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Assessing powder segregation potential by near infrared (NIR) spectroscopy and correlating segregation tendency to tabletting performance

Xiaorong He [a,*], Xi Han [b], Nadia Ladyzhynsky [a], Richard Deanne [a]

[a] Boehringer-Ingelheim Pharmaceutics Inc., Ridgefield, Connecticut, USA
[b] Department of Chemical Engineering, New Jersey Institute of Technology, USA

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ABSTRACT

Segregation is one of the common problems associated with low drug load formulations, particularly for those made by a direct compression process. Segregation of an active pharmaceutical ingredient (API) from excipients can lead to variation in content uniformity, which in turn may result in failure to meet product specification. Segregation not only stems from variation of material properties such as differences of API and excipient particle size, shape and cohesion, but also is highly specific to process handling and specific equipment used. The objective of this study was to examine the effects of particle size and cohesion on the segregation tendency of pharmaceutical powders measured by bench scale sifting and fluidization segregation testers. The test blends consisted of 5% aspirin, 64.5% lactose, 30% microcrystalline cellulose (MCC) and 0.5% magnesium stearate with various aspirin particle size and cohesion value. Aspirin cohesion was varied by coating aspirin particles with Cab-O-Sil M5P. The blends were compressed into tablets by a high speed rotary press using a specially designed hopper, which was intended to simulate segregation tendency at large scale tablet manufacturing. The segregation tendency of the blends was also assessed using bench scale sifting and fluidization segregation testers. Near Infrared (NIR) methods were developed to analyze aspirin content uniformity of blends, segregation samples and tablets. The sifting segregation tester and testing protocol (ASTM D 6940-04) were modified to provide better correlation between the test results and tablet content uniformity. It was found that coating aspirin with Cab-O-Sil M5P can significantly reduce aspirin's cohesion but had little impact on its segregation tendency. The effect of particle size on segregation tendency was quite intriguing. It is commonly believed that large particle size difference between the drug and excipients is a primary factor contributing to segregation. However, our study indicated that one has to consider not only just the particle size difference but also the interaction between aspirin and excipients. Contrary to the common belief, the batch with larger particle size difference had lower segregation potential, which was probably attributed to favorable interaction between aspirin and MCC. In addition to identify the critical physical properties of the blends that influence segregation tendency, the study also highlighted the usefulness of NIR for quantitative analysis as well as the importance of using performance based approach to establish correlation between bench scale powder testing and larger scale manufacturing performance.

1. Introduction

Segregation occurs when one component of a particulate mixture separates from the other component(s) due to differences in their physical attributes (such as size, shape, surface properties etc.) and induced by forces such as gravity, vibration and/or shear. Segregation is an ubiquitous problem that can occur during handling, processing, manufacturing and/or storage of particulate materials [1,2]. It is a problem for virtually all dry-powder-handling industries such as pharmaceutical, food, agriculture, and mining. For the pharmaceutical industry, segregation can cause expensive batch failure because the content of active pharmaceutical ingredients (API) vary from tablet to tablet and fails to meet content uniformity criteria set by the United States Pharmacopeia [3,4].

As many as 13 segregation mechanisms have been documented in the literature, which include trajectory, rolling, displacement, percolation, sieving, air current, fluidization, agglomeration, concentration-driven displacement, push-away, impact/bouncing, embedding, and angle of repose [5–7]. Carson et al. and Johanson have simplified these into five primary mechanisms, which are trajectory, sifting, fluidization, air current, and angle of repose [8,9].

Many factors may influence segregation tendency. The primary factor is particle size difference among components of mixture [10,11]. Secondary factors are particle shape [12,13], density [14–16] and etc. In addition, equipment and process used to handle the particulate

* Corresponding author. Tel.: +1 203 791 6675.
E-mail address: xiaorong.he@boehringer-ingelheim.com (X. He).

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mixture are just as important as material properties in influencing segregation tendency [17,18]. For example, during the filling process, reducing the size of heap formation lowers the trajectory and sifting segregation tendency. Reducing the free fall height also helps control fluidization segregation such that entrainment velocity required for separating out the fines is not reached. In addition, hoppers, which are designed to have mass flow pattern during discharge tend to alleviate segregation problems [19–21].

Given the impact of segregation on product and process quality, it is highly desirable to be able to predict segregation tendency based on material properties and use this information to design a robust product and process prior to manufacturing. Currently, there are two approaches in predicting powder segregation tendency. The first approach is using computational modeling to predict powder segregation tendency based on input parameters such as particle size. Such models can be generally categorized into three types: continuum models, kinetic theory models, and discrete models [22]. Unfortunately, the computational approach cannot handle the complexity of real powder system given the current state of technology. Most of these mathematical models only deal with simulating the effect of particle size of an ideal sphere on segregation tendency of simple binary mixture [23].

The second approach is using a bench scale tester to experimentally measure segregation tendency of a given powder system. To our knowledge, there are three commercially available segregation testers. Jenike and Johanson developed two of them. These are sifting segregation tester [24] and fluidization segregation tester [25]. The third one, SPECtester, was recently developed by Material Flow Solutions, Inc., which uses NIR to assist segregation sample analysis.

Xie et al. used design of experimental approach (DOE) to optimize sifting segregation testing conditions and used the optimum conditions to study the effect of particle size on segregation tendency of a binary mixture [26]. However, the work did not address the important question whether the blend was uniform prior to the segregation test, making it difficult to separate mixing problem from segregation issues. Shah et al. also attempted to correlate performance of commercial blends to results from the segregation testers and obtained a good correlation [27]. However, in this study, it is not clear whether the four commercial batches were manufactured under the same controlled conditions, making it difficult to link blend and content uniformity results to segregation testing data. So far, there is a lack of systematic studies where powder samples were handled and manufactured under the controlled condition. This is mainly because doing well controlled studies require significant resources to analyze hundreds of samples for blend uniformity, tablet uniformity and segregation testing. Near infrared (NIR) spectroscopy has been widely accepted as a process analytical technology (PAT) to assess tablet and blend uniformity [28–30]. Although SPEC Tester uses NIR to assist content analysis, this tester constructed the calibration models based on only NIR spectra of pure components, therefore lacking the ruggedness and accuracy in predicting content uniformity of powder mixture.

The objectives of this study were to: (1) evaluate the feasibility of using bench scale segregation testers to predict powder segregation potential at larger scale manufacturing; (2) examine the utility of NIR in analyzing uniformity of blends, tablets and powder segregation tendency; (3) modify a lab scale tablet press to simulate segregation tendency at a larger scale manufacturing; (4) study the effect of physico-chemical properties on the powder's segregation potential. The study was conducted using a typical direct compression formulation, which contains 5% (w/w) aspirin, 64.5% fast-flo lactose (lactose), 30% microcrystalline cellulose Avicel PH 200 (MCC) and 0.5% magnesium stearate. In some cases, the aspirin particle surface was coated with 1% Cab-O-Sil M5P to reduce cohesiveness of aspirin. A systematic study was conducted to study how particle size and cohesion influence segregation testing results and how it may correlate to tabletting content uniformity.

2. Material and methods

2.1. Materials

Aspirin USP (Acetylsalicylic acid), Jilin Pharmaceuticals, USA/AnMar International, Bridgeport, CT, lot 20110253; microcrystalline cellulose or MCC (Avicel PH200, NF), FMC Biopolymer, Newark, DE, lot PN08819395 (referred as MCC PH200); lactose monohydrate NF, modified-spray dried, Foremost Farms, Baraboo, WI, lot 8510092362 (referred as Fast Flo 316 or simply lactose); magnesium stearate vegetable grade, Mallinkrodt, Covidirn, St. Lois, MO, lot J07623; silicon dioxide, Cab-O-Sil M-5P (untreated fumed silica), Cabot, Bullerica, MA, lot #1372158 were used in this study.

2.2. Sample preparation methods

2.2.1. Aspirin milling

Aspirin was milled using jet mill or hammer mill to obtain different particle size distribution.

2.2.1.1. Jet-milling. Sturtevant 2 inc mill (Hanover, MA) equipped with Syntron Power Pulse vibrator (FMC) and magnetic feeder FTO-C (FMC Technologies, Huston, TX) was used to mill aspirin to D50 of ~10 μm and ~20 μm by adjusting feed and grinding pressures to appropriate values. Aspirin particle size with D50 of 10 μm was obtained by setting feed pressure at 30 psi and grind pressure at 20 psi. To obtain aspirin particle size with D50 of 20 μm, the feed pressure was kept at 30 psi but grind pressure was decreased to 10 psi.

2.2.1.2. Hammer-milling. L1A FitzMill (The Fitzpatrick Company, Elmhurst, Il) equipped with impact blades and screens was used to obtain aspirin particle size with D50 of ~160 μm by using 1722-020 round-hole screen size and setting blades rotation velocity to 4008 rpm.

2.2.2. Aspirin coating

Aspirin cohesion properties were modified by coating the aspirin particle surface with Cab-O-Sil M5P. The required amount of Cab-O-Sil M5P for 100% coverage of aspirin particles was calculated using Eqs. (1) and (2) [31]. The calculated amount of Cab-O-Sil M5P was about 1% by weight.

$$G = \frac{\left(Nd^3\rho_d\right)}{\left(D^3\rho_D\right) + \left(Nd^3\rho_d\right)} \times 100 \tag{1}$$

$$N = \frac{4(D+d)^2}{d^2} \tag{2}$$

where

G is the percent by weight of Cab-O-Sil required for 100% surface coverage of aspirin particles;
N is the number of Cab-O-Sil particles;
D is the median particle size by volume distribution of aspirin (i.e., 10, 20 or 160 μm);
d is the median particle size by volume distribution of Cab-O-Sil (which is 0.015 μm);
ρ_D is the true density of aspirin (1.3984 g/ml), measured using a helium gas displacement pycnometer (Type AccuPyc 1330, Micromeics®, Bedfordshire, UK);
ρ_d is true density of Cab-O-Sil (2.65 g/ml, information provided by the supplier, Cabot).

Aspirin surface was coated with Cab-o-Sil using two different methods (i.e. comil coating and high shear mixer coating)