



Particle size-based segregation of pharmaceutical powders in a vertical chute with a closed bottom: An experimental evaluation



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ABSTRACT

Vertical chute transport is a common and widespread means of transporting powders and powder blends in the pharmaceutical industry; conversely, it is also a ready source of segregation. All components of powder mixtures (i.e., active pharmaceutical ingredients, as well as excipients) are subjected to particle size-based segregation, and therefore all properties of the final product, which depend on the particle size of its constituents, may be affected (e.g., compressibility, dissolution rate, API content, and content uniformity). Segregation of single-component pharmaceutical powders with continuous size distributions (excipients or model API) based on particle size was experimentally investigated. Single-component pharmaceutical powders were subjected to fall in a laboratory-scale vertical chute with a closed bottom, and powder samples from various powder bed heights were collected and analysed for particle-size distributions. The results show particle size-based segregation in all materials tested, and the segregation extent and pattern are material-specific. Certain segregation effects were explained with the flow patterns of falling powder and powder bulk properties. An interesting finding is that less cohesive materials with better flowability exhibit increased segregation of smaller sized-D(0.1) particles, which has been attributed to the vertical chute system with a closed, airtight bottom. The size limit, below which particles concentrate at the top of the sediment, and above which particles concentrate at the bottom of the sediment, seems to be universal at 0.46 of D(0.9) value for tested materials.

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1. Introduction

Gravity-driven flow of granular material in vertical chutes (also referred to as ‘channels’, ‘pipes’, or ‘ducts’) is a simple and widespread means of bulk powder transportation across a wide array of industries. The pharmaceutical production of final dosage forms utilizes vertical chutes for bulk powder transport between processing phases, typically from a powder container to a processing machine (e.g., from a hopper to a tableting machine) [1].

Transport in vertical chutes is a ready source of powder segregation [1,2]. Segregation is based on several mechanisms and can occur at every step of powder handling and transport [2–4]. The mechanisms involved are air entrapment in the form of bubbles or slugs (granular material fluidization) and particle entrapment (particles dispersed in air flow) [1]. Segregation in vertical chutes is further promoted by air escaping through the powder bed, which occurs if the bottom of the chute is closed airtight [5]. Powder properties that have the most influence on segregation, and that also determine particles’ aerodynamic diameter are particle size, shape, and density [4] – in other words, every property

that changes the ability of an individual particle to move faster than neighbouring particles in the airstream.

There are two major approaches to testing segregation in vertical chutes: the first one strives to mimic the escape of fluidization air through the falling powder by air fluidization of material in a vertical cylinder [5,6] or a modified version for smaller sample sizes with an adjustable fluidization pattern [3]. The second approach utilizes a scaled-down version of vertical chutes in which powder fall tests are performed [7,8]. A testing apparatus that utilizes a combination of both approaches has also been described in which the powder is subjected to falling in a short segment of a vertical chute, which is followed by short-term fluidization [9]. In all of the approaches described, the segregated material is sampled in layers for further analysis.

Studies of powder segregation in vertical chutes suggest that a high particle-size ratio [8], chute dimensions (long chutes with small diameters) [7,8], and the effect of counter-flow air [3,9] are the factors that result in largest segregation extent. On the other hand, approaches to reducing segregation include powder flow restriction, reducing dust generation (i.e., particle entrainment), and air venting [1].

A study of binary mixture segregation in vertical chutes based on particle size was performed by Liss et al. [8], which is a valuable study revealing the influence of chute diameters and length on segregation propensity. There are, however, several limitations of their research.

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The bottom of the chute – as can be deduced from the experiment description – is not designed to be air tight, nor was the airtightness confirmed. In their research, segregation testing of pharmaceutical materials was performed only on a 12.3 mm diameter vertical chute, where segregation is overly expressed. The results can be therefore used as a worst case scenario segregation predictor. One tested material was glass beads of two different sizes and very sharp binary distribution. The other examples were sieved fractions of microcrystalline cellulose and dicalcium phosphate, which is an unrealistic condition. The authors have furthermore used polymethacrylate chutes, and in order to avoid electrostatic charging, a high humidity was imposed, which is an unrealistic condition within pharmaceutical applications.

Segregation of the active pharmaceutical ingredient (API) can have a substantial influence on content uniformity in the final dosage form, which is of highest concern for health authorities and the pharmaceutical industry: thus, most research focuses on API segregation. However, pharmaceutical powder mixtures usually contain substantial amounts of multiple excipients, which are also subjected to segregation processes: the excipient's function in the final dosage form is often concentration-dependent [10], and in some cases the excipient's function also depends on its particle size.

The influence of excipient particle size on product process-ability and product properties is being extensively tested because it is recognized by everyone involved in drug product development, production, and authorization that particle size is often a critical material attribute that affects key product performance attributes. Granule particle size influences the compactability of tableting mixtures, with larger particles yielding harder compacts [11]. Matrix-forming polymers (e.g., high viscosity hypromellose) used in controlled-release tablets are a typical example in which differences in concentration lead to substantial differences in drug dissolution [12]. Furthermore, even small variations in the particle size of release-controlling polymers employed in matrix systems may lead to significant differences in dissolution rates [12,13]. Disintegrants are another group of excipients for which performance increases with increasing particle size [14–16].

The influence of vertical chute transport on excipients' particle size-based segregation has not been examined closely thus far, although, as presented above, it is theoretically important. Accordingly, the aim of our study was to measure the extent of segregation of single-component pharmaceutical powders (excipients) on a model laboratory chute with an airtight closed bottom, and to identify the key factors promoting segregation. Our working hypothesis states that segregation based on particle size will also occur in pharmaceutically applicable, unfractionated single component materials, i.e., for unimodal, continuous size distribution with the particle size span used in the industry. This area of research has important implications because many functional properties of excipients are related to particle size.

2. Materials and methods

2.1. Single-component pharmaceutical powders

In our study, real unfractionated pharmaceutical powders used in mixtures for direct compression were subjected to segregation in a vertical chute with a closed bottom. The criteria for material selection were as follows: the material could actually be used in a direct compression process, and the amount of material used in a formulation is substantial (>30% w/w). Seven different powdered materials were identified and tested, all of them of commercial grade: Pharmatose 80M (lactose monohydrate, sieved; L80M) was obtained from DFE Pharma (Veghel, the Netherlands, B.N. 10683635). SuperTab 14SD (spray-dried lactose; SDL) was obtained from DMV-Fonterra Excipients GmbH (Nörten-Hardenberg, Germany, B.N. 10671590). Avicel PH 102 and Avicel PH 200 were obtained from FMC BioPolymer (Cork, Ireland, B.N. 71250C and M1247C, respectively; MCC102, MCC200). Paracetamol D.C. 273N (granulated paracetamol for direct compression; PAR) was obtained

from Mallinckrodt, Inc. (Greenville, IL, USA, B.N. 425512H062). Emcompress AN (dicalcium phosphate anhydrous; DCPA) was obtained from JRS Pharma (Mnf. Chicago Heights, IL, USA, B.N. 124741). Methocel K4M Premium CR (hypromellose 2208, 4000 mPas; HK4M) was obtained from DOW Chemical (Mnf. Bay City, MI, USA, B.N. 1D24012N03).

Particle size distributions of tested materials are shown in Fig. 1. Distributions of tested materials show median particle sizes between 80 and 300 μm . Sieved lactose monohydrate (L80M), microcrystalline cellulose (MCC200), and dicalcium phosphate anhydrous (DCPA) show narrow particle size distributions, whereas spray-dried lactose (SDL), microcrystalline cellulose (MCC102), and hypromellose (HK4M) show wider distributions. Paracetamol granules (PAR) show a pronounced shift in distribution to the left. L80M shows a pronounced fraction of small particles around 30 μm .

According to material mean particle size and material densities, we can classify powdery materials according to the Geldart classification diagram for fluidization [17] with MCC102, HK4M, PAR, and SDL falling into Class A and L80M, MCC200, and DCPA falling into Class B.

2.2. Laboratory-scale model of a vertical chute

The experimental apparatus consisted of two transparent borosilicate glass tubes (Schott, Duran®, 80 mm tube with 5 mm wall thickness) with an inner diameter of 70 mm aligned in a vertical position, one above the other, and with a knife valve (stainless steel) separating both (Fig. 2, left photograph). The upper glass tube was the powder container (800 mm high, top open to air), and the bottom part was a vertical chute with a 1200 mm fall. The knife valve (Fig. 2, top right photograph) was spring loaded and equipped with a triggering mechanism that allowed the instantaneous release of the powder bed from the powder container. The bottom of the chute was closed with a specially-designed sampling valve that allowed airtight closure of the chute during powder fall and equi-volumetric, vertically stratified sampling of powders from the chute during the sampling phase (Fig. 2, bottom right photograph).

The crucial part of the sampling valve was a thick sliding plate (10.5 mm) with two 70 mm diameter openings on either side (Fig. 2, bottom right, Fig. 3): in the central position, the sliding plate functioned as a closing valve for the chute. Two holes positioned left and right from the central position allowed layer-by-layer sampling of the powders from the chute (each layer having a thickness of approximately 10.5 mm). Sampling of the powder from the chute was accomplished by sliding the plate left and right. In the right position, a hole on the left side of the plate was aligned with the chute: powder from the chute filled the cavity. When the plate was shifted to the left, powder in the left hole was transferred laterally and released into the container; at the same time, the hole on the right was filled with powder. The volume of each powder sample was approximately 39 ml.

The moving parts of the knife blade and sampling valve were first layered with self-adhesive PTFE foil in order to reduce friction. After several materials were tested, it was observed that this setup adequately restricts material flow; however, it is not airtight. The results from these experiments are reported as “non-airtight.” In order to ensure airtightness, both the knife and sampling valves were equipped with silicon rubber seals. Airtightness of a sealed knife blade valve and a sampling valve has been tested with smoke test in conditions of over and underpressure.

The apparatus was additionally equipped with LED lighting, which illuminated the white background behind the chute, thus allowing evenly back-illuminated footage of the falling powder (Fig. 2, left photograph).

2.3. Segregation experiments

A segregation test for each material was performed by brief pre-mixing of a single-component test material in a polyethylene bag,

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