Powder Technology 297 (2016) 349–356

Contents lists available at ScienceDirect

Powder Technology

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

Characterization of resonant acoustic mixing using near-infrared chemical imaging

Juan G. Osorio [a,*], Eduardo Hernández [b], Rodolfo J. Romañach [b], Fernando J. Muzzio [a]

[a] Department of Chemical and Biochemical Engineering, Rutgers University, Piscataway, NJ, USA
[b] Department of Chemistry, University of Puerto Rico, Mayaguez, PR, USA

ARTICLE INFO

Article history:
Received 21 October 2015
Received in revised form 12 February 2016
Accepted 24 April 2016
Available online 27 April 2016

Keywords:
Powders
Blending
Micro-mixing
Pharmaceuticals
Aggregates
Resonant acoustic

ABSTRACT

This study presents the first investigations on the micro-mixing properties of pharmaceutical powder blends from a resonant acoustic mixer using near-infrared chemical imaging. All experiments were done in a laboratory resonant acoustic mixer (RAM). The powder blends were studied using near-infrared chemical imaging (NIR-CI). Qualitative (i.e. chemical images) and quantitative (e.g. mean diameter of aggregates) results were obtained using this analytical method. The quantitative results were correlated to the acceleration (mixing intensity) and total mixing time. Overall, the resonant acoustic mixing performance increased with increasing acceleration and mixing time. Therefore, larger aggregates of the active pharmaceutical ingredient (API) were found at lower accelerations (mixing intensity) and shorter mixing times. Mixing in the RAM efficiently reduced the overall aggregate size of the cohesive API (semi-fine APAP, ~45 μm) used in a common blend of filler (microcrystalline cellulose, ~110 μm) and lubricant (magnesium stearate, ~10 μm).

1. Introduction

Powder mixing is an important process in a wide range of industries, such as cosmetics, pharmaceuticals, agrochemicals and cement. Regardless of the manufacturing route used in pharmaceuticals (i.e. direct compression, wet granulation, dry granulation or hot melt extrusion); powder mixing is almost always performed, sometimes in multiple occasions [1]. The role of powder mixing is to homogenize the active pharmaceutical ingredient (API) in an excipient matrix and to lubricate this blend, making it suitable for follow-up processing such as compression, or capsule filling [2]. Often the API is crystallized and/or milled to obtain a specific, small particle size to increase its solubility [3]. While this is beneficial for obvious reasons, agglomerates are formed during the API manufacturing process, packaging, transportation and storage [4]. These agglomerates make the homogenization (mixing) of such APIs challenging.

While powder mixing has focused in understanding the effects of process parameters on the bulk (macro) mixing performance of several types of blenders for cohesive materials (e.g. API and lubricant) [5–8], the micro-mixing performance has been studied much less [9,10]. Macro-mixing focuses on the quantification of the homogeneity of the relevant ingredients. Micro-mixing, on the other hand, is the process that describes how particles from the different ingredients interact with each other to form a blend and to impart the blend with properties such as flowability, hydrophobicity, and charge capacitance. Thus, studying the micro-mixing performance of any blending process is important to understand powder mixing as a whole as well as the specific process under investigation. In this study, the degree of agglomeration (aggregation) of the API and lubricant in the blends investigated is taken as the main indicator of the micro-mixing performance of the blender used. Agglomeration can be directly related to insufficient or inefficient micro-mixing in a blend.

Various techniques have been used to measure the micro-mixing properties of powder blends. Near-infrared chemical imaging (NIR-CI) has been shown to be the most suitable method to study pharmaceutical powders when compared to other techniques such as digital imaging (DI) [11–14], magnetic resonance imaging (MRI) [15–17] and scanning electron microscope (SEM) [18]: DI requires color distinction between the materials under study, MRI has poor resolution and requires particles to be doped for detection, and SEM is laborious, destructive and not representative of scale. In contrast, NIR-CI is rapid and non-destructive method able to chemically distinguish among virtually any ingredient in a powder blend [19]. NIR-CI measures the drug aggregates present in the blend or other formulations, in contrast to light diffraction particle size methods that require that particles be dispersed. NIR-CI provides valuable information on API aggregate size, a key parameter in the evaluation of micro-mixing for cohesive APIs.

NIR-CI and Raman spectroscopy are complementary techniques that may be used in the study of the microstructure of pharmaceutical formulations [20]. Raman spectra consist of spectral bands that may be

* Corresponding author at: Department of Chemical Engineering, Massachusetts Institute of Technology, 77 Massachusetts Avenue, E19-532, Cambridge, MA 02139, USA.
E-mail address: josorio@rutgers.edu (J.G. Osorio).

http://dx.doi.org/10.1016/j.powtec.2016.04.035
0032-5910/

Table 1
Particle size of materials used.

Material	Mean particle size (μm)
Semi-fine acetaminophen (APAP)	45
Magnesium stearate (MgSt)	10
Prosolv HD90	110

assigned to functional groups or bond vibrations, while NIR-CI is based on wide and overlapping bands that result from multiple vibrational modes. The intensity of Raman spectra depends on the polarizability of bonds, while NIR bands vary according to the changes in dipole moment during vibrations. Raman imaging methods provide superior spatial resolution in comparison to NIR-CI methods, however at increased analysis time [21,22]. A single Raman image based on linear mapping of a 10 × 10 μm area requires 1 h versus 3 min of analysis time with NIR-CI [20]. Thus, NIR-CI may be used first to quickly pinpoint drug rich aggregates in a formulation, followed by Raman mapping to determine the particle size distribution of the aggregates [23]. Novel Raman imaging methods are currently under development which could significantly reduce analysis time [24].

Several studies have shown that NIR-CI is suitable for determining the micro-mixing properties of pharmaceutical powders blends. NIR-CI was used to study and compare the macro-mixing dynamics of pharmaceutical powder blending and the micro-mixing properties of final blends [4,25–28]. Most of these studies focused in understanding the technique (NIR-CI) itself, and the chemometric (univariate or multivariate) analysis required using small vials as blenders. In a recent study, Šašić et al. investigated the effects of processing on the micro-mixing properties of powder blends and tablets [4]. The effect of milling a powder mixture after bin-blending on the micro-mixing performance (API agglomerate size) was investigated. The results showed significant agglomeration in blends and tablets from the un-milled process. In our previous studies, we used an in-line NIR-CI technique to measure the micro-mixing dynamics of cohesive APIs in a bin-blending process [28,29]. These previous studies demonstrated that in-line NIR-CI can be used to measure several micro-mixing properties during powder blending while distinguishing among three different cohesive APIs.

In this study, powder blends from a new resonant acoustic mixer (RAM) are characterized using NIR-CI for the first time. NIR-CI was chosen for this study because many samples could be easily analyzed in a short period of time and the higher spatial resolution obtained from Raman spectroscopy was not required in this study. We previously characterized the mixing performance of the RAM [30] showing the RAM efficiently mixes pharmaceutical powders with low concentrations of cohesive APIs. The RAM is a new type of mixer that works on the application of low frequency, high intensity acoustic field facilitating the movement of the loose powder mass to induce mixing. The acoustic mixing principle works on the creation of micro-mixing zones throughout the entire vessel while facilitating bulk movement of the materials. It was found that the RAM is capable of mixing cohesive APIs in as low as 30 s while the amount of energy input can be used to control the materials properties of lubricated blends as well as the properties of final product (i.e. tablets). However, API in low concentrations are typically highly potent and formulations must be developed without drug agglomerates which could have a serious effect on patients. Therefore, the main objective of this study was to investigate the effects of process parameters, acceleration (mixing intensity) and blending time, on the agglomeration and dispersion of the API and lubricant in a common pharmaceutical powder blend produced in a laboratory resonant acoustic mixer (RAM). Qualitative NIR chemical imaging (i.e. chemical images) and quantitative analyses (e.g. mean diameter of aggregates) were obtained. The information obtained through NIR chemical imaging strengthened the understanding of mixing mechanisms necessary to reduce aggregation of APIs in lubricated pharmaceutical powder blends and to develop safer formulations without drug aggregates that could affect patients.

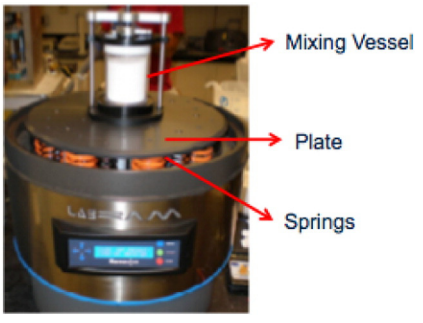

Fig. 1. Laboratory scale resonant acoustic mixer with a 236-mL mixing vessel used in all experimental studies.

2. Materials and methods

2.1. Materials

The materials used in all experiments were semi-fine acetaminophen (Mallinckrodt, Raleigh, North Carolina, USA), magnesium stearate (non-bovine, Tyco Healthcare/Mallinckrodt, St. Louis, Missouri, USA) and silicified microcrystalline cellulose (Prosolv HD90, JRS Pharma, Germany). The mean particle size of each material used is listed in Table 1. The particle size was measured using a Beckman Coulter laser diffraction particle size analyzer.

2.2. Resonant acoustic mixing

A laboratory resonant acoustic mixer (LabRAM, Resodyn, Butte, MT, USA), shown in Fig. 1, was used to make all the powder blends examined in this study. The principles by which the RAM works have been explained previously [31].

A preliminary study was performed to develop the near-infrared chemical imaging method used in all experiments here. The mixing parameters are specified in Table 2. The APAP concentration used in this case was 10% w/w. A commonly used concentration of MgSt (0.75% w/w) was used in two of the blends. Two blending parameters, acceleration (shear rate) and total blending time (total strain), were used. The first combination of blending parameters was 20*g* of acceleration and 2 min of total mixing time for blends 1 and 2. The second combination of blending parameters was 70*g* of acceleration and 4 min of mixing time for blends 3 and 4. These two sets, based on what was previously learned for the RAM [30], yielded distinctive blends, which could be categorized as "poorly mixed" (blends 1 and 2) and "well mixed" (blends 3 and 4) blends with and without lubricant. This preliminary study was performed to confirm that the NIR-CI technique was indeed measuring the materials of interest.

A second set of blends was used to characterize the effect of resonant acoustic mixing on the degree of agglomeration of the semi-fine acetaminophen and the lubricant (MgSt) at 3% w/w and 1% w/w, respectively. Nine conditions (three mixing times by three accelerations) were explored (Table 3). A 236-mL vessel, filled up to 60% by volume, was used for all the experimental work presented here.

2.3. Sampling

Since the objective for the first set of blends was to characterize the near-infrared chemical imaging method, only one sample from each blend was examined. For the second set of experiments, ten samples were extracted from the mixing vessel. A1-mL disposable powder