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Review article

A concise summary of powder processing methodologies for flow enhancement

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ABSTRACT

The knowledge of powder properties has been highlighted since the 19th century since most formulations focus on solid dosage forms, and powder flow is essential for various manufacturing operations. A poor powder flow may generate problems in the manufacturing processes and cause the plant's malfunction. Hence these problems should be studied and rectified beforehand by various powder flow techniques to improve and enhance powder flowability. The powder's physical properties can be determined using compendial and non-compendial methods. The non-compendial practices generally describe the powder response under the stress and shear experienced during their processing. The primary interest of the current report is to summarize the flow problems and enlist the techniques to eliminate the issues associated with the powder's flow properties, thereby increasing plant output and minimizing the production process inconvenience with excellent efficiency. In this review, we discuss powder flow and its measurement techniques and mainly focus on various approaches to improve the cohesive powder flow property.

1. Introduction

As a solid state, powders have diverse applications in different manufacturing fields, such as dyes, ceramics, petroleum, cosmetics, pharmaceuticals, and food. On average, 75% of manufacturing processes in chemical industries involve particulate solids or powders at least once or twice throughout the cycle. In the pharmaceutical industry, where most of the products are solid dosage forms, transport and handling of powdered solids are especially important [1]. Free-flowing powders are desirable to enable robust powder processing operations such as bin filling, hopper discharge, and capsule and die filling. In a pharmaceutical plant where the powders undergo different processes, there is significant variation in the physical particle properties, which affect the powder flow. Thus, it is

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essential to understand the processes and critical parameters to ensure product quality and efficient manufacturing performance. Being such an integral part of all the manufacturing processes, it is essential to understand the phenomenon of powder flow, which finally dictates the process efficiencies of fluidization, blending, crushing, granulation, tableting, and flow from the storage tanks. Powder flow properties are critical, particularly in the pharmaceutical, food, cosmetic and ceramic industries. Really for the development, conveyance, packaging, and transport of goods, powder flow activity is essential [2]. Powder flow can be of diverse types, i.e., "static" and "dynamic"; measurement of the former involves shear cell and wall friction analyses of a consolidated state of the powder, and the latter requires flow studies using a rotating helical blade in a less consolidated state of the powder sample. The static flow determinations, such as shear cells, highlight the dominant friction and mechanical interlocking in some process operations, such as wall friction [3]. The behavior of the powder flow is measured by various material properties, mainly pertaining to the physical and chemical properties of the substance [4]. As a simple observation, poor flow gives poor product uniformity and causes undesirable process breakdown, affecting the production line's required speed and thereby providing substantial financial losses.

Flowability is a derived powder property, unlike other physical properties, which are not inherent but dependent on a range of fundamental powder properties and other material and environmental parameters. The complex phenomena of powder flow are known to be affected by factors such as particle size distribution [5–7], particle geometry [8,9], moisture content, inter-particle forces which eventually reflect the particle surface energies [10,11]. Most of these properties affect the interparticle interactions within the bulk of the powder. Various interparticle forces, such as van der Waals, capillary forces, electrostatic forces, mechanical interlocking, and other frictional and gravitational forces, exert their effects and determine the powder flow [12]. For fine dry particles, the van der Waals force is the most influential type of force responsible for the cohesiveness of powder [13]. The decreased particle size causes gravitational forces to be less dominant. At specific particle sizes (<100 μm), inter-particulate weak polarizing van der Waals forces begin to overcome gravity, dominating powder behavior. When these attractive forces exceed the particle weight by at least an order of magnitude, the powder becomes very cohesive, and the particles no longer flow individually but as aggregates. The small particles' comparatively high specific surface area results in a very high degree of surface sticking and interaction with neighboring particles.

On the other hand, the massive particle is to pass over each other when shear pressure is applied and represents the lower coherent and stable behavior. This is because, for broader particle size, external forces such as gravity are significantly more critical than interparticle troops due to the cohesive forces resulting from electrostatic, capillary, or van der Waals interaction. The reduced particle size increases the surface area per unit mass for any given powder, providing a greater area for surface cohesiveness, interactions, and flow obstructions. The flow properties of the bulk powder would be significantly increased if these coherent forces could be minimized [5]. A study proved that it is more efficient to improve the pharmaceutical powder flow by lowering the interparticle cohesive forces than by reducing the inter-particle frictions [14]. Similar-sized powders can exhibit different flow behaviors due to particle morphologies and surface roughness variations. Both flowability and compactibility depend on the attraction of interparticle forces [15]. Flow occurs in pharmaceutical powders with detachment and breakage of irregular lumps, also called intermittent flow. Such an undesirable flow pattern generally causes a scatter in powder mass deposited into the die and weight variation in solid dosage forms [6]. Moisture is another important factor that highly affects the ability of the powder to flow smoothly. The high liquid content increases the strength of liquid bridges formed between particles causing hindrance to the powder flow. It is common to observe depreciated flow with increasing moisture content, but this may not always hold true. The added moisture improves the density of the material and hence the flow of fluffy powders.

Similarly, Coelho et al. deduced that van der Waals forces are strengthened by adsorbed moisture, decreasing inter-particle distance. Electrostatic forces decrease with added moisture content because of the conductive properties of water. Friction and interlocking, which obstruct powder flow, are diminished by moisture since moisture reduces the surface roughness of the particulate solids [1]. A study on microcrystalline cellulose (MCC) indicated that the mechanical properties of the powder vary significantly in the presence of moisture. The influence was described by the fact that the water acts as a plasticizer and therefore affects the flow of the powder [16].

The size and shape of the particles [17], along with the mechanical properties [10,18] of the particulate solids, affect the

Table 1
Parameters affecting powder flow.

Parameter	Effect
Particle size	The smaller particle size of powder causes increased surface area and hence higher degrees of forces of adhesion and cohesion to neighboring particles and surfaces. Larger particles roll over other particles when pressure is applied and exhibit lower interactive behavior. In such cases, the gravitational forces exceed the interparticle forces; hence, overall, the flow of the particles is better than that of fine particles.
Particle morphology	The smoother the particle morphology, the better the flow. Therefore, spherical particles flow better than those with sharp edges, such as cubical, rhomboid, or needle-shaped crystals. The spherical particles may glide over each other and give a good flow, as compared to the crystalline shapes of the particles.
Moisture content	Environmental humidity can promote the formation of liquid bridges, increasing interparticle forces. As a cause of capillary forces, these liquid bridges lead to increased powder cohesion and negatively impact powder flow.
Temperature	The environmental temperature may affect powder flow if there are low melting or low Tg (glass transition temperature) components in the powder blend. The higher temperature may cause softening of these materials and further obstruct powder flow. On the other hand, higher temperatures may also lead to static development on the particle surfaces, which significantly hinder smooth powder flow.
Intermolecular Interactions	All the above-stated parameters finally affect the intermolecular interactions, which eventually determine the flow of the powder particles. The more cohesive interactions between two particles within a powder, the poorer the flow of the same and vice-versa.

flowability. The type and magnitude of interactions between individual particles at the micron level affect the flow properties [10]. Concerning particle shape as one of the determining factors, spherical particles flow effortlessly with a gliding action. In contrast, irregular-shaped particles usually exhibit poor flow properties due to enhanced friction between the particles [7]. The effect of shape on the flow properties can be traced to its impact on the bulk powder properties, such as the bulk density, particle size distribution, and interparticle forces.

On the other hand, environmental factors such as temperature and humidity also affect the powder flow unless the powder is inert and non-hygroscopic [19]. The addition of formulation excipients, even in small quantities, affects the powder flow properties [20]. Table 1 summarizes powder flow parameters and their effect on powder properties.

1.1. *Types of powder flow*

All the factors mentioned above finally give different types of flow patterns. The reliability for getting a consistent and uniform flow of powders from hoppers or feeders without spillage, wastage, sticking, and dust generation, and the flow patterns inside the silo are of utmost importance. It is, therefore, crucial to have a background of the flow patterns and obstructions that can occur within and out of the storage vessels. Powder flow through a hopper or silo exhibits two principal patterns (1) core flow and (2) mass flow.

An ideal flow pattern is the mass flow wherein the powder's content is in a constant flow motion when released from the hopper. All the material within the hopper is live and flows towards the opening from its middle and periphery as a bulk. A flow pattern called 'funnel flow', like that of mass flow, is when the powder flows out from a central "funnel" formed within the bulk of the material [21]. Mass flow in hoppers also provides a first-in-first-out flow sequence, minimizes stagnant material, reduces the separation of sifting, and provides a good bulk density and flow that is even and well-regulated with a steady discharge [22,23]. Arching seems to be the flow barrier in a mass-flow vessel in which a static powder arch develops over the outlet of a hopper or converging walls, thus preventing powder flow [24]. Mass flow through a container is only possible when the walls are steep and smooth, so there is no resistance to flow. The friction between the powder and the hopper wall should preferably be below a critical value. To evaluate the suitability of the hopper design for an application, a wall friction test can be performed, which gives a fair idea about the possibility of mass flow from the hopper by its design. The discharge of the product from the hopper can be controlled by a feeding valve which allows intermittent powder flow through the entire area of the outlet, which is usually the determining factor for a possibility of a mass flow. The mass flow

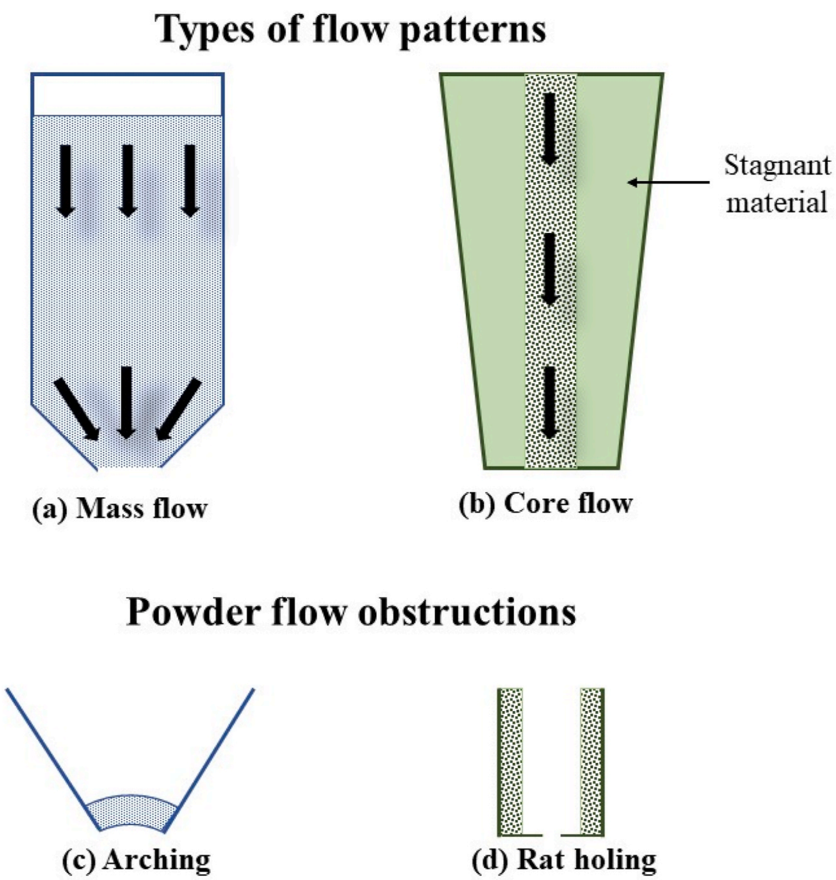

Fig. 1. Representative diagram indicating powders' flow types and their respective flow problems.

process continues until the last remain in the silo or until there's any obstruction to the flow. In a mass flow pattern, the stress on the powder is usually low, and there are no stagnant regions in the hopper [25]. A funnel flow gives a lot of flow problems that can be avoided by modifying the properties of the powder. The worst-case scenario is no flow which happens over time at the funnel's opening. In the case of cohesive powders, "arching" may occur near the hopper's outlet, which blocks the powder flow [26]. Arching is the flow obstruction in a mass-flow vessel, wherein an arch forms across the hopper's outlet. The arch with sufficient strength within is self-supporting and completely prevents powder flow.

The core flow pattern also called the standard flow, is determined by powder discharged into the desired flow direction just above the drawdown points of the outlets. The powder is pulled into the flow channel from the upper free area of the powder. This provides some first-in, last-out discharged systems during funnel flow to source powder caking [22]. Still, if employed in a continuous (instead of batch) process, the powder across walls in the bottom part would remain stationary in the vessels until discharged out to empty. This is a type of flow where the powder material on top cascades toward the center and down the middle while the material at lower levels waits to move until the fill level reduces to that location [26]. Most of the flow problems occur in the core flow pattern, as the cohesive powders move as a central funnel, causing no flow of the powder at the periphery of the funnel near the inner walls giving a stagnant layer [27]. This can lead to a stable rat-hole [24]. The "core" or "funnel" in the middle may be referred to as a "rathole" because, should flow stop before the bin empties, the channel down the middle of the bin from top to bottom remains vacant of powder. The area outside the rathole is filled with consolidated powder, so the movement of particles under gravity alone is impossible. The core flow pattern increases the extent of the segregation effect on the discharge of the powder.

It should be noted that to ensure reliable discharge of the powder, the critical outlet dimension of the hopper should be exceeded. These are the critical rat-hole and arching diameters for core and mass flow patterns. Fig. 1 is a representative diagram indicating powders' flow types and their respective flow problems.

1.2. *Measurement of powder flow*

As we see, powder flow is an important parameter to be evaluated before the start of any process to avoid any hindrance and losses along the production line. Determining powder flow is equally important to ensure product performance and to design a hopper through which powder can flow. From the above discussion, it can be deduced that the prediction of powder behavior is a multidimensional problem such that a single measured parameter or property cannot wholly describe powder behavior [28]. Hence, a single characterization tool cannot suffice to differentiate between good and bad flow powders. On the other hand, when a single powder or a blend is evaluated by different powder testers, the results cannot be well correlated. Moreover, the conditions for the suitability of each tester are not well-defined. Therefore, understanding powder properties as evaluated by different testers and their inter-relationship is a subject matter of interest. Such a study would help discern and establish the rank order of other powders [13]. A lack of basic knowledge of powder flow and subsequent hopper design may cause problems in the manufacturing unit in the industries [29].

Various powder characterization techniques are available to determine how powders perform their processes and are also used to analyze powders in normal conditions [30]. The available methods can be classified into pharmacopeial methods and advanced characterization techniques. The conventional methods include the evaluation of parameters such as the angle of repose, bulk, and tapped density and derived parameters from these evaluations, such as the Carr index and the Hausner ratio. These are elaborated in the consequent sections.

1.2.1. *Pharmacopeial methods for evaluation of powder flow properties*

Powders, being of great importance in the pharmaceutical industry, have developed innovative methods for evaluating powder flow. Attempts have been made to assess the powders with different techniques and further correlate the results to better understand the powder flow behavior. The pharmacopeial chapter on powder flow reviews the most frequently used methods. It is also stated therein that no single method is sufficient for the powder flow evaluation; therefore, standardization of the methods is a prerequisite. The four most commonly reported methods are (i) angle of repose, (ii) compressibility index or Hausner ratio, (iii) flow rate through an orifice, and (iv) shear cell. Pharmacopeial standards state that any method for the evaluation of powder flow must be practical, functional, reproducible, sensitive, and yield meaningful results. Therefore, an appropriate strategy would be the use of multiple standardized test methods, which would evaluate various aspects of the powder flow properties.

1.2.1.1. *Angle of repose.* The angle of repose is the most common evaluation parameter used in several branches of science to analyze

Table 2
The scale of flowability for the angle of repose.

Flow property	Angle of repose (degrees)
Excellent	25–30
Good	31–35
Fair	36–40
Passable	41–45
Poor	46–55
Very Poor	56–65
Very, very poor	>66

powder flow. The repose angle indicates the inter-particulate friction or resistance to movement between particles. As European Pharmacopeia defines, "the angle of repose is the constant, three-dimensional angle (relative to the horizontal base) assumed by a cone-like pile of material formed." Though it is a very dependent method, difficulties arise with materials that undergo segregation and consolidation or aeration of the powder as the cone is formed. From the variety of angle of repose test methods described in works of literature, the two most common experiment variables include (i) the height of the 'funnel' through which the powder passes may be fixed relative to the base, or the height may be varied as the pile forms; and (ii) the base upon which the pile forms may be of fixed diameter or the diameter of the powder cone may be allowed to vary as the pile forms. The drained angle of repose and dynamic angle of repose are the two variations in the angle of repose methods. The general scale of flowability for the angle of repose is usually according to the classification by Carr, as shown in Table 2 [31].

When the angle of repose exceeds 50°, the flow is rarely acceptable for manufacturing purposes. The angle of repose is determined by measuring the height of the cone of the powder and calculating the angle of repose, α, from the following Eq. (1):

$$\tan(\alpha) = \frac{height}{0.5 \times base} \tag{1}$$

1.2.1.2. Compressibility index and Hausner ratio. In recent years the compressibility index and the closely related Hausner ratio have become simple, fast, and popular methods of predicting powder flow characteristics. The compressibility index has been proposed as an indirect measure of bulk density, size and shape, surface area, moisture content, and materials cohesiveness because these can influence the observed compressibility index. The compressibility index and the Hausner ratio are determined by measuring both the powder's bulk volume and tapped volume. The basic procedure is to measure the apparent unsettled volume, V_0, and the final tapped volume, V_f, of the powder after tapping the material until no further volume changes occur. The compressibility index and the Hausner ratio are calculated by the following Eqs. (2) and (3):

$$Compressibility\ Index = 100 \times \frac{V_0 - V_f}{V_0} \tag{2}$$

$$Hausner\ ratio = \frac{V_0}{V_f} \tag{3}$$

Alternatively, these parameters can be calculated by replacing the volumes with their respective density values. For the compressibility index and the Hausner ratio, the generally accepted scale of flowability is given in Table 3 [31].

Like the angle of repose, the two properties are not intrinsic and dependent on the methodology used. Thus, there have to be experimental considerations for evaluating these, including the diameter of the cylinder used, the number of times the powder is tapped to achieve the tapped density, the mass of material used in the test, and the rotation of the sample during tapping.

1.2.1.3. Flow through an orifice. Several particle-related and process-related factors affect the powder flow rate, which can significantly measure powder flow ability. However, determining the flow rate through an orifice is useful only with free-flowing materials. The flow rate through an orifice is generally measured as the mass per time flowing from any container. The three important experimental variables include the type of container used to contain the powder, the size and shape of the orifice used, and the method of measuring powder flow rate. Either mass flow rate or volume flow rate can be determined. Mass flow rate is a more accessible alternative, but it biases the results to favor high-density materials. Since die fill is volumetric, determining volume flow rate may be preferable. No general scale is available because the flow rate is critically dependent on the method used to measure it. The flow rate through an orifice is not an intrinsic property of the powder and is, therefore, dependent upon the methodology used.

1.2.1.4. Shear cell methods. Various powder shear testers and methods that permit a more thorough and precisely defined assessment of powder flow properties have been developed to correlate the powder flow with the hopper design. These methods enable the scientist to obtain several parameters such as yield loci, the angle of internal friction, the unconfined yield strength, the tensile strength, and a variety of derived parameters such as the flow factor and other flowability indices. These methods have been successfully used to determine critical hopper and bin parameters. A cylindrical shear cell forms a shear plane between the lower stationary base and the upper movable portion of the shear ring. Annular shear rings require less material; however, the design does not allow a uniform shear distribution inside and outside the annulus. The plate type of shear cell consists of a thin sandwich of the powder

Table 3
The acceptable scale of flowability for compressibility and Hausner ratio.

Compressibility	Flow character	Hausner ratio
1–10	Excellent	1.0–1.11
11–15	Good	1.12–1.18
16–20	Fair	1.19–1.25
21–25	Passable	1.26–1.34
26–31	Poor	1.35–1.45
32–37	Very poor	1.46–1.59
>38	Very, very poor	>1.60

between a lower stationary rough surface and a rough upper surface that is moveable. A significant advantage of shear cell methodology is greater experimental control. The methodology generally is rather time-consuming and requires substantial amounts of material and a well-trained operator [32].

All these methods, though simple and conventional, hold a great significance in formulation development in the pharmaceutical industry. These basic methods are simple to perform and give a fair idea about the powder flow behavior. Over years now, the pharmaceutical industry has been completely dependent on the Pharmacopeial methods for powder flow evaluation to compare powders and predict their behaviors during large scale processing. However, with growing trends, research and developments of novel APIs and excipients for complex processing in the pharmaceutical industry, the nature of the newer materials differs greatly and therefore, advanced characterization tools for powder flow evaluation become inevitable.

1.2.2. Modern methods for evaluating powder flow properties

Despite the simplicity of these methods in terms of execution and result interpretation, reproducibility, predictability, and sensitivity are the general issues. It is also challenging to establish correlations between the derived values and the actual flow behavior of the powders. Also, these compendial powder flow characterization methods are semi-quantitative and do not indicate the powder flow behavior under shear when subjected to downstream processing such as tableting [33]. A proper characterization technique should mimic the stress and powder compaction state of the powder process condition. Such limitations have paved the way for developing advanced characterization techniques [34]. With technical developments, newer methods such as powder flow categorization techniques to determine cohesivity, determination of avalanches, dielectric imaging, microscopy of atomic force, and penetrometers are coming into practice. Such strategies suffer from multiple factors that contain reproducibility, conditions of efficiency, and predictability. E.g., measurement of the angle of repose and avalanching has limitations for a cohesive powder that does not flow through the funnel, and vibrating the funnel creates inherent complexity and variability in measurement. When the cohesive powder is subjected to vibrations, it reduces interparticle friction and locks the particles into certain positions, which causes inherent variability and may obstruct the flow [35]. Although the smaller avalanches may get suppressed due to the vibration, the vibration consolidates small amounts of powder on the slope of the equipment until sufficient powder is built up to cause a larger avalanche [36]. Another way of calculating powder flow requires using a photovoltaic array with a proprietary technology called “AeroFlow” [37]. But this method includes a narrow disk which imposes a significant frictional barrier and doesn’t accurately mimic the mixing or filling process. Another method to evaluate the flow properties of a powder under shear is a shear cell method which is most commonly used and is convenient [19]. In recent years, image analysis techniques based on high-speed imaging and particle image velocimetry (PIV) are being used to measure flow patterns and agglomeration behavior of fluidized powder using luminous intensity and powder movement inside a cuvette. This direct optical evaluation of powder is suitable for testing a wide range of pharmaceutical powders, even with a small sample size [12,38].

These standard techniques cannot measure the entire range of powder flowability/cohesion. Flow meters require a funnel to flow through the powder or granular material and are thus ineffective for cohesive powders. The method known as miniaturized powder flow through an orifice introduced state-of-the-art image analysis for powder flow analysis. It recognized that measuring large powder volumes has prevented a detailed description of the cohesive phenomena that govern many industrial processes. Since the sample size was drastically reduced, which introduced powder flow measurements into pharmaceutical pre-formulation stages, this method can be applied to process operations such as die and capsule filling, mixing, powder coating and conveying, and to applications such as dry powder inhalers, in which particle-level behavior dominates over bulk behavior. Blanco, D. et al. have successfully predicted die-filling efficiency for the first time in pharmaceutical literature [12].

For highly cohesive powders, tap density testers are often insufficient because the tapping pressure is insufficient to resolve the tight inter particular cohesive bonds. When tapped, the powder bed will not consolidate. Another issue with this research approach when dealing with granular materials would be that the heavier or denser particles are far more likely to stack easily under their weight, resulting in excessively low efficiency. For large granular compounds, commercially available approaches are not commonly available due to particle size limitations. There is no precise method for calculating powder flow throughout all four flow regimes (plastic, inertial, fluidized, and entrained gas) [11].

In the modern innovative powder flow method techniques, different instruments can measure powder characteristics, such as powder flow tester, FT4 powder rheometer, ring shear tester, and gravitational displacement rheometer [39]. The advanced powder flow analyzers, mainly shear cell testers, are trends in the industry to determine good flow behaviors of powder due to the strong theoretical and science-based processing and design. The Powder Flow Tester evaluates powder flow properties in industrial processing equipment rapidly and efficiently [40,41]. Flow Function, Wall Friction, Bulk Density and Time Consolidation Test with Flow Function, Arching diameter, Rat-hole Dimension, Hopper Half Angle, etc. be determined and calculated with the help of simple function in powder flow tester [24,42]. The FT4 Powder Rheometer was initially developed to explain powder rheology or powder flow properties. This range of measuring capabilities makes the FT4 a universally functional powder tester and perhaps the most reliable instrument to test and evaluate powder behavior. A powder rheometer has been discovered to provide a reproducible and straightforward calculation of the powder response to different conditions [34].

The Gravitational Displacement Rheometer (GDR), an experimental apparatus used to characterize the cohesiveness and flowability of powders based on their avalanching behavior, quantifies the flow properties of the mixture under unconfined conditions [43]. A flow index is calculated from GDR measurements. It is directly associated with the flow via hoppers, providing a hopper design predictive approach and simple experimentation for evaluating materials and assessing their suitability for a particular hopper system [39]. Jenike was the pioneer of the shear cell tester. Shear cell measurements are distinguished by Schwedes, 2003 in two variants-direct (major principal stress rotates during the test) and indirect (major principal stress is fixed during the test) tester [44].

Historically, the shear cell process and design were more complex and time-consuming. It required one and half days to collect test measurement, chart recorder output, and produce yield locus, for example, Walker annular ring shear cell (the 1980s). The Jenike shear tester was even more complex because it required manual pre-consolidation stress and multiple sample preparation to define a single yield locus. It could be done by only a trained, experienced and skilled person. Another type of shear tester is the constant -volume shear tester with a lower movable shear mechanism, as reported by Y. Shimada et al., 2018 [45]. The proposed method of evaluation allowed to obtain powder yield locus, consolidation yield locus, critical state line, shear cohesion, powder bed void fraction, and stress transmission ratio by with a single shear test [46]. In order to overcome these difficulties variety of automated and computer-controlled shear cell techniques have been proposed which include uniaxial, biaxial and triaxial compression testers, rotational ring shear cells like FT4 rheometer, Schulze, and most recently powder flow tester (Brookfield PFT).

Uniaxial, biaxial, and triaxial compression testers are indirect types and generally not commercially available; therefore, little research is found in the literature relating to pharmaceutical and other industry-relevant powders. Table 4 summarizes the principle, pros, and cons of these non-commercial testers collected from several reviews on testers [44,47,48].

The availability of several advanced powder flow testers makes their selection and understanding a prerequisite for evaluating powder flow behaviors. Therefore, a comparative study of these powder flow testers would better assist in selection [49]. Table 5 is one such comparative summary of the different powder flow testers.

Compared to conventional techniques, these novel techniques are successful. These new techniques offer automatic handling with no errors and fast results. On the other hand, the inter particulate forces, which also affect the powder flow, can be determined by vibration, centrifugation, or impact separation. Such methods allow the determination of the adhesion forces by measuring the number of particles detaching from a surface at a given force [50].

2. Approaches to enhance powder flow properties

2.1. Addition of glidants

Although the addition of glidants must have resolved several failures in pharmaceutical manufacturing operations, this category of excipients usually does not gain the required attention during product development. As a well-known fact, adding glidants affects the powder mixture's tablet properties and flow behavior in a specific concentration range. The small glidant particles bind to the powder and granule surface, enhancing the separation between the two particles and thereby reducing the attracting forces between the particles. Glidants on the powder or granulate particles form a monoparticulate coating that allows movement over one other. Thus, the rough surface is softened completely, reducing the friction and adhesive forces among materials [50]. Though not clearly known, there are two mechanisms by which glidants improve the flow properties of the powders. Since the interparticle force hinders the powder flow, reducing this friction is one of the most important techniques to promote powder flow. This reduction can be achieved by modifying the surfaces of the powders, increasing the distance between two particles, which in turn leads to a reduction of the

Table 4
Comparison criteria for indirect uni, bi, and triaxial testers.

Indirect testers	Principle	Pros	Cons
Uniaxial	Bulk density and unconfined yield strength can be obtained, sample filled into a cylinder and consolidated using normal consolidating stress to get the bulk density Sample loaded again after removal of the cylinder using normal stress, which leads to unconfined yield strength	Quick and easy Time consolidation of the coarse particle can be measured.	Can be used for testing cohesive powder only (stable after removing cylinder) Low accuracy Determination in the low-stress region is not possible for cohesive powder Consolidation by vertical force cannot guarantee a steady state flow
Biaxial	Four steel plates can realize steady-state flow and uniaxial compression on the lateral X and Y axis. It avoids vertical deformation and friction between the plates using rigid plates and thin silicon rubber membranes.	Stress and strain can be controlled on the X and Y axis and measured in all X, Y, and Z directions. Able to determine time-dependent stress-strain behaviors	Time-consuming Not recommended for silo design and quality control purpose
Triaxial	Principal stress can be applied and measured in all three directions. Normal triaxial tester – stress increases in a vertical direction until failure by two movable stamps True triaxial tester – deformation in all X, Y, and Z directions can be possible with six wall boundaries of the sample.	Both the tester used in soil mechanics A true triaxial tester can measure all three principal strains and stresses. The advantage of a true triaxial tester is the complete determination of the state of stress and the state of strain, because all three principal stresses and strains are measured.	Over consolidated samples cannot be tested after unconfined failure strength

Table 5
Comparison criteria for FT4, Ring Shear Tester, and PFT shear cell testers.

Commercial instrument	Characterized features and differences
FT4 powder rheometer	• A blade, piston, and shear head are applied to rotate a compact and incremental load that interacts and allows particles to flow, resist (axial and rotational force), and measure the bulk flow of the powder sample. • Initial consolidation stress is not included in the data collection • Measures applied normal force (torque) at the bottom of the powder bed and displayed force, torque, and height data • The range of volume of vessel available is 10–400 ml, providing the capability to test variable sample range • The instrument can control and maintain the stress on highly dilating powder • The initial compaction load range for FT4 powder rheometer is 3–15 kPa
Ring shear tester (RST)	• The bottom ring (annular) of the solid specimen's shear cell is rotated while the lid is fixed by two tie rods and connected to the load beam. The extorted force on the lid is transferred to the solid specimen to measure the flow behavior at different shear stress. • Initial consolidation stress is not included in the data collection • The ring (annulus) is used to load the sample • Measure the applied normal force at the top of the powder bed (force), and the torque is displayed • High spillage of sample due to scrapping of overfilled powder • At low normal stress (below 2 pKa), the tester does not control/respond to force created by rapidly dilating (particles roll over each other) powder
Brookfield Powder flow tester (PFT)	• The lid applies the vertical compression downward into the sample contained in the shear cell (annular trough). A calibrated beam controls the compaction stress on the rotating sample trough. Torque experienced on rotating sample trough against the stationary lid is measured to determine the flowability of the powder. • Initial consolidation stresses included in the data collection • The ring (annulus) area used to load the sample • The instrument can measure the low consolidation stresses and determine a flow function from one test with five data points • Initial compaction load can be set in the range of 0.3–5 (4.82) kPa • High spillage of sample due to scrapping of overfilled powder and need separate balance to weigh • Normal stresses during pre-shear and shear steps cannot be set. • The longest shear displacement (measurement of rotational speed and time elapsed to start rotation) is required to attain a steady state.

attraction forces between them. The second mechanism is the theory of ball bearing effect, wherein the tiny glidant particles form a monolayer on the surface of the powder or granule particles, making them roll over each other and giving an enhanced flow. This corroborates with a sandwiched contact system of the small particle between two larger particles. The improved flow behavior greatly depends on the degree and uniformity of the coverage of glidant particles over the host powder particles. Such a covering mechanism of the glidant has been proven by Jonat et al., by scanning electron microscopic studies. The study reports colloidal silicon dioxide particles adhering to the surface of the Microcrystalline cellulose particles, hence improving the latter's flow. The addition of colloidal silicone dioxide increased the bulk and tapped density and reduced the angle of repose of the MCC powder. In another study, the work done by the mixing blade to mix lubricated and unlubricated granules was compared, and it was found that lubrication done to improve the powder flow can reduce the work done by 75% [51].

The efficiency of the glidant to improve the flow properties also depends on the material attributes and the properties of the glidants. Understanding these factors, which affect the formulation, is therefore essential. A paramount concern in this approach is the particle and the consequent surface energy of the host particles and glidant, which eventually affect the inter-particle forces and the flow properties. Some researchers in their study have shown that the material attributes in terms of the surface energy affect the coating efficiency of the glidant over the host material in dry powder systems [13,21]. Though these are also affected by the mixing process, Jallo et al., concluded that a large difference in the surface energies (i.e., high interaction potential) between the two entities is also required for optimal coating. However, the evaluation of this surface energy has not been validated to predict the glidant effectiveness for pharmaceutical powders [52]. As stated earlier, the mixing process also affects the glidant's effectiveness. The energy type and intensity of the mixing process are crucial for the glidant to disperse uniformly on the host particles. Glidants within themselves do not usually have good flow and exhibit tendencies to agglomerate owing to their small particle size. Therefore, low energy or low shear mixing fails to fully disperse the glidant uniformly on the surface of the host particles giving suboptimal flow improvement. The nature of the glidant, in terms of its hydrophobicity and triboelectric behavior, may also affect the flow properties enhancement because of the direct effect on the inter-particle force [11]. It has been reported that the combined use of a glidant and a lubricant in the tablet formulation usually has a better impact on the powder flow [53].

One of the commonly used glidants, silica (silicon dioxide), owing to its small particle size and low density, has been identified as the most potent glidant [54]. Generally, an approach of adding glidants separately into two phases, i.e., API-glidant mixture and pharmaceutical excipient-glidant mixture, is used to optimize the glidant distribution. Such a two-step approach enables the various glidant forms to adjust their right concentrations for each particle characteristic at each glidant mixing point [54]. Abe et al. In their study, used a two-step glidants mixing method with an API and lactose, microcrystalline cellulose, sodium starch glycolate, and magnesium stearate as the pharmaceutical excipients. Two types of silicon dioxide were tested as glidants; non-porous silica and porous silica, both of which were mixed in high-shear blender. Their study results show that, with their optimal concentrations, the required glidants combinations improved the flowability of the two-step process relative to the one-step operation. The two-step operation removes the key to powder flow bottleneck and makes it more beneficial to apply direct compression process for improvement trials.

While using glidants for improving the flow of powders, it is essential to know that the order of mixing of glidants in the formulation is a crucial factor that affects the effect of glidants [53]. A specific order of mixing of glidants plays a vital role, as described by Kalyana et al. in their study on two glidants, i.e., Cab-O-Sil (CS) and Magnesium Stearate (MgSt). In their study, the authors reported that the mixing of glidants in the tableting blends leads to the formation of microlayers, affecting the product properties. These microlayers formed on the surface of particles are the reason the mixing order is significant. Three mixing orders were evaluated to obtain blends containing Avicel PH200, Pharmatose, and micronized acetaminophen (mixing order-1: CS added first; mixing order-2: MgSt added first; mixing order-3: CS and MgSt added together). It was found that the mixing order has a significant impact on hydrophobicity and flowability. Both these properties increased when CS mixed into the blend before the MgSt. These observations were mainly attributed to the onion-like ordered mixtures, explicitly formed due to the microlayers on the particulate surface, giving a distinct microstructure. Another critical factor affecting the improved flow properties of the addition of glidants is the nature of the glidant. As reported by the previous authors, the hydrophobicity and hydrophilicity of the glidant affect the flow properties of the blend. Ahamad et al. determined the glidants' effects of hydrophobic and hydrophilic silica on a poorly flowing API using various methods. Ibuprofen was mixed with hydrophobic and hydrophilic silica and evaluated using conventional flow properties like the angle of repose, bulk density, and the advanced technique, i.e., powder flow tester (PFT). The results show that, according to the multiple flow measurements. However, both the silica increased the flowability of ibuprofen to a significant degree, hydrophobic silica performs better than hydrophilic silica in terms of a reduction in angle of repose, cars index values, and hydrophilic silica is considered a good flow enhancement for the flow factor [19]. This observation is due to the simple reason that increased hydrophobicity decreases cohesion and hence improves flow [12].

Similarly, a study by Jonat et al., also revealed that hydrophobic glidants are most effective for hydrophilic drugs [50]. The difference in the glidant geometry structure on the flow properties of powder mixture has also been evaluated. It was noted that porous flow aids improve flow properties more than nonporous agents because porosity contributes to the reduction of adhesion force between the individual host particles [55].

2.2. *Thin coating to the powder with polymers*

Coating fine particles on the surface with a polymeric solution to improve the flow properties of the core particles in a controlled manner is a well-known approach [56]. The flow improvement by such an approach is due to a ball-bearing effect, as stated earlier, which means that the modification of the surface properties helps improve the powder flowability [57]. The formed inter-particulate barrier will decrease attractive forces such as electrostatic and molecular interactions, resulting in improved powder flow and packing properties. This approach to coating particulate systems can also be applicable for taste masking and controlled release properties.

Natalja et al. studied the effect of polymer coating on Ibuprofen's cohesiveness, mainly due to its varying particle size and distribution [58]. The powder was then coated with hydroxypropyl methylcellulose (HPMC) to improve the flow with the help of an ultrasonic nebulizer. The coated powder showed improved physical properties since polymer treatment affected the particle size. Morphology evaluation revealed a decrease in the API's cohesiveness and an improved particle surface homogeneity. The enhancement in flow properties increased as the uniformity of the HPMC layer increased. Because the glidants affect tablet parameters such as hardness, friability, dissolution, etc., the polymer coating can be a preferred method for pharmaceutical industries. Genina et al. (2010) worked on improving the flow properties of Ibuprofen powder by HPMC coating in a top-spray fluid bed granulator. An increased flow of the powder was noted due to the trace amounts of hydroxypropyl methylcellulose deposited onto the particle surfaces [59].

Li et al., in their work, utilized nano-coating by electrostatic deposition to improve the flow properties hindered due to crystal growth. The coating significantly improved physical stability, wetting by aqueous media, dissolution rate, powder flow, and tabletability. Thus, it can be seen that coating cohesive powders with polymeric solution has an essential application in improving the flow of powders. The process can be carried out by several techniques, as discussed above [60].

2.3. *Surface coating of the powder with silica*

Surface modification of particulate solids by dry coating to reduce the cohesion between particles can be done by dispersing guest nano-particles over the surface of host particles of cohesive powders. Coating with nano silica provides nanoscale roughness, which eventually causes a reduction in the contact surface between the cohesive particles and hence reduces the interparticle cohesion force, which is responsible for the reduction in the agglomerate formation [61]. Such a technique for surface modification reduces the cohesiveness of the powders by forming a film or thin coat over the host particles [62]. Van der Waals forces are responsible for keeping the host and the guest particles in contact with each other. The guest remains attached to the host when the force of attraction between the two is more than the guest's weight [63].

Different types of silica produce different results when used to improve a powder's flowability. Microcrystalline cellulose (MCC) coated with hydrophobic colloidal silicone dioxide types showed better flow properties in terms of angle of repose as compared to those coated with hydrophilic silicone dioxide types. Moreover, hydrophobic silica coatings are independent of the mixing conditions, unlike hydrophilic silica, which shows improved flow under forced mixing conditions. The SEM data showed that the coverage by the silica particles on the MCC particles dictates the improvement of the flow properties. The nature of silica particles also determines the extent and uniformity of this coverage. The silica particles are linked to stable MCC aggregates, forming larger aggregates owing to the hydrogen bonds. Hydrophobic silica has a comparatively lesser ability to form hydrogen bonds giving friable aggregates compared to those with hydrophilic silica. Agglomerates of hydrophobic silica are easily breakable, whereas those with hydrophilic silica require higher energies [64]. Generally, the flow of MCC or starch-like particles improves when hydrophilic colloidal silicon dioxide is used with higher mixing time and energy. On the other hand, hydrophobic silica tends to spread evenly on the hydrophobic surface. Higher surface coverage can be achieved by mixing hydrophobic silica with host particles leading to flow improvisation [19].

Qi tony et al., in their study, treated cohesive lactose powder with magnesium stearate and fumed silica using tumbling blending or intensive mechanical dry coating. The results show that a cohesive powder of lactose improves flow properties after treatment with magnesium stearate and fume silica due to reducing inter-particular forces [65]. El-Say et al. improved the rheological properties of cohesive lactose powder by treating the powder with different kinds of acrylic resins [66]. A magnetically assisted impaction coater and a hybridizer have also been to coat cohesive cornstarch powder with silica particles to improve the powder flow. The Hosokawa powder flow tester results showed that nanosized silica provided the best flowability enhancement [67]. Performed a similar study of coating a cohesive API with silica particles in a vibratory mixer. Their study showed that dry coating improves a cohesive powder's bulk density and flow function coefficients. Another method that can be used from such dry coating is comilling, as reported by several researchers [5,68]. The above observation and results indicate that a dry coating is a simple and easy technique to improve the flow of cohesive materials. In addition, the problems faced in a polymeric coating involving liquid solution spray, that can be devoid in a dry coating include lumps formation, degradation of drugs from moisture, heat, etc. The dry coating is helpful for light and moisture-sensitive drug. Fig. 2 illustrates the mechanism of flow enhancement by silica coating.

Silica coating helps to improve the flow properties by counteracting the different forces which hinder the powder flow, such as van der Waals forces, liquid bridging, electrostatic charge, mechanical locking, and frictional and gravitational forces. The silica particles, at first, adhere to the material's surface, filling the voids and irregularities on it. Such adherence causes a reduction in mechanical and interlocking friction. The increased distance between the direct particle surfaces reduces van der Waals forces and electrostatic interactions. Thus, the silica particles act as barriers and lubricant to enhance the powder flow. Such a mechanism is mostly observed for hydrophobic silica. On the other hand, the hydrophilic silica retains moisture, preventing liquid bridging [12,69].

Surface modification should be used in conjugation with micronization to together obtain benefits of enhance dissolution properties as well as good flow. Micronization is another widely used technique to improve poorly soluble drugs' surface area and solubility – dissolution rate [70]. However, this process usually leads to highly cohesive fines forming agglomerates due to electrostatic interactions between the particles. Though micronization may lead to enhanced dissolution characteristics, it hampers the flow properties and density of the powders. Simultaneous micronization and surface modification can be achieved by milling the particles with nano silica, which provides fine surface-modified particles with a lower tendency to agglomerate. A water-soluble polymer can be an alternative to such a process which would further assist water wettability. Along similar lines, X. Han et al. have used a water-soluble Polyvinyl pyrrolidone for co-milling the drug particles along with nano-silica to give a combined advantage of water wettability and nano-silica to improve the flow in a lower mechanical stress fluid energy mill. A reduced electrostatic charging tendency on the surface of the micronized powder is observed due to the coating of nano-silica, which prevents agglomeration of the powder and enhances

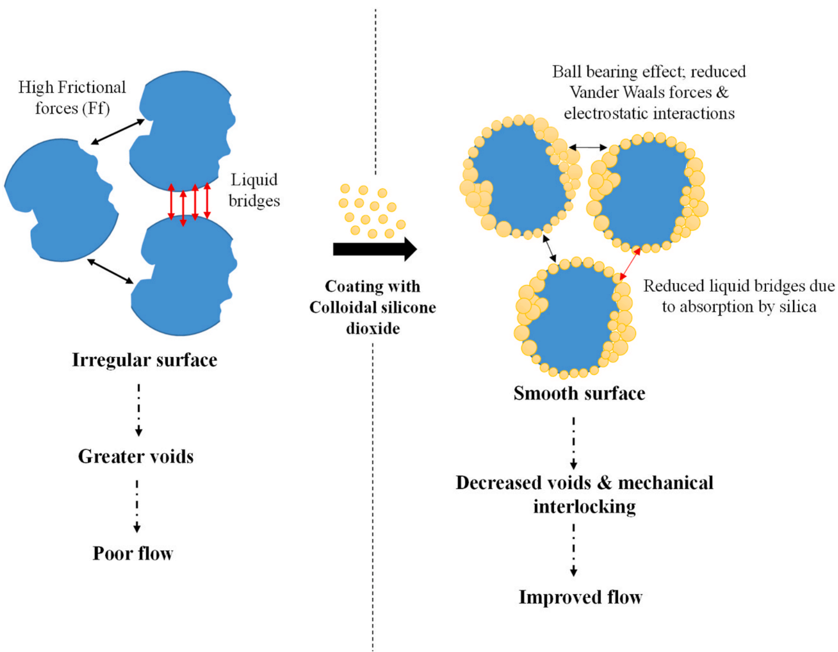

Fig. 2. Schematic representation of the mechanism of flow improvement by silica coating.

flowability. In such a process, the mill operating conditions and amount of silica used significantly affect its flowability and compressibility [61]. With increasing grinding air pressure, smaller median particle size was obtained due to more energy input, leading to more intense and faster particle-particle and particle–wall collisions. A higher feeding rate results in larger ground particles owing to the shorter residence time of the particle in the grinding chamber and lower kinetic energy available for grinding. The amount of silica increases the flow properties, but beyond a certain value, no significant improvement is obtained. Such a coating and co-grinding process also increases the powders' compressibility compared to pure or pure micronized powder. As also dispersibility of the powder drug. Thus, such surface modification improves the flow properties and the powdered drug's dissolution characteristics.

2.4. Addition of anticaking agents or flow conditioners

One of the significant issues in handling solid hygroscopic powders is agglomeration or caking to form lumps, mainly due to partial dissolution of particles and subsequent recrystallization due to environmental moisture content [71]. Deliquescence is the phenomenon responsible for the chemical and physical instabilities of powdered materials, which is nothing but a first phase temperature-induced, moisture-dependent phase change from solid to liquid which appears for crystalline deliquescent ingredients at a particular relative humidity [72]. The absorbed moisture forms a stable bridge causing what is called caking—during manufacturing, processing, storage, and consumer use, caking and lumping cause severe problems in powdered products [73]. The anticaking substances, also called the flow conditioners, overcome flow issues inside the manufacturing units (Barbosa-muriet Canovas et al., 2005). Anticaking agents are usually crystal growth inhibitors [74]. A flow conditioner is sub-sieve particle size and is typically very fine powder. The added flow conditioners compete for moisture uptake with the host molecules and form a protective moisture barrier on the surface of the particles or physical barriers between ingredient particles [73]. This physical barrier eliminates surface friction and further inhibits crystal growth. For optimal agent effectiveness, interactions between the anti-caking agent and the host molecules are necessary [4].

Various forms of fine silicon oxide, sodium aluminum silicates, tricalcium phosphate, and calcium stearate powder are widely used as anti-caking agents. In a study by Nurhadi and Roos, calcium silicate and calcium stearate were added to honey powder as flow conditioners. A comparative analysis was performed to evaluate the agents' performance by influencing water sorption and flowability. Calcium silicate did not seem to affect the water sorption properties of honey powder, whereas calcium stearate showed an inhibitory effect on recrystallization. The addition of flow conditioners improved the flow of honey powder from easily flowing to free-flowing powder. Calcium stearate was a better aid since it reduced interparticle friction. The flow conditioners also improved honey powder's bulk density and flow factor index [75]. Rebeca et al. also studied the impact of anticaking agents on the action of delicate ingredients and blends on moisture sorption, flowability, and caking characteristics. Out of the anti-caking agents evaluated, Calcium stearate showed a delay in the onset of deliquescence, reduction of moisture sorption, and the preservation of flowability at different humidities over time whereas the addition of calcium silicate decreased the overall moisture sorption event [76].

Silicon dioxide makes a barrier between the host particles, which can be decreased powder stickiness and slow down the deliquescence [72]. One another research done by M. Peleg et involves the study of anticaking agents like calcium stearate with aluminum silicate for improving the flow of sugar powder. Using a Jenike Flow Factor Tester, the evaluation showed decreased cohesion and compressibility upon the addition of anticaking agents. The incorporation of calcium stearate caused a reduced angle of internal friction [23]. Another work done by Christopher et al. on egg powder reported particle surface alteration by flow conditioner such as silica and sodium silica-aluminate, which eventually increased the flowability of egg powder. Without a conditioner, it was found that whole egg powder could absorb more water and the same powder with flow conditioners yet retain strong flow properties [77]. In another work, the scientist Konstance et al. researched Sucrose, lactose, and flour; these three powders as encapsulated materials for butteroil, and Sylox is used as an anticaking flow agent for the same. They reported that encapsulated powders are less flowable, but flow characteristics are improved by the addition of the anticaking/flow agent [78].

2.5. By changing the particle shape and size

Researchers have attempted to improve this powder property to enhance flow by considering particle size and shape as critical factors in powder flow properties. Particle morphology plays a vital role for powders that must be directly compressed to form tablets. Consequently, it is possible to improve the flow as well as compaction properties of the powders by modifying the particle shape of the particles. One example is Ascorbic acid; wherein spherical agglomerates were prepared using a spherical crystallization process by a binder. The process involved precipitation of the crystals in the form of spherical agglomerates by a bridging liquid which eventually enhances the micrometric properties, flowability, packability, and compactibility required for direct tableting. The improved compactibility of the spherical agglomerates was attributed to enhanced fragmentation, increased contact points during compression, and improved plasticity of the particles [79].

It is known and studied that lowering the particle size minimizes the flowability. Detergent powder with particle sizes of 125–180 μm and 180–250 μm gave more significant bulk powder flow properties because their circular shape makes them roll or move over each other when the shear stress is applied to them. However, the particles (<125 μm) having a high surface area to volume ratio showed flow suppression of powders and particle interaction when pressure was applied [25]. The powder flowability range of these particles (125–355 μm and 710–1000 μm) is quick to flow, and other powder size ranges indicated poor flowability [80].

Preparation of granules of powders to modify the particle size and morphology is yet another approach to improve powder flow. Granules improve flow, handling, and compression properties [81]. Depending on the method used to enable powder particle agglomeration, the granulation method can be divided into two types: dry granulation and wet granulation. Wet granulation means increasing the size using a liquid binder; fine particles are agglomerated into bigger ones into permanent structures. The granulation method has unique benefits, enabling powders' mechanical processing without loss of blend consistency. The flow properties of a powder mixture are enhanced by growing the size and surface area of the particles—the uniformity of powder density increases and the strength. The process minimizes air trapping between granules and reduces particle and cross-contamination levels [82].

In a study reported by El-Say et al., the physical and technological properties of the poorly-flowing and remarkably coherent drug Bezafibrate were addressed. Bezafibrate's flow property and compression properties were enhanced by wet granulation. The result showed that the flow property improves in terms of enhanced micromeritic parameters, including acceptable mean size, narrow size distribution, low lump percentage, low fines percentage, and no sticking to the wall surface [66]. Another group of researchers also prepared granules by adding water as a binding agent, using two pre-processed excipients, such as lactose monohydrate and cellulose, and evaluated their flowability. Using the wet granulation process, all these excipients can be directly compressed. The result shows that the wet granulation method enhanced the flow and improved permeability properties and compression, which is not observed in dried powder [83]. Granulation can be done using different techniques and various instruments; hence, Limin et al. [84] prepared granules in a high-shear granulator and scientifically assessed the effects of massing on flowability. This study evaluated microcrystalline cellulose as an excipient, and the granulating agent was distilled water. The process enhanced flowability due to dramatic changes in granule porosity, morphology, and specific surface area [84]. Hence agglomeration is one process implemented to enhance the powders' functionalities involving flow properties [85]. Agglomeration improves the flow property of fine powders since it results in a powder with higher bulk density and lots of reduction in its wall friction and the cohesive strength [86]. From all the above studies, it can be concluded that granulation is the most widely used technique to improve powder flow and minimize production process problems in different industries.

2.6. *Sprouting the crude drug*

Sprouting is another technique that has been found to improve powder flow, as reported by a few studies, mainly for food powders. Sprouting of food seeds and nuts significantly affects the nutritional value since the bioavailability, and improved digestion of the nutrient leads to better nutrient utilization. The sprouting process leads to the release of metabolic enzymes, such as proteinases, that increase the amino acid content of the food products [87]. Apart from improved nutrition, few researchers studied the effect of sprouting on the flow properties of the sprouted material compared to their counterparts. The raw and sprouted onion powders were examined for their individual flow properties, and the flow indicators such as bulk density, Hausner's ratio, Carr's index, angle of repose, coefficient of friction cohesion index, and caking index indicated the improvement in the flowability of the powder. Powder flow analysis also showed the more coherent nature of the powders obtained from sprouting, which is the free-flowing nature. Also, the caking tendency of the sprouted onion powder can be reduced, which provides reduced segregation potential during transportation and storage [88]. Sprouting leads to increased density of the powders. The improved flow properties of the sprouted powder can be the plausible reason for enhanced flow properties. Sprouting process parameters like sprouting days affect the flowability of the powder. Likewise, the increased number of sprouting days increases the flowability of powder [89]. Thus, it can be concluded that sprouting improves the functional potential of the food powders and the powder rheology and flowability. By considering the above results of different scientists, we could conclude that sprouting is a novel technique to enhance powder rheological characteristics.

2.7. *Crystallization technique*

Crystallization is another study that has proven to improve the flow properties of poorly flowable materials. The technique allows researchers to modify the crystal habit of various materials which affects their powder flow properties. Garekani et al. showed different sizes and shapes of ibuprofen particles crystallized from multiple solvents showed varied flow properties. Crystals obtained from methanol and ethanol were lath/plate-shaped and exhibited better flow properties than the needle-shaped crystals from hexane [90]. Crystallization modifies the particle size and shape, eventually modifying the powder flow properties [7]. C. Sun studied poorly flowing citric acid anhydrate by exposing it to relative humidity to prepare pure monohydrate with almost equal particle size and morphology but varying surface properties than citric acid anhydrate. Results by ring shear cells indicated that hydration could significantly increase the anhydrous citric acid flowability [91]. Kawashima et al. carried out another method of crystallization to improve ascorbic acid flow, i.e., spherical agglomeration technique by emulsion solvent diffusion. In this study, ascorbic acid crystal agglomerations with the mechanism of emulsion solvent diffusion (ESD) and spherical agglomeration (SA) were precipitated by a solvent to alter the system. In contrast with the initial pharmaceutical crystals, the resulting angle for agglomerated crystals decreased significantly. These results showed that agglomerated crystals' flowability and packability were ideally enhanced for direct tableting [79]. Information from the above research work reveled that the crystallization techniques is effective for poorly flowable anhydrous drugs for improving the drug flow properties. If the anhydrous drug can be converted into hydrous form, it improves their compaction, flow and tableting performance. One more research performed by Kaerger et al., in 2004 reported the influence of the size and shape of paracetamol particles blends on the flow and compression behavior. The engineered particles by SAXS (Solution Atomization and Crystallization by Sonication) technique exhibited improved properties in bulk, tapped density, and overall flow compared to the blend with micronized particles [92].

To summarize, there are several proposed and implemented methods for enhancing flow properties of pharmaceutical powders. Based on the material properties and suitability of the technique, either of these can be explored for an application. Literature reports a vast array of examples which employ the above-described methods and the results are promising for all. A summary of a few of these examples is tabulated for reference in Table 6, indicating the approach, instruments, observations and inferences reported for those.

Table 6
Summary of some reported studies for improvement of powder flow with different techniques.

Sr. No.	Methods	Techniques/materials used	Instruments used for checking powder flow	Observations	Reference
1	Two steps glidants mixing process	Silicon dioxide mixed with the help of high shear mixer (HSM)	Powder tester (PT-R, Hosokawa Micron Corporation, Japan) and critical orifice diameter tester	Decreased repose (AOR) angle, required minimum hopper outlet diameter, and improved powder flow.	[54]
2	Thin coating to powder	Used ultrasound-assisted mist of HPMC (Hydroxy propyl methyl cellulose)	In-house designed flowability testing method	Superficial changes occur	[58]
3		Used HPMC solution by using top spray fluidized bed granulator	In-house designed flowability testing method	Small improvements in particles	[59]
4		Deposition of chitosan by Electro-statistic deposition over powders	Compendial methods	Inhibit crystallization and reduce AOR.	[60]
5		Dry coating of silica	FT4 powder tester	Enhance flow function coefficients (FFC) and bulk density (BD)	[67]
6		Mixed hydrophilic nono silica via continuous fluid energy mill	FT4 powder tester and conventional methods	Increase BD and FFC and reduce electrostatic forces (ESF)	[61]
7		Intensive mechanical dry coating of silica	FT4 powder rheometer and conventional methods	Reduce inter particular forces, cohesiveness, AOR, compressibility, and increase in pour and tapped density.	[65]
8		Used acrylic resin via phase separation techniques	Conventional methods	Reduce AOR, Hausner ratio (HR), and increase in density	[93]
9		The coating is done by using Magnetically assisted impaction coater (MAIC) and the hybridizer (HB)	Hosokawa powder flow tester	Reduction in AOR due to uniformed coating to powder	[94]
10	Adding anticaking agents	Calcium silicates and calcium stearate are used as anticaking agents by using manual mixing	Powder flow tester (PFT) Brookfield's engineering	Inhibit recrystallization, collapse structure of amorphous honey powder, reduce internal friction and enhance BD and flowability index.	[75]
11		Calcium silicates, calcium stearate, and silicon dioxide are used as anticaking agents via manual mixing	Revolution powder analyzer	Reduce moisture sorption, delaying the onset of deliquescence and preventing the caking	[76]
12		Silica and sodium silico-aluminate are used and mixed by using a hand wire mixer	Compendial methods	Enhance Surface smoothness, fill inter particular voids, absorb powder and bulk density moisture, and reduce inter particular forces.	[77]
13		Sylox is used as an anticaking agent and mixed by manual mixing	Conventional or compendial methods	Reduction in cohesion in powder hence enhances powder flow	[78]
14	Mixing order of glidants and lubricants	Cab-o-sil and magnesium stearate are used as glidants, mixing done via a v-shape blender	Gravitational displacement rheometer (GDR)	An increase in hydrophobicity and mixing order also affects powder flow properties	[53]
15	By altering particles' shape and size	Three different shapes and sizes of lactose powder use	Shear cell	Spherical size particles, similar size distribution, large size particles, less specific energy, and low compressibility are all parameter that increases powder flowability.	[9]
16		Black soybean has different particles sizes, powder use	PFT	Increased high sensitivity circularity (HSC) reduces internal friction and requires minimum critical hopper opening diameter as it reduces HSC and particle size decreases the powder flow.	[25]
17		The detergent powder having different sizes was used	Schulze ring shear cell tester	The spherical shape particles have a higher flow than less spherical shape particles. The particles having small sizes having higher surface area increase particle interaction and reduce flow.	[80]
18		Paracetamol and microcrystalline are prepared by using novel engineered Solution Atomization and crystallization by Sonication (SAXS)	Compendial methods	Improve powder flow because of increased spherical morphology, BD, and tapped density (TD).	[95]
19	Addition of hydrophilic and hydrophobic glidants	Hydrophobic and hydrophilic silica is used as glidants mixing done in a v-shape blender	PFT and compendial methods	The reduction in AOR, carr index (CI), and enhanced flow factor indicated enhanced powder flow.	[19]
20		Hydrophobic and hydrophilic colloidal silicon dioxide utilize similar to a glidant mixing done via different mixers (free fall mixer, high-speed mixer, pin mill)	Conveyer belt and compendial methods	Uniformed distribution of glidants, as well as protection from moisture, improves powder flow.	[50]

(*continued on next page*)

Table 6 (*continued*)

Sr. No.	Methods	Techniques/materials used	Instruments used for checking powder flow	Observations	Reference
21	By prepare granules	Prepare granules of Bezafibrate by using wet granulation techniques (high shear granulator).	Compendial methods	After granulation, the narrow size distribution minimizes lumps formation, and fine powder percentage minimizes sticking property, required low ejection force indicated improved powder flow.	[66]
22		Prepare granules by using wet granulation techniques (Cuisinart mixer)	FT4 rheometer and compendial methods	Increasing particle size reducing size distribution and increasing density indicated that it improves powder flow.	[83]
23		Granules prepare by using wet granulation techniques (high shear granulator)	Ring shear cell tester	Increasing circularity, granules size, and reduced specific surface area and porosity indicated that enhanced powder flow	[84]
24	By sprouting the crude drug	Sprouted (Freeze-dried) onion powder is utilized	Powder flow analyzer and compendial methods	An increase in particle size and a decrease in the CI, cohesive index, and caking strength indicated improved powder flow properties.	[96]
25		Sprouted sorghum grains powder is utilized	Compendial methods	A decrease in CI indicated that enhanced flow of powder	[89]
26	Crystallization techniques to improve powder flowability	Crystal hydration of citric acid is done with anhydrous citric acid	Ring shear cell tester	It reduces crystal surface interaction and increases density, enhancing powder flow.	[91]
27		Ascorbic acid is used by utilization of emulsion solvent diffusion (ESD) techniques	Compendial methods	Increase plastic deformation, lower elastic recovery and AOR indicate that enhance powder flow.	[79]

3. Conclusion

Powder flow is a crucial parameter necessary for the smooth functioning of a pharmaceutical production line. Freely flowable powder improves feed parameters' reproducibility, resulting in efficient processing. From a pharmaceutical point of view, it gives reliable tablet hardness, friability, dissolution rates, and ease in manufacturing. There is an increase in plant output when the powder is smoothly flowing. Poor or uneven powder flow can result in excessive trapped air inside powders, thereby facilitating capping or laminating or even creating lubrication issues in high-speed tableting operations. This problem can be solved to improve powder flow properties. It will diminish air-pocket forming by a smooth downward flow of the material. The dosage cavity is filled very precisely, which increases the average weight and eliminates the deviation in the average weight coefficient, and induces force during compression, decreasing stress on system components. In a nutshell, the powder flow evaluation is crucial for understanding the suitability of a manufacturing process and for giving efficient drug development strategies. With the help of the techniques mentioned above, novel ways and means of powder flow enhancement can be used to provide overall benefits.

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Data availability statement

Data will be made available on request.

Declaration of competing interest

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

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