in such systems and further research is needed to establish the upper and lower size limit. In any case, free-flowing materials are unlikely to pose significant challenges with respect processability in or inside the tablet press. A more comprehensive testing strategy, incorporating complementary techniques such as powder rheometer and shear cell measurements, can facilitate a deeper understanding and enhanced control of powder flowability throughout the drug development process.

The operational window of the miniaturised funnel test covered a broad range of powder flow behaviours, from cohesive to free-flowing materials, although repeatability decreased with increasing cohesion. As such, is applicable to most excipients and intermediate products used in the manufacture of solid dosage forms: powders with good flowability generally maximise filling performance and allow for higher processing speeds. In contrast, highly cohesive materials, such as lactose L200M and acetaminophen (APAP), exhibit poor flowability under very low consolidation stresses, often forming clusters both in the tablet press and the miniaturised system. Micro-dynamic flow properties described material behaviours relevant to filling performance, particularly in cases where cohesive forces and powder agglomeration predominantly governed flow behaviour. Highly cohesive powders were best differentiated in the quasi-static regime (shear cell analysis), where higher

consolidation stresses helped mitigate the spatial (cohesive) distribution at very low stresses. However, results obtained from quasi-static methods cannot be extrapolated to dynamic flow conditions and/or filling processes, as discussed in *Section 5.4.1 "Flow properties at very low stresses"*, and the large material quantities required for such analyses present additional limitations.

The experimental work presented in this thesis has primarily focused on eccentric tablet presses during early-stage formulation development. However, the translation of these results to rotary presses in later development stages may not be straightforward, due to the presence of distinct and concurrent mechanisms governing die filling in rotary systems, as discussed in *Section 2.4.1 "The importance of effective filling"*. While it can generally be assumed that a powder exhibiting good flowability in an eccentric press will benefit from these additional mechanisms and flow well in a rotary press, this is not always the case. The complex dynamics in rotary systems, such as centrifugal forces, rapid turret speeds, and suction filling, may either facilitate or hinder powder flow depending on the material properties. Therefore, although good performance in eccentric presses provides valuable insights for formulation development and process design, it does not guarantee equivalent behaviour under the high-throughput conditions of rotary compaction and should be validated accordingly. Moreover, the effect of processing speed may not be able to be characterised in this method.

Future perspectives

Despite the theoretical foundations discussed in this thesis, micro-dynamic flowability remains an emerging and largely unexplored area within powder technology. To date, powder flow analysis has primarily focused on bulk powder volumes, while flow behaviours at very small scales and/or very low stress conditions have received limited attention. A comprehensive understanding of this novel approach and its broader applicability will require addressing several factors. First, the operational stress range of the method should be quantitatively defined using numerical models, such as DEM, to fully understand the processing conditions represented. Moreover, the influence of additional formulation constituents on the measurement is not fully established; the upper particle size limit for coarse materials remains unclear, and the sensitivity of the method to different shear (or flow) rates according to particle properties needs further investigation. While the method may not reach the higher consolidation stresses characteristic of traditional bulk flow measurements, its capability to operate under very high strain rates may provide new insights into the frictional behaviour of powders.

Most industrial processes operate within the dynamic range, where cohesive flow and powder agglomeration often constitute the main bottleneck [Ghadiri et al., 2020]. Future research should explore the role of interparticle cohesive forces in diverse

applications, such as surface modification, blending, fluidisation, segregation, and spreadibility. Other relevant areas may include particle engineering techniques such as co-crystallisation, granulation, spray drying, or supercritical fluid processing, which could provide new insights into powder behaviour in complex formulations. In this context, the image analysis approach introduced in this work presents significant opportunities for innovation, particularly through the integration of artificial intelligence (AI) and machine learning for advanced visual inspection and automated characterisation of powder and/or particle characteristics. Complementary optical techniques, such as spectroscopic and microscopy, could further enhance the resolution and accuracy of the analysis.

Future work may also extend this approach to other solid dosage forms and advanced manufacturing technologies. Applications such as dry powder inhalers (DPIs) and certain emerging additive manufacturing (AM) processes require uniform and consistent powder flow in small volumes and/or very low stress conditions [dos Reis et al., 2021; Mellin et al., 2017; Mathias et al., 2024]. In such cases, micro-dynamic flowability becomes a powerful tool for ensuring efficient processing and product quality while reducing resource consumption. Furthermore, the potential contribution of these advances to the development and optimisation of cost-effective direct compression (DC) platforms should not be overlooked. Similarly, continuous manufacturing (CM) could benefit from the integration of micro-dynamic flow analysis, as reliable and consistent powder flow is critical throughout the manufacturing route to ensure uninterrupted processing and product uniformity [ICH, 2023].

6 · Conclusions

This thesis work contributes to the body of knowledge on powder technology and sheds light on how particle-level understanding of flowability is key to enhancing flexibility and capacity to the manufacturing of pharmaceuticals. Effective filling of materials into cavities is a ubiquitous and decisive aspect of solid dosage form manufacturing. The long-standing challenge of characterising the flow properties inside the tablet press during die filling was investigated.

Powder flow properties were found to depend on the applied consolidation stress: the resulting physical mechanisms (or shear stress) dictate material performance. Regardless of the feed system, very low stresses were detected in eccentric R&D tablet presses; thus, the interparticle cohesive forces determined the filling performance. Higher stresses were increasingly affected by frictional contacts and less by cohesion. For instance, non-flowing (cohesive) materials in the tablet press performed well under an applied load. The weight of the powder bed, along with other external factors inherent to the measuring principles, was identified as an additional source of consolidation stress, helping to explain why available bulk flow testers may not adequately represent these processing conditions. Within this context, the mechanistic differences observed in comparison with bulk solid systems highlight the need for further research, as small powder volumes may be governed by a distinct flow regime.

The miniaturised test method closely reproduced the operational stress (and strain) range observed in small-scale R&D tablet presses. Flow behaviour at very low stresses depended on the particle properties and the environmental factors affecting interparticle cohesive forces, such as particle size, surface roughness, moisture or the number of fines in the powder specimen. Particle-level flowability exhibited greater sensitivity to material differentiation driven by cohesive mechanisms compared to measurements performed at higher consolidation stresses. Additionally, machine vision brought new insights into powder flow analysis. Beyond the visualisation and interpretation of results, digital imaging enabled the quantitative detection of powder agglomeration as a primary descriptor of cohesion, particularly under low-stress conditions. Highly automated, fast and reproducible measurements were produced with minimal operator intervention, and the measuring principle was patented.

Standardised measurements using this method may address the challenge of ‘normalising’ flow properties inside the tablet press so that formulations can be compared, and operating ranges can be considered in advance. In this way, the focus can shift away from final product testing and towards building quality throughout the development process. Notably, powder dynamics within the feed frame are complex and the results, although informative, may not necessarily be representative in all manufacturing scenarios. Die-filling performance must ultimately be assessed for each formulation and tablet press. In any case, process-relevant flow data can be generated

from the lab to commercial production for enhanced understanding, monitoring and control of powder products and processes. This translational capacity is paramount in the evolving pharmaceutical landscape, which is characterised by recent regulatory initiatives, such as Quality by Design (QbD), and the growing implementation of continuous manufacturing (CM).

To summarise, early assessment of filling performance leads to more informed decision-making. A more robust formulation design and a trouble-free scale-up process can considerably reduce the need for extensive testing of the final product, as well as the time-to-market and associated costs. For the patient, this can mean more affordable drugs. Key advances in drug development will include: (i) early characterisation of active pharmaceutical ingredients (APIs) at pre-formulation stages, (ii) fine-tuned formulations from the beginning of formulation work, and (iii) filling process–relevant characterisation of raw materials and intermediates for quality control (QC) and validation strategies. Micro-dynamic flow studies address major challenges in the design and manufacture of pharmaceuticals and offer promising opportunities for advancing powder flow research.

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