EFFECT OF OPERATIONAL AND DESING PARAMETERS ON THE EARLY STAGES OF HIGH SHEAR WET GRANULATION PROCESSES

by

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ABSTRACT

The development of new technologies, active ingredients and regulatory initiatives, has increased the need for a scientific understanding of the pharmaceutical manufacturing processes. In this context, solid dosage forms (i.e., tablets, capsules, etc.) receive special attention since they represent more than 66% of the medications in the market, due to their ease of administration, handling and production.

This work is focused on the study of high shear wet granulation, a widely used intermediate operation in the production of solid dosage forms. The main objective is to contribute to the understanding of the effect of initial formulation conditions (i.e., hydrophobicity), operational parameters (i.e., impeller velocity), and design factors (i.e., impeller blade design) on the early stages of granule growth.

The effect of the dry premixing stage in the initial wettability of hydrophobic formulations was studied. Results indicate that the concentration of the hydrophobic component and the applied premixing shear strain affect significantly the hydrophobic conditions of the formulation. They also suggest that the mixing mechanism of the hydrophobic ingredient should be taken into account in the design and analysis of these systems. Those findings were further explored carrying out an experimental design to study the high shear granulation of lubricated formulations. Although this is not a common practice in the industry, the results show that the addition of small amounts of lubricant can help as an internal controller of the granulation, decreasing the growth velocity and reducing the amount of over-granulated material.

Another study was developed to determine the influence of the impeller velocity and blade angle on the granulation behavior. The analysis of the granulated material confirmed that both factors impact significantly the growth kinetics and can be used to modify the performance of a high shear granulation process. The data also allowed the generation of useful processing maps and dimensionless groups to describe the process.

In general, this research provides scientific elements to analyze high-shear granulation processes and demonstrates the applicability of those elements in formulation and process design. Experimental conditions and data sets are also valuable for the development of theoretical models and simulations.

RESUMEN

El desarrollo de nuevas tecnologías, ingredientes activos e iniciativas regulatorias ha aumentado la necesidad de entender científicamente los procesos de manufactura en la industria farmacéutica. En este contexto, las formas orales sólidas (tabletas, cápsulas, etc.) han recibido especial atención ya que representan más del 66 % de los medicamentos en el mercado, debido a la facilidad en su administración, manejo y producción.

Esta investigación está enfocada en el estudio de la granulación húmeda de alto esfuerzo, que es una de las operaciones más importantes en la producción de formas de dosis sólidas. El objetivo principal es contribuir a comprender el efecto de condiciones iniciales de la formulación (i.e., hidrofobicidad), parámetros de proceso (i.e., velocidad del agitador) y factores de diseño (i.e., diseño de aspas del agitador) en las etapas iniciales del crecimiento del gránulo.

Se estudió el efecto de la etapa de premezclado en la humectabilidad inicial de formulaciones hidrofóbicas. Los resultados indican que la concentración del componente hidrofóbico y el estrés aplicado durante la etapa de premezclado afectan significativamente las condiciones hidrofóbicas de la formulación. También sugieren que el mecanismo de mezclado del ingrediente hidrofóbico debe tomarse en cuenta en el diseño y análisis de estos sistemas. Las implicaciones de estos hallazgos fueron exploradas mediante de la ejecución de un diseño experimental cuyo objetivo era estudiar la granulación de formulaciones lubricadas. Aunque esta práctica no es común en la industria, los resultados demuestran que la adición de lubricante en bajas concentraciones puede ayudar como un controlador interno de la granulación, disminuyendo la velocidad de crecimiento y reduciendo la cantidad de material sobre-granulado.

Otro estudio fue desarrollado para determinar la influencia de la velocidad del agitador y el ángulo del aspa en el comportamiento de la granulación. El análisis del material granulado confirmó que ambos factores impactan significativamente la cinética de crecimiento y pueden ser utilizados para modificar el desempeño de un proceso de

granulación de alto esfuerzo. Los datos también permitieron la generación de mapas de procesamiento y grupos adimensionales útiles para describir el proceso.

En general, esta investigación provee elementos científicos para analizar procesos de granulación de alto esfuerzo y demuestra la aplicabilidad de estos elementos en la formulación y diseño de dichos procesos. Además, las condiciones experimentales y los datos obtenidos son valiosos para el desarrollo de modelos teóricos y simulaciones.

To my mother

Concepción Aguilar Bran (R.I.P.)

for her love, strength and courage;
for her unconditional support and
inspiration; for all her lessons and
memories, those I keep as a treasure,
those that draw the path of my life.

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CHAPTER 1
INTRODUCTION

1.1. Background

Nowadays, approximately 60% of the products in the chemical industry are produced in granular form (i.e., particles or powders) [1,2]. They are widely used as raw materials, intermediates or final products in the manufacturing industry (e.g., pharmaceuticals, detergent, food, fertilizers, ceramics, etc.) due to their multiple processing advantages (e.g., stability, ease of handling and transportation, etc.).

In the pharmaceutical industry, powders are essential since most excipients and active ingredients are synthesized in this state [2]. They are used in the production of virtually all solid dosage forms (e.g., tablets, capsules, powders, etc.), which represent more than 66% of the drugs in the market according to an estimate published by GBI Research in 2011 after considering more than 20,000 marketed drugs [3]. The most popular solid forms are tablets and capsules, which represented an average of 55% of the US Food and Drug Administration (FDA) approvals in the period from 2003 – 2008 [4].

The production of solid medications involves various processes and technologies that are used according to the raw material properties or the required final product characteristics [2,4]. Thus, a solid dosage manufacturing line could include the following processes: dispensing, feeding or loading, granulation, drying, mixing or blending, milling, tablet compression, capsule filling, coating, branding and packing. Figure 1.1 illustrates a generic process of tablet manufacturing that uses high shear granulation and fluid bed drying (FBD).

The continuous development of new drug delivery systems and active pharmaceutical ingredients (API) requires a deeper and scientific understanding of the manufacturing processes, materials, products, equipment, etc. As the standards for drug production and quality control are becoming more rigorous, initiatives such as the pharmaceutical analytical technologies (PAT) and related concepts such as quality by design (QbD) and *particle engineering* are gaining importance. In this context, this work presents a scientific approach to study the granulation process as it plays an important role in particle design and solid dosage manufacturing lines.

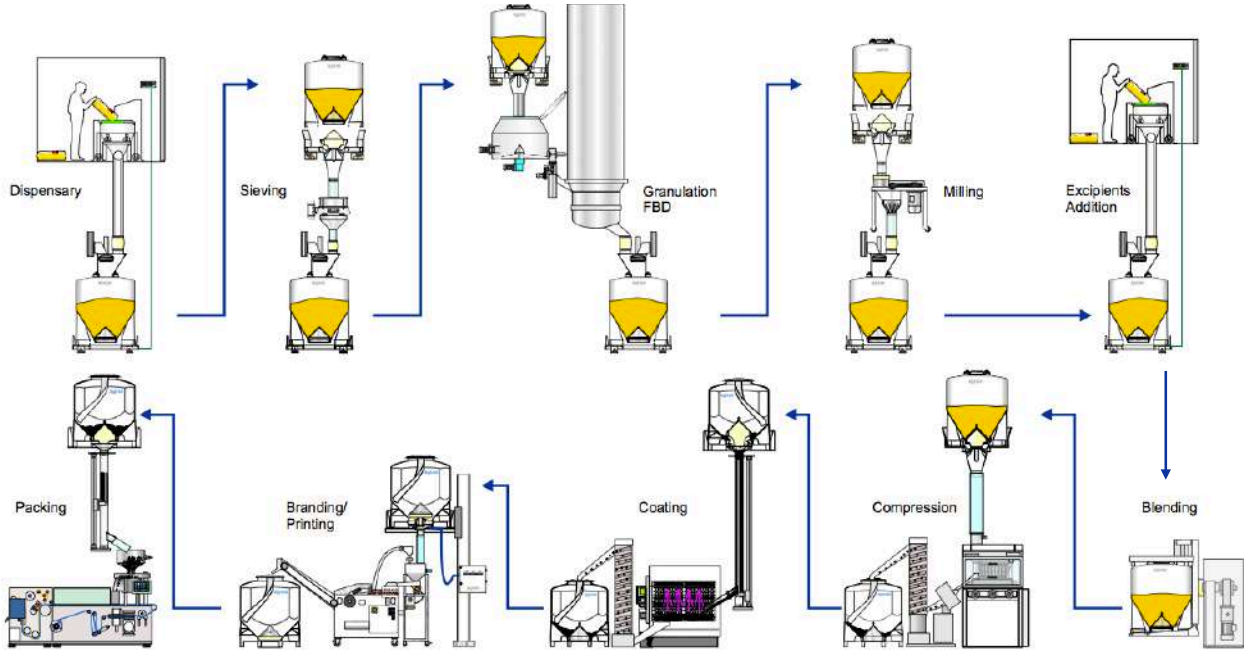

Figure 1.1. Generic tablet manufacturing process based on high-shear wet granulation [5].

1.2. Granulation in the pharmaceutical industry

Granulation has been known as the principal method to increase the particle size of powders in the pharmaceutical industry. Its objective is to join together small particles into larger semipermanent aggregates, called granules. It has been studied since the early 1950's but it was in the 1970's when this industry adopted granulation as one of its main processes in solid dosage manufacturing as high-speed tablet and capsule filling machines with automated controls were introduced [6]. Since then, it has been widely used as an intermediate process usually performed to prepare the material before the compression stage (i.e., for tablets) or the filling stage (i.e., for capsules). Its popularity is due to its many advantages [6–8]:

- It improves the flow properties of powders so that they can be exposed to high-speed machines (e.g., compression, filling stations, metering stations).
- It decreases segregation of ingredients, narrowing particle size distributions of the formulations and reducing differences in density of the materials.
- It increases the bulk density of the materials, which is useful in transfer or storage operations.
- It modifies the compressibility of the powder mixture.

- It modifies the uniformity of the API distribution.
- It reduces dust to minimize losses and handling hazards (i.e., inhalation and explosion risks).
- It reduces the formation of lumps or cakes, specially in hygroscopic materials.
- It modifies the final product appearance, hardness, porosity, etc.

1.3. Types of granulation

Granulation methods are divided according to the origin of the granule binding force. Generally, granulation is carried out by size enlargement of primary particles *(wet granulation)*, but it is also common to obtain a desired particle size by reducing previously compacted materials *(dry granulation)*.

Wet granulation is the most common type of granulation method, where a liquid binder promotes the agglomeration of powders. Bonding mechanisms on this type of granulation are due to the adhesion produced by capillary pressure or liquid bridges. The formation of solid bridges during drying is also relevant. Liquid binding forces are responsible for the resultant particle size, whereas solid bridges are the primarily responsible for granule strength [7]. This granulation method requires a drying step to remove the moisture from the granulated material before further processing.

Dry granulation is based on external mechanical pressure exerted to powders. Its popularity has risen in the last 20 years since a number of new APIs cannot be processed using wet granulation and drying due to their chemical fragility and/or sensitivity. Typically, in this type of granulation powders are exposed to high stresses leading to the formation of large tablets (i.e., tableting) or compact films (i.e., roller compactor) that are further grinded in a disintegrator or mill [6] to obtain the final granules.

Extrusion processes are a combination between wet and dry granulation since wet powders are kneaded and pressed to form a strand that is cut or broken to form the final agglomerates [9]. Although there is a growing interest in dry granulation and extrusion processes, this work is focused on wet granulation since it is still the most popular technology, used in most solid dosage manufacturing lines.

1.4. Wet granulation processes

In wet granulation, the particle growth is mainly promoted by the addition of a liquid binder to an agitated powder bed. The motion of the particles is fundamental to increase the particle collisions frequency, which is the responsible for the coalescence or granule growth. Wet granulation involves four key mechanisms or rate processes that take place simultaneously and continuously inside the granulator (Figure 1.2): **wetting (nucleation)** [10–15]**, coalescence or growth** [16–19]**, consolidation and breakage** [20–25]**.** The interaction between the mechanisms determine the final size distribution and other attributes of the granulated product (e.g., density, porosity, etc.) [26]. Each mechanism involves specific micro-level phenomena, hence a different physical and mathematical analysis. Ennis (1991) and Iveson (2001) presented a comprehensive analysis and review of the mechanisms fundamentals [8].

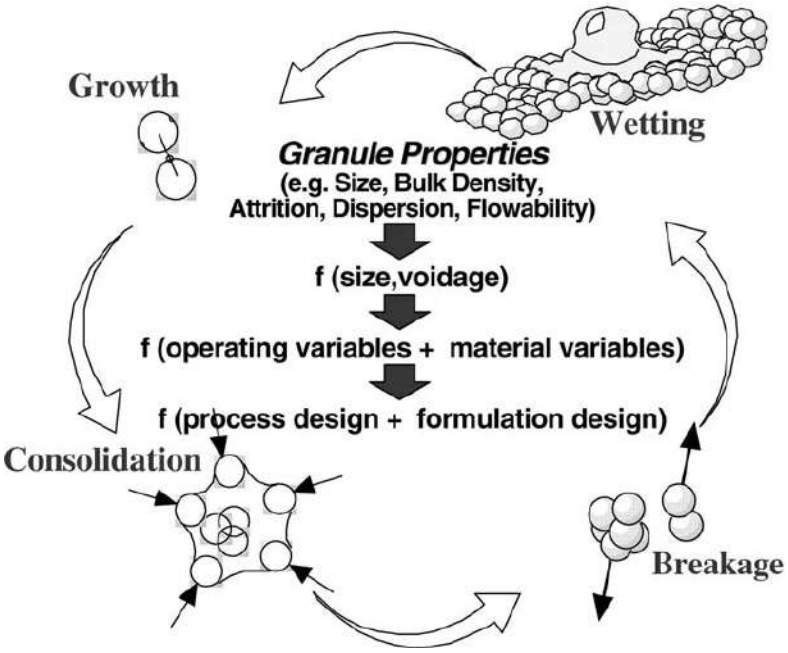

Figure 1.2. Rate processes of wet granulation [6].

Wet granulation technologies are commonly classified according to the equipment. Although there exist other options in the market (i.e., low-shear, hot melt, etc.), the most popular are the *high-shear granulators* and the *fluid bed granulators*. The main difference between them is the way in which the powder is agitated during the granulation; however there exist other specific factors that characterize their operation, which are summarized below.

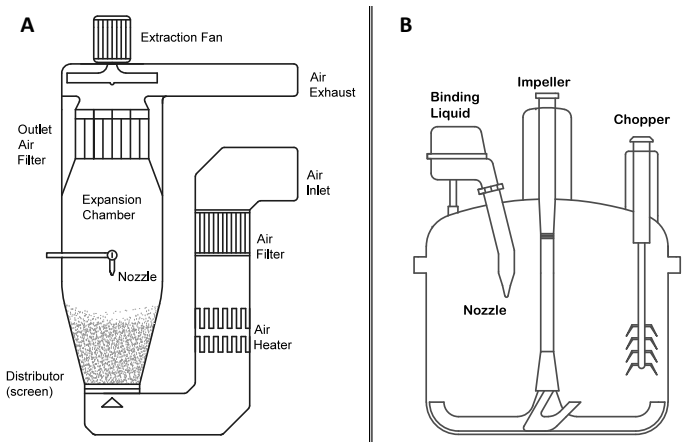

Figure 1.3. Principal components of a fluid bed granulator (A) and a high-shear granulator (B).

1.4.1. Fluid bed granulation (FBG)

The first application of this process to the pharmaceutical industry was firstly reported on 1959. It has been widely adopted in this field mainly because it allows granulating and drying in the same equipment (i.e., one-pot processing technology). The process typically begins when the formulation is loaded into the granulator. Then, hot filtered air is pumped into the bottom of the system (some processes use vacuum) and after a short fluidization period (i.e., pre-mixing), the liquid binder is added to the fluidized bed in the form of fine droplets using a spray nozzle (i.e., wetting stage) that promotes the granule growth. When the endpoint is reached (e.g., addition time, liquid content), the binder addition is terminated and the granules are allowed to further grow or dry as air continues fluidizing the system. Commonly, a milling stage is performed after this process to homogenize the particle size of the granulated product. A representative diagram of the equipment is shown in Figure 1.3A. The distribution screen and the filtration units prevent that particles scape the container [27] during processing.

In this technology, the granules are mainly formed by a layering process, which generates friable and porous granules. In addition, the fluidization of the powder bed frequently creates the conditions for the prevalence of the breakage or attrition phenomena. Several studies have been published in the last years regarding this type of granulation, including experimental research [28–38], control strategies (e.g., fuzzy logics, neural networks, etc.) [6,39–42], modeling (e.g., partial least squares, discrete element method, computational fluid dynamics, etc.) [32,43–49] and PAT initiatives (e.g., near-infrared, focused beam reflectance, etc.) [39,50–53].

1.4.2. High-shear wet granulation (HSWG)

This technology is the main focus of this research. It is characterized by the presence of a rotating impeller that distributes the liquid binder, promotes the particle collisions and generates high densification of the granules. The process is commonly performed in batch mode where the materials are firstly loaded into the granulator, followed by a short period of dry pre-mixing. Then, the impeller and chopper agitate the powder bed while the liquid binder is dripped or sprayed using a nozzle (i.e., wetting stage). After all the liquid has been added, the agitation continues (i.e., massing stage) until reach the set endpoint (i.e., particle size, time, etc.) [54]. The granulated material is often processed in a wet-mill to break the large lumps before being transferred to an external dryer (i.e., convective ovens, fluid bed dryers, etc.); however some equipment allow granulating and drying in the same vessel (i.e. *one-pot processing*) using either oscillating bowls, vacuum, gas-assisted, or microwave instruments [55]. A final milling stage is common after drying to homogenize the granule size before the next processing stage (e.g., excipients blending, compaction).

High-shear granulators could be horizontal or vertical (top or bottom-driven) depending on the position of the impeller and most of them are equipped with the accessories shown in Figure 1.3B. The impeller speeds usually range from 100 to 500rpm with a tip speed in the order of 10 m/s [56], while the chopper operates from 1000 to 3000rpm. The purpose of the chopper is to decrease the amount of lumps.

This technology has been used since the early 1980's and today is a main operation in many production lines. Its advantages over other granulation processes include [54]:

- Short processing times.
- Flexibility to handle cohesive powders or materials with significant differences in particle size or density. It can also process hydrophilic polymers, which is not achievable with other technology.
- Usually uses less amount of liquid binder.
- Produces highly densified and low friable granules than FBG and low shear granulation.

However, the latter can be counterproductive since the granules tend to have lower compressibility. Another challenge is that the process should be carefully controlled to detect

the granulation endpoint and avoid over-granulation. Indirect measurements of torque [56–59], power consumption [60–63], sound and vibration [64–67], electrical capacitance [68], etc., have been used as they have proved relation to the formulation characteristics during granulation. On the other hand, recent advances in the field of *in-line* PAT instruments are boosting the efficiency of direct methods to monitor granule size and other physicochemical properties (e.g., conductivity, shape) during the course of granulation. In that sense, recent technologies such as image analysis [69,70] (e.g., Eyecon, Innopharma Labs) or focused beam reflectance measurements (e.g., FBRM, Malvern Inc.) [71,72] offer an interesting alternative that would be worth studying for industrial applications. Despite the pros and cons of both approaches (i.e., indirect and direct measurements), the endpoint has to be established according to the formulation, process and required final granule size distribution [60].

A comprehensive characterization of the formulation and a fundamental knowledge of the interaction between operating parameters and equipment design are required for a scientific understanding of high shear granulation [73]. The process is technically simple and a strong body of empirical knowledge supports its application; however there is a lack of scientific understanding of the fundamentals, mainly due to the number of variables involved. Several researchers have studied the influence of these factors, which are summarized in Table 1.1.

Table 1.1. Factors that affect high-shear granulation processes and relevant publications.

Type	Factors	Selected publications
Formulation	Ingredients and initial blend: particle size, porosity, cohesion, solubility, thermal stability, hydrophobicity, mechanical properties, etc.	[59,74–90]
	Binder: Loading (i.e., liquid to solid ratio), method of incorporation (i.e., wet or dry), viscosity, surface tension, thermal behavior, concentration, etc.	[91–103]
Process parameters	Pre-mixing time	
	Impeller / chopper speed	[103–112]
	Binder addition method: flow rate, dripping/spray, number of nozzles and location, spray pattern, drop size, etc.	[37,104,113–115]
	Massing time	[104,107]
Equipment design	Scale	[73,83,116–127]
	Vessel design (e.g., geometry, material, etc.)	[128,129]
	Fill level	[56,130,131]
	Impeller / chopper position and design	[56,63,132]

1.5. Justification and scope of the dissertation

Design and analysis of industrial granulation has been rooted in empiricism and continue to be one of the least understood and one of the most inefficient processes in the pharmaceutical industry. It is often considered more as an art than a science, as stated by Litster [73], since it is commonly based on routine practices rather than on systematic scientific strategies.

The disperse nature of particulate systems has been a barrier for a complete understanding of the phenomena. This situation exposes the necessity to study the characteristics of the process towards a deeper knowledge of the whole mechanism of granulation, its micro-scale phenomena and macro-scale implications of the operational conditions. This work focuses on the study of high-shear wet granulation as an effort to contribute to the scientific understanding of the process. It stands as an attractive area to develop experimental and theoretical research due to its potential application in the pharmaceutical industry and the lack of systematic studies on its fundamentals.

This dissertation is aimed to provide a theoretical and experimental study to understand the macro-scale impact of formulation and operating parameters on batch HSWG. Specifically, the main contributions of the work are: the study of the impact of the dry premixing stage on the conditions of hydrophobic formulations; the experimental analysis of the early stages of HSWG of lubricated formulations, and the evaluation of the effect and interaction between an operational parameter (i.e., impeller velocity) and a design parameter (i.e., impeller blade angle) on the early stages of a HSWG process. In addition, the methodology also allowed generating processing maps, diagrams and dimensionless parameters that take into account the studied variables and that can be used in other experimental studies.

Although the study was focused in batch high-shear wet granulation, some findings can also be useful in the analysis of other granulation technologies. They also can be of interest in formulation and process design, scale-up, trouble-shooting, equipment design, optimization, and process control.

1.6. Dissertation overview

This dissertation is presented as a chronological description of the experimental and theoretical work. Each chapter is aimed to cover a specific stage of a granulation process.

Chapter 2 presents the general experimental setting and a comprehensive characterization of the ingredients that were used in the study. It includes the specifiations of the equipment and a general description of the characterization methods that were used in the study.

Chapter 3 describes the results of a study aimed to determine the impact of the premix stage on formulations that contain a hydrophobic ingredient. It presents a quantitative and qualitative approach to understand how the applied premixing shear and the concentration of the hydrophobic component can modify the wettability of a formulation before the wetting stage. The implications of these factors are further studied in Chapter 4 where a series of high-shear granulation experiments were conducted to determine the influence of the formulation hydrophobicity on the early stages of growth. The study evaluates the use of a lubricant to control the granulation.

Chapter 5 presents an experimental study aimed to quantify the effect and interaction of a process parameter (i.e. impeller velocity) and a design parameter (i.e., blade angle) on the growth kinetics of a lactose-based binary formulation. It presents a statistical and theoretical analysis that allowed proposing a set of dimensionless parameters and a processing map that takes into account the studied parameters.

Other interesting areas of study were detected during this work. They have not been fully explored, hence they can be considered to generate future research and expand the present work. Those recommendations and the final remarks of the dissertation are summarized in Chapter 6.

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CHAPTER 2
GENERAL EXPERIMENTAL METHODS

2.1. Formulation ingredients

Placebo formulations were used as model systems for this study. The ingredients were chosen due to their importance in the pharmaceutical industry and their low hazard potential. The specifications are presented in Table 2.1. Two ***lactose*** grades were used as the main ingredients since lactose is the most popular excipient in the production of commercial solid dosage forms. It is extensively used as filler or diluent due to its stability, availability, safety, and compatibility with most of the small molecular weight drugs [1].

Magnesium stearate was chosen for its hydrophobic nature (Chapter 3) and for its lubricant properties (Chapter 4). It is the most popular lubricant in the industry and it is known to form thin layers around other ingredients of the formulation, which decreases the friction between particles and equipment [2], enhancing the compression process.

Aqueous solutions of ***polyvinylpirrolidone*** (i.e., Povidone) were chosen as the liquid binder for the granulation experiments. Povidone is an inert synthetic polymer primarily used in wet granulation processes due to its solubility, binding power and wetting properties [3–5]. It is powder available in different molecular weights (MW) and commonly used in diluted solutions (i.e., 1 – 25% w/w) [6].

Table 2.1. Specifications of the formulation ingredients used in the study.

Ingredient	Supplier	Grade/Brand	Empirical Formula	MW (g/mol)
Anhydrous lactose	Kerry Bio-Science	NF, Direct tableting	$C_{12}H_{22}O_{11}$	342.30
Lactose monohydrate	Meggle	Granulac 140	$C_{12}H_{22}O_{11}*H_2O$	360.31
Magnesium stearate	Peter Greven	Ligamed MF-2-K	$C_{36}H_{70}MgO_4$	591.34
Povidone	ISP Technology	Plasdone K29/32	$(C_6H_9NO)x$	30,000 – 50,000

2.2. Characterization of formulation ingredients

An initial characterization was performed to establish a database of physicochemical properties of the raw materials and to understand their behavior at the processing conditions of the experiments. Samples were taken directly from the top and bottom of the containers using scoops and sample thieves as necessary.

2.2.1. Particle Size Analysis

Analytical sieving: This gravimetric method was used to approximate the mass-based particle size distribution (PSD) of the raw materials. It is usually the method of choice for classification of coarser grades of single powders or granules. The samples (500-800g) were placed in the top of a stack of analytical sieves each having different mesh size, descending from top to bottom. The stack was agitated for a specific period of time (i.e., 10min) separating the sample in size ranges. The PSD was obtained plotting the weight percentage (%w/w) of material retained in each sieve after agitation, against the size range. Figure 2.1 shows the differences between the modal sizes of the main components of the formulation, a typical scenario in wet granulation processes. The PSD of magnesium stearate is not presented since this technique is not recommended for materials with such high cohesion and small particle size [7].

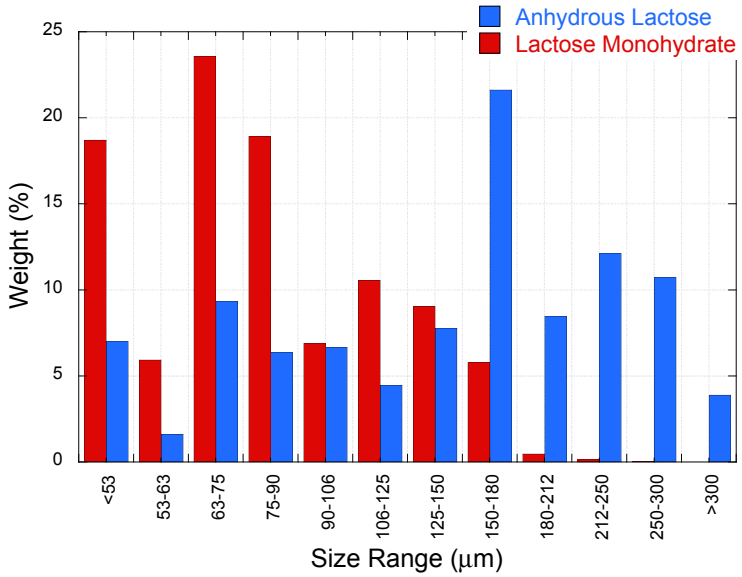


Figure 2.1. Mass-based PSD of the main ingredients of the formulation showing the modal size of anhydrous lactose (150-180µm) and lactose monohydrate (63-75µm)

Laser diffraction: This analysis was performed to obtain the volume-based PSD of the materials. Samples were analyzed using a laser diffraction instrument (Insitec T, Malvern Inc.) coupled with a data analysis software package (RTSizer V7.20, Malvern Inc.). The method measures the diffraction angles of a laser beam when it hits the particles in a dispersed environment. The data analysis is based on the Mie's solution to Maxwell equations, calculating the PSD as the radius of an equivalent sphere with the same volume. It is more reproducible and efficient than the sieving analysis because it uses less amount of sample (from 10 - 30g approximately) and results are available in a shorter period of time.

Figure 2.2 show the log-normal distributions of the raw materials. Relevant statistics are shown in Table 2.2. Results are in agreement with the sieving analysis and confirm the differences between both grades of lactose more precisely. The small particle size (Dv_{50} = 5.43µm) and wider distribution (Span = 3.36) of the magnesium stearate is also noticeable. The size differences between ingredients should be taken into account in process design to understand the behavior of the formulation and avoid possible segregation.

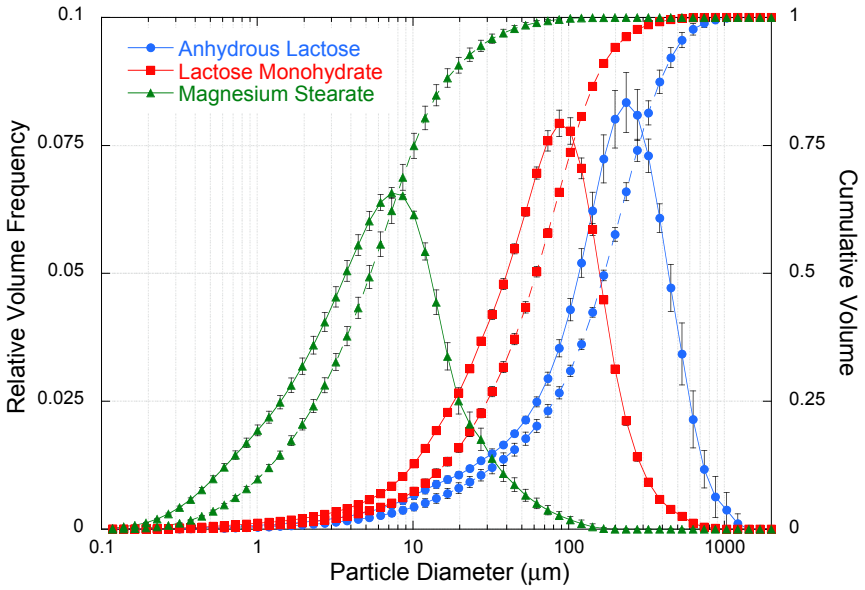


Figure 2.2. Volume-based PSD of the formulation ingredients: Relative frequency (solid lines) and cumulative distributions (dashed lines). Error bars indicate the standard deviation of 3 replicates (each replicate includes more than 10 recorded values fitted to log-normal distributions).

Table 2.2. Relevant statistics of the raw materials particle size distribution *.

Variable	Description	Anhydrous lactose	Lactose monohydrate	Magnesium stearate
Dv_{50}	Median size (μm)	167.67 ± 6.75	62.34 ± 1.29	5.43 ± 0.26
Dv_5	5^{th} percentile (μm)	11.50 ± 1.06	7.90 ± 0.34	0.64 ± 0.02
Dv_{10}	10^{th} percentile (μm)	25.01 ± 2.75	13.89 ± 0.42	1.03 ± 0.04
Dv_{90}	90^{th} percentile (μm)	383.65 ± 22.27	159.75 ± 3.44	19.27 ± 1.62
Dv_{95}	95^{th} percentile (μm)	473.41 ± 32.70	206.37 ± 6.55	29.93 ± 2.57
Span	Distribution width, calculated as: Span = $(Dv_{90} - Dv_{10})/Dv_{50}$	2.14	2.34	3.36
GSD	Geometric standard deviation (μm)	3.30 ± 0.10	2.85 ± 0.04	3.13 ±0.06
SSA	Optical specific surface area (m^2/cc) assuming non-porous particles of 1g/ml.	0.17 ± 0.01	0.27 ± 0.01	2.44 ±0.09
N	Records averaged	14	14	22

* Mean value ± standard deviation of *N* records.

2.2.2. Compessibility index and Hausner ratio

They are qualitative methods used to characterize the powder flow of the ingredients based on their bulk and tap density (Table 2.3.). Hence, the results are indirectly affected by the size, shape, moisture and cohesiveness of the material. Both densities (i.e., tapped and bulk) were determined according to USP <616> Methods using a 100g cylinder and a drop height of 14mm for the tapped density measurements (Vankel Tap Denser, Germany).

Table 2.3. Density and flow character of formulation components [b].

Component	Bulk Density (g/mL)	Tap Density (g/mL)	Hausner Ratio $\frac{\rho_{Tap}}{\rho_{Bulk}}$	Carr Index (%) $100 * \frac{(\rho_{Tap} - \rho_{Bulk})}{\rho_{Tap}}$	Flow character
Anhydrous lactose	0.592 ± 0.004	0.847 ± 0.009	1.43 ± 0.01	30.1 ± 0.6	Poor
Lactose Monohydrate	0.591 ± 0.01	0.833 ± 0.001	1.41 ± 0.03	29.0 ± 1.4	Poor
Magnesium Stearate	0.249 ± 0.003	0.335 ± 0.003	1.35 ± 0.02	25.7 ± 1.05	Passable/Poor

[b] Mean ± SD (*N=3*).

2.2.3. Scanning electron microscopy (SEM)

It was mainly used to identify the morphological differences of the raw materials. Samples (~0.5g) were coated with a gold layer using a vacuum sputter (Standard Desk IV, Denton Vacuum) and photographs were taken at different magnifications in a Jeol JSM-6390 microscope. Figure 2.3 depicts examples of SEM images of the ingredients. The images show that both lactose grades were formed by particles of irregular porous morphology while magnesium stearate was characterized by agglomerations of *flake-like* particles of smooth surface. The images length scales are also useful to qualitatively confirm the particle size that was previously measured with other methodologies.

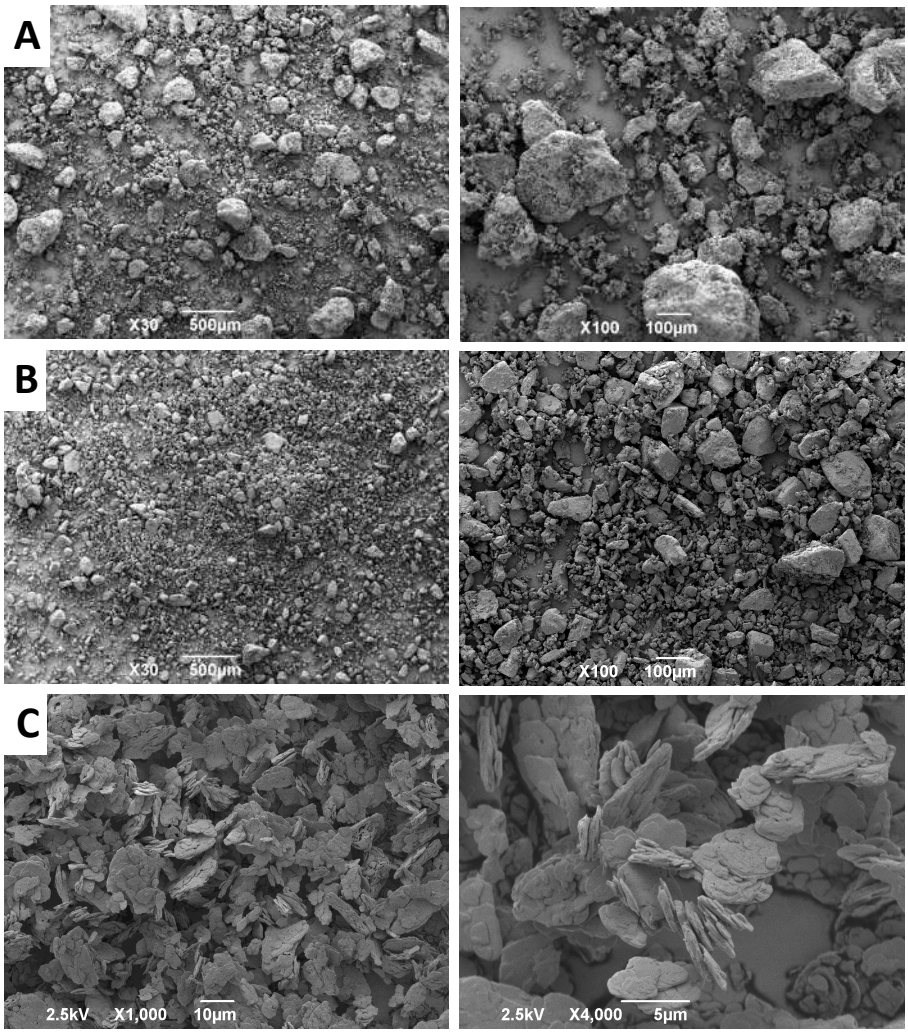
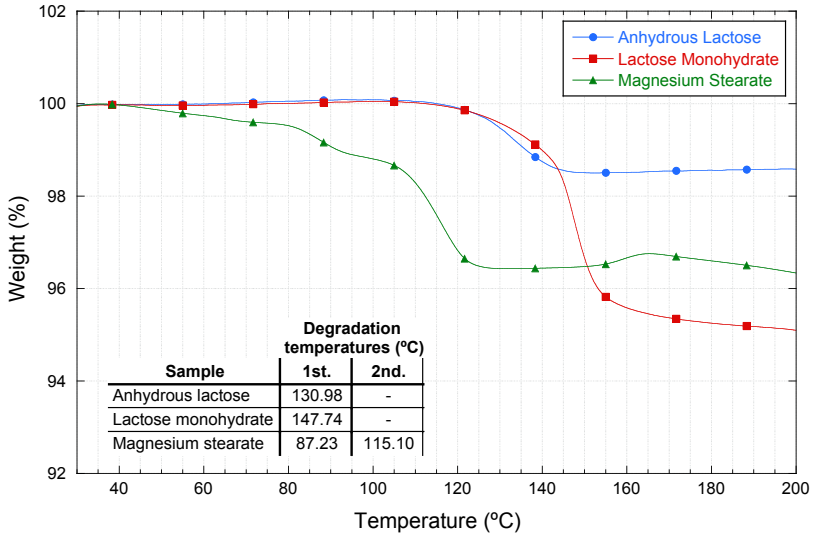


Figure 2.3. SEM images of the ingredients (at 2.5kV of incident voltage). Anhydrous lactose (A), lactose monohydrate (B) and magnesium stearate (C). Magnification and length scale is shown in each image.

2.2.4. Thermogravimetrical analysis (TGA)

It was performed to evaluate the thermal stability of the formulation components and detect possible changes or weight losses at typical processing temperatures (40-55°C). A sample (~6mg) was heated up to 200°C in a TGA/SDTA 851 (Mettler Toledo) at a constant heating rate of 10 °C/min under a nitrogen atmosphere. Weight percentage profiles (Figure 2.4) indicate that the three components are thermally stable up to 87.23 °C, where the first weight loss is observed for magnesium stearate. Other losses were identified at higher temperatures as indicated in the inserted table of the figure.



Sample	Degradation temperatures (ºC) 1st.	2nd.
Anhydrous lactose	130.98	-
Lactose monohydrate	147.74	-
Magnesium stearate	87.23	115.10

Figure 2.4. TGA curves of the formulation ingredients. Inserted table shows the degradation temperatures observed in the studied range.

2.2.5. Differential scanning calorimetry (DSC)

This method was implemented to identify the phase transitions of the raw materials. Samples (~6mg) were heated from 25 to 200 °C at a constant heating rate of 10 °C/min under a nitrogen atmosphere in a DSC 822^e (Mettler Toledo). The results (Figure 2.5) show that the materials do not have phase transitions in the processing temperature range (40-55ºC); however melting points (i.e., endothermic transitions) were identified at higher temperatures as indicated in the inserted table.

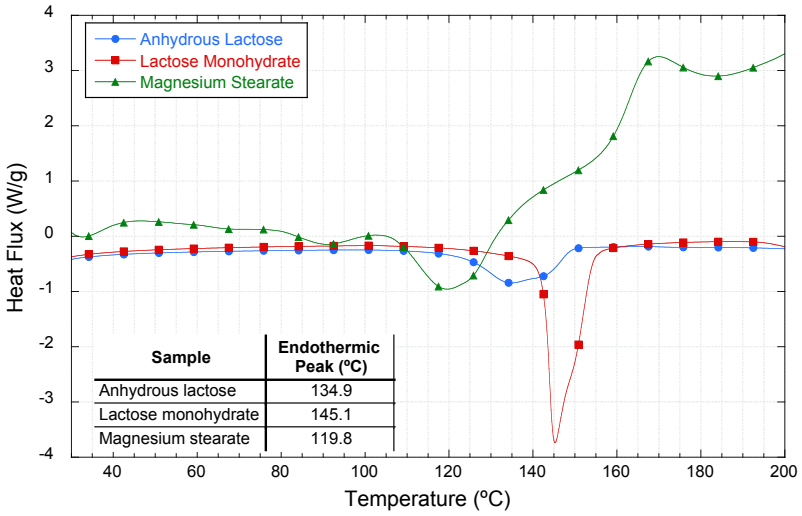


Figure 2.5. DSC curves of the formulation ingredients. Inserted table shows the melting temperatures observed in the studied range.

2.2.6. Fourier transform infrared spectroscopy (FTIR)

A Varian 800 FTIR Scimitar Series Spectrometer with a ZnSe ATR was used to obtain the spectra of the raw materials in transmittance units in the wavenumber range from 600 to 4000 cm^{-1} using 100 scans and a resolution of 4 cm^{-1}. Results are shown in Figure 2.6. This method was performed to identify characteristic bands of the components and determine the spectral differences that were used in further analysis.

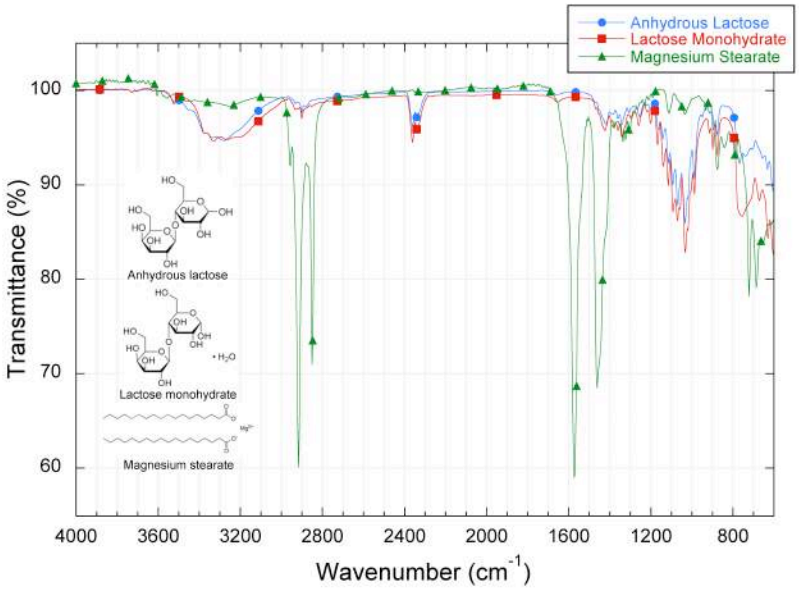


Figure 2.6. FT-IR spectra of the raw materials used in this study.

Similar spectra were obtained for both lactose grades, where a band from 2900 to 3300cm^{-1} can be highlighted corresponding to the vibration of the OH bond, broader for the monohydrate lactose as expected. Characteristic peaks of magnesium stearate are noticeable at 1462 and 1574 cm^{-1} (typical CO bands of a carboxylate salt); also at 2851 and 2916 cm^{-1} corresponding to the CH stretch vibration of the long aliphatic chain.

2.2.7. Rheological analysis of the liquid binder:

The solutions that were used as binder in the granulation experiments (i.e., Povidone 2.5% and 5% w/w) were analyzed to determine the impact of the operating temperature range (40-55 ºC) in the viscosity. Figure 2.7 shows the results of the dynamic test performed from 20 to 60ºC at 1ºC/min using a Reologica Instruments Stresstech HR equipped with a double gap Couette geometry. The figure demonstrates that the viscosity of both solutions decreased slightly in the range of interest. According to previous reports, these changes will not affect significantly the growth rate of the formulation [8].

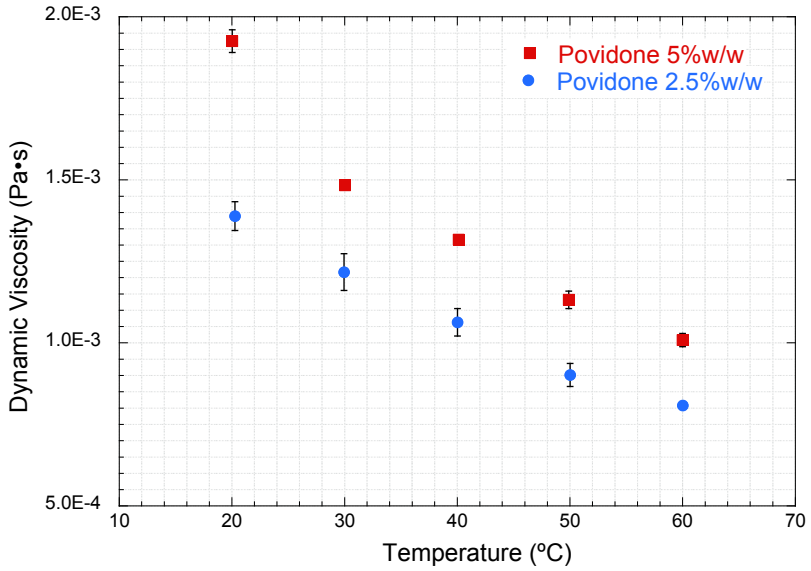


Figure 2.7. Rheological analysis of the Povidone solutions used as binder in the granulation experiments.

2.3. Equipment:

All the experiments were performed in laboratory scale high-shear granulators that allowed processing small batches (200 – 2000g) under controlled conditions. Their flexibility facilitated the evaluation of the macro-scale effects of operational variables on different stages of the granulation. Figure 2.8 illustrates the general granulation setting. Given that the study was focused on the growth behavior, experiments were conducted without the aid of a chopper to avoid additional granule breakage.

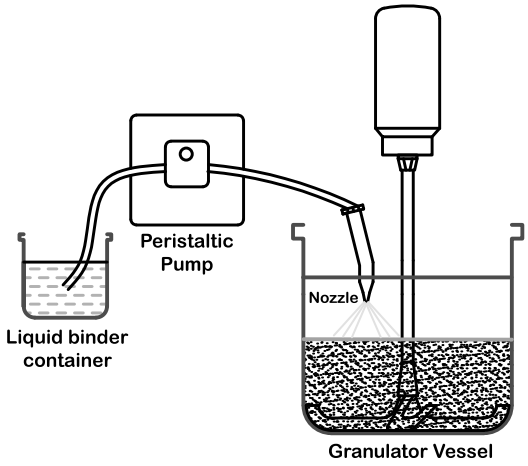


Figure 2.8. Laboratory-scale granulation setting.

2.3.1. Specifications of the equipment and accessories:

Mixing and granulation:

- 2 custom made top-driven granulators (shown in Appendix A).
    - RYOBI 12" bench drill press (280 – 3000rpm).
    - Scale: 2L
    - 3-blade impeller (three different geometries)
- 1 automatic bottom-driven granulator (shown in Appendix A)
    - Model: MHS-6-10b Mendel Co.
    - Scale: 10L
    - 3-blade impeller (100 – 940 rpm)
    - 8-blade chopper (300 – 2800 rpm)

Liquid binder addition:

- Peristaltic pumps:
    - Masterflex. Cole-Parmer. Model 7521-40. 115VAC. 6 – 600 rpm
    - Masterflex. Cole-Parmer. Model 7523-60. 0.1 HP. 10 – 600 rpm
    - Tubing: Masterflex Tygon.
- Nozzles:
    - HDPE spray nozzle.
    - Stainless steel nozzle (MW125, Bette)

Drying:

- Convection oven. Lindberg Blue (60 – 75ºC)
- HDPE trays.

2.4. Experimental methods:

Formulations were prepared using the ingredients described in Section 2.1 and 2.2 and processed according to structured experimental designs to evaluate the effect of selected operating parameters on different stages of a high-shear granulation. The specific factors, methodologies, experimental conditions, and characterizations performed in each study, are discussed in the following chapters as indicated in Table 2.4.

Table 2.4. Summary of the experimental factors included in this work.

Studied factors	Granulation stage	Main response variables	Chapter
Magnesium stearate loading and applied premixing shear strain	Dry premixing	Hydrophobicity and magnesium stearate distribution.	3
Magnesium stearate loading and applied premixing shear strain	Early massing times (growth)	Particle size distribution, morphology.	4
Impeller velocity and blade design	Early massing times (growth)	Particle size distribution, morphology and flow properties.	5

2.5. References

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CHAPTER 3
IMPACT OF THE DRY PREMIXING STAGE OF A WET GRANULATION PROCESS ON HYDROPHOBIC FORMULATIONS

3.1. Summary

Wet granulation processes typically start with a dry premixing stage. Its objective is to homogenize and prepare the material for further granulation steps. This work was aimed to study the influence of premixing conditions on the wettability of formulations that contain a hydrophobic component.

A binary lactose-based formulation was chosen as model system and magnesium stearate (MgSt) as the hydrophobic ingredient. They were processed in a laboratory-scale high shear granulator following a factorial experimental design to evaluate the effect of MgSt concentration and applied premixing shear strain on the hydrophobicity of the formulation. The design included four 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 Washburn Method was implemented to determine the hydrophobicity of the samples and hyperspectral images, collected in a NIR Chemical Imaging system, were used to assess the spatial dispersion of MgSt.

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

3.2. Introduction

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

Although agitation continues during all the stages of a granulation process, the dry premixing stage will determine the conditions of the formulation before wetting. Therefore, the study of this stage (i.e., operating parameters and formulation properties) could help to strengthen the understanding of the early stages of granulation (i.e., nuclei formation) since there is still a lack of knowledge in this regard [4]. The effect of this stage could be particularly important in equipment with low mixing capabilities (i.e., high fill volume, low impeller swept volume, etc.) where the conditions of the initial blend may prevail for longer periods of time [5]; or in processes where granulation happens shortly after the binder addition.

Pharmaceutical formulations often contain hydrophobic components, such as active ingredients, glidants, etc. Recent studies have demonstrated that these ingredients affect the granulation and the final product properties since they 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 [6–11]. Other studies have reported the influence of the applied shear on the hydrophobicity of the formulation using shear cells with axial dispersion to create controlled environments of nearly uniform shear conditions [12–14]. However, there is a lack of experimental studies in real high shear mixers where the flow patterns and shear profiles are non-homogeneous.

This work is aimed at studying the effect of the 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.

3.3. Materials and methods

3.3.1 Formulation

A lactose-based formulation was chosen as the model system and magnesium stearate (MgSt) as the hydrophobic component. MgSt is usually used as a lubricant in solid dosage formulations and is not commonly added before granulation, however it was chosen since its hydrophobic properties and mixing mechanism could be of interest in granulation experiments. Relevant properties of the formulation components are presented in Table 3.1 (a detailed characterization is presented in Chapter 2).

Table 3.1. Specifications and physical properties of the components used in the hydrophobicity studies.

Component	Grade / Supplier	Dv_{50} [a] (µm)	Particle Morphology [b]	Bulk Density (g/mL) [c]	Tapped Density (g/mL) [c]
Anhydrous lactose (AL)	Direct Tabletting, Kerry Bio-science, USA	167.7 ± 6.8	Irregular	0.593 ± 0.005	0.847 ± 0.010
Lactose Monohydrate (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] Determined in a Malvern Insitec T. See Table 2.2. Mean value ± SD ($N_{AL}=14$; $N_{ML}=14$; $N_{MgSt}=22$).
[b] Observed in SEM (Jeol, JSM 6390). [c] Mean value ± SD ($N=3$)

3.3.2 Experimental design and data analysis

Binary blends (3.8AL:1ML) were prepared according to a full factorial design using five levels of MgSt concentration: 0%, 0.5%, 1%, 2% and 3% w/w and three levels of premixing time: 15s, 30s and 60s (Figure 3.1). The 0% MgSt blends were used as control. A minimum of three randomized replicates was run for each condition. The analysis of variance (ANOVA) was carried out in Minitab 16 (Minitab Inc., USA).

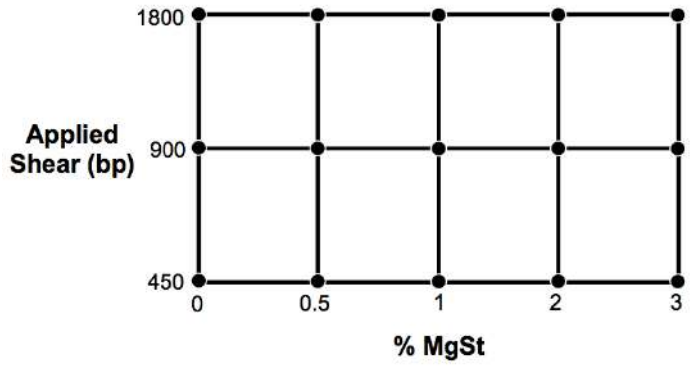

Figure 3.1. Experimental design used to evaluate the effect of the MgSt concentration and applied premixing shear strain on the hydrophobic conditions of the formulation.

In this work, the relative shear strain was calculated and reported as blade passes (bp) using the Equation 3.1:

$$\text{Blade Passes (bp)} = \frac{N_b * \omega * t_{PM}}{60} \qquad \text{Equation 3.1}$$

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

3.3.3 Equipment and Method

Laboratory-scale batches (250g) were prepared in a cylindrical laboratory-scale high shear mixer (1L vessel; diameter = 0.12m) equipped with a top-driven three-bladed impeller (diameter = 0.11m), shown in (Figure 3.2). The impeller shear velocity was set at 600rpm (tip speed = 3.6m/s). MgSt tends to fluidize when agitated due to its small particle size and density (See Table 3.1); hence, an adjustable lid was used to minimize the empty space inside the vessel decreasing the volume of suspended MgSt but leaving enough space for powder bed to dilate while mixing.

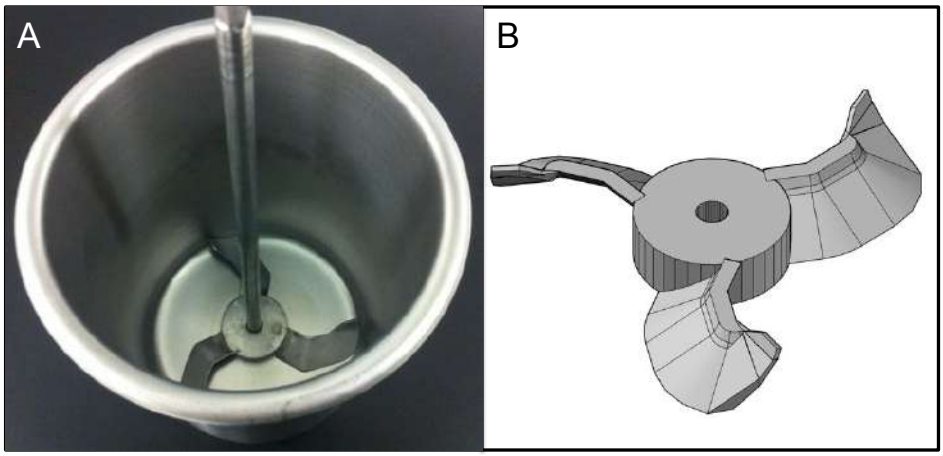

Figure 3.2. Laboratory-scale high-shear granulator (A) and impeller geometry (B).

Formulation components were weighted and loaded into the granulator vessel in horizontal layers (Figure 3.3). Material was premixed according to the experimental design and samples were collected using a customized sampler that allows collecting a layer of material from the surface of the powder bed. Although the formulations were granulated after sampling, the results of the granulation experiments will be presented in the near future.

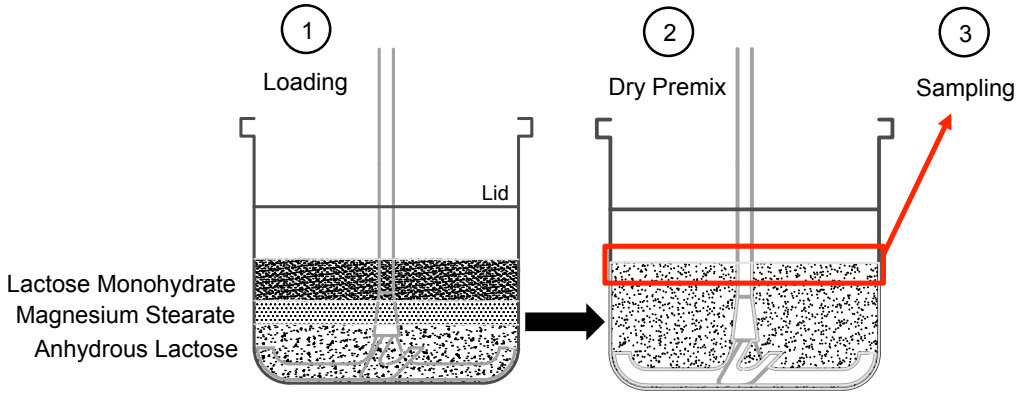

Figure 3.3. Loading order of the ingredients and general experimental methodology.

3.3.4 Characterization

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 the 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]:

$$t = \frac{\eta m^2}{C\rho^2\gamma Cos(\theta)} = \Phi m^2 \qquad \text{Equation 3.2}$$

where θ is the contact angle between the 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 is related to the packing condition of the material. 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 high value of Φ due to large contact angles (θ).

Samples (30g) were poured into a chromatographic column equipped with a sintered glass layer in the bottom (Chromaflex SZ 233) and tapped for 3min (VanKel Vanderkamp®) to reproduce the same packing conditions in all the experiments. The column was attached to a stand and placed on a balance (Explorer Pro, Ohaus Co.). Weight measurements started exactly after the column was immersed slightly into a saturated lactose solution (barely above the sintered glass layer). Data were recorded automatically for 15min at intervals of 5s using an acquisition software package (Balance Talk, Labtronics Inc.). A graphical description of the experimental setting can be found in the work of [14]. Hidrophobicity was calculated as the slope of a lineal regression (i.e., t vs. m^2). Figure 3.4 illustrates the average profile of lactose monohydrate and anhydrous lactose. MgSt is not reported since the permeation of the solution was undetectable due to its high hydrophobicity. Other studies have reported similar observations with highly hydrophobic materials [14].

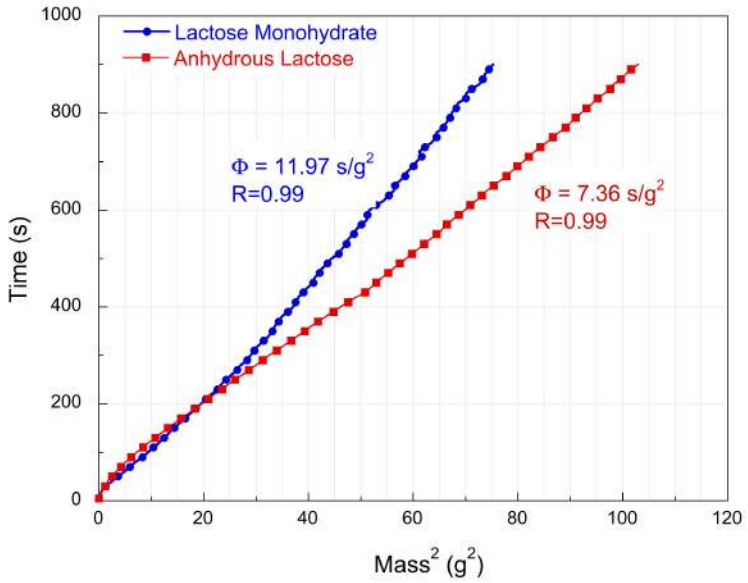

Figure 3.4. Results of the hydrophobicity test performed to lactose monohydrate and anhydrous lactose (**Φ** = hydrophobicity).

Analysis of MgSt Dispersion using NIR-Chemical Imaging (NIR-CI)

Hyperspectral images were obtained to determine the spatial distribution of MgSt in the samples (20g). Images were collected in reflectance mode using a Near Infrared Chemical Imaging system (SyNIRgi; Malvern Instruments, UK) in the spectral range from 1200 to 2400nm. The selected optical magnification provided a test area of 34mm x 42mm. Data was treated and analyzed using ISys Software Version 5.0.0.14 (Malvern Instruments, UK).

This spectroscopic methodology has been used as a process analytical technology (PAT) to facilitate the quality assessment in intermediate and final pharmaceutical products since it is a non-invasive and non-destructive method that allows a description of components in heterogeneous samples [21–24]. Some publications have reported difficulties in the quantification of MgSt when implementing methods that do not require previous calibrations [25]. Therefore, a partial least squares discriminant analysis (PLS-DA) classification model was developed using the spectra of pure components as predictors [26–28]. The degree of similarity or membership between a sample and the predictors defines the intensity of the pixels in the resultant images; hence, any variation

in the intensities is related with the abundance of a component in the sample at a given wavelength. The PLS-DA model was developed using the spectral range from 1300 to 1800nm with 8 factors given the low concentration range of MgSt. This approach has been used in other studies that have reported good quantification results for analytes at low concentrations [28].

Spectra were first converted to absorbance units and a correction was applied to remove unresponsive pixels and areas of bad illumination. All spectra were normalized using Standard Normal Variate (SNV) and a second derivative (Savitzky-Golay, filter length 9, filter order 3) to eliminate baseline differences and multiplicative/additive effects [21,26,27]. Spectra of pure components are shown in Figure 3.5 after these transformations. The most significant differences between the spectra of MgSt and the other components are observed at 1410nm and 1720nm.

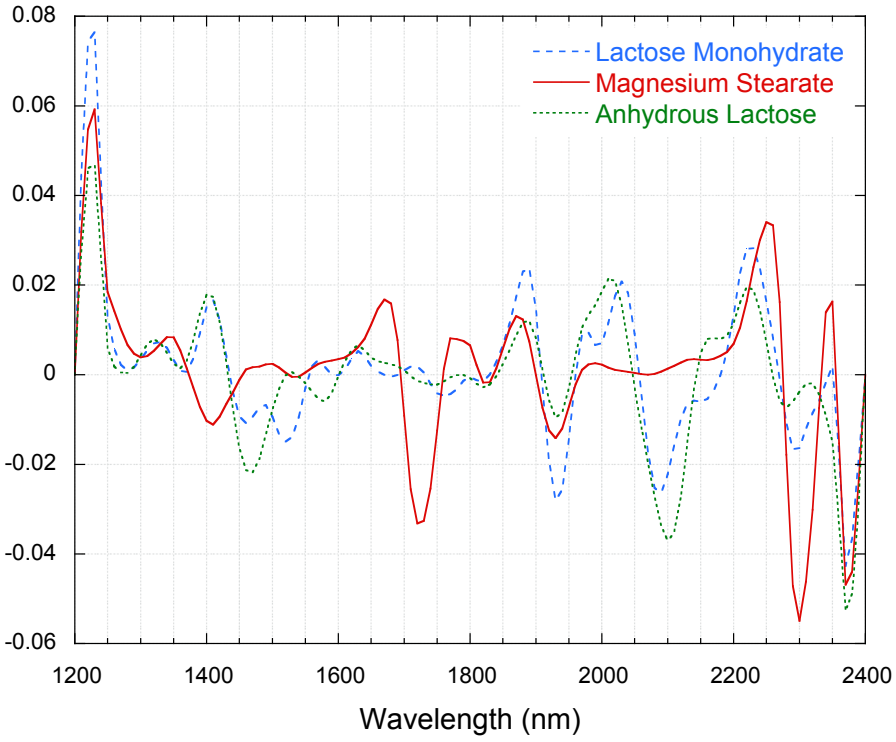

Figure 3.5. NIR spectra of pure components after SNV and 2nd derivative.

Model Validation

Validation samples (20g) at known concentrations of MgSt ranging from 0.5% to 3.0% w/w were prepared in a **low shear** tumble mixer for 3min at 10rpm. Figure 3.6 depicts the spatial distribution of the MgSt in the validation samples. The score distribution maps (top row) give a semi–quantitative description of the MgSt abundance in the samples. The color bar indicates the relative contribution of MgSt to any pixel (e.g., an area of pure MgSt would have a value of 1.0). The figure also includes the binary images collected at 1410nm (bottom row) since the MgSt has lower absorbance than the other components at this wavelength (as shown in Figure 3.5). Hence, a dark color was assigned to all the pixels below the mean absorbance minus two standard deviations (i.e., mean absorbance – 2SD) to highlight the areas rich in MgSt. Notice that the model shows good distribution of MgSt at low concentrations and a tendency to agglomerate as the concentration increases, which has been previously reported for low shear mixing processes [29,30].

Table 3.2 summarizes the abundance of MgSt in the samples. The mean scores (i.e., pixel concentration) show that the model has fair quantification capabilities and it is sensitive to small changes in concentration, which is useful for qualitative comparisons.

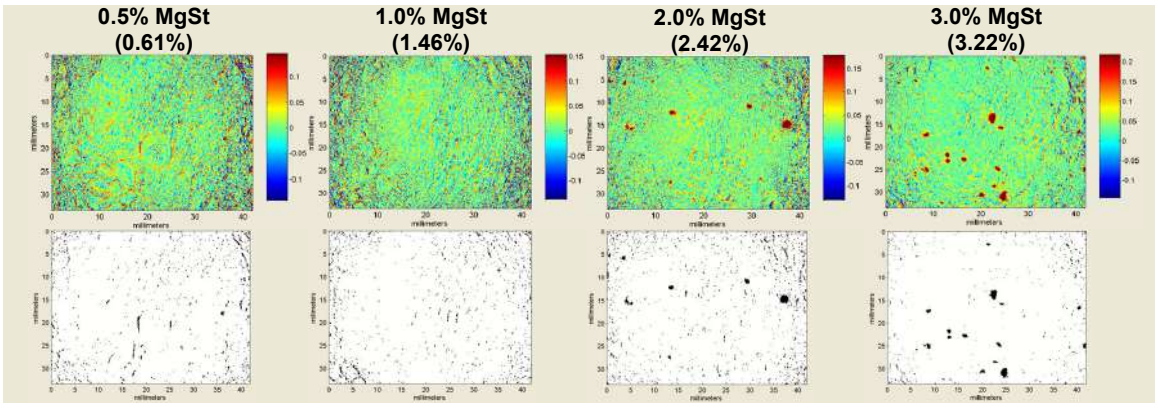

Figure 3.6. NIR-CI images of validation blends prepared in a low shear mixer (3min at 10rpm). Nominal values and PLS-DA predicted values (in parenthesis). Score images (top row) indicate MgSt abundance and binary images at 1410nm (bottom row) indicate the areas rich in MgSt.

Table 3.2. Predicted abundance of MgSt in the validation blends prepared in a low shear mixer (3min at 10rpm).

Blend Composition	Nominal MgSt Concentration (%w/w)	PLS-DA Model Mean Score [a] (%)
3.8LA:1LM + 0.5% MgSt	0.50	0.55 ± 0.11
3.8LA:1LM + 1% MgSt	1.00	0.82 ± 0.15
3.8LA:1LM + 2% MgSt	2.00	2.48 ± 0.13
3.8LA:1LM + 3% MgSt	3.00	3.35 ± 0.30

[a] Mean Score ± SD (*n=2*)

3.4. Results and discussion

3.4.1. Effect of premixing shear and MgSt concentration on the hydrophobicity

Samples were collected after the premixing and analyzed with the modified Washburn method. Results are summarized in Figure 3.7 where the hydrophobicity is plotted in logarithmic scale.

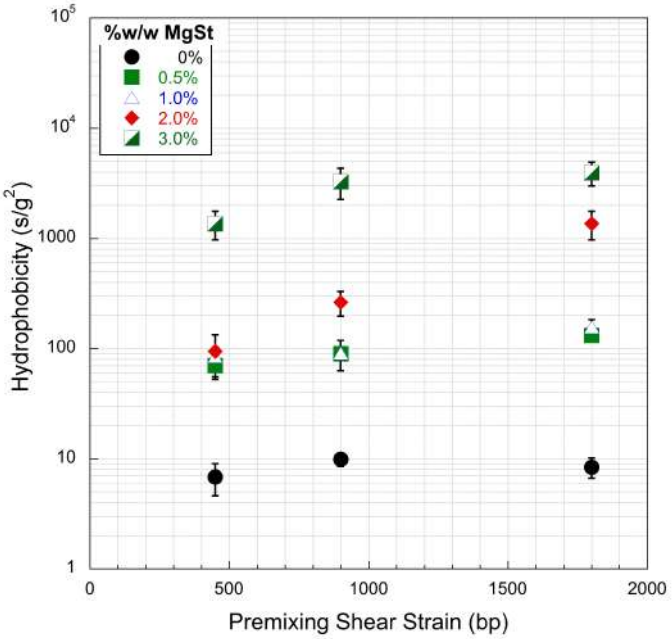

Figure 3.7. Hydrophobicity profiles of binary formulations (3.8AL:1LM) at different MgSt concentrations. Error bars correspond to the standard deviation of three replicates.

It is observed that the premixing shear did not affect the wettability of control samples (i.e. 0%w/w MgSt). Hence, any change in the hydrophobicity was the result of the addition of MgSt and/or the applied premixing shear conditions. The addition of MgSt increased the hydrophobicity of the formulations for all the shear conditions. Results also show that the applied premixing shear increases the hydrophobicity of the formulation at any concentration of MgSt. This indicates that the wettability is not only determined by the concentration of the hydrophobic ingredient but also by the mechanism that governs its mixing grade. In this regard, MgSt is known to form layers around the carrier particles [29,31–34] and the results suggest that homogeneity of those layers is increased at high concentrations and high-shear conditions.

The figure shows that the formulations with 0.5% and 1%w/w MgSt have similar behavior at all shear conditions, however formulations with 2%w/w MgSt presented a drastic increase in the hydrophobicity when the premixing shear raised from 450 to 900bp which may indicate the transition to an over-blending state that has been reported in other publications when MgSt is added at concentrations higher than 2%w/w [33]. The results are in agreement with this practice since the formulation with 3% w/w MgSt turned highly hydrophobic even at 450bp. A decrease in the reproducibility of the process at high shear conditions and high concentrations of MgSt was also observed, which is confirmed by the error bars in Figure 3.7 considering the logarithmic scale of the hydrophobicity axis.

The ANOVA results (Table 3.3) demonstrate that both studied factors (i.e., %MgSt and applied premixing shear strain) and the interaction between them, have a significant impact on the hydrophobicity ($p<0.001$). The average influence of the factors is shown in Figure 3.8 where the hydrophobicity is plotted in natural logarithmic scale. The magnitude of the effects confirms that the wettability of the formulation is highly sensitive to changes in MgSt concentration; however, the applied premixing shear strain can also be considered as a process design factor since it produces gradual changes in the wettability of the formulation. The tendency of the results is in agreement with recent studies performed in confined cells that produces controlled shear conditions [12–14], however this work extends that knowledge to the conditions of a high-shear mixer, where a convective and dispersive mixing environment is promoted.

Table 3.3. ANOVA test of the effects of MgSt concentration and applied premixing shear strain on the formulation hydrophobicity (α=0.05; R^2=93.64%)

Source	Degrees of freedom	F	*p-value*
%MgSt	4	107.12	<0.001
Premixing Shear Strain	2	15.31	<0.001
%MgSt * Premixing Shear Strain	8	9.10	<0.001
Error	37		
Total	51		

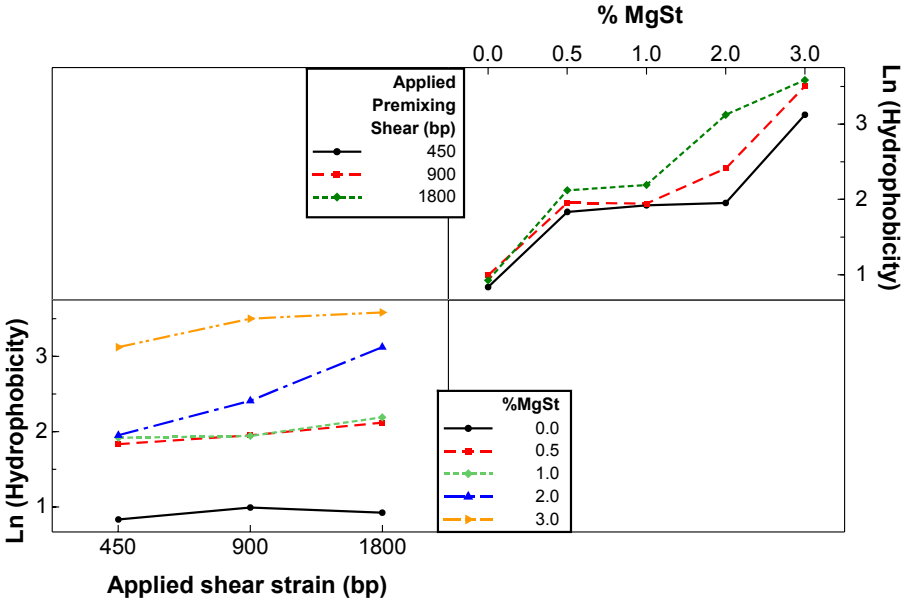

Figure 3.8. Interaction plots of %MgSt and applied premixing shear strain (values in natural logarithmic scale).

3.4.2 MgSt dispersion after the premixing stage

Previous experimental work has indicated that the physical characteristics of the pure ingredients (i.e., particle size and morphology) do not change considerably after high shear processing (Table 3.1); therefore, the validated PLS-DA model (Section 3.3.4) was implemented to assess the distribution of MgSt in the samples collected after the premixing stage. Figure 3.9 shows the score images of one set of experiments. The colors indicate the MgSt abundance in each pixel of the image and the mean value can be identified in the middle section of each color bar.

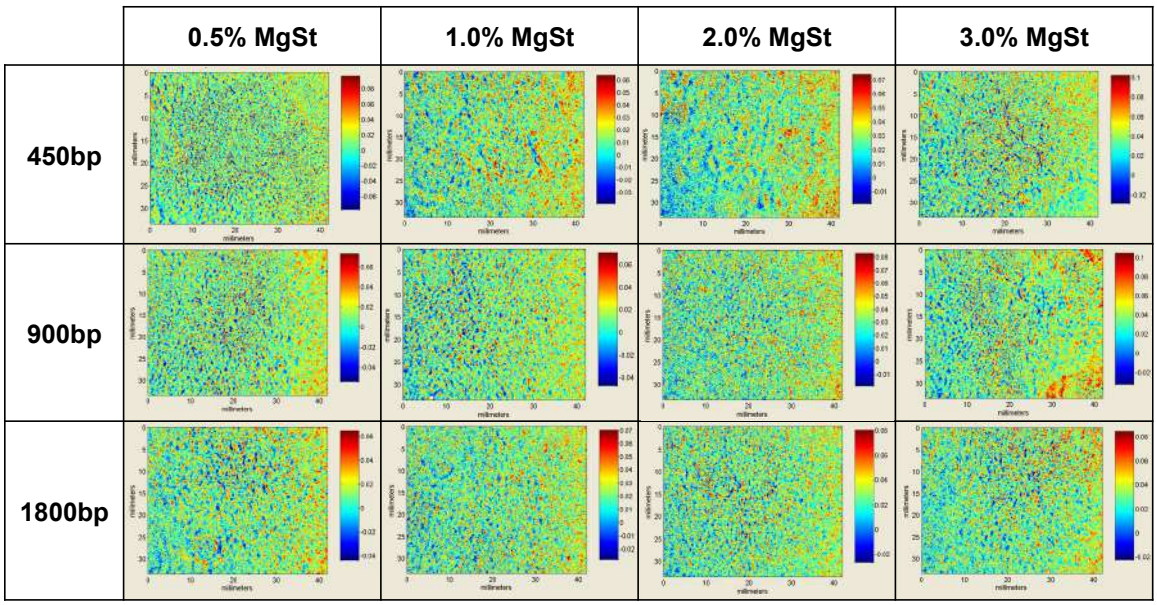

Figure 3.9. Score images of samples collected after the premixing stage.

Mean values are summarized in Table 3.4 and they show that the MgSt abundance is higher than expected which could also be a result of the mixing mechanism of MgSt. The layering process would cause an increase in the amount of MgSt particles in the surface of the powder bed as it spreads over the other components of the formulation. This means that, although the global concentration of MgSt in the sample is known, the abundance in the surface of the formulation particles is higher than the nominal value due to the high-shear processing.

Table 3.4. %MgSt abundance (mean scores) in the samples collected after the premixing stage.

Formulation	Premixing Conditions (time; blade passes)		
	15s; 450bp	30s; 900bp	60s; 1800bp
3.8LA:1LM + 0.5% MgSt	0.93	1.02	1.04
3.8LA:1LM + 1.0% MgSt	1.40	1.14	1.63
3.8LA:1LM + 2.0% MgSt	2.73	3.15	2.62
3.8LA:1LM + 3.0% MgSt	3.68	3.68	3.06

Figure 3.10 shows the binary images of the same samples indicating the areas rich in MgSt (black pixels). These images were obtained following the same procedure described in the model validation (Section 3.3.4) and they confirm that high-shear conditions promote a good distribution of MgSt regardless of its concentration. This is in agreement with other authors that suggest that the mixing of MgSt particles is governed by shear, as well as by dispersive and convective mechanisms, which are present in high-shear granulators [29].

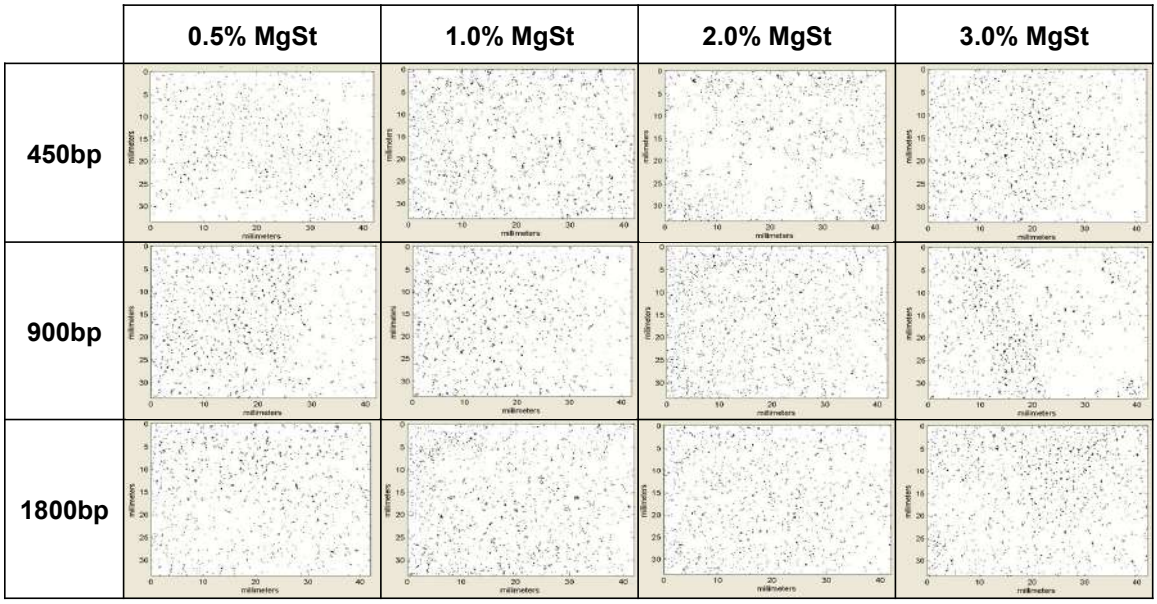

Figure 3.10. Binary images (at 1410nm) of samples collected after the premixing stage. Black pixels indicate the areas rich in MgSt.

Unlike the validation samples (i.e., low shear blends), the high-shear process did not allow the formation of agglomerates. Given the homogeneous distribution of MgSt at all the studied conditions, it is suggested that the differences in the hydrophobicity described in the previous section would be the result of the formation of thin layers of MgSt. Therefore, some areas of the samples may not be rich in MgSt but the degree of spreading would be enough to increase its hydrophobicity, which is directly related to the results obtained in Section 3.4.1.

In the context of granulation, results show that high shear strains during premix will generate high dispersion of MgSt in the surface of the formulation increasing the

liquid penetration time and the solid/liquid contact angle. Results also indicate that the hydrophobicity of the formulation can be modified by the applied premixing shear strain and by the addition MgSt. Preliminary granulation experiments that will be published in the future suggest that this approach could be useful in process or formulation design to modify the performance of a high-shear granulation process.

3.5. Conclusions

The analysis of the hydrophobicity results demonstrated that the concentration of the hydrophobic ingredient (i.e., MgSt) and the applied premixing shear strain both increased significantly the wettability of the blend after the premixing stage. Although the concentration of MgSt has a stronger effect, the applied premixing shear should also be taken into account in process design. A chemical imaging analysis confirmed that MgSt is well dispersed in the samples regardless of the applied shear strain. This supports the hypothesis that MgSt particles form a thin layer over the carrier particles (i.e., layering mechanism) and its mixing grade determines the final hydrophobicity of the blend.

These findings are important in the analysis of granulators with low mixing capabilities (i.e., high fill volume, low impeller swept volume) where the conditions of the initial blend may prevail for longer periods of time during other stages of granulation. From another perspective, the results could be of interest in formulation and process design since they indicate that the addition of small amounts of MgSt before granulation can be considered as an alternative to control the wettability of the formulation before wetting. Although this practice is not typical before a wet granulation, it could offer an alternative to control further stages of the granulation process.

In general, it can be concluded that the shear conditions of the premixing stage of a wet granulation process can affect the wettability of hydrophobic formulations. The magnitude of this effect will depend on the formulation properties, operational conditions and mixing mechanism of the ingredients at the studied shear conditions.

3.6. References

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CHAPTER 4

HIGH-SHEAR GRANULATION OF LUBRICATED FORMULATIONS

4.1. Summary

This study explores the effect of a lubricant on the performance of high shear wet granulation. Although the addition of a lubricant before granulation is not common in pharmaceutical manufacturing, recent studies led to hypothesize that it could be useful in process design as it offers an alternative to modify the wettability of the blend before granulation.

Lactose-based formulations were prepared at four concentrations of lubricant (i.e., magnesium stearate) and applying three different shear strains in the premixing stage. Formulations were processed in a laboratory scale high shear granulator using a diluted povidone solution as binding agent. The evolution of the particle size of the formulation during the massing stage was monitored off line by means of standard laser diffraction and standard sieving analysis. Fourier Transform Infrared was used to evaluate the segregation of the lubricant after granulation and morphological characteristics of the granules were assessed with scanning electron microscope images. Dissolution profiles of Acetaminophen tablets were obtained as a preliminary test to evaluate the feasibility of lubricated granules compared with a direct compression method.

Results demonstrate that the addition of lubricant before granulation could provide advantages in formulation design. It was found that low concentrations of lubricant (<1.0% w/w) slow the growth kinetics of the formulation, decrease the formation of lumps and enhance the controllability of the process. Dissolution profiles of Acetaminophen tablets demonstrated that lubricated granules could provide a feasible alternative to common direct compression processes; however more research is needed to understand the impact of this process on other characteristics of the final product.

4.2. Introduction

Wet granulation is a widely used intermediate process in the production of solid dosage forms (i.e. tablets, capsules, powders, etc.). Its main objective is to enhance the flow properties of the excipients and/or active ingredients for downstream stages (i.e. transfer, filling, compaction, etc.) by increasing their particle size. Although several studies have been dedicated to this process, it is not fully understood and it is still difficult to control its performance based on *a priori* knowledge of the formulation properties.

In that sense, this work is dedicated to the study of high shear wet granulation of hydrophobic formulations. Although there have been other studies in this regard [1–3], this work deals with the specific case where the hydrophobic component is a solid lubricant. This is not a typical practice in tablet manufacturing; however recent studies have shown its potential in formulation design (Chapter 3). This work explores the practical challenges of the process and the feasibility of the production of lubricated granules that can be used in tablet compression.

4.2.1. Lubrication

Usually, in tablet manufacturing, a lubricant is mixed with the formulation in low shear mixers after granulation and prior to compression. Although it can improve the flowability of the material and the appearance of the final product [4], the main objective of lubrication is to reduce the friction between the material and the metal surfaces of the equipment enhancing the performance and efficiency of the compression process and tablet ejection [5–8].

Solid boundary lubricants are preferred for pharmaceutical applications due to their properties and friction coefficient (i.e., 0.15–0.50). Some examples of this kind of lubricants are: metallic salts of fatty acids, fatty acids, hydrocarbons, fatty alcohols, fatty acid esters, alkyl sulphate, inorganic materials and polymers [7]. Among them, the magnesium stearate (MgSt) has been the most popular for decades. It is as a mixture of

magnesium salts of different fatty acids, mainly stearic and palmitic [9], obtained from animal or vegetable sources, although the pharmaceutical industry prefers the latter due to the potential human risks of the animal-derived MgSt [6,7,10].

4.2.2. Magnesium stearate

The main attractiveness of MgSt in solid dosage manufacturing lies in its cost and physical properties (Table 4.1.). It has been reported that its small particle size and large specific surface area favor its tendency to smooth the irregularities and form thin layers around the carrier particles and metal surfaces. This effect reduces the interfacial interactions and the contact area between the formulation and the equipment [7,11–14]. It also has shown a capacity to decrease electrostatic charges of the materials possibly due to its apolar chemical structure [13–17].

Table 4.1. Physical properties of magnesium stearate reported in the literature.

Physical Property	Value	Implication
Maximum shear stress	85 kg/cm^2	Little affinity with metal surfaces.
Particle size (D_{50})	2 – 15 μm	High spreading capacity (key factors of its lubrication efficiency) [5–7,17–20]. Trihydrate MgSt can reach up to 30 m^2/g [21].
Specific surface area	1.6 – 14.8 m^2/g	
Melting point	117 – 150 °C	Stable in the compression temperatures [7,18].
Moisture content	4.8 – 5.2%	Lubrication properties can be improved with moisture and polymorphic form [7,21].

MgSt is a poorly flowing cohesive material and, as many other lubricants, it is highly hydrophobic, which may negatively affect final product attributes such as hardness, friability, tensile strength, release time, disintegration, dissolution kinetics, bioavailability, and even the stability of the active drug [5,10,12,14,19,22,23]. These negative effects may increase with prolonged mixing or excessive shear (i.e., *over-lubrication*) [6,8,12,13,17,18,24]. Hence, in order to balance the effects of lubricant, the formulation design needs to be optimized taking into account two main variables: concentration of lubricant and applied shear [4,5,25].

The influence of MgSt concentration on the final product characteristics (i.e. hardness, dissolution, bioavailability, etc) is widely recognized but its impact on specific downstream processes is not yet fully understood [26]. Several studies have shown that MgSt has its best performance in low concentrations, commonly from 0.25 to 3% w/w; a critical point over which its lubrication properties do not longer increase and the material flowability tends to reduce as the MgSt cohesiveness begins to prevail [5–7,14,17].

4.2.3. Practical challenges in the granulation of lubricated formulations

In addition to the adverse effects that lubricants can have on the final product (see previous section), it is important to take into account the operational challenges that can arise as consequence of high shear processing:

Fluidization: Usually, lubricants have low density and small particle size compared with other excipients (i.e., Chapter2, Table 2.2). Both characteristics are beneficial for their lubrication purposes but they also promote significant fluidization in agitated beds. This implies that the lubricant will be in less contact with the rest of the formulation during the granulation and it can result in losses, segregation, non-lubricated granules and large amounts of lubricant adhered to the equipment walls and filters.

Wettability: Most lubricants are highly hydrophobic and this property could have a significant effect on granulation. Most liquid binders are prepared as aqueous solutions; therefore the hydrophobicity would affect the binder distribution during the wetting stage and the collision efficiency of the particles during the massing stage.

Detection: It has been challenging to detect and quantify MgSt in pharmaceutical blends due to its low concentration and small size. Analytical methods, such as HPLC and wet-chemistry tests, are difficult to implement mainly because of MgSt poor solubility in water. Some studies have reported characterization methods based on energy-disperse X-Ray (EDX), near infrared spectroscopy (NIR) and radioactivity [14,27–29] while others have implemented indirect approaches measuring the effect of the lubricant concentration on the hydrophobicity of formulations [4,25].

Other considerations: *Cohesiveness* could also be a significant factor in low shear mixers but the processing conditions of a high shear granulator could overcome this issue according to previous studies (Chapter 3). It has been reported that when MgSt reaches a certain concentration, it did not make much difference whether the lubricant is in granular form or powder form in terms of how it performed its lubrication function [12]. The *applied shear* can also affect the mixing grade and dynamics of lubricants [4,14,26]. Recent studies have demonstrated that the *dry premixing* stage is important to define the dispersion of the lubricant and the initial conditions of the material before the wetting stage (Chapter 3). Some researchers have evaluated this effect using shear cells with axial dispersion to create controlled environments of nearly uniform shear conditions [4,25], but there is a lack of experimentation in real high-shear equipment.

The main objective of this work is to study the implications of the lubricant addition (i.e., magnesium stearate) on the early stages of granule growth. The hypothesis was that the MgSt could act as an internal controller of the granulation due to its hydrophobic properties and mixing mechanism (reported previously in Chapter 3).

4.3. Materials and methods

4.3.1. Materials

Blends (3.8:1) of anhydrous lactose (Kerry Bio-science, NY, USA) and lactose monohydrate (Meggle, Granulac® 140, Germany) were prepared adding magnesium stearate (Ligamed MF-2-K, Peter Greven, Germany) as lubricant. Aqueous solutions (2.5% w/w) of povidone (Plasdone K29/32 USP, ISP Technology, NJ, USA) were used as binder agent. Physical properties of the components are detailed in Chapter 2.

4.3.2. Equipment

Experiments were performed in a top-driven laboratory scale high shear granulator (Figure 4.1). The equipment consists of a 2 L stainless steel vessel and a top-driven vertical shaft with a three-bladed impeller located at 5 ± 0.5mm from the vessel walls and 3 ± 0.5mm from the bottom. Impeller velocity was set at 600 rpm for all the experiments. Given the tendency of the magnesium stearate to fluidize, the mixer was equipped with a lid that minimized the empty space inside the granulator but allowed the powder to dilate during the process. This made possible a significant reduction in the fluidization of the lubricant.

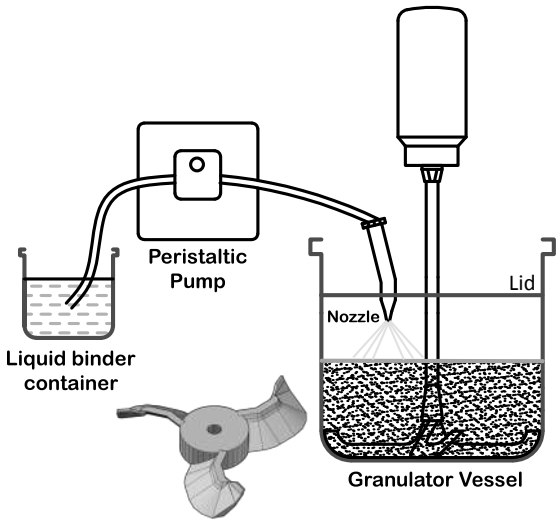

Figure 4.1. Impeller geometry and experimental setting used to process the lubricated formulations.

4.3.3. Experimental design and data analysis

Three levels of applied premixing shear strain were chosen: 450, 900, and 1800 blade passes (bp); corresponding to 15, 30, and 60s, respectively (following the explanation of Section 3.3.2). MgSt was added at four concentrations (i.e., 0.5%, 1%, 2%, and 3% w/w) and the granulation kinetics study was performed at four massing times (i.e., 15, 30, 60, and 90s). A randomized full factorial design with two replicates was performed (Figure 4.2) (Total = 96 treatments). A complete granulation process (i.e., loading – dry premixing – wetting – massing – drying) was performed for each treatment to have representative samples and maintain a constant mass of material inside the granulator minimizing the influence of sampling.

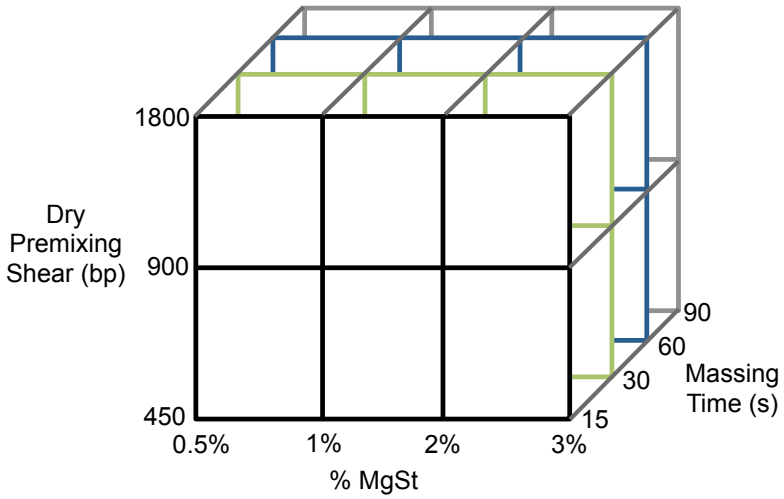

Figure 4.2. Experimental design used to evaluate the granulation kinetics of lubricated formulations.

4.3.4. Granulation process

Premixing

Formulation (250g) was loaded to the granulator adding the ingredients in horizontal layers as shown in Chapter 3 (Figure 3.3). The vessel was closed to reduce suspended particles or losses, and a dry premixing was performed at 600rpm according to the experimental design. The suspended particles were allowed to sediment for 60s before the binder addition. Sample (50g) were taken for characterization at the end of this stage.

High-shear granulation

Liquid binder was sprayed at 1.6 ± 0.1 ml/s using a peristaltic pump drive (Cole-Parmer, MasterFlex Model 7521-40) until reach 12.5%w/w of humidity. The agitation started after 5s of binder addition to decrease the fluidization of fines. Once the binder was completely added, a wet massing period was performed according to the experimental design. The granulated product was dried in trays using a convection oven at 75 °C for 1h.

4.3.5. Characterization

Particle size analysis

Particle size distributions were determined at-line using a laser diffraction method (Insitec T, Malvern, UK) and a data acquisition and analysis software package (RTSizer v.7.20). The method is based on the Mie's solution to Maxwell equations applied to light scattering and was implemented to obtain a volume-based particle size distribution of the samples smaller than 1410μm. Larger granules were separated and manually sieved (Gilson, U.S.A. Standard Test Sieves No. 3, 4, 10, 14) to obtain a mass-based distribution of coarse granules and lumps.

Morphology analysis

Samples were analyzed by scanning electron microscopy (JSM-6390, Jeol) to observe the morphological differences between the initial and granulated product. This technique was also useful for a qualitative identification of MgSt in the surface of the granules considering the morphologies of the formulation components (Chapter 2, Figure 2.3.). Samples (~0.5g) were collected from the granules smaller than 1410μm at three random points. Images of each point were obtained at three magnifications.

Fourier-transform infrared spectroscopy

This technique was used as a qualitative way to determine the presence of MgSt in the fines (<90μm) and find the maximum concentration of MgSt that can be added to have a

non-segregated granulated product. Spectra were collected with a 800 FTIR Scimitar Series (Varian, US) in the range from 1300 to 1800 cm^{-1} using 100 scans at 8 cm^{-1} resolution.

Dissolution test

The dissolution test was performed to assess the impact of the lubricated granules on the final tablet performance. The lubricated granules obtained in the study were used to prepare 10% w/w Acetaminophen (i.e., APAP) tablets using a manual tablet press (Carver, US) at 8 metric tons of compressive force. Another set of tablets was prepared by at the same conditions using direct compression of a blend containing the same concentration of APAP, monohydrate lactose (Dv_{50} = 120μm; Tablettose 70, Meggle, Germany) as diluent and magnesium stearate as lubricant. The dissolution profiles for both types of tablets were obtained following the corresponding USP monograph in an SR8-Plus Dissolution Test Station (Hanson Research, USA) at 50rpm and using 900mL of a phosphate buffer solution (pH = 5.8).

4.4. Results and discussion

4.4.1. Effect of lubricant and premixing shear on the granulation kinetics.

The effect of the applied premixing shear and the concentration of MgSt on the granule growth kinetics was evaluated at different massing times. It was observed that the granulation of non-lubricated blends produced larger granules compared with the lubricated formulations as illustrated in Figure 4.3 that shows the growth profiles of the formulations granulated after 900bp of applied premixing shear strain. Previous studies demonstrated that the addition of MgSt increases the hydrophobicity of the studied formulation as it covers the surface of the carrier particles (Chapter 3). Therefore, the results of Figure 4.3 demonstrate that the MgSt is acting as an internal controller of the granulation, creating regions of low binder affinity on the surface of the particles, which decreases the particle collisions success (i.e., collision efficiency) and slows the granule

growth kinetics. Figures 4.3B-C exemplifies this effect: the distributions show a gradual increase in the particle size at low MgSt concentrations (i.e., 0.5% and 1%w/w). While Figures 4.3D-E demonstrates that high concentrations of MgSt (i.e., 2% and 3% w/w) inhibit the granule growth, producing a single significant size enlargement at the beginning of the massing time. These results supports the hydrophobicity studies presented in Chapter 3, and demonstrates that concentrations above 2%w/w of MgSt produces highly hydrophobic conditions (i.e., over-lubrication) that limit the growth and predictability of the granulation.

A liquid binder layer on the surface of the particles is critical for a successful coalescence process [30]. The results demonstrated that the hydrophobic nature of the MgSt and its mixing mechanism are useful to control the granule growth since it increases the liquid/solid contact angle and restricts the formation of the binder layer. Thus, the lubricant reduces the capacity of the viscous layer to dissipate the kinetic energy of the collisions, decreasing the efficiency of the coalescence mechanism.

Experimental results also indicated that the breakage mechanism was present since the early stages of granulation. For example, Figure 4.3 shows a reduction in the granule size at 30s illustrating the weakness of the granules at short processing times. It is also confirms that the liquid bridge between particles becomes weaker with the addition of lubricant.

The applied premixing shear strain also modified the granulation behavior at short massing times as shown in Figure 4.4. The profiles show that the final granule size decreased with applied premixing shear, which is in agreement with previous work (Chapter 3) that demonstrated that the hydrophobicity of the formulation increases with the premixing shear strain causing smaller and weaker granules.

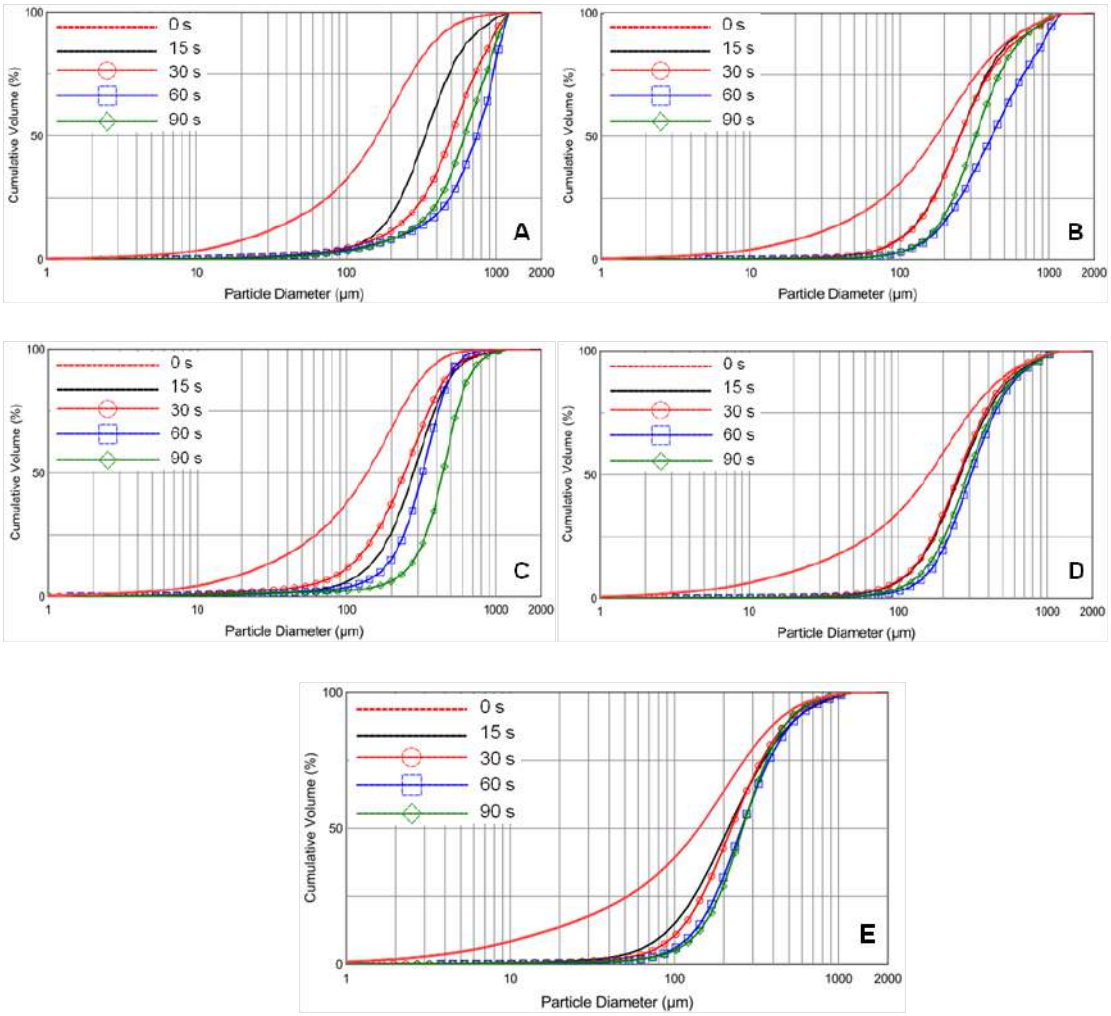

Figure 4.3. Growth profiles of formulations granulated after 900bp of applied premixing shear strain and 0% w/w MgSt (A); 0.5% w/w MgSt (B); 1% w/w MgSt (C); 2% w/w MgSt (D) and 3% w/w MgSt (E).

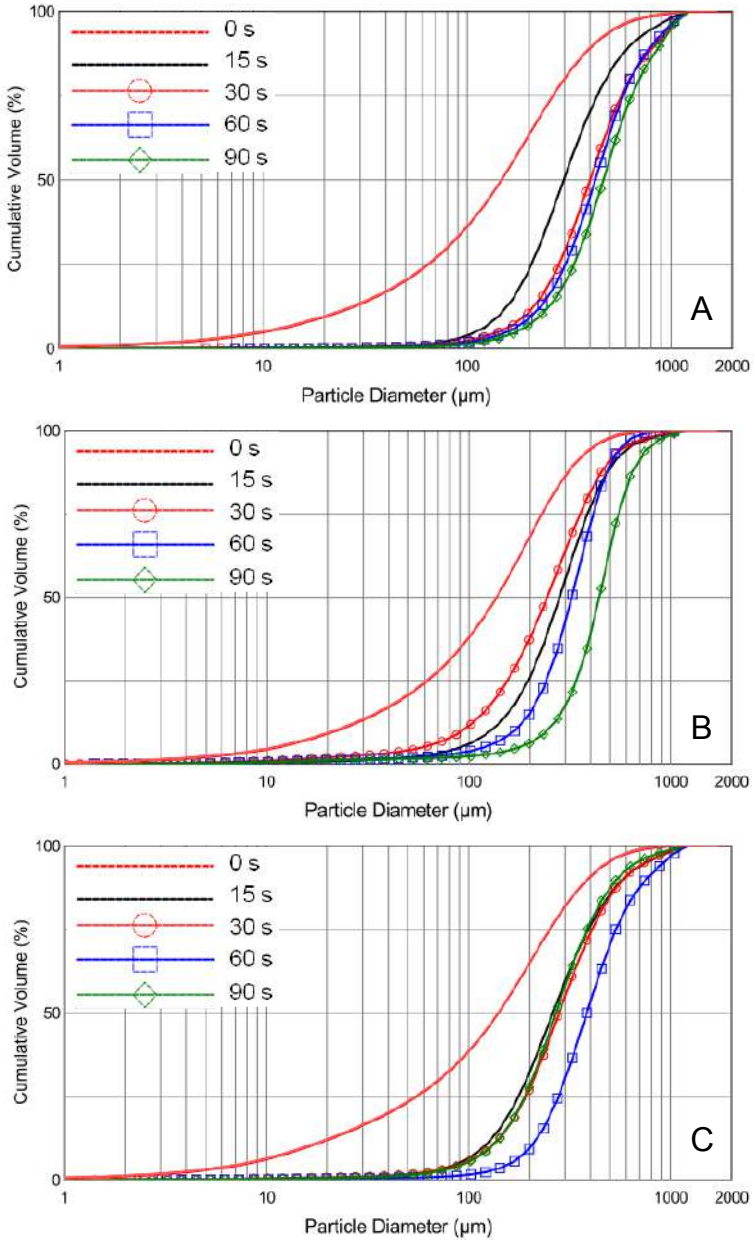

Figure 4.4. Growth profiles of formulations containing 1% w/w MgSt granulated after 450 bp (A); 900bp (B) and 1800 bp (C).

4.4.2. Effect of lubricant addition on the amount of over-granulated material

The conditions inside a high shear granulator usually promote strong interactions between particles that results in large amounts of over-granulated material (i.e., lumps). A poor distribution of liquid binder in the powder bed also produces large lumps that should be milled after granulation. The effect of lubricant on the amount of particles larger than 1410µm was analyzed using analytical sieving (Figure 4.5). The results are in agreement with the granule growth behavior discussed in Section 4.4.1 and demonstrates that the addition of small amounts of MgSt (i.e., 0.5% and 1% w/w), not only offerred a way to control the particle growth, but also decreased the amount of over-granulated material, which would produce a narrower distribution and will reduce the work done by the mill. Although high concentrations of MgSt (i.e., 2% and 3% w/w) decreased the formation of lumps to a higher extent, the hydrophobicity analysis (Chapter 3) and growth study (Section 4.7) demonstrated that they are not adequate to control granulation due to the high hydrophobicity of the formulation and the adverse effects that can cause to the final product performance (e.g., dissolution profiles, bioavailability).

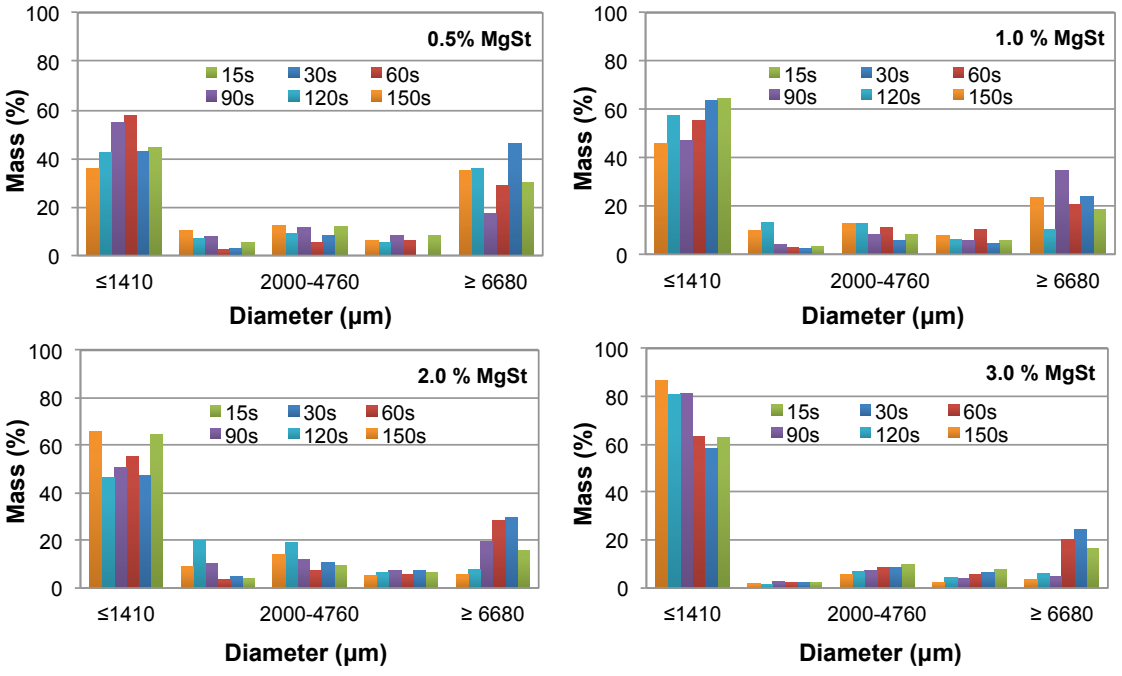

Figure 4.5. Analytical sieving of particles larger than 1410µm obtained after granulating at 900bp of premixing shear strain.

4.4.3. Qualitative assessment of segregated lubricant

Granulated samples were sieved and the granules below 90µm were analyzed by FT-IR. The objective of this experiment was to detect, but not quantify, the MgSt segregation after granulation. Figure 4.6 illustrates the results of the analysis for the granules obtained after 900bp of applied premixing shear strain. The analysis is focused on the wavelengths from 1570 to 1575 cm^{-1}, which correspond to the spectral range with the most significant differences between the MgSt and the rest of the components of the formulation. The results indicated that MgSt was not detectable at low concentrations (i.e., 0.5% and 1% w/w) at any massing time, suggesting low segregation of MgSt. The phenomena was different at high concentrations of MgSt (i.e., 2% and 3% w/w) where it was found in the fines of the granulated formulation at all massing times, demonstrating that the lubricant tends to segregate inside the granulator at concentrations above 1% w/w.

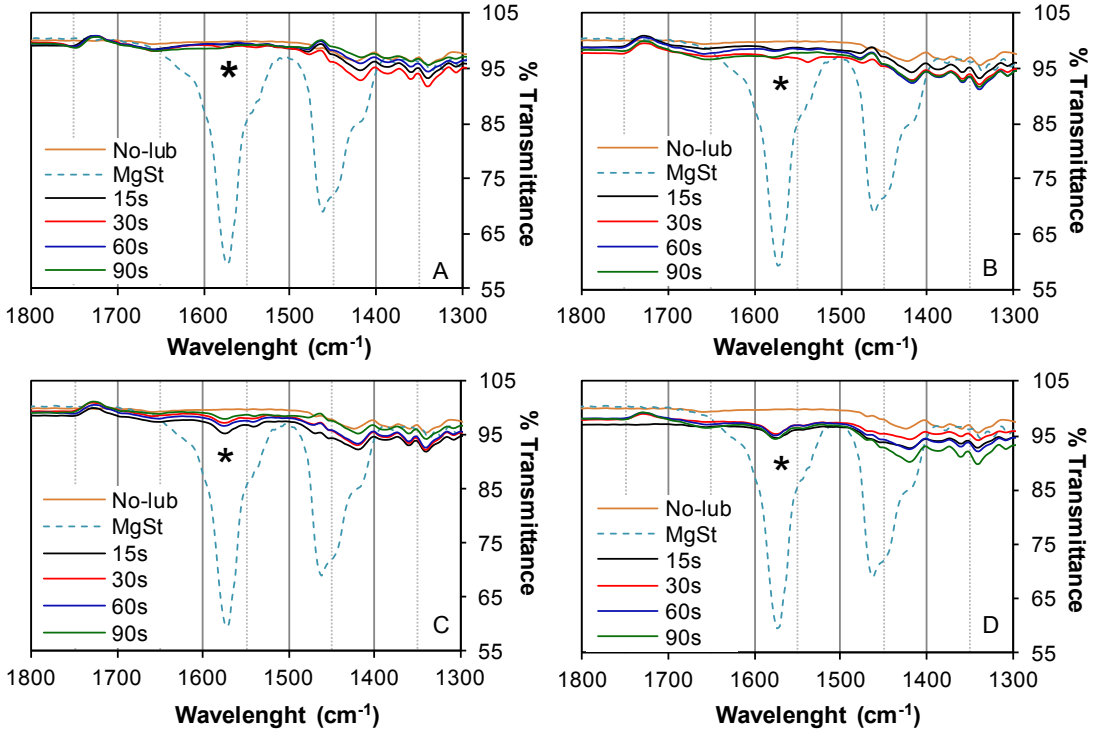

Figure 4.6. FT-IR spectra of samples below 90µm obtained after 90s of massing time. MgSt concentration: 0.5% w/w (A); 1% w/w (B); 2% w/w (C) and 3% w/w (D).

The results were complemented with a morphological analysis of the granules using scanning electron microscope (SEM) images. Considering that MgSt is the

smallest component in the formulation (Dv_{50} = 5.4μm) and the only one that has a flake-like shape (Chapter 2), the images were useful to identify the presence of non-granulated MgSt and its location on the final granules (i.e., granules below 90μm), as shown in Figure 4.7. However, further studies should be carried out to determine the exact location of the lubricant in low concentrated formulations (i.e., below 1%w/w MgSt).

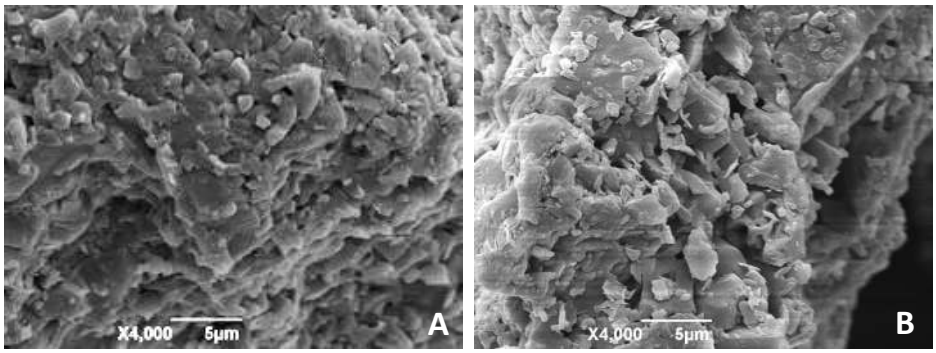

Figure 4.7. SEM images of the granules below 90μm obtained after 900bp of premixing shear strain, 90s of massing time and 0.5% w/w MgSt (A) or 3% w/w MgSt (B).

4.4.4. Effect of lubricated granules in the dissolution profiles of APAP tablets

Lubricants, such as MgSt, are typically added after granulation. They are blended for short times in low shear mixers to avoid over-lubrication that could negatively affect the final product. Considering the high shear conditions of the experiments it was important to evaluate the performance of the obtained granules in the preparation of tablets to understand the effect of the process on the final product. The objective was to compare the dissolution performance of tablets prepared by direct compression using two methods:

- Method 1: Two-step low shear blending process: firstly mixing APAP with lactose monohydrate and then adding the MgSt.
- Method 2: One-step low shear mixing process: mixing APAP with the lubricated granules obtained in this study.

Both types of tablets were prepared at the same compressive force (i.e., 8mtons) and all of them had a comparable hardness (~10 ± 1.4 kp).

Figure 4.8 depicts the average dissolution profiles of the tablets. The results for non-lubricated formulations (i.e., 0% w/w MgSt) show that the tablets prepared by direct compression have a slower dissolution rate than the ones prepared using the prelubricated granules. This behavior was expected since the granulated material is more consolidated than the direct compression formulation. In addition the wide particle size distribution of the granulated material contributes to a better particle arrangement during the compression stage as reported elsewhere [4,23,31].

The dissolution profiles demonstrated that the lubricant concentration increased the dissolution time of the tablets for both preparation methods; however the most interesting result was that all the lubricated tablets had similar dissolution time regardless of the preparation method. This effect confirms the lubrication of the granules and demonstrates that the dissolution time of APAP tablets was not changed by the use of previously prepared lubricated granules. However, this is a preliminary study of the feasibility of lubricated granules and further studies should be developed to understand the impact on other properties of the final product

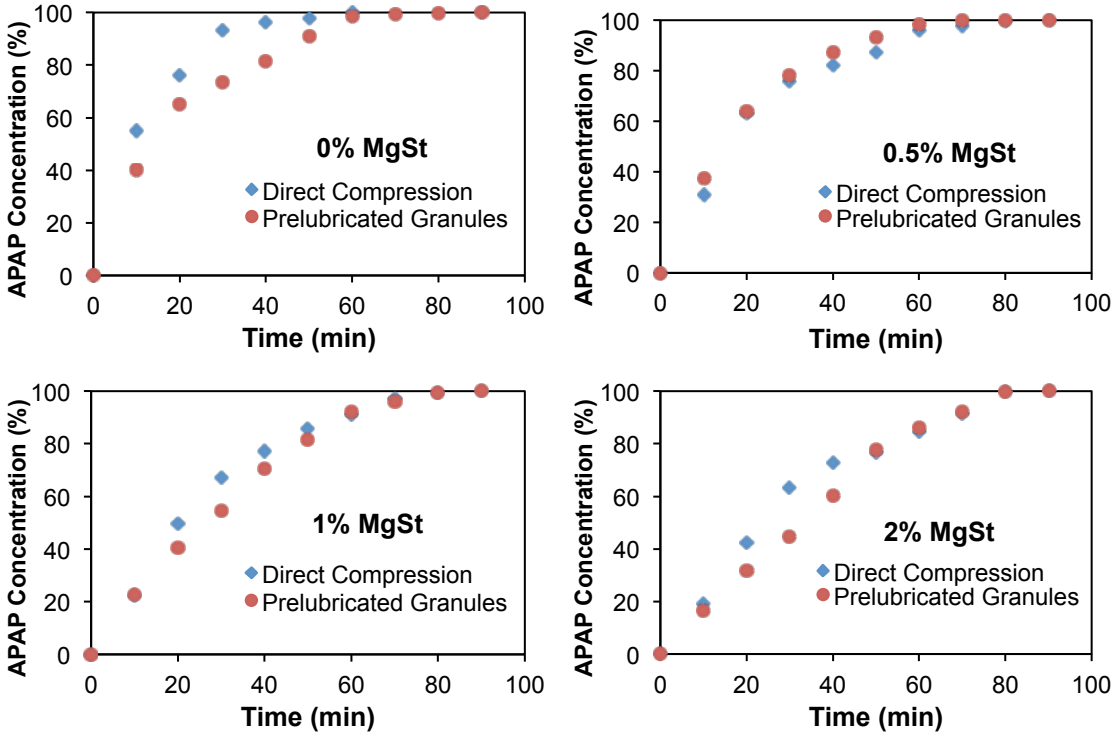

Figure 4.8. Dissolution profiles of 10% w/w Acetaminophen tablets prepared by two methods: direct compression and using prelubricated granules.

4.5. Conclusions

The granulation of lubricated formulations was explored. Binary lactose-based formulations were processed in a laboratory scale high shear granulator at different concentrations of magnesium stearate. The results demonstrated that the lubricant acted as an internal controller of the growth and the final size of the granules. Concentrations below 1% w/w of MgSt produced a growth behavior characterized by a slow and gradual increase in particle size. As the concentration of MgSt increased, the growth was limited by the hydrophobic conditions of the formulation observing only one step of significant granule growth.

The efficiency of the granulation, in terms of the amount of large lumps, was also enhanced with the addition of MgSt, promoting the formation of less over-granulated material. A qualitative analysis showed that the lubricant tends to segregate at concentrations above 1% w/w when processed in a high shear granulator. Lubricated granules were used to prepare Acetaminophen tablets in order to compare their applicability in direct compression. Results showed that the dissolution profiles of the tablets are comparable with a typical direct compression process.

The approach presented in this study can be of interest in formulation design to enhance the predictability of high shear granulation processes. It also opens research areas to understand the production of pre-lubricated excipients, the mechanisms involved, the implications of this material in downstream processes, and the feasibility to use it as a feedstock for continuous processes.

4.6. References

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