Advanced Powder Technology 27 (2016) 1141–1148

Contents lists available at ScienceDirect

Advanced Powder Technology

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

Original Research Paper

Effect of resonant acoustic mixing on pharmaceutical powder blends and tablets

Juan G. Osorio *, Koushik Sowrirajan, Fernando J. Muzzio

Department of Chemical and Biochemical Engineering, Rutgers University, 98 Brett Road, Piscataway, NJ 08854, USA

ARTICLE INFO

Article history:
Received 30 November 2014
Received in revised form 21 March 2016
Accepted 24 March 2016
Available online 7 April 2016

Keywords:
Powders
Mixing
Resonant acoustic
Pharmaceuticals
Tablets

ABSTRACT

Blending in a resonant acoustic mixer (RAM) was shown to be highly effective for low concentrations of cohesive active pharmaceutical ingredients (APIs) and lubricant (Osorio and Muzzio, 2015). However, changes in material properties of the final blend were observed. Those changes, and their effects on tablet characteristics, are discussed in this paper. Variations in particle size, powder flow properties and hydrophobicity of the blend were examined. The final blend was compressed into tablets. The tableting compression force, and tablet hardness, weight and dissolution were investigated. Overall, powder blend and tablet properties were significantly affected by acceleration, blending time and total energy input. The total energy input to the blend can be efficiently calculated within error in the RAM; this is not true for most mixers. Trends between total energy input and the material properties of the blends and tablets were obtained. Resonant acoustic mixing is a good choice for blending low concentrations of cohesive APIs. Care must be taken when blending hydrophobic lubricants in the RAM; the high energy input can adversely affect critical tablet properties such as hardness and dissolution. The known energy input can be used to predict the performance of blends and final products processed in a RAM.

1. Introduction

Bulk properties of fine powders are dependent on both their physicochemical properties and their processing histories such as feeding, mixing and delumping [1,2]. This is particularly true for mixtures where two or more ingredients experience substantial changes in properties from those displayed by the raw materials. Shear rate (which is proportional to the energy input rate per unit mass) and total strain (which is proportional to the total energy input per unit mass) experienced during blending greatly affect properties of powder blends such as particle size distribution [3], hydrophobicity or contact angle [4–6], electrical conductivity [7,8] and powder flow properties [7,9,10]. In addition, the efficiency of processing steps after blending and the properties of finished products are dependent on the rate and extent of mechanical energy dissipation during blending. For example, the performance of the tableting [4,6,11,12] and capsule filling [13–16] processes is dependent on the powder flow properties of blends. Tablet hardness and dissolution are dependent on the powder flow properties and the extent of hydrophobic lubrication of the final blends [4,6,11,17].

The ultimate goal from any blending process is to have a high quality (uniform) finished product that performs as specified. For instance, tablets need to have good homogeneity and low weight variability in order to ensure that the dose delivered is the same every time, i.e., that they achieve acceptable content uniformity. Thus, content uniformity is a direct indicator of the efficiency of the blending process. Content uniformity is usually achieved through high mechanical energy input, which can also lead to over-lubrication when a hydrophobic lubricant (most commonly magnesium stearate, MgSt) is used. Over-lubrication (i.e. high hydrophobicity) can also lead to low tablet hardness and delayed dissolution [4,6,18]. It would be ideal if the final properties of the finished product could be predicted from defined process parameters and that such process parameters could be directly transferred for scaling of the process. Therefore, studying the effects of processing parameters of a particular blending process on the properties of blends and finished product is critical.

Our recent work presented the mixing performance of a laboratory-scale resonant acoustic mixer (RAM) for pharmaceutical powders. It was shown that the RAM is a good candidate for

* Corresponding author at: Department of Chemical Engineering, Massachusetts Institute of Technology, 77 Massachusetts Avenue, E19-532, Cambridge, MA 02139, USA. Tel.: +1 617 324 3943.

E-mail addresses: josorio@rutgers.edu (J.G. Osorio), ks784@scarletmail.rutgers.edu (K. Sowrirajan), muzzio@sol.rutgers.edu (F.J. Muzzio).

http://dx.doi.org/10.1016/j.apt.2016.03.025
0921-8831/

mixing cohesive APIs and pharmaceutical powders, especially during the formulation stage where the amount of API is limited [19]. In those studies, the blend uniformity correlated well to the energy input per unit mass. Changes in bulk density were visually detected after blending. Therefore, it was suspected that the blend properties of the blends were significantly affected by the process parameters (e.g. total energy input per unit mass). To confirm this, further investigations were conducted and are presented in this article. The only other reported instances in which APIs were used in a RAM were studies performed by Polizzi et al. [20] and Zhonghui et al. [21]. These studies investigated SiO_2 dry coating of various APIs and excipients in the RAM. SiO_2 dry coating led to an increase in the API particle size and bulk density, leading to improved flow properties of the APIs and excipients.

With no reported knowledge of the effect of resonant acoustic mixing on powder blends and finished product properties, the main objective of this study was to investigate the effects of resonant acoustic mixing on the bulk properties of pharmaceutical blends and tablets. For this purpose, a common formulation was used while varying the intensity of mixing (acceleration) and the total blending time yielding different energy inputs. Powder bulk properties, including particle size, bulk density and hydrophobicity, were studied. The tableting performance (compression force), and tablet weight, hardness and dissolution were also investigated. These measured properties were correlated to the resonant acoustic mixing parameters. The main findings of these investigations are presented in this article.

2. Materials and methods

2.1. Materials

The materials used in all experiments were as follows: semi-fine acetaminophen (Mallinckrodt, Raleigh, North Carolina, USA), silicified microcrystalline cellulose (Prosolv HD90, JRS Pharma, Germany), and magnesium stearate (MgSt, non-Bovine, Tyco Healthcare/Mallinckrodt, St. Louis, Missouri, USA). The nominal particle sizes of the materials used are listed in Table 1. The particle size distribution of the raw materials was determined using a laser-diffraction analyzer with a Tornado Dry Powder System (LS-13320, Beckmann-Coulter, Brea, California, USA). Approximately 10 mL of each raw material was used for each measurement.

2.2. Resonant acoustic mixing and blending

All powder blends were prepared in a laboratory scale ResonantAcoutic® Mixer (Resodyn Acoustic Mixers, Butte, Montana, USA) shown in Fig. 1. The RAM is a relatively new mixing technology that works on the application of low frequency, high intensity acoustic field. This facilitates the movement of the loose mass created by micro-mixing zones as well as the bulk movement of the materials throughout the entire vessel. The RAM operates at mechanical resonance, capable of transferring almost all of the mechanical energy created in the springs to the loose mass in the vessel by the propagation of an acoustic pressure wave. The resonant frequency automatically adjusts by fluctuating constantly around 60–61 Hz. The controllable parameters in the LabRAM are the mixing intensity (0–100%), which determines the input acceleration (0–100g's) depending on the load mass, and the mixing time. These two parameter determine the total energy input to the blend.

Table 1
Concentrations and mean particle size of materials in blend.

Concentration (% w/w)	Material	Mean (μm)	d_{10} (μm)	d_{50} (μm)	d_{90} (μm)
3	Semi-fine acetaminophen	48.9	5.6	32.6	122.7
96	Microcrystalline cellulose	143.7	37.0	137.4	250.9
1	Magnesium stearate	8.8	2.1	7.8	16.6

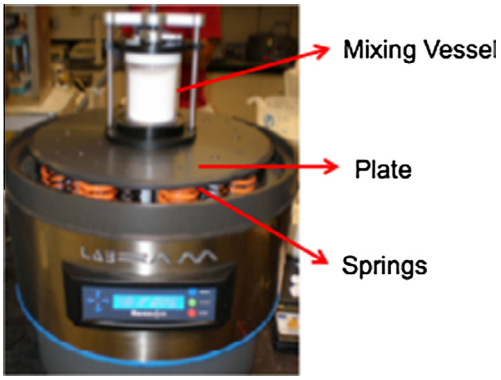

Fig. 1. LabRAM with 236-mL mixing vessel.

The common formulation for each powder blend consisted of 3% semi-fine acetaminophen (APAP), 1% magnesium stearate (MgSt) and 96% Prosolv HD90. In this study, each blend was obtained from a different combination of accelerations and mixing times. For the blend characterization, the experimental design used is shown in Table 2A. The experimental design was slightly changed for the tablet characterization study and is shown in Table 2B. A 236-mL polystyrene vessel, filled up to approximately 60% by volume, was used for all the experimental work presented in this article.

2.3. Blend characterization

To characterize the effect of resonant acoustic mixing on the bulk properties of the final blends, three blends for each experimental condition (Table 2A) were obtained and characterized.

2.3.1. Particle size

The particle size distribution of the finals blends was also determined using a laser-diffraction analyzer with a Tornado Dry Powder System. Approximately 10 mL of blend was used for each particle size distribution measurement.

Table 2
Experimental design used to study the effect of resonant acoustic mixing on pharmaceutical powder (A) blends and (B) tablets.

Time (min)	Acceleration (g's)
(A)	
0.5	20
1	40
2	70
4	
8	
Additional acceleration	
1	80
2	
(B)	
0.5	20
1	40
2	70
4	80