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# Assessment and predictive modeling of pharmaceutical powder flow behavior in small-scale hoppers

Mark A. Polizzi [a,*], Justin Franchville [b], Jon L. Hilden [a]

[a] Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285, USA
[b] Trine University, 1 University Ave, Angola, IN 46703, USA

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ABSTRACT

The propensity of powder to bridge in hoppers and bins is important for a wide variety of pharmaceutical processes, yet it remains difficult to predict large-scale performance from small-scale powder measurements. Despite the availability of various powder flow testing techniques, the prediction of powder bridging has remained elusive. To address this issue, powder flow performance was characterized for several pharmaceutical powders out of small-scale conical hoppers under various conditions. Specifically, the impacts of powder properties, hopper design, hopper fill level and vibration prior to discharge were characterized. The hopper flow regimes were categorized as mass flow, funnel flow, rat-holing or bridging. A Projection to Latent Spaces (PLS, a.k.a. partial least squares regression) model was developed to predict flow behavior from easily measured powder properties such as the Hausner ratio and measured hopper dimensions. The model correctly predicted flow initiation for new materials for ~90% of tests. The variables of Hausner ratio, vibration prior to discharge, and hopper orifice diameter were seen to be most predictive of flow. Surprisingly, powder shear test data such as flow function and unconfined yield strength along with other flow properties were not predictive of hopper performance for the conditions studied. A useful metric, $tan(\phi)/D$, was developed utilizing the hopper semi-apex angle ($\phi$) and orifice diameter ($D$), and was considered as a first-pass scale-up model.



## 1. Introduction

Powder flow is critical to a range of pharmaceutical manufacturing processes. Acceptable flow is required in powder transfer operations such as the emptying of tumble bins and conveyance of powders by gravity or screw feeders. Unit dose uniformity depends on reproducible flow of powders into tablet compression dies or into capsule shells. Failure to maintain consistent flow of materials can lead to costly process interruptions, material losses, or failure to meet product critical quality attributes.

Powder emptying from hoppers and bins is particularly important as it usually occurs multiple times during the course of processing of a single batch of dosage units. For example, a tumble bin may be emptied into a roller compactor which has a separate hopper directing powder into feed screws. Following granulation, a different tumble bin may be emptied into another hopper on a rotary tablet press which directs powder into a feeder assembly. At each step, one of four potential powder flow patterns may be observed. Mass flow occurs when the entire mass of powder moves in unison downward toward the opening. Mass flow is the preferred flow pattern and generally only occurs for very free-flowing powders. Funnel flow occurs when the material in the center flows at a faster rate compared to material near the walls. This creates a deep funnel shape that can be viewed on the top surface of the powder. This flow pattern is less desirable than mass flow, but is perhaps the most commonly observed behavior in pharmaceutical processes. An extreme case of funnel flow is referred to as “ratholing”. Ratholing occurs when material in the center discharges completely while material nearer the walls of the hopper remains in place. Finally bridging, the least desirable condition, occurs when an arch forms at the bottom of the hopper and prevents powder from emptying. Bridging is catastrophic as it completely halts the pharmaceutical production process. Predicting the propensity of a powder to bridge would therefore be highly useful when designing formulations and material handling procedures.

Many techniques (both compendial and non-compendial) have been developed to measure powder flow attributes which may correlate to flow from a hopper. Historically, the Hausner ratio (HR, tapped density/bulk density) and angle of repose have been investigated as simple means to assess powder flow [1–4]. Powder shear-cell testing provides a more complete set of powder flow parameters including the unconfined yield strength (UYS), flow function coefficient (FFC), etc. [5–8]. The shear cell can also be used to determine wall friction angle of powders against various surfaces. The wall friction of a specific powder/surface combination does not significantly impact bridging behavior, but does features prominently in the equations for hopper

* Corresponding author.
*E-mail address:* polizzi_mark_andrew@lilly.com (M.A. Polizzi).

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design which are used to encourage mass flow (vs. funnel flow) [5]. The UYS does theoretically correspond with bridging behavior as it reflects the stress required to break the powder bridge [6]. However, to the knowledge of the authors, no published dataset has shown a direct correlation of UYS to actual observed bridging events in hoppers for pharmaceutically relevant powders.

Other powder rheometry techniques have been developed to assess powder behavior dynamically based on measurements of the torque and normal forces applied on a blade traveling in a helical pattern through a powder bed [9–11]. These instruments optionally provide air pressure gradients across the powder bed, allowing measurement of powder permeability [9]. Another dynamic method, avalanche testing, usually involves measuring the intensity and frequency of avalanches inside a rotating drum [12,13]. Avalanche testing has been empirically correlated to the flow pattern of powders through small-scale conical hoppers of varying wall angles [14,15]. However, this method requires specialized equipment and relatively large quantities of powder. Unfortunately, both static and dynamic flow measurements are sensitive to the internal stress state and loading geometry of the powder and no single measurement is able to capture or predict the flow response of powders under all loading geometries [16].

In addition to bulk powder measurements computational approaches using discrete element modeling (DEM) have been utilized to assess powder flow [17]. This technique simulates the multitude of individual particle–particle and particle–surface interactions in a system. This method has proven useful in predicting powder flow initiation in pharmaceutical hoppers and bins [18,19]. However, these studies require significant expertise/training, special software, and high computational power due to the large number of simulated interactions needed to appropriately represent a real system. As previously reviewed, these simulations often rely upon simplifications (simplified particle shapes and container geometry) and require input parameters for inter-particle forces which are not easily measured [20,21].

Despite the commonplace use of powder flow testing, the prediction of powder flow, especially the propensity for powders to bridge, remains a significant and elusive challenge in the pharmaceutical industry. Ideally, an approach to predict bridging in a hopper would require a simple, non-destructive, powder characterization test using small quantities of material. This would allow for facile assessments of new formulations while predicting scale-up performance based on straight-forward geometrical measurements. Herein, powders were characterized by several independent flow measurement techniques. The powder characteristics were compared to direct observations of powder flow in conical hoppers and a PLS model was applied to the complex dataset. From the complete model, a streamlined approach is distilled to predict flow through conical hoppers using only bulk and tapped density, the angle of the hopper, and the diameter of the opening. The empirical latent variable model (LVM) was shown to be highly predictive of flow initiation for pharmaceutical powders over a wide range of densities. Also, a geometric scale-up parameter is proposed to predict flow initiation (i.e. bridging vs. no bridging) for a given material across scales. This holistic approach may be used to assist with formulation development as well as process equipment design.

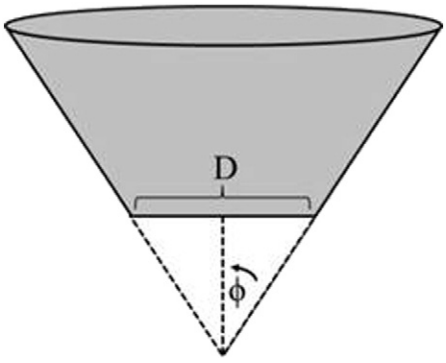


**Fig. 1.** Hopper Diagram.

## 2. Materials and methods

### 2.1. Material selection and characterization

Initially, six pharmaceutical powders with a range of expected flow properties were evaluated as shown in Table 1 (top six rows). These include lactose monohydrate (Fast Flo 316, Foremost labs), three grades of microcrystalline cellulose (Avicel PH200, PH102, and PH101, FMC Biopolymer), a mixture of 95 wt% pregelatinized starch (Starch 1500, Colorcon) with 5 wt% silicone oil (350 cSt, Dow Corning), and Acetaminophen (USP APAP, Mallinckrodt). Each material was characterized for true density ($\rho_{true}$) by He porosimetry, bulk ($\rho_{bulk}$) and tapped density ($\rho_{tapped}$) using the USP method 616 and the HR ($\rho_{tapped}/\rho_{bulk}$) was calculated.

These materials were also characterized using a Freeman FT4 Powder rheometer (Freeman Technology). A standard series of powder rheometry tests were performed on each material. They were the stability and basic flow energy, aeration, permeability and shear-cell (flow function). The powder rheometer data consisted of tests for Basic Flow Energy (BFE), Stability Index, Aeration Ratio (AR), permeability pressure drop, and unconfined yield stress (UYS) and flow function from the shear cell. The standard settings provided by the Freeman Rheometer software were used for each test. For shear cell testing the consolidation pressure was set at 2 kPa to be in the appropriate range for powder beds in pharmaceutical hoppers. The definition and detailed description of each test have been previously described [9].

Two blends were partially characterized for the purpose of testing the flow prediction model (Table 1, bottom two rows). Blend 1 was based on a potential immediate-release (IR) formulation and was comprised of 62% mannitol (Pearlitol SD200, Roquette), 31% microcrystalline cellulose (Avicel PH102, FMC Biopolymer) and 7% Croscarmellose Sodium (Ac-Di-Sol, PMC Biopolymer). Blend 2 was a more poorly

**Table 1**
Properties of the Test Materials.

| Material | $\rho_{true}$ (g/cm$^3$) | $\rho_{bulk}$ (g/cm$^3$) | $\rho_{tapped}$ (g/cm$^3$) | HR | BFE (mJ) | Stability index | SE (mJ/g) | Aeration Ratio | Press. drop (mBar) | UYS (kPa) | Flow function |
|---|---|---|---|---|---|---|---|---|---|---|---|
| FastFlo Lactose | 1.55 | 0.62 | 0.70 | 1.11 | 296.0 | 0.90 | 3.8 | 39.1 | 0.56 | 0.3 | 9.5 |
| MCC Avicel PH200 | 1.57 | 0.36 | 0.43 | 1.19 | 220.7 | 0.97 | 5.5 | 24.1 | 0.18 | 0.6 | 5.6 |
| MCC Avicel PH102 | 1.44 | 0.38 | 0.48 | 1.26 | 300.1 | 1.08 | 5.9 | 13.7 | 0.74 | 0.9 | 5.3 |
| MCC Avicel PH101 | 1.55 | 0.33 | 0.47 | 1.42 | 185.6 | 2.08 | 7.6 | 0.7 | 0.85 | 2.6 | 1.5 |
| Starch + Silicone Oil | 1.48 | 0.48 | 0.83 | 1.73 | 258.8 | 0.99 | 4.9 | 93.0 | 0.42 | 0.6 | 6.2 |
| Acetaminophen (USP APAP) | 1.50 | 0.36 | 0.73 | 2.03 | 181.2 | 0.93 | 8.7 | 3.4 | 1.67 | 1.0 | 3.7 |
| *Blend 1 — IR formulation** | *1.49* | *0.44* | *0.56* | *1.27* | *N/A* | *N/A* | *N/A* | *N/A* | *N/A* | *N/A* | *N/A* |
| *Blend 2 — ODT formulation** | *1.53* | *0.39* | *0.61* | *1.59* | *N/A* | *N/A* | *N/A* | *N/A* | *N/A* | *N/A* | *N/A* |

* Blends 1 and 2 were used to test the predictive model as described below.