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A New Method to Predict Flowability Using a Microscale Fluid Bed

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ABSTRACT

The purpose of this research was to develop a new method to predict the flow behavior of pharmaceutical powders using a multichamber microscale fluid bed. Different amounts of poorly flowing paracetamol were added to various grades of microcrystalline celluloses and silicified microcrystalline cellulose powders. Magnesium stearate was used as a lubricant. Experimental minimum fluidization velocities (u_{mf}) were defined using 2 to 4 g (equal to 10 mL) of material (Video 1). The reference flowability of the powders was determined using a specific flow meter. Also, the weight variation of the compressed powders, using a single-punch press, was measured. When the amount of paracetamol in the excipients was increased, the experimental u_{mf} increased and the fluidization behavior grew worse (Video 2). Principal component analysis (PCA) established that the pressure difference over the bed as a function of fluidization velocity could be used to characterize the behavior of powders. The increase in poor fluidization behavior of the powders was in accordance with the increasing amount of paracetamol and with the increasing weight variation of the tablets. Furthermore, the angle of repose and the flow rate of silicified microcrystalline cellulose powders were predicted using a partial least squares (PLS) model. The developed method to predict flowability is a promising approach for use in the preformulation and formulation stages of new drug candidates, for example.

KEYWORDS: fluid bed, flowability, formulation, preformulation

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INTRODUCTION

The development of new drug candidates is a slow and expensive process. It has been suggested that to speed up the drug development more attention should be paid to study and development (eg, miniaturized screen systems, process measurement technologies, seamless scaling techniques).[1]

Due to the increasing efficiency of lead compound discovery, the drug development processes will focus more and more on the early stages. In the preformulation stage, each lot of active pharmaceutical ingredient (API), excipient, and formulated blends will be characterized as fully as possible.[2] The fact that the availability of new drug candidates is often limited to a few grams sets special demands for formulation and process optimization. Producing an oral dosage form using small quantities of an expensive and scarce drug candidate is the perennial problem of formulation.[3]

Traditionally, pharmaceutical fluid beds have been studied with materials weighing from hundreds of grams to several kilograms. Problems with the fluid beds have been inadequate process control and monitoring, scaling-up, and complexity of the systems (eg, fluid bed granulators). Simplified, precisely monitored, and controlled small-scale systems may allow novel viewpoint for understanding and use of the almost chaotic fluid beds.

Small-scale equipment has been used to study the compression behavior or scalability of the high-shear granulation process.[4,5] Recently, Räsänen et al[6,7] introduced a novel multichamber microscale fluid bed device that could accurately process 2 to 10 grams of pharmaceutical solids. An in-line near infrared (NIR) monitoring and a noninvasive electrostatic measurement for the same fluid setup have also been described.[7,8] Simultaneously performed studies in precisely controlled conditions save time and ensure the high quality of results, although the characterization of process behavior is difficult. Increasing the number of experiments can bring the same kind of effectiveness for the preformulation stage as high-throughput screening techniques, which have been allowed for drug discovery.[9]

Table 1. The Amount of Paracetamol in the Studied Microcrystalline Cellulose and Silicified Microcrystalline Cellulose Mixtures*

Excipient (Brand)	Amount of Paracetamol, % (wt/wt)									
MCC101 (Avicel PH101)	0	2.5	5	7.5	10	12.5	15	-	20	-
MCC102 (Avicel PH102)	0	-	5	-	10	-	15	17.5	20	-
MCC200 (Avicel PH200)	0	2.5	5	-	10	-	15	-	20	-
SMCC (Prosolv 90)	0	2.5	5	-	10	12.5	15	-	20	25
MCC101/MCC200†	0	2.5	5	7.5	10	12.5	15	-	20	-

* MCC indicates microcrystalline cellulose; SMCC, silicified microcrystalline cellulose; and (-), not determined.
† 75%/25%

Flowability is one of the most important factors in drug development.[10-12] Inadequate flow properties of solids can cause serious problems during pharmaceutical unit operations (eg, compression, filling, conveying). Prediction of the flowability on the basis of the physical properties is difficult, and thus a number of experimental methods have been developed. When the amount of drugs is limited, common experimental methods to evaluate powder flow are measurements of bulk density and angle of repose of the powders.[13] Carr[14] and Hausner[15] have developed simple models that can be used to evaluate powder flow properties and compressibility in the preformulation stage. These models are based on the relationship between tapped and bulk densities of the powders. However, results achieved by indirect methods are often difficult to connect to the true process behavior of the powders.

During fluidization, particles contact intensively with gas, wall of the chamber, and other particles. Mechanical stress is considerable, and a number of interparticle forces and interactions occur.[16,17] Understandably, the interactions and interparticle forces that appear during fluidization are the same ones that disturb other pharmaceutical unit operations. When fluidization behavior is connected to more universal process behavior (eg, flowability or compression behavior), valuable information and fundamental advantages can be achieved.

Despite the streamlining of the discovery of lead compounds, average development times for new drugs have remained quite unchanged.[18] To emphasize and to speed up the drug development and the preformulation stage, new miniaturized technologies are required to characterize and to predict the process behavior of pharmaceutical solids. The aim of this study was to introduce a new view for considering the flowability and the process behavior of pharmaceutical powders using a multichamber microscale fluid bed.

MATERIALS AND METHODS

Materials

Studied excipients were 3 types of standard microcrystalline cellulose (MCC, Avicel PH101, PH102 and PH200, FMC International, Ireland), a mixture of MCC101/MCC200 (75%/25%) and silicified microcrystalline cellulose (SMCC, Prosolv 90 Penwest Pharmaceutical, Patterson, NY). Various amounts (**Table 1**) of poorly flowing active pharmaceutical ingredient (Paracetamol, The European Pharmacopoeia (Ph. Eur.) grade) were added to the powders. Magnesium stearate (0.5% wt/wt, Ph. Eur. grade) was used as a lubricant. The prepared powders were mixed for 10 minutes at 14 rpm in glass jars using a laboratory-size mixer (Turbula T10B, Willy A. Bachofen AG Maschinenfabrik, Basle, Switzerland).

Multichamber Microscale Fluid Bed

A multichamber microscale fluid bed (Ariacon Oy, Helsinki, Finland) module consists of 4 fluidization chambers made from glass (**Figure 1**). The inner diameter of the lower part of the conical chamber was 20 mm and of the upper part, 1000 mm. Fluidization mainly occurred in the lower part and the upper part acted as an aerodynamic brake (no bag filters), decreasing the velocity of process air. Each of the chambers was an individual unit, and the process control and monitoring solution was automated.[6,7] Using a process air control unit (Ilmasäätö Oy, Turku, Finland), the moisture content of inlet air was adjusted to be under 0.5 g water/m^3 of dry air. With such an arrangement,

Figure 1. Experimental setup.

the generation of interparticle (electrostatic) forces was emphasized. The temperature of the inlet air was 22°C.

Determination of Process Behavior

Experimental minimum fluidization velocity (u_{mf}) was measured from decreasing air flow rate[19] (Video 1: http://www.pharmtech.helsinki.fi/eeturasanen/). The batch size of the powders was 10 mL, equal to 2 to 4 g of studied powders. First, the powders were fluidized for 2 minutes at a constant air flow rate, 79 mL/s, so that the fluidization mainly occurred in the lower part of the chamber. (The velocity of the process air was 25 cm/s in the lower part of the chamber). Next, the velocity was slowly decreased to zero. The experiments were repeated in an identical manner simultaneously in 4 fluidization chambers (**Figure 1**). In each of the chambers, the pressure difference over the bed was measured as a function of the velocity (in the lower part of the chamber) of the fluidization air.

A reference flow tester was a noncommercial apparatus (Orion Pharma, Helsinki, Finland). The tester consists of a stainless steel funnel, 100 mm in diameter and 120 mm in height, with a wall angle of 40 degrees and a round orifice 10 mm in diameter. A stainless steel wire mixed the powders in the funnel. The measurement started when the valve of the funnel outflow opened. The powder flowed from the filled funnel onto a round plate with a diameter of 100 mm, and the weight of powder on the plate was recorded at intervals of 0.1 second. The powder fell onto the plate until it was full and started to overflow. By using such an arrangement, a powder cone with a regular base diameter was achieved. The flow rate (g/s) was determined from the recorded weight values. The system included electric scales, a control unit, a video camera and a computer (PC).

Powders were compressed using an instrumented single-punch press (Korsch EK-0, Erweka Apparatenbau GmbH, Berlin, Germany). The diameter of round, flat tablets was 9 mm, and the weight was 225 mg. Operating speed was 34 tablets/min and the compression force of the upper punch was 4 kN. Before compression, powders were stored for 3 days under controlled conditions of 55% relative humidity. Weight variations of 20 tablets were measured using a tablet tester (Erweka Multicheck, Erweka GmbH, Heusenstamm, Germany). The relative SD (%) of the tablets was calculated. Both reference flow tests and compression of the powders were performed at ambient conditions.

Data Analysis

Shapes of the pressure difference over the bed curves were compared after principal component analysis (PCA) using SIMCA-P (version 8.0, Umetrics, Umeå, Sweden). The 2 first principal components of the pressure difference curve were drawn as a point on the plane. The values of the 2 first principal components (scores t[1] and t[2]) determined the position of the point on the plane. Pressure difference curves having the same kind of shapes were projected near each other on the plane.

A partial least square (PLS) regression model was build to model the relationship between the fluidization behavior and the flowability (flow rate and angle of repose measured by the reference method) using SIMCA-P. All microcrystalline cellulose powder mixtures (28) were used as modeling data. The entire graph of the pressure difference over the bed as a function of decreasing velocity of the inlet air (25-0 cm/s) was exploited for modeling. Silicified microcrystalline cellulose powders (8) were used as test data, which were not included in building the regression model.

RESULTS AND DISCUSSION

Reference Flowability

Paracetamol was used as a poorly flowing drug substance in the studied excipients. When the amount of paracetamol was increased, the angle of repose increased, and the flow properties of the powders decreased (**Figure 2**). The goodness of fit (r^2) between the angle of repose and the amount of paracetamol was 0.69 using a rising exponential polynome. Average relative SD of the reference flow tester for all measurements was 5.1%. Most probably, the low goodness of fit was due to the deficiency of the reference flow

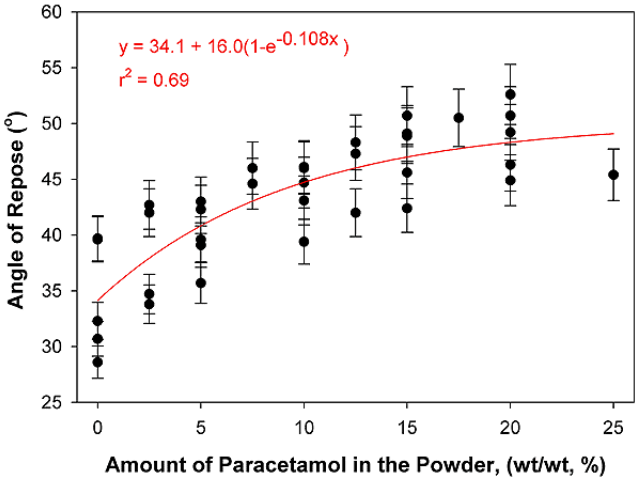

Figure 2. The dependency between the amount of paracetamol and the angle of repose measured by a reference flow tester (n = 3).

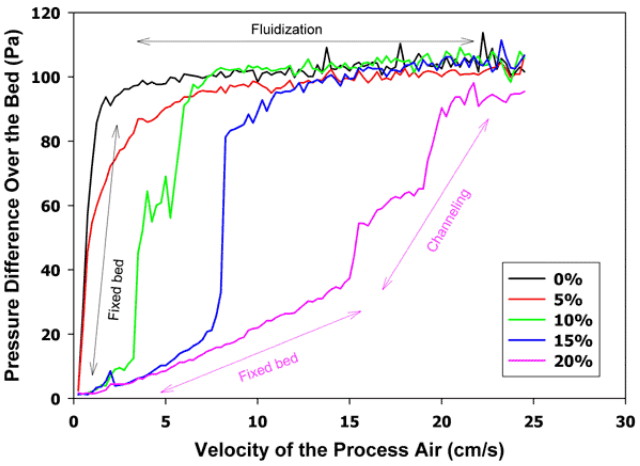

Figure 3. Pressure difference over the bed as a function of decreasing fluidization velocity. Percentages indicate the amount of paracetamol in silicified microcrystalline cellulose powders.

tester.[20] One explanation for the results is a rather low mechanical stress applied to the powders during the measurements. Additional methods are required to predict the real process (ie, tabletting) behavior of these powders.

Fluidization Behavior

A minimum fluidization velocity (u_{mf}) represents the point of transition between fixed and fluidized states. At this point, the drag force of upward moving gas counterbalances the weight of the bed of solid particles. For design and scaling-up purposes, it is important to be able to calculate the value of u_{mf} precisely and thus avoid a large number of experiments. Several authors have published their own detailed models for predicting the u_{mf} in different conditions.[21-26] However, it is well known that all these models are only trend settings, and the exact u_{mf} should be determined experimentally (Video 1).

When the amount of paracetamol in the powders was increased, the fluidization behavior grew worse, and some undesired features (eg, channeling and plugging[19,27]) appeared (Video 2: http://www.pharmtech.helsinki.fi/eeturasanen/). The pressure difference over the bed as a function of fluidization velocity represented the effect of paracetamol on the fluidization behavior of the studied cellulose powders (**Figure 3**). The shape of the pressure curve changed logically as the amount of paracetamol was increased. The experimental u_{mf} moved to the higher values, and increase in poor fluidization behavior (eg, channeling was observed by the pressure difference over the bed. There were also 2 compositions of the powders, MCC200 20% and SMCC 25%, which could not be fluidized at these process conditions (velocity 25 cm/s).

On the basis of the fundamental theory of fluidization,[19,27] the u_{mf} should have decreased when the mean particle size of the powders decreased. However, when the amount of fine paracetamol in the excipients was increased, the experimental u_{mf} increased (**Figures 3** and **4**). The increase in the poor fluidization behavior and the higher experimental u_{mf} (than was expected on the basis of the basic theory) were a consequence of the increasing interactions and the interparticle forces of fine paracetamol particles. The electrostatic forces were especially emphasized due to the low moisture content of the process air (<0.5 g/m^3).

A clear correlation was found between the amount of paracetamol and the experimental u_{mf} (**Figure 4**). Two powders (MCC200 20% and SMCC 25%), which could not properly be fluidized, were excluded from this model. Using a growing exponential polynome, the goodness of fit (r^2) was 0.93, which was much better than the r^2 value 0.69 obtained by the reference flow tester (**Figure 2**). The results showed that the changes in the experimental u_{mf} or in the fluidization behavior can be successfully used to classify the powders process behavior in formulation studies.

Prediction of Flowability

The determination of the experimental u_{mf} may sometimes be difficult and quite subjective, especially with powders that have wide particle size and shape distri-

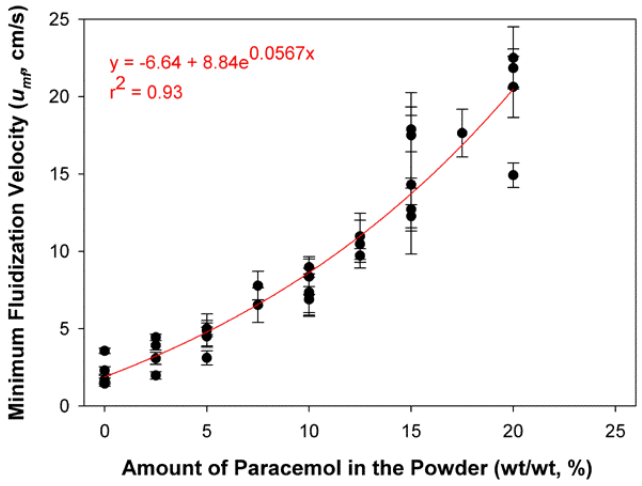

Figure 4. Pressure difference over the bed as a function of decreasing fluidization velocity. Percentages indicate the amount of paracetamol in silicified microcrystalline cellulose powders.

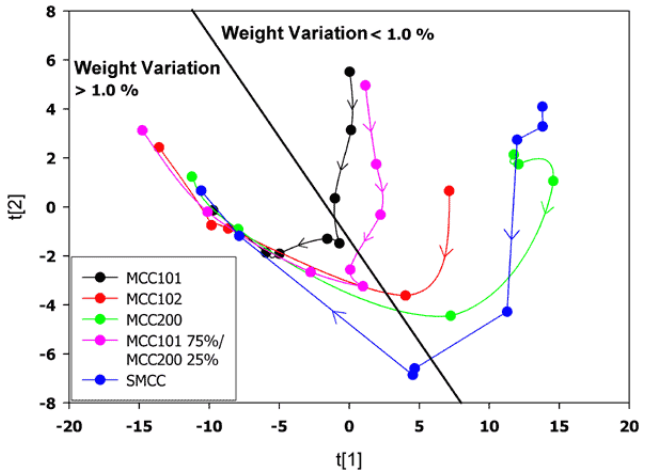

Figure 5. Principal component analysis of the entire pressure difference graphs of the studied powders. Weight variation (%) of the compressed powders is marked as a black line. The amount of paracetamol in the studied excipients and the weight variation of compressed tablets are increased in the direction of arrowheads.

butions and strong interparticle forces, because different modes of fluidization occur and overlap. Consequently, the utilization of the whole graph of the pressure difference over the bed could be more informative and objective than the simple determination of the experimental u_{mf}.

After the PCA, the 2 first principal components of the whole pressure difference over the bed curve were drawn as a point on the plane. When the amount of poorly flowing paracetamol in the excipients was increased causing decreased flowability, the points on the score plot projected along specific paths that started from the upper right part of the plane and ended at the upper left part of the plane (**Figure 5**). The weight variation (%) of the compressed tablets was also increased in the same way. On the upper right side of the plane, weight variation was under 1%, and on the upper left side of the plane weight variation was over 1%.

At the low level of paracetamol, each of the powders was ordered on the basis of the fluidization behavior of the excipients (**Figure 5**). The paths were in reasonable order, MCC101 (finest) on the left side, MCC101/MCC200 (75%/25%), and MCC102. On the upper right side, MCC200 (largest) and SMCC were quite near each other, indicating similar and quite good fluidization behavior. This order was in accordance with a recent study, which established that the silicification improves the fluidization behavior of the standard microcrystalline cellulose powders.[7] When the amount of paracetamol in the powder mixtures was increased, their fluidization behavior became identical and approached the upper left corner of the plane (poor fluidization behavior). Thus, it is concluded that the pressure difference over the bed graphs are able to characterize and to predict the process behavior of powders.

A PLS regression model was used to predict the flow rate and the angle of repose by the curves of the pressure difference over the bed (**Figures 6** and **7**). When the amount of paracetamol increased in the powder mixtures, the flow rates decreased and, correspondingly, the angles of repose increased. The created PLS regression model overestimated slightly the flow rate results. However, the angle of repose was more precisely predicted by the PLS model. A recent note by Schüssele and Bauer-Brandl[20] discussed the real usefulness of the flowability test in the European Pharmacopoeia, and they established that the time per mass unit value might give distorted results in the flow testers. Thus, the limited ability of the reference flow tester could also be one source of the error of the PLS regression model (**Figure 2**). However, another important source of error is the restricted size of the modeling data. When the amount of data is increased and the process conditions (ie, fluidization velocity and amount of powders) are optimized, the accuracy of the developed model should also improve.

The developed method to predict flowability and to characterize process behavior was proved useful in the microscale fluid bed. The fundamental benefits could be achieved using expensive and scarce drug molecules because the same fluid bed can be used for several

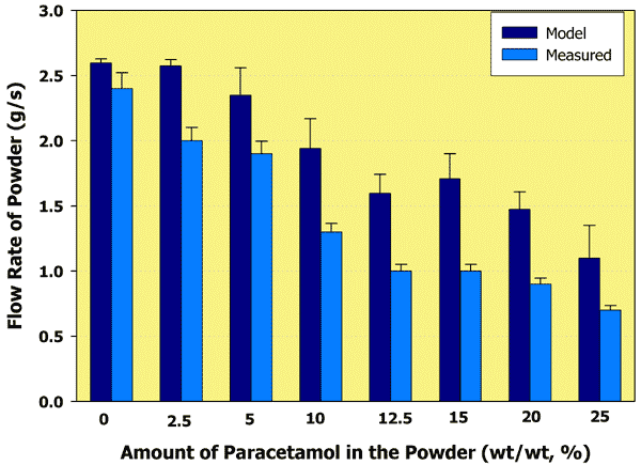

Figure 6. Prediction of the flow rate of silicified cellulose powders by the PLS model.

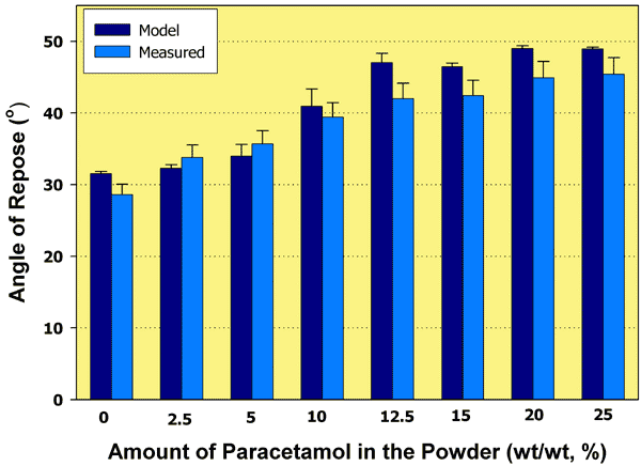

Figure 7. Prediction of the angle of repose of silicified cellulose powders by the PLS model.

pharmaceutical purposes in variable process conditions.[6-8] The developed method to predict flowability of powders could be used successfully for formulation studies in the early stages of drug development.

CONCLUSION

Utilization of the pressure difference graph as a function of fluidization velocity is a potent approach to predict the process behavior of pharmaceutical solids. The interdependency between fluidization behavior and flowability was established. The developed approach in a precisely controlled and monitored microscale fluid bed could offer fundamental advantages for predicting drug formulations behavior in the real process environment.

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