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Dynamics of the dry premixing stage of a hydrophobic formulation and potential implications on the wet granulation process

David A. Mota-Aguilar, Carlos Velázquez *

Center for Pharmaceutical Engineering Development and Learning, Department of Chemical Engineering, University of Puerto Rico at Mayagüez, Call Box 9000, Mayagüez 00680, Puerto Rico

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ABSTRACT

Wet granulation processes typically start with a dry premixing stage in which the objective is to homogenize and prepare the powder materials for further granulation stages. This work was aimed at studying the influence of premixing conditions on the wettability of formulations that contain hydrophobic components and the potential implications on early granulation stages.

A binary lactose-based formulation was chosen as the model system and magnesium stearate (MgSt) as the hydrophobic ingredient. The formulations were processed in a laboratory-scale high shear granulator according to a factorial experimental design to evaluate the effect of MgSt concentrations and applied premixing shear strains on the hydrophobicity of the formulation. The experimental design included five concentrations of MgSt (from 0% to 3% w/w) and three levels of applied shear strain ranging from 450 to 1800 blade passes (bp). A modified Washburn method was implemented to determine the hydrophobicity of blend samples after the premixing and hyperspectral images, collected with a NIR Chemical Imaging (NIR-CI), were used to assess the spatial dispersion of MgSt.

Statistical results demonstrated that both studied factors increase the hydrophobicity of the formulation and suggest that the magnitude of this effect depends on the mixing mechanism of the hydrophobic ingredient. The findings can be of interest in the formulation and process design to modify the wettability of hydrophobic blends before granulation.

1. Introduction

Wet granulation is a widely used intermediate process in the production of solid dosage forms (e.g., tablets, capsules). Its principal objective is to decrease segregation and enhance the flow properties of solid particulate materials by increasing their particle size. This type of granulation is commonly performed in high-shear mixers or fluid bed systems where the particle growth is promoted by the addition of a liquid binder to an agitated powder bed.

A wet granulation process typically starts with a dry mixing stage (i.e., dry premix), in which the principal objective is to breakdown the ingredient layers and to prepare the blend for further processing. A liquid binder is added (i.e., wetting stage) later to promote the formation of nuclei that will coalesce and grow by viscous or capillary forces during the massing stage [1–3].

The premixing stage determines the conditions of the formulation before the addition of the liquid binder. Therefore, a thorough understanding of this stage, in terms of the operational parameters and formulation properties, will contribute to understand the early stages of granulation (i.e., nuclei formation) since there is still a need for knowledge in that regard [4]. The effect of the premixing stage is particularly important when the conditions of the initial blend prevail for longer periods of time, for example: processes with short massing times [5] or equipment with low mixing capabilities (i.e., high fill volume, low impeller swept volume, and low agitation velocity).

Pharmaceutical formulations often contain hydrophobic components (i.e., active ingredients, lubricants, and glidants), which increase the solid/liquid contact angle, affecting the nucleation kinetics (i.e., liquid penetration time) and other thermodynamic relations (i.e., spreading coefficients) that govern the granulation. Recent studies have focused on understanding the effect of hydrophobic ingredients on the granulation performance and the final product characteristics [6–11]. For example, the hydrophobic nature of the materials and the characteristics of the binder can be used to create hollow granules [6]. The level of wettability of the formulation [9] affects the formation of the binder bridge and as such the formation of new granules. In summary, these studies demonstrate that the hydrophobic characteristic of the formulation will affect size, strength, porosity, shape, and density of the final granules.

Other studies have reported and quantified the effect of the mixing degree of hydrophobic ingredients on the final hydrophobicity of the formulations using shear cells with axial dispersion to generate

* Corresponding author.
E-mail addresses: david.mota@upr.edu (D.A. Mota-Aguilar), carlos.velazquez9@upr.edu (C. Velázquez).

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environments of nearly uniform shear conditions [12–14]. However, there is a lack of published studies conducted in high shear mixers where the flow patterns and shear profiles are non-homogeneous.

The objective of this experimental work is to study the effect of the dry premixing stage on the hydrophobic conditions of a pharmaceutical formulation processed in a high-shear granulator. It is driven by the hypothesis that the wettability of a formulation that contains a hydrophobic ingredient will be significantly affected, not only by the concentration of this ingredient, but also by the shear strain applied in the premixing stage.

2. Materials and methods

2.1. Formulation

A lactose-based formulation was chosen as the model system and magnesium stearate (MgSt) as the hydrophobic component. A base formulation consisting of anhydrous lactose and monohydrate lactose in a ratio of 3.8:1 was used for all the experiments. This ratio was found in previous works to produce the best wet-granulation performance. Physical properties of the ingredients are presented in Table 1. Lactose is widely used as filler in solid dosages, while MgSt is the most popular lubricant in tablet manufacturing. MgSt is not commonly added before wet granulation, however it is used here for its hydrophobic properties and mixing mechanism, which can be of interest in the design of this process.

2.2. Experimental design and data analysis

Binary blends (base formulation + MgSt) were prepared according to a full factorial design using five MgSt concentration levels (i.e., 0%, 0.5%, 1%, 2%, and 3% w/w) and three dry premixing times: 15 s, 30 s and 60 s. Non-hydrophobic blends (i.e., 0% MgSt) were used as control and three randomized replicates were run for each condition. The analysis of variance (ANOVA) was carried out in Minitab 16 (Minitab Inc., USA).

In this work, the relative shear strain was calculated and reported as blade passes (bp) using the Eq. (1):

$$bp = \frac{N_b \omega t_{PM}}{60} \quad (1)$$

where N_b is the number of impeller blades, ω is the impeller velocity (rpm) and t_{PM} is the premixing time (s). This shear strain estimator is used to compare results obtained in the same equipment conditions. Other authors have reported a similar approach to quantify the shear conditions inside commercial scale mixers [15].

2.3. Equipment and method

Laboratory-scale batches (250 g) were processed in a top-driven laboratory-scale high shear mixer equipped with a cylindrical vessel (1 L capacity; diameter = 0.12 m) and a three-blade impeller (diameter = 0.11 m), shown in Fig. 1. The impeller shear velocity was set at a tip speed of 3.6 m/s.

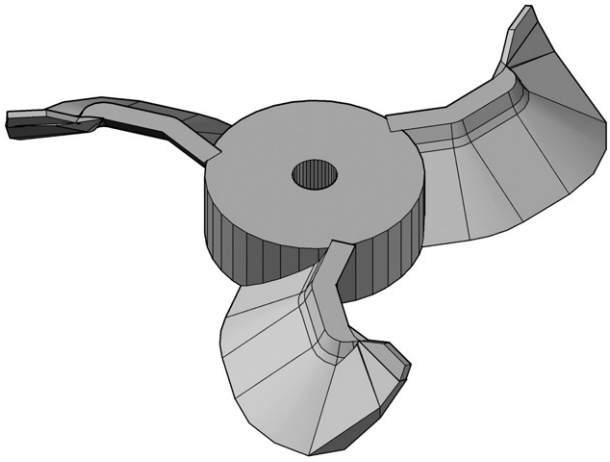

Fig. 1. Geometry of the top-driven three-bladed impeller used in the experiments.

MgSt tends to fluidize when agitated due to its small particle size and low density (see Table 1); therefore, the granulator (Fig. 2) was equipped with a lid, shown in Fig. 2 over the powders, that its distance from the powders can be adjusted to minimize the empty space inside the vessel decreasing the volume of suspended MgSt but leaving enough space for the powder bed to dilate while mixing.

Formulation components were weighed and loaded into the granulator vessel in horizontal layers (Fig. 2). Materials were premixed according to the experimental design and samples were collected using a customized sampler that allowed collecting a layer of materials from the surface of the powder bed. Although the formulations were granulated after sampling, results of the granulation experiments are out of the scope of this article.

2.4. Characterization

2.4.1. Hydrophobicity analysis

Hydrophobicity of the formulations was determined using a modified Washburn method measuring the speed at which a liquid is absorbed by a vertical powder bed [16,17]. According to this method, the wettability is described by a linear relation between the mass (m) of liquid that permeates and the square root of time (t), as follows [14,18–20]:

$$t = \frac{\eta m^2}{C\rho^2 \gamma cos(\theta)} = \Phi m^2 \quad (2)$$

where θ is the contact angle between the powder material and the liquid and η, ρ and γ are the viscosity (Pa·s), density (g/L) and surface tension (g/s^2) of the liquid, respectively. The constant C in Eq. (2) is related to the packing condition of the materials. In this work, Φ is reported as the hydrophobicity. Given that all the conditions were kept constant for all the measurements, an increase in the formulation hydrophobicity will produce a higher value of Φ due to the larger contact angle (θ).

Table 1
Specifications and physical properties of formulation components[a].

Component	Grade/Supplier	D50[b] (μm)	Particle morphology[c]	Bulk density (g/mL)	Tapped density (g/mL)
Anhydrous lactose (AL)	DT, Kerry Bio-science, USA	167.7 ± 6.8	Irregular	0.593 ± 0.005	0.847 ± 0.010
Monohydrate lactose (ML)	Granulac® 140, Meggle, Germany	62.3 ± 1.3	Irregular	0.591 ± 0.012	0.833 ± 0.001
Magnesium Stearate (MgSt)	Ligamed MF-2-K, Peter Greven, Germany	5.4 ± 0.3	Flakes	0.249 ± 0.003	0.335 ± 0.003

[a] Mean value ± SD ($n = 3$).
[b] Determined in a Malvern Insitec T.
[c] Observed in SEM (Jeol, JSM 6390).