Chemical Engineering and Processing 102 (2016) 141–155

Contents lists available at ScienceDirect

Chemical Engineering and Processing: Process Intensification

journal homepage: www.elsevier.com/locate/cep

Micro-mixing dynamics of active pharmaceutical ingredients in bin-blending

Juan G. Osorio[a,*], Gina Stuessy[b], Gabor J. Kemeny[b], Fernando J. Muzzio[a]

[a] Chemical and Biochemical Engineering, Rutgers University, 98 Brett Road, Piscataway, NJ 08854, USA
[b] Middleton Spectral Vision, 8505 University Green, Middleton, WI 53562, USA

ARTICLE INFO

Article history:
Received 30 April 2015
Received in revised form 20 September 2015
Accepted 18 December 2015
Available online 21 December 2015

Keywords:
Pharmaceuticals
Powders
Micro-mixing
Near infrared
Chemical imaging

ABSTRACT

This paper compares the micro-mixing dynamics of three active pharmaceutical ingredients (APIs) varying in particle size, bulk density and cohesion. Chlorpheniramine maleate, acetaminophen and caffeine, in a common blend of excipients, were used in this study. Micro-mixing was studied in a 1-L bin-blender using in-line near infrared chemical imaging (NIR-CI) to monitor the aggregate size distribution of the APIs and excipients. A science-based calibration chemometric method was used to calculate the concentration maps of ingredients in the blends. Chlorpheniramine maleate, smallest in particle size with lowest bulk density, resulted in the highest relative standard deviation (RSD) for all concentrations. The RSDs obtained for acetaminophen and caffeine were similar and dependent on their concentrations. Chlorpheniramine remained in large aggregates throughout the blending process. Overall, other ingredients (e.g. Avicel) required longer blending times to become well dispersed in the presence of chlorpheniramine maleate, as evidenced by the aggregate size measurements. This in-line NIR-CI technique was able to approximate the number of API aggregates and their size during a common blending process. Although further development of this technique is necessary, metrics measured using this technique could potentially be used as a critical quality attributes during pharmaceutical processing.

1. Introduction

Powder mixing is a critical process in the pharmaceutical industry as well as numerous other industries. Important advances in understanding the bulk (macro) mixing behavior of pharmaceutical powders, especially in tumbling blenders, have been made within the last few decades [1,2]. Although understanding the macro-mixing behavior is important, powder mixing also involves micro-mixing processes, which are also important and have been studied substantially less. Micro-mixing is the process that describes how particles of the same and different materials interact with each other to form a blend and impart it with important properties. Micro-mixing controls the degree of agglomeration [3,4], cohesion [5], hydrophobicity [6], and electric conductivity [7]. Hence, investigations of the micro-mixing dynamics of active pharmaceutical ingredients (APIs) and excipients are necessary to better understand powder blending.

Most of the macro-mixing studies have focused on characterizing the mixing dynamics and performance of various blenders for one set of materials with just one model powder (e.g. API). In fewer cases, the macro-mixing dynamics of materials with very distinct material properties (cohesive vs. free-flowing) were compared [8]. However, systematic comparisons among APIs with varying degrees of cohesion have not been performed. Most un-granulated APIs are cohesive in nature and tend to form agglomerates in powder blends, making it more difficult to obtain an adequately dispersed mixture. This can lead to content uniformity problems, especially at low concentrations (≤3% by weight) [9]. As the concentration of the cohesive API is increased, blend uniformity issues become less intense, but powder flow and mixing dynamics are increasingly governed by the API's flow properties. Therefore, in any blending scenario, it is important to consider the material properties of cohesive APIs.

A few previous studies on the micro-mixing dynamics of powder blends have focused on characterizing the micro-mixing state of the final powder blends using digital imaging (DI) [10–13], magnetic resonance imaging (MRI) [14–16], and scanning electron microscopy (SEM) [17]. Although these studies have reported

* Corresponding author at: Department of Chemical Engineering, Massachusetts Institute of Technology, 77 Massachusetts Avenue, E19-532, Cambridge, MA 02139, United States.
E-mail addresses: josorio@rutgers.edu (J.G. Osorio), gina@middletonspectral.com (G. Stuessy), gabor@middletonspectral.com (G.J. Kemeny), fjmuzzio@yahoo.com (F.J. Muzzio).

http://dx.doi.org/10.1016/j.cep.2015.12.008
0255-2701/

important findings, these techniques present disadvantages when used with pharmaceutical powders. DI requires ingredients to be different in color. MRI has poor resolution and particles also need to be doped to be MRI-sensitive. SEM is a laborious and destructive technique, and is not representative of the overall blend.

A newer analytical technique that has proved useful in characterizing the agglomeration and dispersion of pharmaceutical powder blends and final products is near infrared chemical imaging (NIR-CI). This method has been used to compare the dynamics of pharmaceutical powder mixing and the micro-scale state of final blends [18–22]. The focus of these studies was to understand the technique (NIR-CI) itself, and the chemometric and the multivariate analysis required. Not much emphasis was put into understanding powder micro mixing as a process (i.e. process parameters and material properties). Sasic et al. used NIR-CI to study the effect of milling a powder blend before lubrication and compression [22]. The results showed significant agglomeration in blends and tablets from the un-milled process. This has been the only reported study so far that quantified the effect of powder mixing on the final blends. In recent work by our group, we characterized a new in-situ NIR-CI technique and studied the micro-mixing dynamics of acetaminophen during a bin-blending process as a function of process parameters and API concentration [21]. In this case, the micro-mixing dynamics of all components were considered. The results showed that changes in acetaminophen concentration had a great influence on the micro-mixing of the excipients.

As an expansion of our previous published studies, we investigated the micro-mixing dynamics of three cohesive APIs (chlorpheniramine maleate, acetaminophen, and caffeine) blended in common excipients. Generally, cohesive APIs are blended in a high shear mixer to overcome the forces that make them form or remain as agglomerates. In this case, the APIs were mixed in a one-liter bin-blender (low shear) to study the sole effect of material properties on their micro-mixing dynamics. The main objective of this work was to study the effect of material properties of APIs on their micro-mixing dynamics as a function of API concentration and process parameters. The effect of particle size and cohesion on the micro-mixing state of blends as measured by NIR-CI was demonstrated here. This in-line NIR-CI technique could potentially be used to monitor and control the blending process of pharmaceutical powders, including cohesive APIs as shown in this article.

2. Materials and methods

2.1. Materials

The materials and suppliers used in all the experiments reported are described here. The three active pharmaceutical ingredients (APIs) used were chlorpheniramine maleate (USP, Spectrum Chemical MFG. Corp., New Brunswick New Jersey, USA), acetaminophen (semi-fine, USP, paracetamol Ph Eur, Mallinckrodt, Raleigh, North Carolina, USA) and caffeine (anhydrous, USP, CSPC Innovation Pharmaceutical Co., LTD., China). The measured material properties, including particle size, of the APIs used are listed in Table 1. The excipients in all blends were microcrystalline cellulose (Avicel PH101, FMC Biopolymer, Newark, Delaware, USA), lactose (monohydrate N.F., crystalline, 310, Regular, Foremost Farms USA, Rothschild, Wisconsin, USA), amorphous fumed silica (Cab-O-Sil M-5P, Cabot Corporation, Tuscola, Illinois, USA), and magnesium stearate N.F. (non-Bovine, Tyco Healthcare/Mallinckrodt, St. Louis, Missouri, USA). The nominal particle sizes of all excipients used are listed in Table 2.

2.2. Material properties of APIs

Material properties of the APIs were characterized by three metrics: the particle size, the conditioned bulk density, and the compressibility.

2.2.1. Particle size

The particle size distribution of each API used was determined using a laser-diffraction (LS-13 320) analyzer with a tornado dry powder system (Beckmann–Coulter, Brea, California, USA). The APIs were chosen based on their difference in particle size. The mean particle size, and d_{10},d_{50} and d_{90} fractions of each API are recorded in Table 1.

2.2.2. Conditioned bulk density

The conditioned bulk density of the APIs was measured using a powder rheometer system (FT4, Freeman Technology Ltd. Gloucestershire, UK) using a 48-mm cylinder. The conditioned bulk density is the density after the powder has gone through the conditioning cycle which was performed before each compressibility test in the FT4 rheometer. This ensures that the state of each powder is “reproducible”. Thus before each compressibility measurement, the conditioned bulk density for each API was obtained. The values are recorded in Table 1 and are referred to as “bulk density”.

2.2.3. Compressibility

The compressibility of the APIs was also measured using the FT4 rheometer system. The compressibility of a powder is a measure of the change in density as a function of applied normal stress. In this case, the compressibility is the percentage change in volume after compaction at a specific normal stress. The FT4 compresses the powder from 0 to 15 kPa with increasing steps of 0.5 kPa. Cohesive powders show a large change in volume, while non-cohesive powders show little change in volume. The compressibility values used for comparison were obtained at a normal stress of 15 kPa and are recorded in Table 1.

Table 2
Nominal particle size of excipients used.

Material	Mean particle size (μm)
Avicel 101	50.0
Regular lactose	180.0
Cab-*O*-Sil (SiO_2)	0.005–0.02
Magnesium stearate	10.0

Table 1
Material properties of active pharmaceutical ingredients studied. Compressibility value obtained at 15 kPa.

Material	Mean particle size (μm)	d_{10} (μm)	d_{50} (μm)	d_{90} (μm)	Bulk density (g/mL)	Compressibility (%)
Chlorpheniramine	7.1	1.4	6.2	13.3	0.23	45.5
Acetaminophen	47.2	5.5	29.8	116.4	0.39	34.9
Caffeine	54.0	4.8	34.7	135.8	0.54	19.2