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Development of a micro-dosing system for fine powder using a vibrating capillary. Part 2. The implementation of a process analytical technology tool in a closed-loop dosing system

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ABSTRACT

In an earlier study, a micro-dosing system for fine powder using a vibrating capillary which can precisely dose various lactose powders, was introduced. In scaling up to a multi-track dosing system, it was suggested that additional track cut-offs can improve the dosing performance by reducing the overruns. A non-contact in-line control unit within a closed-loop system is required to achieve this goal. Due to its very fast response time (a few milliseconds) a capacitive sensor was integrated together with multi track cut-offs into a closed-loop dosing system. With this improvement a standard dosing deviation as low as 0.1 mg was achieved. The results suggest its application in precise filling of fine pharmaceutical powders.

1. Introduction

Precise filling of fine powders can be found in many industrial operations. Such operations include the micro-dosing of powder in pharmaceutical research, development and production. For instance, the production of dry powder inhalers requires small quantity of fine powder being precisely metered into either capsules or blister pockets. A single dose ranges from only several milligrams up to 20 mg of powder. The validation of mass is done currently volumetrically. However, powders may have very different bulk densities depending on their manufacturing methods and handling processes during production. In some cases, the dosed value can be altered partly by changing the machinery parameter settings. For instance, the dosed weight of vacuum drum filler can be modified by altering the strength of suction pressure. However, in cases of formulation development where different powders are to be filled in small scale or in filling for pre-clinic research where the target dose might vary in a broad range, the only practical way is to change the dosing heads. As a result, it increases the process time and a number of dosing heads with different cavities are needed.

1.1. A micro-dosing system for fine powders using a vibrating capillary

Taking these demands into consideration, a simple dosing system with a straightforward construction was developed. The frequency and the amplitude of applied vibration (Matsusaka et al., 1995, 1996; Yang and Li, 2003; Yang and Evans, 2005; Jiang et al., 2006) were the contributing factors to the mean dosing value and the dosing accuracy. It was found that by careful selection of the capillary orifice, the start/stop of powder flow can be controlled by switching on/off the vibration (Yang and Evans, 2005). In a simple case, the desired dose can be controlled by adjusting the duration of vibration.

A 100% fill weight control can be achieved by implementing a closed-loop control using a weighing cell. However, it is difficult to implement it into an industrial scale production line due to several limitations (Chen et al., 2011). In this case, a closed-loop control using a non-contact in-line detection principle can provide more advantages. With this intention, a sensitive capacitive sensor was integrated into the dosing system presented.

1.2. Measurement of the flow of powder bulk using a capacitive sensor

A simple capacitive sensor has two parallel electrode plates. The permittivity change between electrodes causes a change of

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capacitance when powder passes through the sensor. The measurement is done by comparing the signal with a reference capacitor circuit. For a monolith, for example, a piece of tablet with a size smaller than the height of the electrodes obtains always a peak value. The peak value or the effective capacitance (C_{eff}) can be calculated from the capacitance values of two sensors which are connected in parallel, see Eq. (1):

$$C_{eff} = \frac{C_{solid}C_{gas}}{C_{solid} + C_{gas}} \quad (1)$$

In case of moving powder bulk which approximates to a continuum, its effective permittivity contributes by the fraction ratio of the solid material to the medium and their different electrical permittivity. Therefore, different functions are used to calculate the effective permittivity (Bruggeman, 1935). In recent years the industrial practice has focused mainly on the visualization of the powder flow regime (Rao et al., 2001; Chaniecki et al., 2006; Takei and Zhao, 2008; Sun et al., 2008; Niedostatkiewicz et al., 2010), for instance, to study the material distribution in a pneumatic conveyor for powder. In these studies, the signals collected by a few pairs of electrodes are used to visualize the material distribution in 2D or in 3D electrical capacitance tomography. Due to the complexity of such system and the lack of resolution, the quantitative measurement of a few milligrams of powder is less studied.

1.3. The phenomenon of self-valve and the need of an active track cut-off

Janssen proved that on large scale the weight of powder bed is mainly supported by the wall (Janssen, 1895). By analysing the micro-structures in photo-elastic granular material, it was found that the transmission of static forces in bulk powder is through a network built by anisotropic force chains (Howell et al., 1999a). They are formed by the spatial connections among particles (Howell et al., 1999b; Corwin et al., 2005).

In a capillary with a narrow orifice, the formation and the release of such micro-mechanical structures are influenced not only by the material properties but also by the local arrangement of particles. When the capillary has an orifice with the proper size, powder could be enclosed in it even without the need of a valve under the exit (Yang and Evans, 2005), which is called the *self-valve phenomenon*.

Once external vibration is applied to the powder bed and if the induced shear force exceeds the elastic threshold value, the network of force chains will be broken and powder starts to flow under gravity force. When the vibration is stopped, the particles rearrange themselves rapidly and establish a new network of force chains that stops the flow. The release and rebuild of such clogging structure take only several milliseconds in the setup presented here. Hence, discharge of powder is possible using a narrow capillary in a controlled manner by switching the vibration on/off.

On the other hand, the strength of these connections renders the cohesiveness among the particles. Feng and Hays (2003) compared the cohesive forces among particles and their forces of gravity. When the particle size decreases to 10 μm, the van der Waals forces between two particles are estimated to be at least a hundred-fold larger than their forces of gravity (10–500 nN to 0.005 nN). Consequently, the shear forces induced by the vibration alone might not be sufficient to overcome the cohesive forces among primary particles. However, most of large agglomerates break into small agglomerates due to the collision induced by the vibration (Matsusaka et al., 1995).

The effectiveness of such self-valve phenomena depends on a geometric factor: the ratio of the orifice diameter to the average particle size of powder. A small orifice has an increased risk to block the capillary even in presence of vibration, a too large orifice may lead to overrun even in absence of vibration. Furthermore, it could be problematic when powders have relative broad particle size distribution. In this case, the orifice of the capillary is often chosen for particles with large diameter in order to reduce the possibility of blockage. Consequently, the possibility of overruns is increased. An additional track cut-off is supposed to be helpful. Further, in scaling up to a multi-track dosing system, the fluctuation of powder flow and the minor difference of flow rate among diverse dosing heads could increase the flow rate variability. Again, a mechanism for individual adjustment of every single track is needed to meet the requirement of 100% control of fill weight.

In general, two conceivable strategies can be followed:

- the individual control of the vibration generators, and
- the individual cut-off of powder flow with one common vibration generator.

In the first concept, multiple actuators and signal controllers are needed which increases the complexity of the system and the cost. Accordingly, the system described here is based on the latter principle.

2. Materials and methods

2.1. Material

Several kinds of inhalation grade lactose powder were used in the experiments: Inhalac 70, Inhalac 120, Inhalac 230, Sorbolac 400 (all from Meggle GmbH, Germany, Wasserburg) and Respitose SV 003 (DFE Pharma, Germany, Goch). Their particle sizes and size distribution as well as other powder properties are shown in Table 1. A laser diffractometer (Sympatec HELOS GmbH, Germany, Clausthal Zellerfeld) was used to measure the volume particle size distribution. Powders were measured in dry form after dispersing in air using compressed air at a pressure of 3 bar (RODOS dispersion module). The bulk density, the tapped density and the Carr's index were taken from the specification provided by the manufacturers. The angle of repose were measured using a tester built according to DIN ISO 4324. The results were taken from the average value of five experiments with exception of Sorbolac 400, which did not pass the orifice despite stirring.

2.2. The machinery assembly and the procedure

A multi-track micro-dosing system for fine powder was assembled as shown in Fig. 1.

Powder was introduced through a small reservoir (1) into three capillaries (2) and from there to be dosed into cavities (5). The capillaries were bolted together to the actuator. An additional track cut-off (4) was installed under the capillaries, see Fig. 1. Under the cut-offs a capacitive sensor (3) was applied as the in-line non-contact controller. In Fig. 1 the track cut-offs (4) were removed to expose the capacitive sensor (3) (Advance Mass Verification sensor, Uhlmann VisioTec GmbH, Germany, Laupheim); in Fig. 1 the capacitive sensor (3) is removed to expose the additional track cut-offs (4).

The vibration parameters are set on frequency 338 Hz, amplitude corresponding to an input voltage 30 V. The strength of vacuum applied on the capillaries was measured with a pressure transmitter CPA2500 (WIKA Alexander Wiegand GmbH & Co. KG, Germany, Klingenberg). For ease of use, the vacuum was triggered on/off manually.

A few milligrams of powder pass through the sensor and cause the change of capacitance, which can be instantaneously calculated with a strength-time curve. The integral of curve is compared with a given target. Once the target value is achieved in one single track,