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Evaluation of resonant acoustic mixing performance

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ABSTRACT

An experimental investigation was carried out to study the mixing performance of a laboratory-scale ResonantAcoustic® Mixer (LabRAM). The first part of the study summarizes the results of a fractional factorial design of experiments used to determine the main effects of process parameters (fill level, acceleration, and blending time) on blend homogeneity. Studies were carried out for several blends having various values of particle size, cohesion and concentration of the active pharmaceutical ingredient. The second part of the study describes the LabRAM mixing performance as a function of process parameters (fill level and acceleration) and total blending time. The blend homogeneity was quantified by estimating the relative standard deviation (RSD) for low concentration of active pharmaceutical ingredient (acetaminophen, 3% w/w) and lubricant (magnesium stearate, 1% w/w) blend. Overall, the LabRAM reached the minimum blend homogeneity in as low as 30 s depending on process parameters. The temperature of the final blend increased with fill level, time and acceleration. Resonant acoustic mixing can significantly reduce blending time, making it a good candidate for improving the efficiency of powder mixing processes.

1. Introduction

Powder mixing is a required operation in a wide range of industries such as food, chemicals, ceramics, and pharmaceuticals. Just in the pharmaceutical industry, around 80% of all finished products are solid dosage forms made from powder blends [1]. However, despite several decades of active research, powder mixing is still not well understood. This is attributed to the complex material characteristics of powders, and chiefly among them, their rheological properties. The wide range of material properties such as particle size distribution, particle shape, particle density, surface properties, powder cohesion, and variable bulk density make powder mixing a complex process. In addition, the high blend uniformity standards, required by regulatory agencies and needed to ensure high quality products, make powder mixing a complex task [2]. This becomes even more challenging when mixing either low concentrations of active pharmaceutical ingredient (API) in large amounts of excipient or large amount of API with small quantity of excipient to achieve functionality [3].

Numerous batch blenders, varying in size, geometry and mixing mechanisms, have been developed. Out of all types of mixers used in the pharmaceutical industry, the most common are tumble mixers and convective mixers. Tumble mixers induce gentle mixing reducing the risk of overheating the materials and are relatively easy to clean [4]. Convective mixers are used for materials that cannot be easily mixed in tumble mixers. The mechanisms and performance of these blenders have been investigated and reported in the literature, including V-blenders [5–9], bin-blenders [4,5,10–12] and ribbon blenders [1]. In most cases, "mixing curves" or blending profiles (the evolution of the variability in the concentration of the "critical" ingredient in the blend as a function of mixing time) comparing blender designs, rotation rates, fill levels and fill patterns were reported [1,5,6,10–12].

In the literature cited above, blender performance has been studied using design and process parameters as input variables. However, since performance is material-dependent, blending performance can only be compared by the final blend uniformity at a specific mixing time when materials with similar properties are used. The blending performance of batch blenders has been found to be dependent on blender type, material properties of powders and even environmental conditions [13]. Moreover, they have been found to be vulnerable to significant variations in performance depending on fill level [10,14] and loading method [6,10], and the final outcome can be strongly affected by segregation [7,9,15] and agglomeration [16,17] tendencies of the powder.

New technologies that can improve mixing efficiency and performance are of significant interest, in particular for processes that involve cohesive and/or highly potent ingredients [18]. Moreover, for pharmaceutical applications, it is also important to consider the blender's potential for over-lubrication [19,20], which is usually the result of long mixing times for lubricated blends. In this paper, the goal is to evaluate the mixing performance of a new mixer, a resonant acoustic mixer (RAM), using common pharmaceutical powders. This mixer works on a different principle than those commonly used for pharmaceutical processing, using resonant vibration to induce fast motion and homogenization of powders. No work on the RAM has been reported in previous peer-reviewed literature for any pharmaceutical application. Although, the

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RAM used in this work was a laboratory scale mixer, there currently exist other commercially available versions with higher volume capacities (i.e. 5 gal and 55 gal) of the RAM.

The experimental evaluation carried out in this article was divided in two main components. In the first part the RAM mixing performance was studied as a function of API particle size, fill level, mixing intensity (acceleration) and blending time, using a fractional factorial design of experiments to determine the RAM main effects. The second part was a more detailed study to define the mixing dynamics of both API (acetaminophen, APAP) and lubricant (magnesium stearate, MgSt) as a function of blending time, acceleration, and fill level. It was found that better mixing performance is obtained at higher accelerations and longer mixing times. The fill level for all mixing parameters and materials used did not show significant effects on the mixing performance. Overall, the RAM is capable of mixing low concentrations of API and lubricant in as little as 30 s and 10 s, respectively. Longer mixing times at higher accelerations significantly increased the temperature of the powder bed without necessarily improving performance.

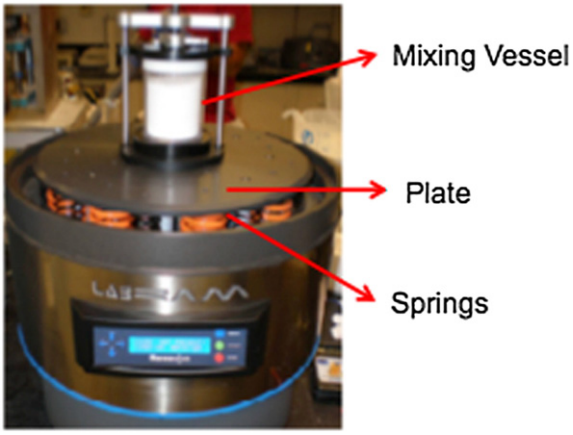

Fig. 1. Laboratory scale resonant acoustic mixer (LabRAM) with 236-mL mixing vessel used in all experimental studies.

2. Materials and methods

2.1. Materials

The materials used in the first set of experiments reported here were the following: micronized acetaminophen (Mallinckrodt, Raleigh, North Carolina, USA), granulated acetaminophen (Compap-L, Mallinckrodt, Raleigh, North Carolina, USA), and caffeine (CSPC Innovation Pharmaceutical Co., LTD., China). Microcrystalline cellulose (Avicel PH 200, FMC Biopolymer, Newark, Delaware, USA) was used as the main excipient. The materials used in the second set of experiments were the following: semi-fine acetaminophen (Mallinckrodt, Raleigh, North Carolina, USA), silicified microcrystalline cellulose (Prosolv HD90, JRS Pharma, Germany), and magnesium stearate (non-Bovine, Tyco Healthcare/Mallinckrodt, St. Louis, Missouri, USA). The nominal particle sizes of the materials used are listed in Table 1.

2.2. Resonant acoustic mixing

The experimental studies described here were used to characterize the mixing performance of a ResonantAcoustic® Mixer (Resodyn Acoustic Mixers, Butte, Montana, USA). The specific mixer used in the studies was the laboratory scale RAM, or LabRAM (Fig. 1). The RAM is a new mixing technology 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 (Fig. 2). The RAM is designed to operate at mechanical resonance, transferring almost all of the mechanical energy created by the mixer to the loose mass in the vessel by the propagation of an acoustic pressure wave. The RAM operates around 60 Hz, defined as the resonant frequency, at which the potential energy stored in the springs can be efficiently transferred to the plates. The principles by which the RAM works are explained in more detail elsewhere [21,22]. The resonant frequency automatically adjusts by fluctuating constantly around 60–61 Hz. The only controllable parameter in the LabRAM is the mixing intensity (0–100%) which determines the amplitude of the mechanical vibration, translating into acceleration values (0–100 g's) depending on the load mass. Therefore in all the experimental work presented here, the acceleration is used (instead of the intensity) for comparison purposes between experiments.

Table 1
Materials used for both experimental designs with their respective mean particle size.

Material	Mean particle size (μm)
Experimental design 1	
Micronized acetaminophen	18
Caffeine	54
Granulated acetaminophen	195
Avicel PH200	220
Experimental design 2	
Semi-fine acetaminophen	45
Prosolv HD90	110
Magnesium stearate	10

2.3. Blending

All experiments were conducted using a 236-mL mixing vessel. Fresh powder and a new mixing vessel were used for each experimental condition. The two experimental designs, along with the blending method used are described next.

2.3.1. Experimental design 1

In order to determine the critical mixing parameters and overall efficiency of the RAM, various concentrations of APIs with varying particle sizes were blended in a common excipient. A 3-level fractional factorial experimental design with 5 factors was used to determine the main

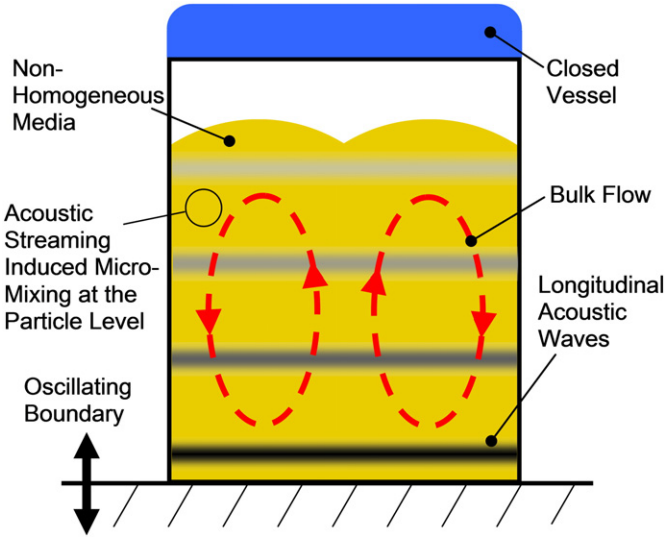

Fig. 2. RAM mixing mechanisms.