The effect of lactose fines, magnesium stearate, choice of mixer and mixing process on the performance of adhesive mixtures for inhalation

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“The effect of lactose small particles and mixing process on the ability of medicine powders to reach the lungs.”

Popular language summary

Dry powder inhaler (DPI) preparation is a key area of interest since they are used by the healthcare system to treat relevant persistent diseases like asthma. Earlier research has shown that the making process and composition of DPI are key for the medicinal ingredient to reach the lungs and have medicinal effects for dry powder inhalers.

The objective of this study was to research the effect of the non-medicinal components in the DPI medicine and mixing processes on the ability of the composition to be used in dry powder inhalers and have medicinal value. The following research work was conducted by using two mixers: Low mixing force (Turbula®) and high mixing force (Diosna®) for the fabrication of the preparations. Three preparations were prepared varying the amount non-medicinal components and mixing time, 27 batches were produced. Small microparticles of budesonide were used as the medicinal ingredient.

Quality control considerations like poured powder density, medicine content evaluation, and mixing consistency were done. Preparation performance was analyzed by using equipment that can filter the particles by their size and it is used to predict the preparation ability to reach the lungs. The chosen device was Novolizer®, 27 devices were filled with each preparation. They were connected to this equipment and the powder quantity in each filter was analyzed.

It was found that adding small particles of lactose and a non-pharmaceutical ingredient that helps the preparation to have less agglomeration can improve the preparation performance. Also, the high mixing force mixer helped the preparations that were made in this mixer to have more probabilities to reach the lungs, than the ones prepared by the low mixing force mixer.

In conclusion, these findings suggest adding small particles of lactose and other non-active ingredients help the formulation to have less agglomeration thus improving performance. In addition, a high mixing force mixer is necessary to boost preparations for DPIs.

ABSTRACT

Introduction: Dry powder inhaler (DPI) formulation is a major area of interest since they are employed by the healthcare system to treat relevant chronic diseases like asthma.

Background: Previous research has established that the manufacturing process and formulation composition are key for the active pharmaceutical ingredient to reach the lungs and achieve therapeutic effects.

Aim(s): The aim of this study was to research the effect of lactose fines and magnesium stearate as well as mixing processes on the performance of adhesive mixtures for inhalation.

Methods: The following research work was conducted by employing two mixers: Low shear (Turbula®) and high shear (Diosna®) for the manufacturing of the formulations. Three formulations were prepared varying the amount of excipients and mixing time, 27 batches were produced and filled into Novolizer® devices. Micronized budesonide was used as the active pharmaceutical ingredient.

Quality control parameters like poured bulk density, drug content assay, and mixing homogeneity were executed. Formulation performance was analyzed by doing particle-size distribution analyses done mostly in an Andersen Cascade Impactor, although Next Generation Impactor was also used. Fine Particle Fraction (FPF) and Fine Particle Dose (FPD) were the central parameters to judge formulation performance.

Results: It was found that both lactose fines and magnesium stearate can improve formulation performance. In addition, high shear mixer formulations presented higher FPF values than low shear formulations.

Conclusion: These findings suggest that lactose fines and magnesium stearate are key ingredients for an improved formulation performance and that high shear mixing is preferred to enhance FPF for DPIs.

Keywords: High shear mixing, low shear mixing, lactose fines, coating agent, budesonide, mixing energy, dry powder inhaler, carrier-based formulations, mixing time.

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The high shear mixer batches were produced thanks to Galenica. I would like to extend my gratitude for the opportunity to use their Diosna® mixer and R&D facilities, especially to Ann-Marie Lyberg for the guidance during the manufacturing.

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PROJECT AIM

- Understand how the addition of fine lactose particles and magnesium stearate can lead to improved delivery of dry powder formulations to the lungs.
- Perform analytical investigations to assess key quality parameters for each formulation.
- Study how the mixing time can impact the quality of a formulation.
- Compare the performance between mixers: (Diosna®) high shear and (Turbula®) low shear.

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LIST OF ABREVIATIONS

ACI	Andersen Cascade Impactor
API	Active Pharmaceutical Ingredient
CDER	Center for Drug Evaluation and Research
COPD	Chronic Obstructive Pulmonary Disease
DI	Deionized
DPI	Dry Powder Inhaler
FDA	Food and Drug Administration
FPD	Fine Particle Dose
FPF	Fine Particle Fraction
g	Gram
GSD	Geometric Standard Deviation
HS	High Shear
IR	Infrared
kPa	Kilopascal
l	Liter
LC	Liquid Chromatography
LS	Low shear
ME	Mixing energy
Mg	Magnesium
min	minutes
mm	milimeter
MMAD	Mass Median Aerodynamic Diameter
NGI	Next Generation Impactor
PS	Pre-separator
PSD	Particle Size Distribution
rpm	Revolutions per Minute
RSD%	Relative Standard Deviation Percentage
UV-VIS	Ultraviolet–visible spectroscopy
WHO	World Health Organization
µm	Micrometer

1. INTRODUCTION

Chronic respiratory diseases like asthma and chronic obstructive pulmonary disease (COPD) have a considerable impact on world health. According to the World Health Organization (WHO), 262 million people have asthma [1], [2]. Asthma is an inflammatory disease, which is characterized by the constriction of the airways causing breath difficulties [3] To treat these diseases, dry powder inhaler (DPI) formulation is a major area of interest since they are propellant-free, they can deliver larger drug doses and they are breath-actuated which makes them easy to use for different age groups [4].

Two important aspects of an effective inhalation therapy are formulation composition and device design [5]. Optimization of powder formulation properties can improve pulmonary drug delivery. DPI formulations contain an active pharmaceutical ingredient (API), and excipients that can be carriers and other particles like fines and coating agents [6]. The API is the most important molecule since it will be responsible for the therapeutic effect. Formulations for DPI aim for the respiratory tract as a target and a delivery route because for drugs to be administrated locally in the lungs, they must travel through the upper and lower conducting regions of the respiratory tract that are designed to prevent the entry of foreign particles. For instance, formulations must be optimized to be able to reach the desired target [4]. The present research utilized budesonide as an API, which is a corticosteroid that is used to treat inflammatory conditions that affect the respiratory system [6], [7].

For an API to reach the lungs, the particle size is essential because it determines the deposition in the respiratory tract. The micronized API has to have an aerodynamic diameter between 1- 5 µm to reach the lungs because at this size both gravitational settling and inertial impaction are favored for lung deposition [4], [5], [6]. In contrast, bigger particles (>5 µm) will deposit in the oropharynx, and smaller particles (<0.5 µm) are less prone to be deposited with the risk of being exhaled *(Figure 1).* The amount of API particles that can be delivered (1 – 5 µm) per loaded dose is defined by the Fine Particle Fraction (FPF) [8], [9]. However, micronized particles (1 - 5µm) present high adhesive and cohesive forces that cause powder agglomeration which leads to a decrease in the powder aerosolization and the capacity of the API to reach the lungs [5], [6].

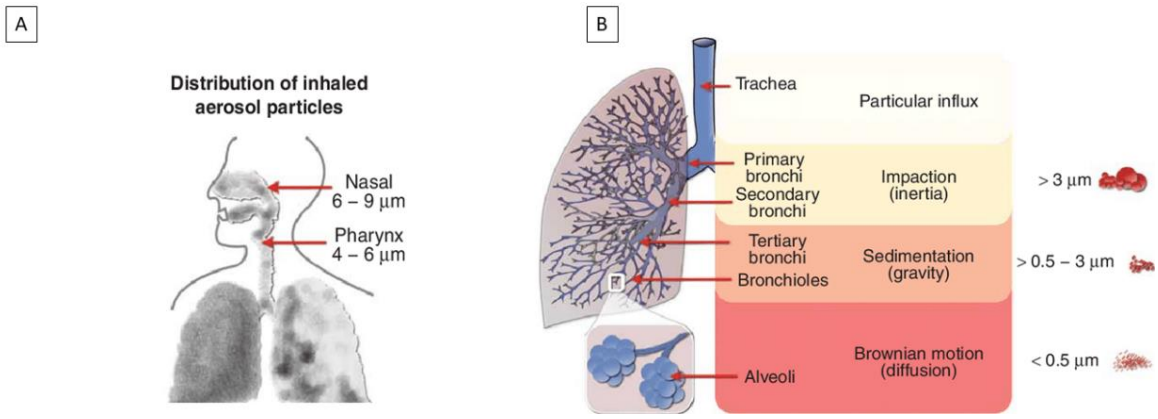

Figure 1 Pulmonary particle size deposition, A= upper respiratory track distribution. B= lower respiratory track distribution. Figure adapted from [10].

This presents a challenge for formulators and that is why excipients are key components of a DPI formulation because they can help to avoid aggregation and improve the fluidization of the powder by adhering to the high-energy sites of the API particles. This distribution of the API over the surface of the carrier forms an adhesive mixture [6], [8], [9], [11].

Lactose is a widely used excipient in DPI formulations because its physicochemical properties like stability and crystalline structure make it an excellent excipient. Manufacturers produce it in several sizes and morphologies that can be used both as carriers and fine particles. These last ones are believed to support the dispersibility of the API by decreasing particle agglomeration [6], [8], [9], [11]. However, the mechanism behind this effect is not well understood. The degree project will address this topic by studying formulations with different lactose fines percentages manufactured at various times and speeds.

In addition, coating agents can be used to enhance the fluidization and dispersion properties of the formulation. In a study conducted by Chan et al. [12], it was found that coating agents can decrease the *"microscopic surface roughness of the carrier"* which can lead to an increase in the detachment of the API from the carrier surface and increase the drug delivery [9], [12]. A second aim of the present research work is to study how the addition of magnesium stearate as a coating agent can lead to improved delivery of dry powder formulations.

The manufacturing process impacts the formulation performance, especially when it comes to adhesive mixtures where mixing variables like mixer choice, rotation speed and time have a critical impact on mixing homogeneity as well as drug delivery in the lungs [6]. At the mixing stage, the formulation powder is subject to inertial, frictional, and shear forces that impact drug/carrier adhesion [8]. This research work studied the aforementioned variables, two types of mixers were employed: Low shear mixer (Turbula®) and high shear mixer (Diosna®).

Shear mixing is recommended for DPI formulation because the shear force will promote deagglomeration. The low shear mixer (Turbula®) has a rotary vessel where the formulation powder tumbles around inside, the mixing process occurs due to shear and diffusive mixing. In contrast, the high shear mixer (Diosna®) has a stationary vessel with impeller mixer blades that can achieve high rotational speeds that produce high shear forces and mixes the powder by convection and shear forces [8].

For high shear mixers, it has been found by Thalberg et al. [9], that the performance of adhesive mixtures for inhalation can be controlled using the mixing energy concept which explains the forces that are applied on particles and their effects on formulation performance. This research work aims to explore this concept in terms of dispersibility through FPF [8], [9], [13].

To study the FPF and other quality parameters for each formulation special instruments that measure aerodynamic particle size distributions of the aerosol cloud from the DPIs are used. These instruments are called impactors and are recognized by regulatory agencies as an *in vitro* methodology to predict lung drug delivery and formulation efficiency. The science behind their action is based on particle separation at different stages according to their aerodynamic size [14], [15]. The two types of impactors that were used in this research were the Andersen Cascade Impactor (ACI) and the Next Generation Impactor (NGI). These techniques allow the determination of the Fine Particle Dose (FPD), FPF, MMAD (Mass Median Aerodynamic Diameter), Delivered Dose (Sum NGI or Sum ACI), and distribution profiles [15].

There are several DPI devices available on the market. This research used a multidose device called Novolizer®, which utilizes refill cartridges, and has a triggering feedback mechanism that can be activated at low inspiratory flow rates (35-50 l/min). Powder dispersion during inhalation in the Novolizer® device is achieved by the presence of a cyclone inside the device that causes centrifugal energy, which allows it to produce an effective particle flow and deagglomeration. In addition, the metering dose system of this device is characterized by being robust and accurate [5], [14], [16].

The purpose of the present degree project was to understand the effect of lactose fines and magnesium stearate as well as mixing processes on the performance of adhesive mixtures for inhalation. Three formulations were manufactured using different strategies like excipient quantities, mixer choice, time, and speed, in total 27 batches were produced. Impactor investigations were used to assess key quality parameters for each formulation and the concept of mixing energy was explored for high shear mixer formulations. Further details about the formulation composition and mixing strategies can be found in the next section.

2. MATERIALS AND METHODS

The current investigation involved manufacturing and analytical investigations to study the effect of lactose fines, magnesium stearate as a coating agent, choice of mixer, and mixing parameters on the performance of adhesive mixtures for inhalation.

2.1. Manufacturing

Budesonide was used as an API, and the excipients employed were: LH206 as the lactose carrier, LH 300 micronized as lactose fines, and magnesium stearate as the coating agent *(Table 1).*

Table 1 Raw materials used to manufacture the formulations.

Material type	Grade	Supplier	Batch number
API	Budesonide	AstraZeneca	4211059-01
Lactose carrier	LH 206 Lactose carrier	DFE Pharma	600365
Lactose carrier	LH 206 Lactose carrier	DFE Pharma	733729
Lactose fines	LH 300 Micronized	DFE Pharma	1083C67
Coating agent	Magnesium stearate	Peter Greven	C723845

Three formulation types were produced, and the API amount was constant. However, the excipient quantities varied. An overview is given in *Table 2.*

Table 2 Formulation composition.

Raw material	Formulation 1 Amount (%)	Formulation 2 Amount (%)	Formulation 3 Amount (%)
Budesonide	2.0	2.0	2.0
LH 206	96.0	94.0	93.0
LH 300	2.0	4.0	4.0
Magnesium stearate	0.0	0.0	1.0

To study the manufacturing strategies to optimize the DPI's formulation, two mixers were used: Low shear mixer (Turbula®, *Figure 2*) and high shear mixer (Diosna®, *Figure 3*). For low shear mixer (Turbula®), three mixing times were tested (10, 30, and 60 min) each time representing a batch for each formulation. The mixing process required dividing the total mixing time into two halves and in the stop the powder mixture was sieved (Mesh: 0.710 mm). Examples of batch records can be found in the appendix.

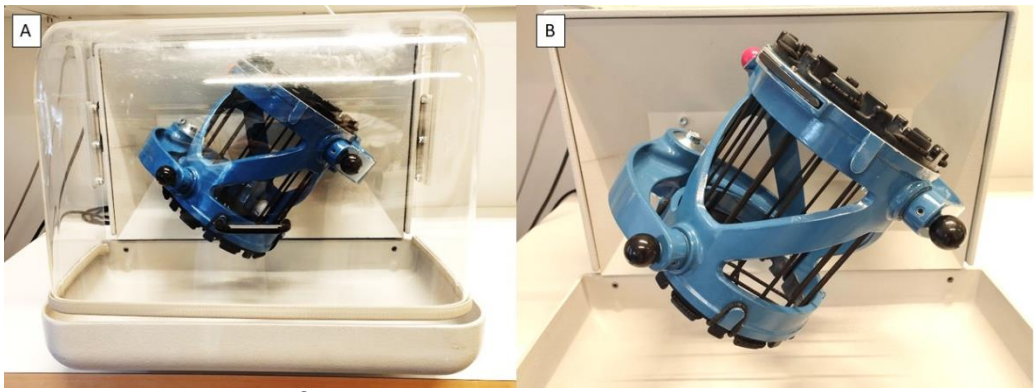

Figure 2 Low shear mixer (Turbula®) A: Full picture of the mixer. B: Place for the mixer vessel. Pictures taken courtesy of Department of Food Technology, Engineering and Nutrition. The rubber rings held tightly the container.

A codification name system was used to refer to the individual Turbula® batches *(Table 3).* The speed during the process was constant (68 rpm) and the batch size was 80 g of powder mixture for each batch.

Table 3 Low shear mixer batch names.

Mixing time (min)	Formulation 1	Formulation 2	Formulation 3
10	LS1A	LS2A	LS3A
30	LS1B	LS2B	LS3B
60	LS1C	LS2C	LS3C

LS stands for "Low Shear", the numbers refer to the formulation number and the letters refer to the mixing time.

For the high shear mixer (Diosna®, *Figure 3).* An initial premixing step at 150 rpm for 1 minute was performed. When this was completed, three mixing times (3, 6, and 9 min) were tested for each formulation at two different mixing speeds (700 and 1000 rpm). Each time and mixing speed representing a batch for each formulation, an overview is given in *Table 4*, and examples of batch records can be found in the appendix.

The total intended batch size was 250 g of the powder mixture. However, the production process in the high shear was continuous, the mixing time represents stops during the process. Samples of approximately 40-50 g, were taken from different parts of the bowl while avoiding lumps into the plastic container for each time stop. For the last mixing time (9 min) a sieving step was performed using a mesh (size 1.00 mm).

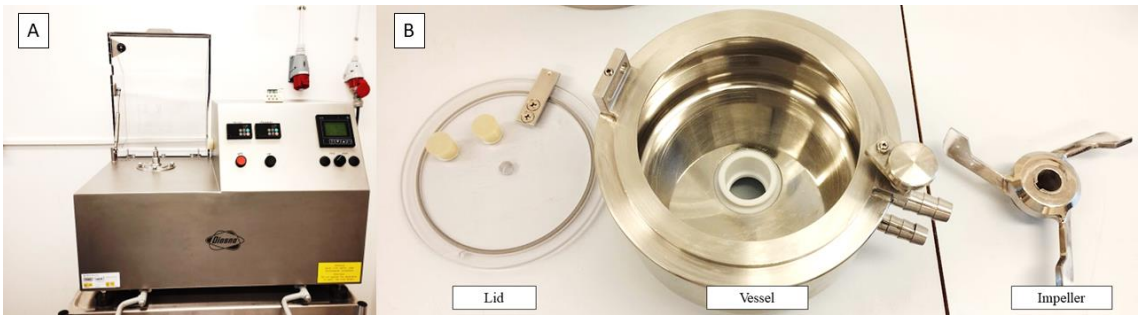

Figure 3 High shear mixer (Diosna® mixer P1-6). A: Full picture of the mixer. B: Mixer parts, the mixer vessel had a 1 liter capacity. Pictures taken courtesy of Galenica.

Table 4 High shear mixer batches names.

Mixing speed (rpm)	Mixing time (min)	Formulation 1	Formulation 2	Formulation 3
700	3	HS1A	HS3A	HS5A
	6	HS1B	HS3B	HS5B
	9	HS1C	HS3C	HS5C
1000	3	HS2A	HS4A	HS6A
	6	HS2B	HS4B	HS6B
	9	HS2C	HS4C	HS6C

HS stands for "High Shear", the numbers refer to the manufacturing order and the letters refer to the mixing time where A= shortest mixing time (3 min), B= middle mixing time (6 min), C= longest mixing time (9 min). 18 batches were produced.

For high shear formulations, the temperature was taken at each time stop using a Testo® Thermometer IR. For safety reasons, before opening the mixer lid 1 minute had to pass after that the temperature was recorded. There was no heating for the low shear mixer batches. The raw materials were weighted in analytical and semi-analytical scales according to each formulation composition *(Table 2).* The order to incorporate the raw materials in the mixing vessels followed the "sandwich method" where the first half of the lactose carrier was added, followed by the API and the lactose fines, and last the rest of the lactose carrier was added.

For formulation 3 a coating step was carried out for the lactose carrier with magnesium stearate. The “sandwich method” was used where half of the lactose carrier was added to the mixer vessel, followed by the magnesium stearate and then the rest of the lactose carrier was added. For the low shear mixer, it required mixing for 15 min, followed by sieving (Mesh: 0.710 mm), then another mixing for 15 min. After this the API and the lactose fines were added using the “sandwich method”.

In comparison, the coating step for the high shear mixer required a premixing step at 700 rpm without stopping for 4 minutes. No sieving was performed, after the coating, the API and the lactose carrier were added using the “sandwich method”. After the mixing process, the batches were stored in airtight light protected containers at room temperature of at least 250 ml capacity.

2.2. Filling

The filling process was performed manually into the Novolizer® device. The dose reservoir of the device was opened, emptied, and cleaned. Each inhaler contained a batch sample between 1.5 - 2.5 g of the powder mixture. Before performing further methodological steps a waiting time of at least 3 days had to pass after the filling.

For ACI analysis, three wasting doses were performed for each device before the official analysis, a waiting time of at least one day had to pass before the ACI major analysis. For NGI, one wasting dose was performed and the NGI analysis was performed right after the wasting. The same inhaler device was used for both analyses *(Figure 4).*

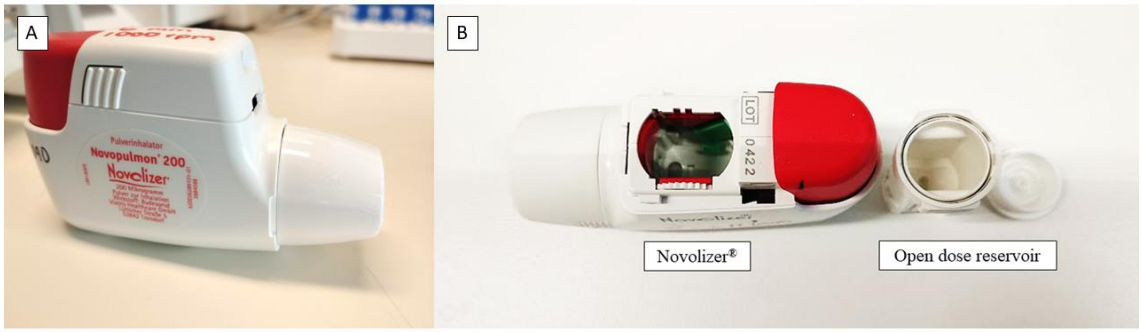

Figure 4 Novolizer® A: Device B: Clean device ready for filling

2.3. Analytical investigations

There was a waiting time of at least one week before starting the analytical investigations to allow the relaxation of the powder mixture for every batch. This was performed to reduce the electrostatic energy that can cause variability in the results.

2.3.1. Mixing homogeneity and drug content assay

Mixing homogeneity or blend uniformity and budesonide content assay, are a quality parameter essential to determine the efficacy of the mixing and target dose concentration [17]. These analyses were performed for the shortest mixing time and slowest speed batches *(Table 5)*, samples of between 20-50 mg were taken from at least 6 points (3 from the surface + 3 from the middle) of each batch container. The samples were reconstituted in a solution of ethanol/water 50% v/v, and a calibration curve was prepared to determine the concentration of budesonide in each sample. To detect budesonide in each sample a Varian Cary® 50 Bio

UV-Vis Spectrophotometer instrument and software was used. Budesonide was measured at a wavelength of 245 nm. The relative standard deviation percentage (RSD%) and the average concentration of budesonide (%w/w) were calculated for every batch in *Table 5* [18]. Fabric gloves were used while weighing to reduce electrostatic formation that could affect the analyses.

Table 5 Mixing homogeneity and drug content assay analyzed batches.

Mixing time (min)	Low shear mixer	Mixing time (min)	High shear mixer (700 rpm)
10	LS1A	3	HS1A
10	LS2A	3	HS3A
10	LS3A	3	HS5A

LS= Low shear HS= High shear

2.3.2. Poured bulk density.

Bulk density is a measure of the flowability of the powder [18]. The densities were measured by using a 20 ml density tester cylinder. At least three replicates were performed for each batch. The lactose carrier LH206 was used as a reference material. The standard deviation of the replicates was calculated to assess the variability of the results the process can be found in *Figure 5.*

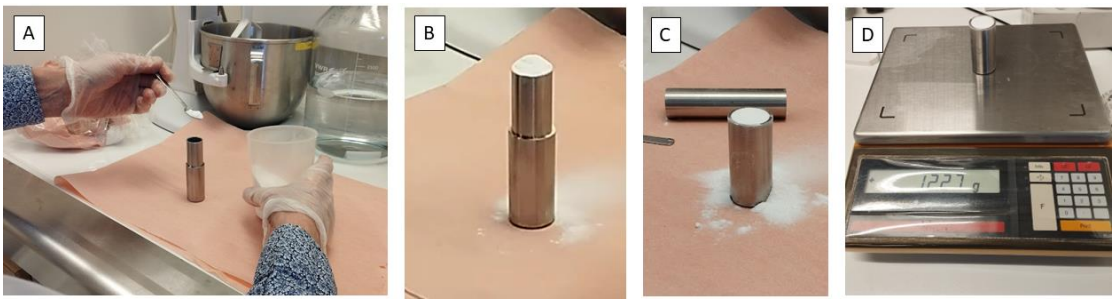

Figure 5 Poured bulk density process. A: Pouring of the powder mixture. B: Filled density test cylinder (20 ml). C: Scraped density test cylinder (20 ml). D: Weighted density test cylinder (20 ml).

2.3.3. Andersen Cascade Impactor (ACI)

The cascade impactors analyze the aerodynamic size distribution of the aerosol particles [5]. The ACI analysis was performed at least 24 hours after the wasting process for every batch. The ACI plates for each stage were coated with BRIJ/glycerol and the pre-separator (PS) was filled with 15 ml of an ethanol/water 50% v/v solution to avoid particle bouncing [19]. The ACI system was calibrated before the analysis where the flow was adjusted to 80 l/min corresponding to a pressure drop of 4 kPa. The device was triggered by a critical flow controller and pump *(Figure 6).*

Six doses were discharged from the filled device to the ACI. The analysis was done with at least two replicates for each batch. The formulation powder that impacted each plate was reconstituted with 15 ml of ethanol/water 50%v/v solution. The throat and the mouthpiece adapter were washed with the same solution. The budesonide concentration in each stage was analyzed by a Varian Cary® 50 Bio UV-Vis Spectrophotometer employing a calibration curve. Budesonide was measured at a wavelength of 245 nm.

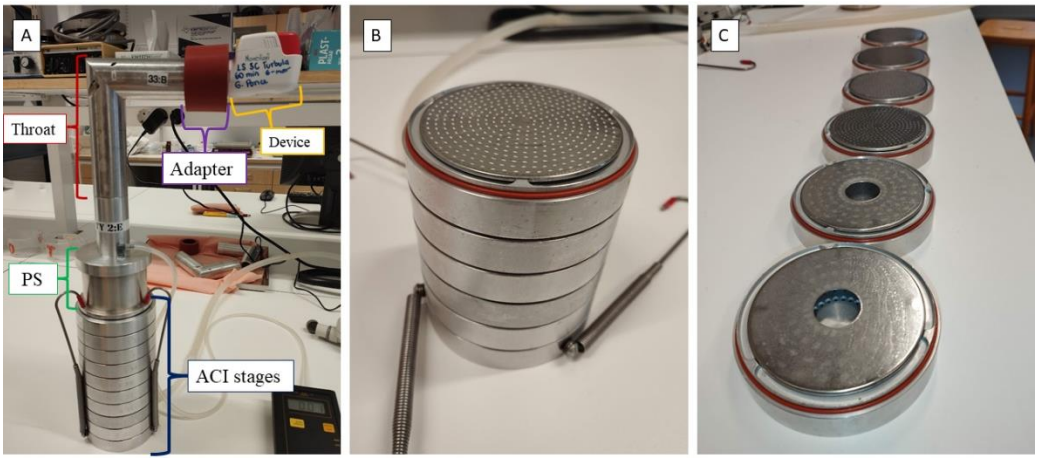

Figure 6 Andersen cascade impactor (ACI). A: ACI full system. B & C: ACI plates impacted with powder mixtures. Pictures taken courtesy of Department of Food Technology, Engineering and Nutrition.

2.3.4. Next Generation Impactor (NGI)

The NGI *(Figure 7)* is a useful and efficient aerodynamic particle size analyzer that has seven stages in a built-in tray single unit [15]. This instrument was used courtesy of Emmace Consulting. NGI was used to analyze formulation 1 high shear mixer 700 and 1000 rpm *(Table 4)*. One waste dose was performed before the analysis for every inhaler device. The NGI plates for each stage were coated with BRIJ/glycerol, and the pre-separator (PS) was filled with 15 ml of an ethanol/water 50% solution. The NGI system was calibrated before the analysis where the flow was adjusted to 80 l/min corresponding to a pressure drop of 4 kPa. The device was triggered by a critical flow controller and pump.

Six doses were discharged from the filled device. The analysis was done with at least two replicates for each batch, the formulation powder that impacted each plate was reconstituted with 15 ml of an ethanol/water 50% solution. The throat and the mouth adapter were washed with the same solution. Budesonide concentration in each stage was analyzed by LC with a UV-VIS detector, and the concentrations of the API were calculated employing a calibration curve.

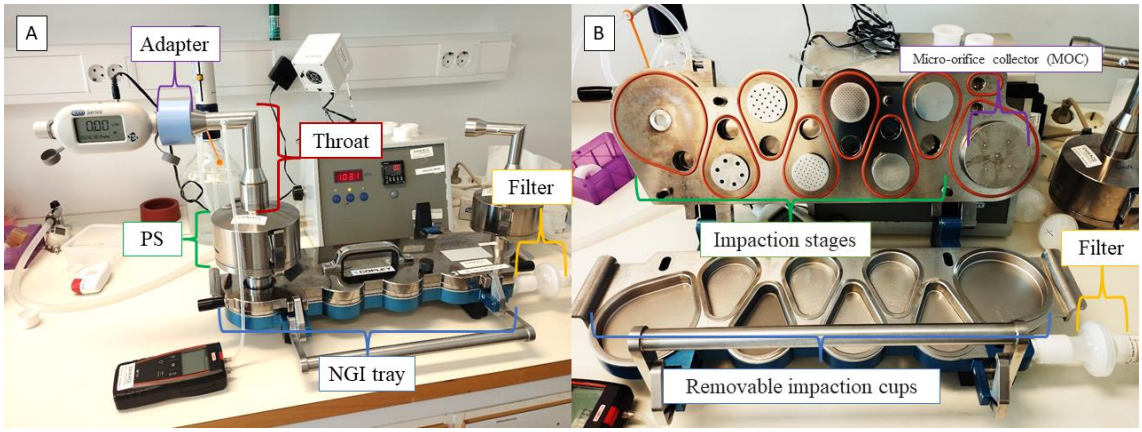

Figure 7 Next Generation Impactor (NGI). A: Full picture of the NGI system. B: Open NGI tray. Pictures taken courtesy of Emmace AB.

2.3.5. Particle size

There were two batch numbers for the Lactose Carrier LH206 *(Table 1)*. The batch number 600365 was used for the manufacture of all the batches except for formulation 3 high shear mixer 700 and 1000 rpm *(Table 4)* where the batch number 733729 was used since the quantity of the first excipient (600365) was not enough for the production of the last formulation batches (formulation 3, high shear mixing 1000 rpm), *(Table 4)*.

Therefore, it was necessary to determine if both carriers presented the same particle size distribution. A particle size distribution analysis using laser diffraction (wet and dry dispersion) was performed for both batches. A Malvern Mastersizer 3000 instrument *(Figure 8)*, equipped with a 300mm reverse Fourier lens was employed.

For wet dispersion, the solid samples were introduced directly to the Hydro HV unit with a spatula. Measurement was performed during stirrer dispersion and after internal sonication at 20% power for 1 minute. In comparison, for dry dispersion, the samples were introduced directly into the Aero S feeder funnel at 2 bar pressure.

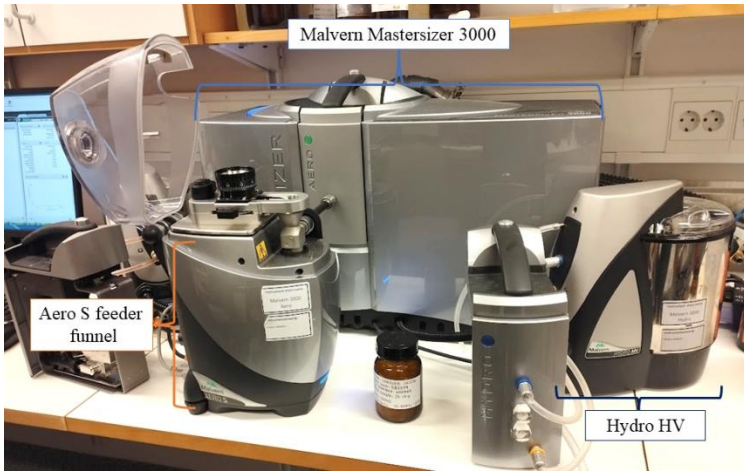

Figure 8 Malvern Mastersizer 3000 instrument. Pictures taken courtesy of Magle Chemoswed AB.

2.3.6. Calculations

The concept of Mixing Energy (ME) was explored for the high shear mixer batches *(Table 4)*, to understand how the forces applied to the particles during the mixing process influence the formulation performance [9]. The forces that cause centrifugal motion and the mixing vessel radius combined with the carrier particle mass are behind the expression of the mixing energy [9], [13], *Equation 1*:

$$ME = m_{carrier} * \frac{v^3}{r} * t$$

m=carrier particle mass, v=peripheral velocity, r=mixing vessel radius, t=mixing time.

If rotational speed in the mixing process is expressed in terms of revolutions per minute, instead of the peripheral velocity, the mixing energy equation used in this research work will be, *Equation 2*:

$$ME = 8\pi^3 m_{carrier} * (\frac{rpm}{60})^3 r^2 t$$

m=carrier particle mass, rpm=revolutions per minute, r=mixing vessel radius, t=mixing time.

3. RESULTS AND DISCUSSION

3.1. Particle size

From the overlay of the graphs in *Figure 9*, it can be inferred that there is not a significant difference between the carriers from different batches. This was important to measure because the carrier particle mass is a value used for the mixing energy calculation [9].

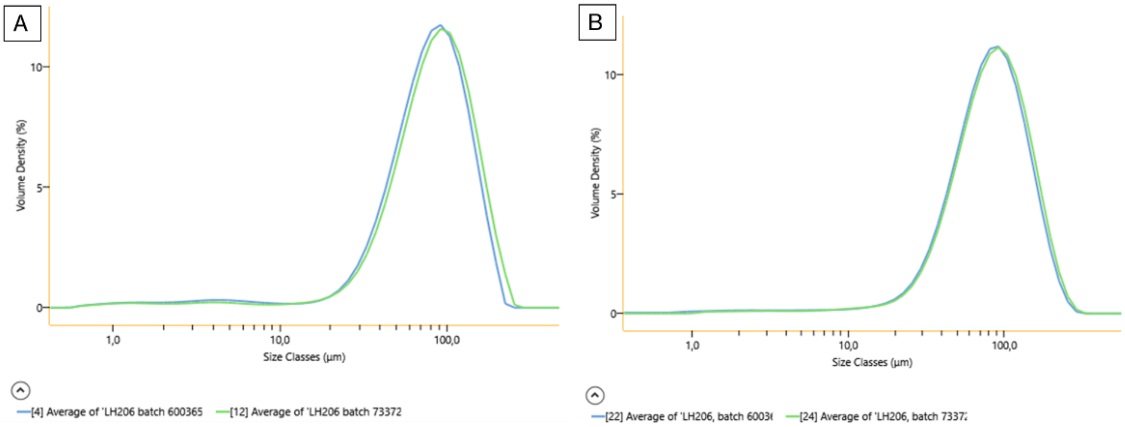

Figure 9 Overlay of Particle Size Distribution (PSD) graphs Lactose carrier LH206: A: Wet dispersion batch 600365 (blue) and batch 733729 (green). B: dry dispersion 2 bar batch 600365 (blue) and batch 733729 (green). Graphs courtesy of Magle Chemoswed.

3.2. Manufacturing

Table 6 presents the obtained production yield for low shear mixer (Turbula®). High production yields (>98%) were consistently obtained for all the batches regardless of the mixing time of formulation composition.

Table 6 Production yield for Low shear mixer batches

Formulation	**1**			**2**			**3**		
Batch	**LS1A**	**LS1B**	**LS1C**	**LS2A**	**LS2B**	**LS2C**	**LS3A**	**LS3B**	**LS3C**
Mixingtime (min)	10	30	60	10	30	60	10	30	60
Production yield (%)	98.9	100.1	99.5	99.9	99.8	100.0	99.1	98.8	99.1

For batch composition see Table 3.

Table 7 reports the obtained production yield for high shear mixer (Diosna®) at a mixing speed of 700 rpm, where it can be noted that Formulation 3 (Budesonide 2%, lactose fines 4%, magnesium stearate 1%, and lactose carrier 93%) had the lowest total production yield percentage. Nevertheless, all the batches presented yield values above 90 %.

Table 7 Production yield for high shear mixer batches at 700 rpm.

Mixing speed	**700 rpm**								
Formulation	**1**			**2**			**3**		
Batch	**HS1A**	**HS1B**	**HS1C**	**HS3A**	**HS3B**	**HS3C**	**HS5A**	**HS5B**	**HS5C**
Mixing time (min)	3	6	9	3	6	9	3	6	9
Formulation produced (g)	44.1	42.3	157.4	42.2	44.5	155.2	48.6	54.7	133.3
Total production yield (%)		97.5			96.8			94.6	

For batch composition see Table 4

Table 8 shows the obtained production yield for high shear mixer (Diosna®) at a mixing speed of 1000 rpm, where it can be noted that formulation 3 (Budesonide 2%, lactose fines 4%, magnesium stearate 1%, and lactose carrier 93%) had the lowest total production yield percentage. Nevertheless, all the batches presented yield values above 90 %.

Table 8 Production yield for high shear mixer batches at 1000 rpm.

Mixing speed	**1000 rpm**								
Formulation	**1**			**2**			**3**		
Batch	**HS2A**	**HS2B**	**HS2C**	**HS4A**	**HS4B**	**HS4C**	**HS6A**	**HS6B**	**HS6C**
Mixing time (min)	3	6	9	3	6	9	3	6	9
Formulation produced (g)	46.6	46.5	141.9	50.7	49.4	137.3	64.1	43.5	119.1
Total production yield (%)		93.9			95.0			90.7	

For batch composition see Table 4

The difference between the yields obtained for formulation 3 (Budesonide 2%, lactose fines 4%, magnesium stearate 1%, and lactose carrier 93%) might be due to the coating agent since it is known that blending time can increase the shearing of magnesium stearate layers and produce surface adherence between particles. This might have produced an adherence between the surface of the blender and the particles and it was observed at the end of the manufacturing process [20], [21], *(APPENDIX, Figure 35).*

Figure 10 shows that high mixing speed (1000 rpm) and longer mixing time (9 minutes), formulations presented higher temperature increase. This was expected because the impeller movement can cause friction between particles which can cause an increase in temperature [22]. In formulation 3 (Budesonide 2%, lactose fines 4%, magnesium stearate 1%, and lactose carrier 93%) the presence of magnesium stearate 1% helped to maintain the temperature at a medium level, compared to formulations 1 and 2.

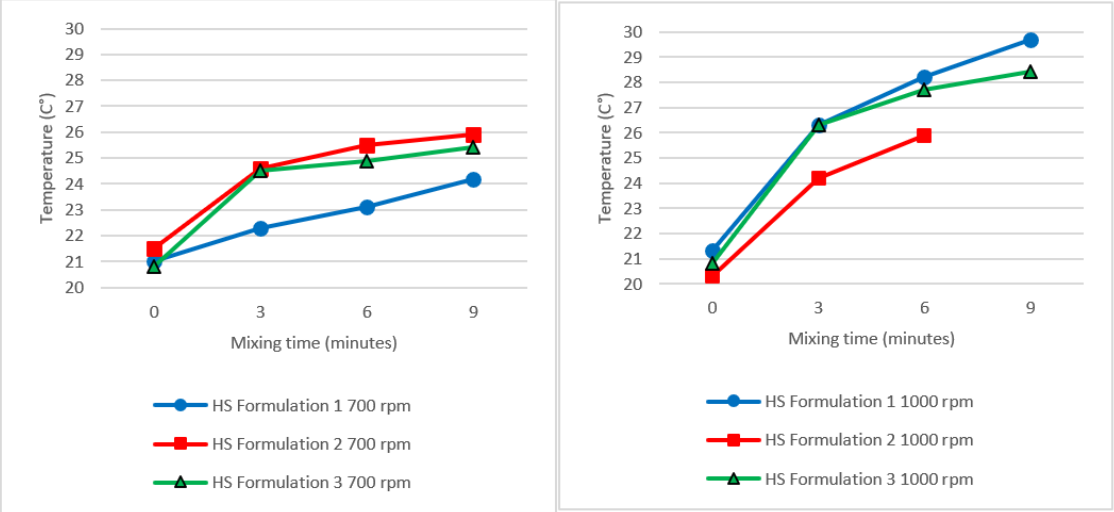

Figure 10 Temperature measurements for high shear batches. There is a missing value at 9 minutes, for the batch HS Formulation 2 1000 rpm, due to human error. Formulation composition details can be found at Table 2.

3.3. Budesonide content assay and Mixing homogeneity

Figure 11 reports that the low shear mixer results are closer to the target concentration (budesonide 2%), compared to the high shear mixer batches, where HS3A and HS5A have lower budesonide concentrations.

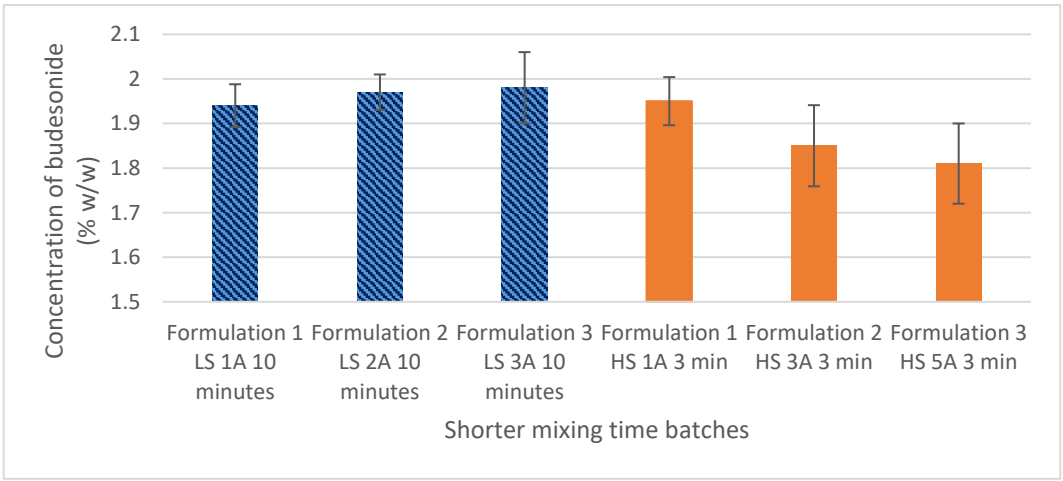

Figure 11 Concentration of budesonide in percentage for the shorter mixing time batches and lower speed. Formulation composition details can be found at Table 2.

Figure 12 bar graphs show that the low shear mixer results presented less variability than the high shear batches. Nevertheless, all the batches followed the FDA/CDER criteria for validation in batch powder mix homogeneity that state: *"RSD (relative standard deviation) of all individual results ≤ 5.0 percent and all individual results are within 10.0 percent (absolute) of the mean of the results"* [23].

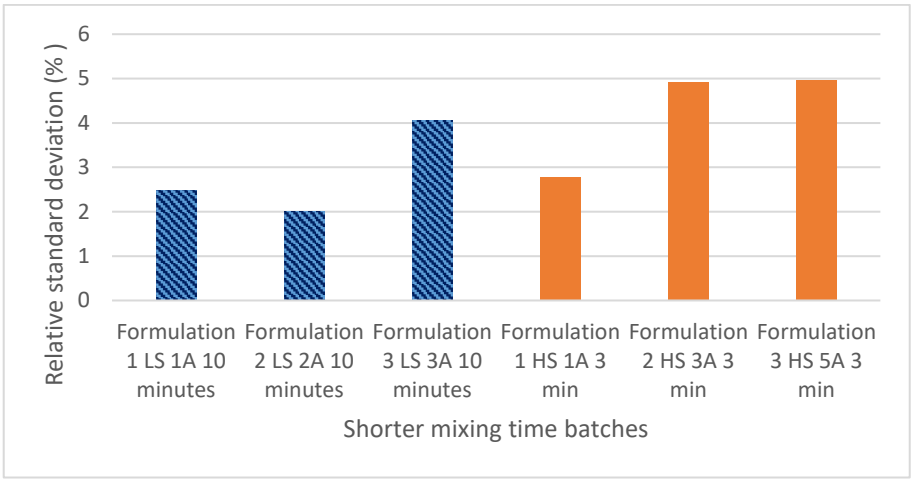

Figure 12 Mixing homogeneity shows the relative standard deviation in percentage for the shorter mixing time batches and lower speed.

The mixing homogeneity result *(Figure* 12*)* was somewhat unexpected, because according to Sarkar et al. [24], high shear mixers are shown to produce more homogeneous mixes. Nevertheless, since the values obtained followed the quality parameters both mixers had acceptable results [23], [24]. The findings imply that the powder mix for the low shear batches has a satisfactory degree of homogeneity. Furthermore, the homogeneity is expected to improve the longer the mixing time for both mixers.

3.4.Bulk density

Figure 13 shows that there is an increase in the pored bulk density for Formulation 3 (Budesonide 2%, Lactose fines 4%, Mg stearate 1% and Lactose carrier 93%) (green). The red dot presents the result of the pure lactose carrier LH206 it can be used as a reference.

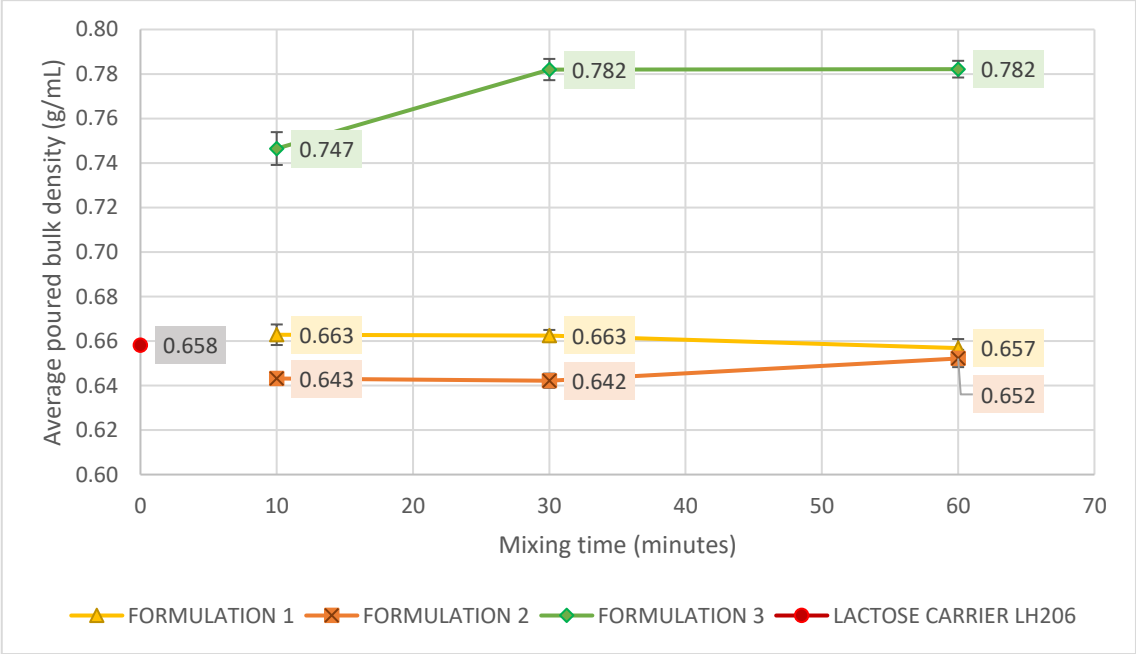

Figure 13 Poured bulk density for low shear mixer formulations average values are presented. For formulation detail composition refer to Table 2.

Figure 14 shows the average values for 700 and 1000 rpm batches. Formulation 3 (Budesonide 2%, Lactose fines 4%, Mg stearate 1%, and Lactose carrier 93%) had a higher level of bulk density than the formulation 1 and 2, for both low speed (700 rpm) and high speed (1000 rpm). The red dot presents the result of the pure lactose carrier LH206, it can be used as a reference. The increase in poured bulk density means that the formulation has a higher flowability [25].

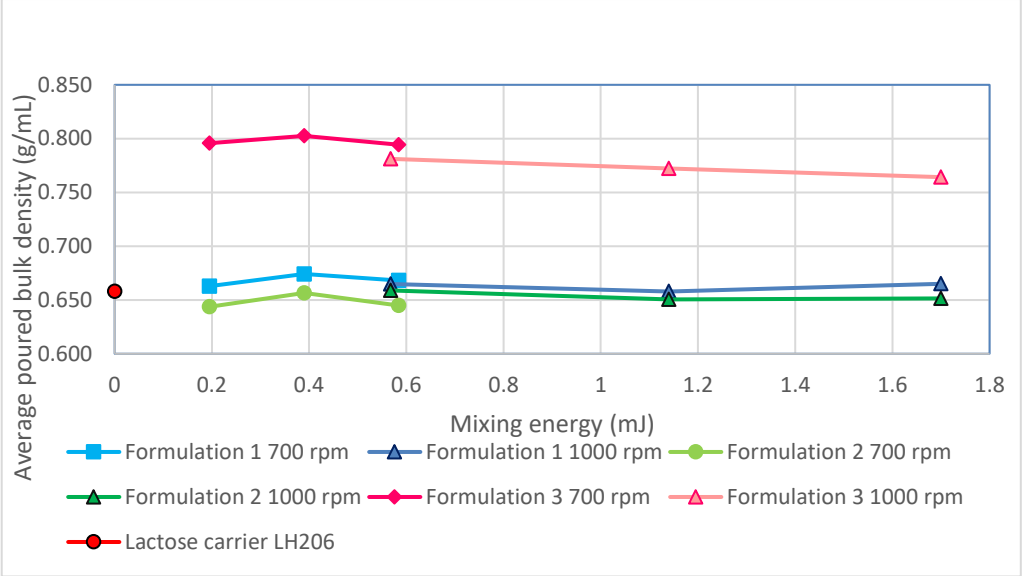

Figure 14 Poured bulk density for high shear mixer formulations. For formulation detail composition refer to Table 2.

The poured bulk density decreases for formulation 2 (Budesonide 2%, lactose fines 4%, and lactose carrier 94%) compared to the lactose carrier LH206 for both mixers. This was expected and it was previously observed by Thalberg et al. [26]. The overall results propose that adding magnesium stearate as a coating agent increases the poured bulk density of the powder mixture for both low and high shear mixing processes.

3.5. ACI

3.5.1. Low shear mixer batches

The results in *Figure 15* suggest that for formulation 1 (Budesonide 2%, lactose fines 2%, and lactose carrier 96%) there is an increase in FPD at a mixing time of 60 minutes. For instance, a lower percentage of lactose fines leads for a need of longer mixing times to achieve a higher FPF.

In comparison, formulation 2 (Budesonide 2%, lactose fines 4%, and lactose carrier 94%) and formulation 3 (Budesonide 2%, lactose fines 4%, magnesium stearate 1%, and lactose carrier 93%) had their highest FPD at a mixing time of 30 minutes. The lowering of the FPD for these formulations at 60 minutes was expected, similar results for low shear mixer were found by Grasmeijer et al. [27], who theorized that longer mixing times caused drug detachment to decrease [27].

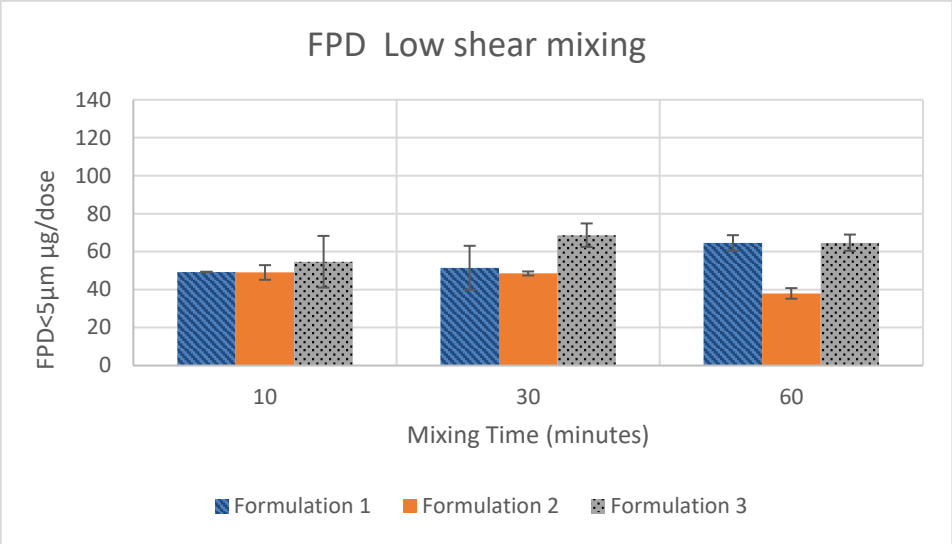

Figure 15 Fine Particle Dose (FPD) assessment for ACI analyses for low shear mixer formulations. For formulation detail composition refer to Table 2.

Figure 16 provides a graphic description of the FPF values obtained from the ACI analyses; it can be noted that the FPF was increased at a mixing time of 60 minutes. Formulation 3 (Budesonide 2%, lactose fines 4%, magnesium stearate 1%, and lactose carrier 93%) had the highest FPF. A high FPF means that a significant amount of fine drug particles can reach the lungs and have therapeutic value [28]. It can be concluded that the addition of magnesium stearate and a longer mixing time increased the FPF at least for low shear mixer. The distribution profiles can be found in the *APPENDIX, (Figures 36, 37, and 38).*

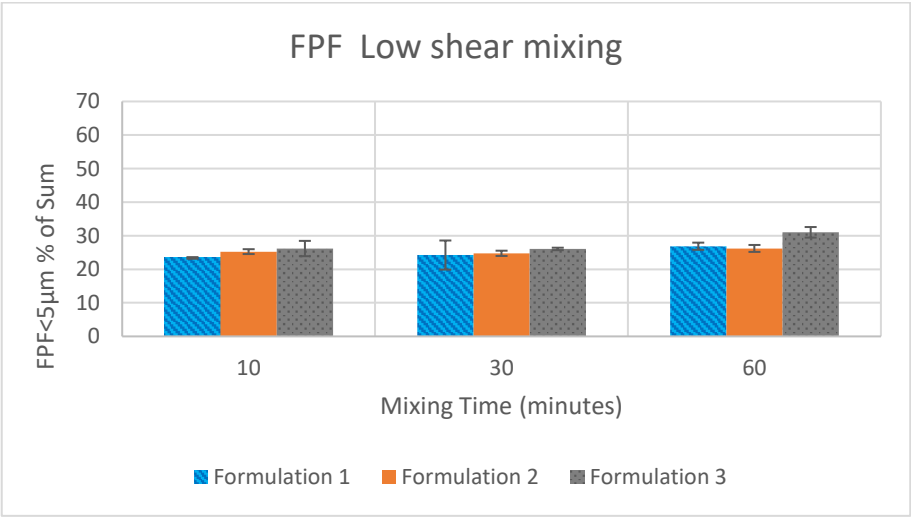

Figure 16 Fine Particle Fraction (FPF) assessment for ACI analyses low shear mixer formulations. For formulation detail composition refer to Table 2.

Figure 17 shows the MMAD values obtained from the ACI analyses. There was a uniform tendency for all the values where formulation 3 (Budesonide 2%, lactose fines 4%, magnesium stearate 1%, and lactose carrier 93%) had the highest MMAD value for all the mixing times. This was somewhat unexpected in view of the higher FPF values for formulation 3 [5], [29].

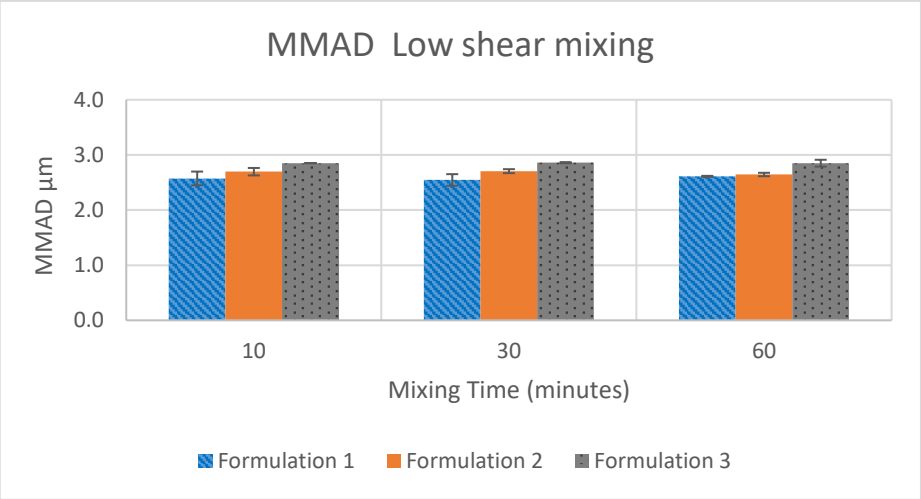

Figure 17 Mass median aerodynamic diameter (MMAD) for ACI analyses low shear mixer formulations. For formulation detail composition refer to Table 2.

The bar graphs in *Figure 18* indicate that for a mixing time of 30 minutes, there will be a higher Sum in ACI for formulations 2 and 3. However, for formulation 1 the higher Sum in ACI was obtained at 60 minutes.

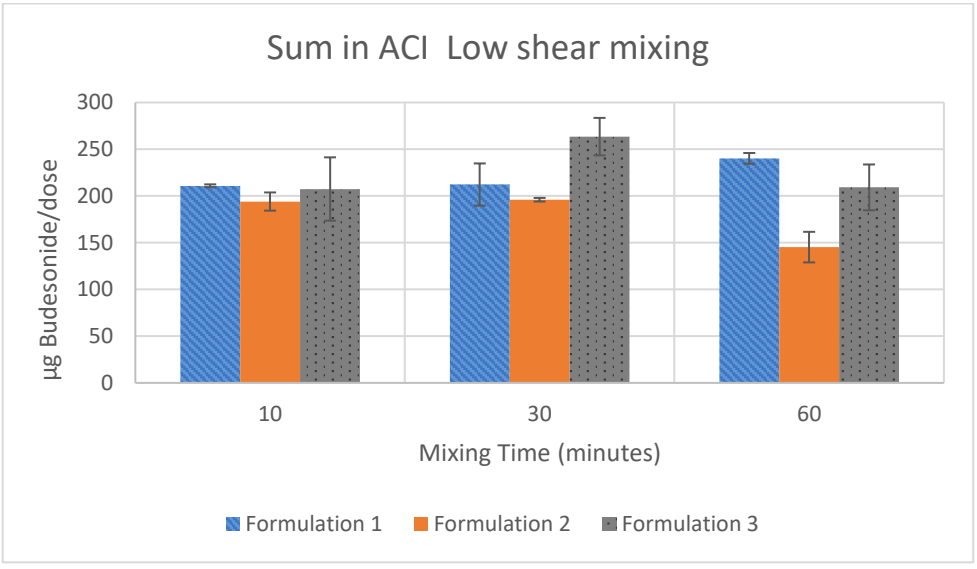

Figure 18 Delivered dose (Sum in ACI) for analyses low shear mixer formulations.

3.5.2. High shear mixer batches (700 rpm)

The results in *Figure 19* suggest that for formulation 1 (Budesonide 2%, Lactose fines 2%, and Lactose carrier 96%) there is an increase in FPD at a mixing time of 30 minutes. While formulation 2 (Budesonide 2%, Lactose fines 4%, and Lactose carrier 94%) had a directly proportional FPD increase according to the mixing time. In contrast, formulation 3 (Budesonide 2%, lactose fines 4%, magnesium stearate 1% and lactose carrier 93%) had the highest FPD regardless of the mixing time. It can be concluded that the addition of magnesium stearate increased the FPD in the high shear mixer (700 rpm). These results confirm the findings of Kumar, et. Al. [30] in another device type (PlastiApi®) where it is believed that magnesium stearate lubricant properties are responsible for this effect [30].

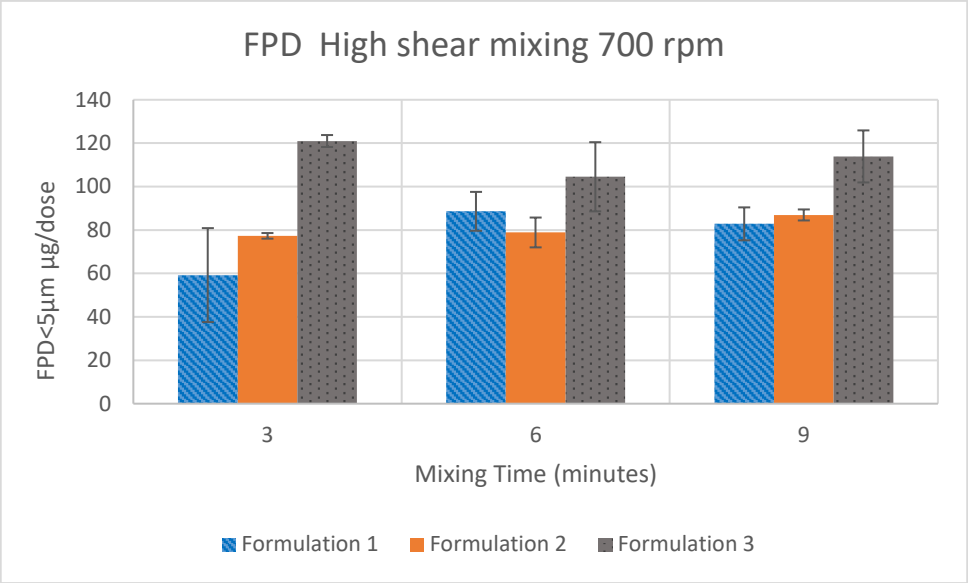

Figure 19 Fine Particle Dose (FPF) assessment for ACI analyses high shear mixer formulations (700 rpm).

Figure 20 provides a graphic description of the FPF values obtained from the ACI analyses; it can be noted that the FPF values were almost increasing with the increase in the mixing time. Formulation 3 (Budesonide 2%, lactose fines 4%, magnesium stearate 1%, and lactose carrier 93%) had the highest FPF. In addition, formulation 2 (Budesonide 2%, lactose fines 4%, and lactose carrier 94%) had higher FPF than formulation 1 (Budesonide 2%, lactose fines 2%, and lactose carrier 96%). Several studies have supported the idea that varying the amount of fines added to a formulation increases FPF. It is believed that the mechanism behind this is that the lactose fines will adhere to the carrier's areas of high adhesion, thus allowing the API's dispersion and deaggregation [31], [32].

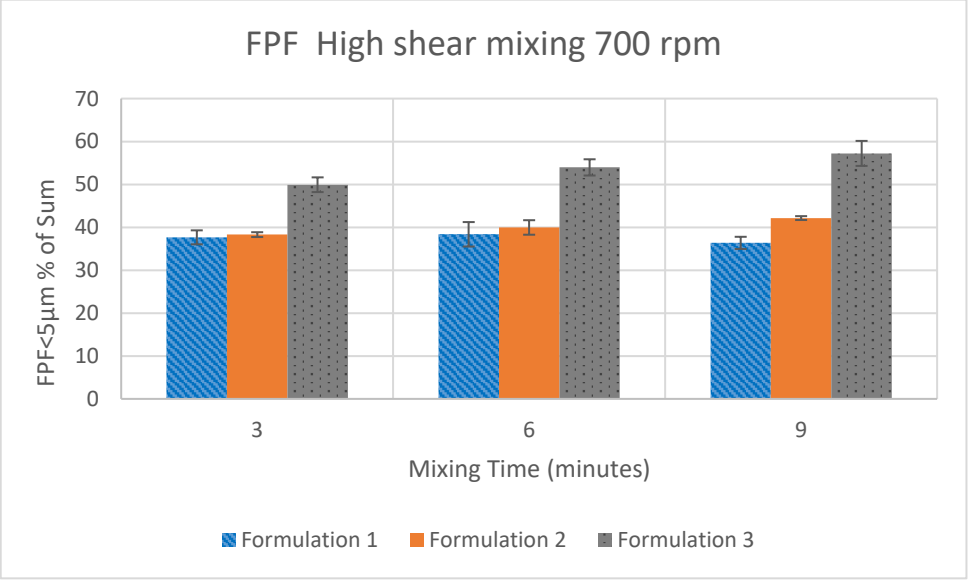

Figure 20 Fine Particle Fraction assessment for ACI analyses high shear mixer formulations.

A high FPF means that a significant amount of fine drug particles can reach the lungs and have therapeutic value [28]. It can be concluded that the addition of magnesium stearate, lactose fines, and a longer mixing time increased the FPF at high shear mixer (700 rpm). The distribution profiles can be found in the *APPENDIX, (Figures 39, 40, and 41).*

Figure 21 bar graphs show that there was a uniform tendency for all the values where formulation 3 (Budesonide 2%, lactose fines 4%, magnesium stearate 1%, and lactose carrier 93%) had the smallest MMAD value for all the mixing times. However, all the values were satisfactory because for inhalable particles the requirement is that the aerodynamic particle size for bronchial deposition of drug particles is <5 µm [33], [34].

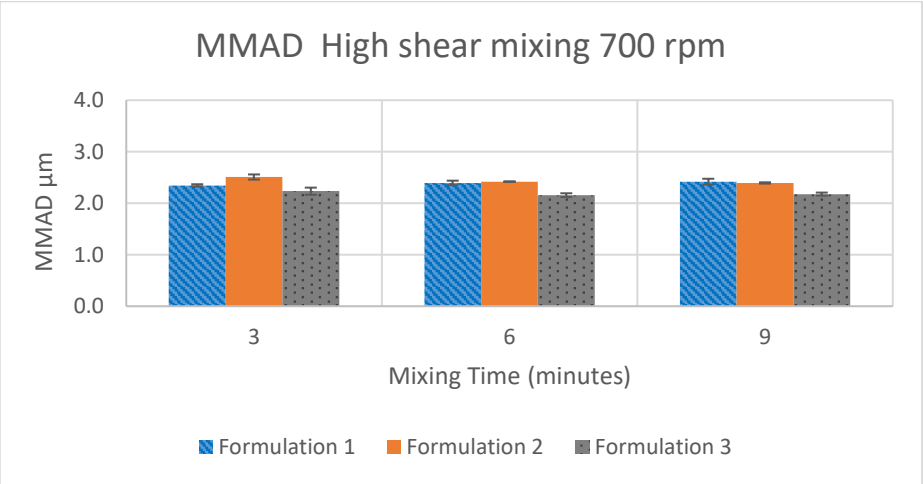

Figure 21 Mass median aerodynamic diameter (MMAD) for ACI analyses high shear mixer samples at 700 rpm.

Figure 22, the bar graphs showed a similar pattern at 6 and 9 minutes where formulation 1 had the highest delivered dose. However, at 3 minutes this pattern was different since there was a higher delivered dose for formulation 3 (Budesonide 2%, lactose fines 4%, magnesium stearate 1%, and lactose carrier 93%).

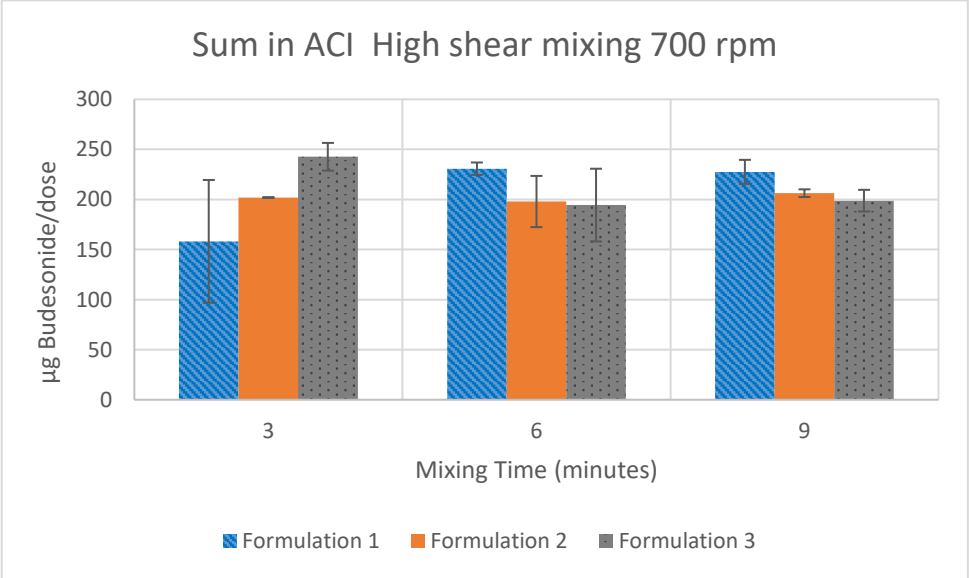

Figure 22 Delivered dose (Sum in ACI) analyses for high shear mixer formulations.

An explanation for this phenomenon could be that formulations with less lactose fines need longer mixing times to ensure a high delivery dose. In comparison, the magnesium stearate and a higher percentage of lactose fines helped to achieve a higher degree of delivered dose.

3.5.3. High shear mixer batches (1000 rpm)

It can be noted in *Figure 23* that a mixing time of 6 minutes is favorable for formulation 2 (Budesonide 2%, lactose fines 4%, and lactose carrier 94%) and formulation 3 (Budesonide 2%, lactose fines 4%, magnesium stearate 1% and lactose carrier 93%). At a mixing time of 9 minutes there is a decrease of FPD for almost all the formulations, the reason behind this might be due to the fact that high shear mixing at longer mixing times might cause drug detachment to decrease and lower the fine particle dose [27].

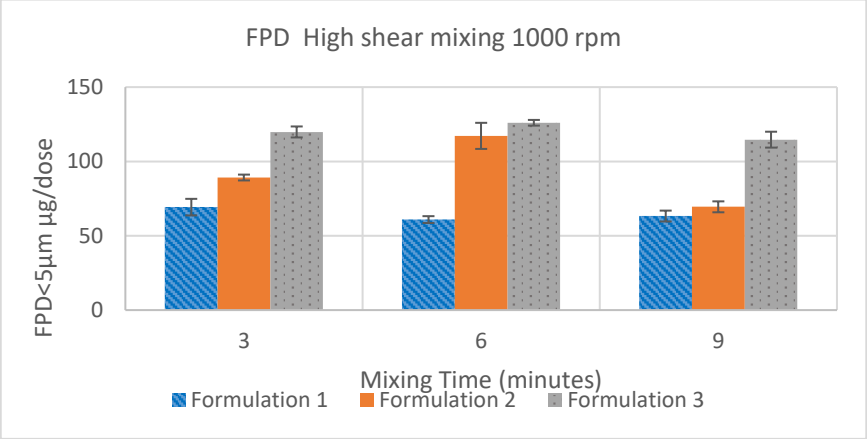

Figure 23 Fine Particle Dose assessment for ACI analyses high shear mixer formulations.

Another explanation for this decrease was found by Balducci et al. [35], who believe that a decrease in drug content can be associated with an increased drug adhesion to the mixing vessel walls [35].

Figure 24 provides a graphic description of the FPF values obtained from the ACI analyses. It can be noted that formulations (2 and 3), with higher amounts of lactose fines and coating agent, had higher FPF values in comparison with formulation 1. At a mixing time of 9 minutes, it was observed a decrease in FPF values for all formulations in comparison with the previous mixing time (6 minutes). In a study conducted by Selvam, P and Smyth, H. [36], it was observed that increases in speed while mixing can cause increases in press-on forces, which can reduce drug dispersion [36]. The distribution profiles can be found in the *APPENDIX, (Figures 42, 43, and 44).*

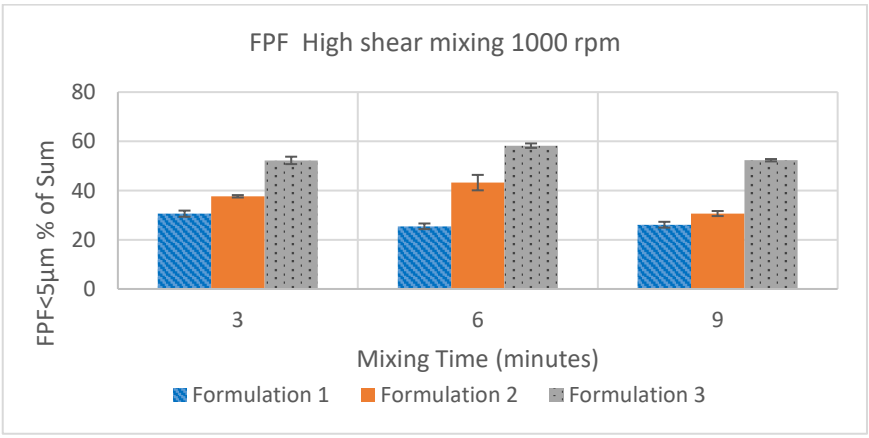

Figure 24 Fine Particle Fraction assessment for ACI analyses high shear mixer formulations.

Figure 25 shows that there was a uniform tendency for all the values where formulation 3 (Budesonide 2%, lactose fines 4%, magnesium stearate 1%, and lactose carrier 93%) had the smallest MMAD value for all the mixing times. Nevertheless, all the values were satisfactory because for inhalable particles the requirement is that the aerodynamic particle size for bronchial deposition of drug particles is <5 µm [33], [34].

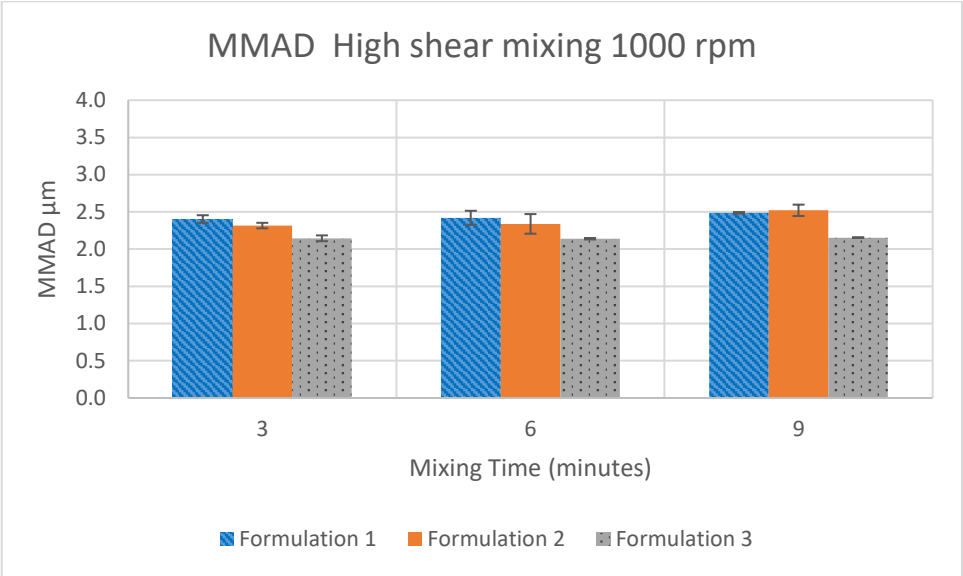

Figure 25 Mass median aerodynamic diameter (MMAD) for ACI analyses high shear mixer formulations.

Figure 26 shows that Formulation 2 (Budesonide 2%, Lactose fines 4%, and Lactose carrier 94%) had the highest delivered dose, especially at 6 minutes. However, at 9 minutes this pattern was different since there was a higher delivered dose for formulation 1 (Budesonide 2%, lactose fines 2%, and lactose carrier 96%). The same tendency was observed in the low shear mixer, where longer mixing times favored the formulation with fewer lactose fines.

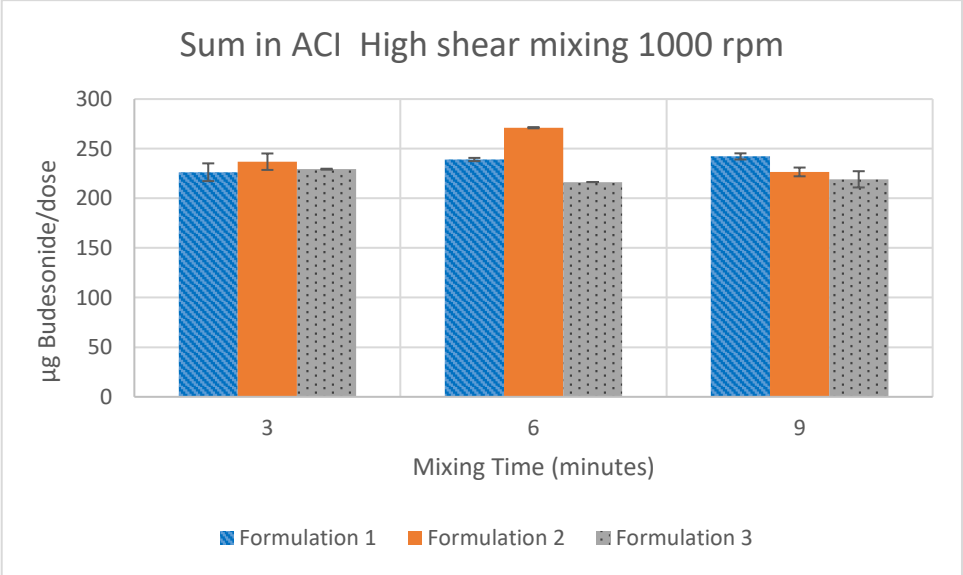

Figure 26 Delivered dose for Andersen Cascade Impactor analyses for high shear mixer formulations.

3.6.NGI

In *Figure 27* the results suggest that at 700 rpm there is a higher FPD than at 1000 rpm. At 700 rpm FPD is relatively constant regardless of mixing time. The decreasing tendency for 1000 rpm was the same as detected in ACI.

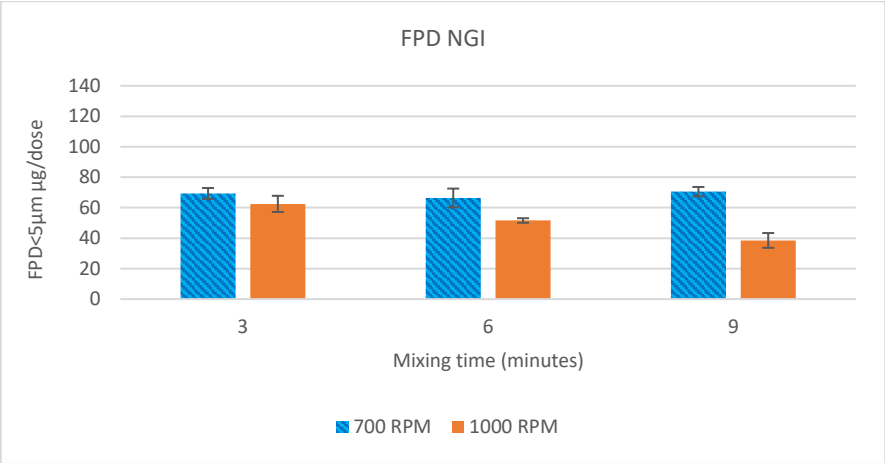

Figure 27 Fine Particle Dose (FPD) assessment for NGI analyses for high shear mixer formulation 1.

In *Figure 28* the results confirm the FPD trend that 700 rpm gives better dispersibility than 1000 rpm. The distribution profiles can be found in the *APPENDIX, figures 45, 46, 47, and 48.*

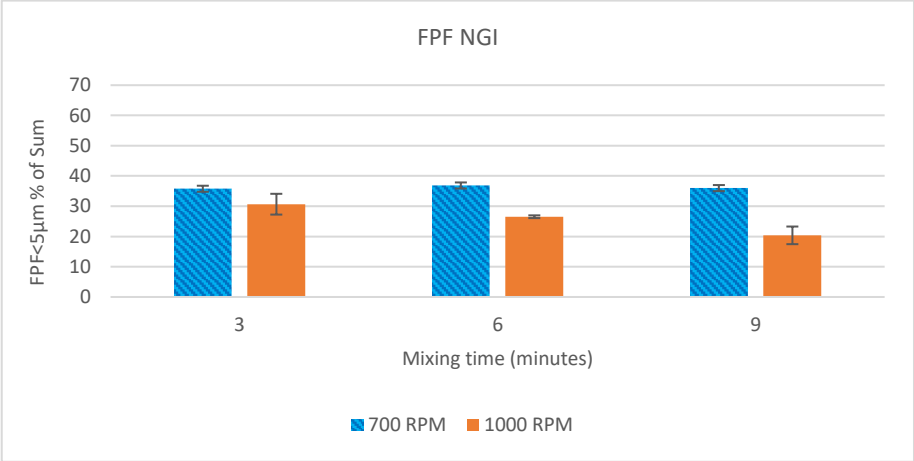

Figure 28 Fine Particle Fraction (FPF) assessment for NGI analyses for high shear mixer formulation 1.

Figure 29 results indicate that the MMAD is higher for 1000 rpm formulation 1 batches. However, all the values were satisfactory because for inhalable particles the requirement is that the aerodynamic particle size for bronchial deposition of drug particles is <5 µm [33], [34].

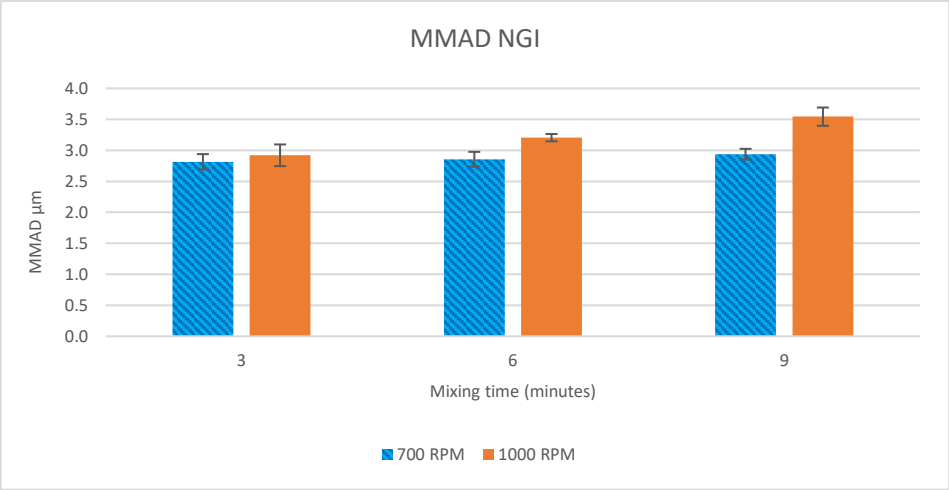

Figure 29 Mass median aerodynamic diameter (MMAD) for NGI analyses for high shear mixer formulation 1.

Figure 30 shows that the delivered dose (Sum NGI) is rather constant, however, there is slightly less at a mixing time of 6 min 700 rpm speed.

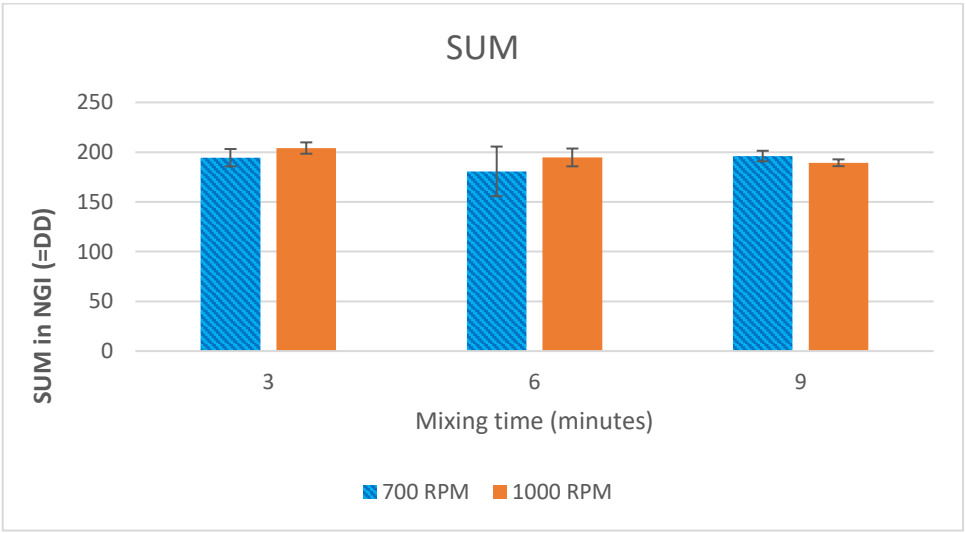

Figure 30 Delivered dose for NGI analyses for high shear mixer formulation 1.

3.7.Mixing energy analysis

Figure 31 shows that the Fine Particle Dose varied between the NGI and ACI analyses, this variability might be due to the differences in both systems and analyses process. There was furthermore a time lag between the ACI analyses and NGI analyses.

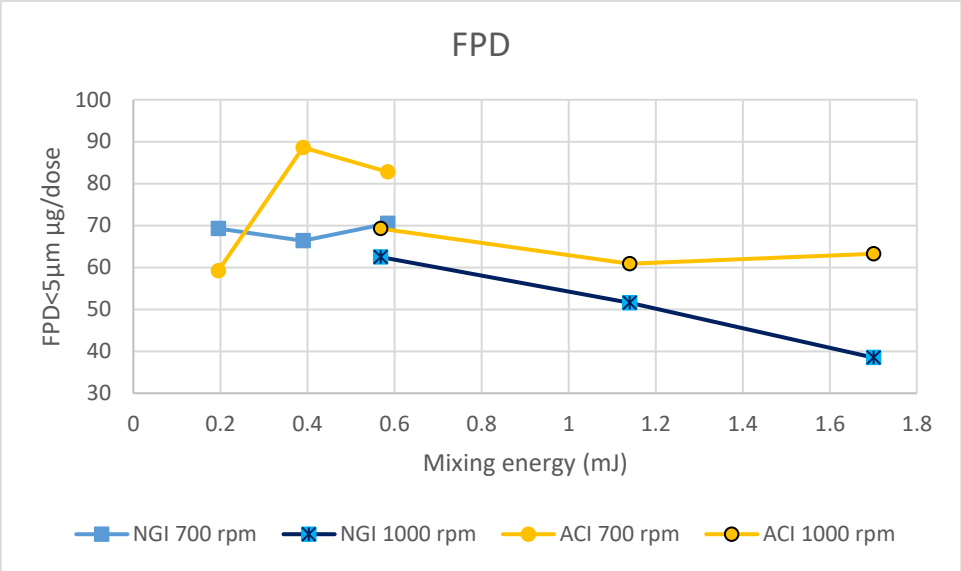

Figure 31 Fine Particle Dose (FPD) assessment for NGI and ACI analyses for high shear mixer formulation 1.

Figure 32 suggests that there is a correlation between the NGI and the ACI results in terms of FPF. It can be seen a decrease observed during mixing at high speed, these results confirm the findings by Thalberg et al. [9], where they explained that the FPF decrease is due to strong incorporation of the fine particles (including the API) into the carriers [9].

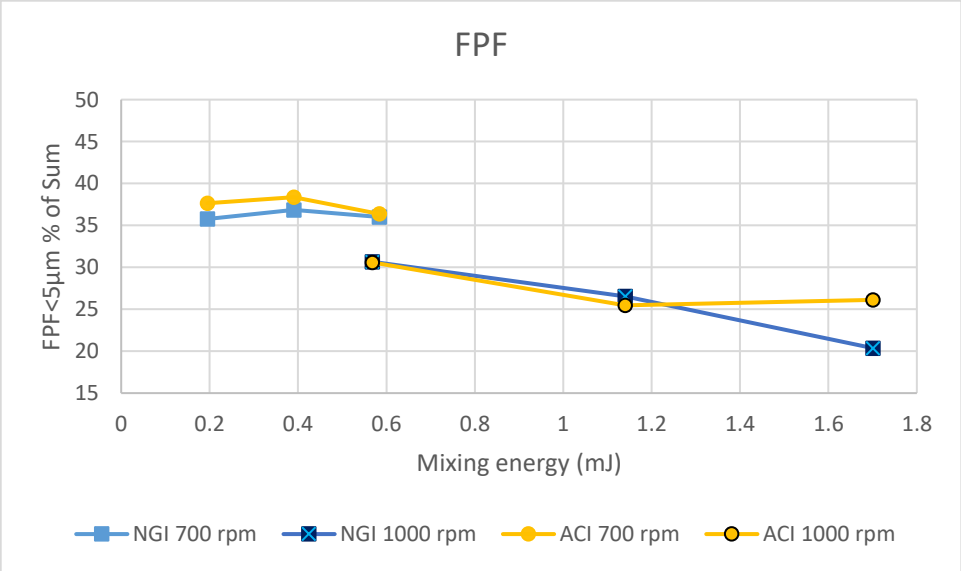

Figure 32 Fine Particle Fraction (FPF) assessment for NGI and ACI analyses for high shear mixer formulation 1.

Figure 33 shows that there is a correlation between the longest mixing time low speed formulation and the shortest mixing time high speed formulation, even though there is a gap between the values. These findings corroborate the concept of mixing energy proposed by Thalberg et. al [9], and that the FPF peak increase was followed by a decrease at a longer mixing time was expected.

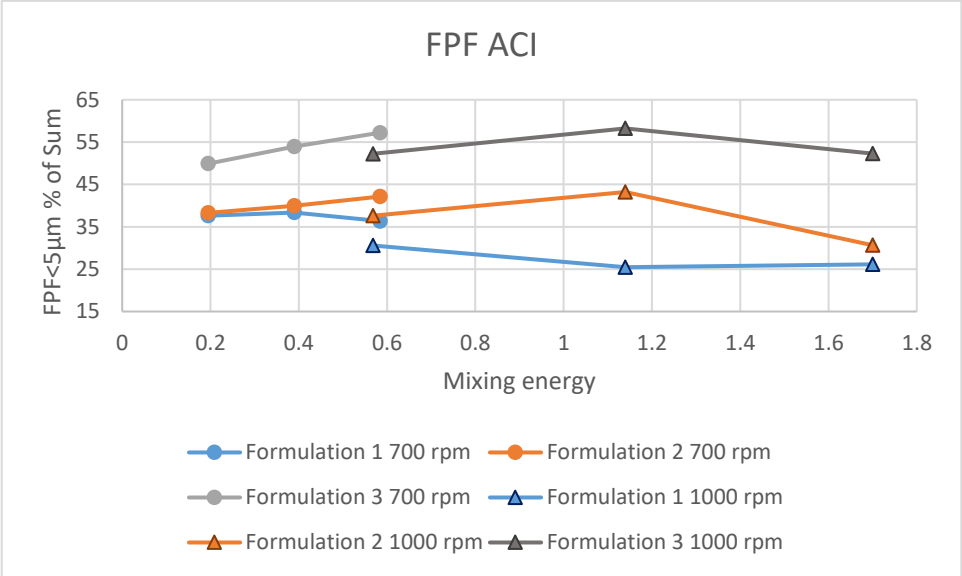

Figure 33 Fine Particle Fraction (FPF) assessment for ACI analyses high shear mixer formulations in terms of mixing energy.

Formulation composition impacted the FPF, formulation 3 (Budesonide 2%, lactose fines 4%, magnesium stearate 1%, and lactose carrier 93%) had the highest FPF values. This was explained by Thalberg et. al, where the increase of FPF is due to *"the transfer of coating agent from the coated carrier to the API"* [9].

Mixing energy increases with mixing time and speed, lower levels of FPF at shorter mixing times are the result of the formation of drug agglomerates during the mixing process [8] and lower levels of FPF at longer mixing times are the result of the incorporation of API into the carrier particles [9]. Optimum mixing conditions were found at intermediate mixing energy values.

Figure 34 shows that the MMAD values between the formulations correlate with each other for the two speeds. The lowest MMAD values were achieved at intermediate mixing energy values. However, all the values were satisfactory because for inhalable particles because the requirement is that the aerodynamic particle size for bronchial deposition of drug particles is <5 µm [33], [34]. Formulation 3 containing magnesium stearate presented the lowest MMAD values.

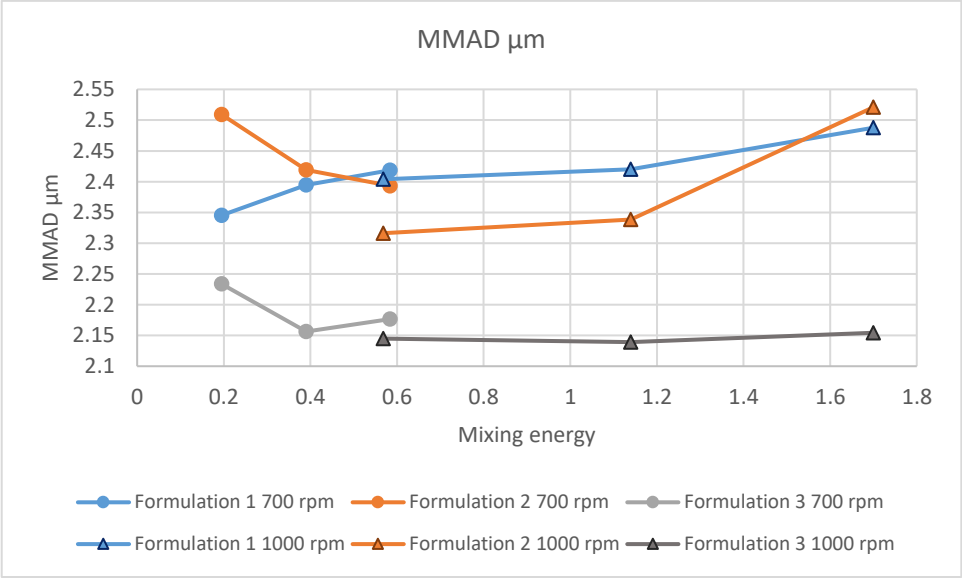

Figure 34 Mass median aerodynamic diameter (MMAD) for ACI analyses high shear mixer formulations in terms of mixing energy.

3.8. Comparison of low (Turbula®) and high (Diosna®) mixers

In the manufacturing section *(Tables 6, 7, and 8)*, it was found that the low shear mixer had higher production yields than the high shear mixer. The forces exerted during high shear mixing applied to the confined particles, can cause particle adhesion to the mixing vessel walls resulting in higher losses of powder mixture compared with low shear mixing where the mixing process is more gentle [13] [9]. However, time efficiency in high shear mixers is an advantage for the manufacturing process.

In addition, interesting results were found for the budesonide content assay and the mixing homogeneity *(Table 5, figures 11, 12, 13, and 14)*. For both analyses, low shear mixer batches had higher compliance values. This was not expected because it is known that high shear mixer is characterized to have a higher mixing homogeneity than low shear mixers because increasing the shear forces improves the homogeneity of DPI mixtures [8]. However, as mentioned before the results obtained had a satisfactory degree of homogeneity and if mixing time is compared high shear mixing achieves homogeneity faster than low shear mixing [24]. The results obtained for poured bulk density were similar between both mixers.

Continuing with the comparison of the two mixers, for the aerodynamic particle-size distribution analyses performed by ACI, it was found that high shear mixing batches both 700 and 1000 rpm had higher FPF, regardless of the formulation composition or mixing time than the low shear manufactured formulations. The FPF and FPD values were almost doubled in high shear mixer batches, this is because high shear mixing improves the distribution of the API in the mixing causing a reduction of drug particle aggregates. The impeller blade places a key role by slicing the powder bed thus improving the deagglomeration [35], [8], [37]. It can be concluded that high shear mixing is more suitable for DPI powder mixture manufacturing *(Figures 15, 16, 19, 20, 23, and 24)*.

The exceptionally high performance of formulation 3 (Budesonide 2%, lactose fines 4%, magnesium stearate 1% and lactose carrier 93%) for high shear mixer batches was the result of the efficient spreading of the coating agent that can be achieved in this mixer type [38], combined with magnesium stearate's flowability enhancement properties [39].

4. CONCLUSIONS

In this degree project, three types of formulations were manufactured in low shear and high shear mixers using budesonide as the API at a 2% drug load. The amount of lactose carrier, lactose fines, and magnesium stearate (coating agent) were varied according to their composition:

1. Lactose fines 2%, and lactose carrier 96%.
2. Lactose fines 4%, and lactose carrier 94%.
3. Lactose fines 4%, magnesium stearate 1%, and lactose carrier 93%.

Following the project aims, first it can be concluded that adding 4% of lactose fines and magnesium stearate 1% lead to an improvement in FPF. In terms of formulations, formulation 3 presented the highest values of FPF and FPD in both mixers, and this tendency was seen at all mixing times. The coating agent was a key component of the formulation. In addition, formulation 2 presented higher FPF values in high shear mixing batches in comparison with formulation 1. Although this difference was not that remarkable in low shear mixer, it can be concluded that higher amounts of lactose fines improved the formulation performance.

Second, regarding the mixing time in low shear and high shear mixer at 700 rpm, it can be concluded that longer mixing times increased the FPF values for almost all formulations. In comparison, in high shear mixing at high speed (1000 rpm) intermediate mixing times presented higher FPF values, this corroborates the mixing energy concept, and it was found that long mixing time at high speed should be avoided.

Finally, in the comparison of the performance between the mixers (Diosna®) high shear and (Turbula®) low shear. It can be concluded that both mixers (low and high shear) had satisfactory levels of homogeneity and drug content. Production losses were higher for high shear mixer, particularly at high speed with a coating agent. In addition, high shear mixer formulations presented the highest performance in the aerodynamic particle assessments, judged in terms of FPF and FPD. It was found that these values were almost double for high shear mixing formulations.

5. FUTURE DIRECTIONS

The future steps of this degree project would be to research how cooling during high shear mixing can have an impact on the formulation performance. In addition, analyses like TOF-SIMS can be useful to research about smearing of the coating agent on the lactose carrier surface [9].

For low shear mixer, since it was observed that longer mixing times favored the FPF of the formulation, researching if even longer mixing times could be worth it. Moreover, testing different inhaler devices and APIs would be valuable to corroborate the finding in this research work.

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7. APPENDIX

7.1. Manufacturing

Figure 35 High shear mixer (Diosna® mixer P1-6) picture taken after the production of formulation 3. It can be seen high amounts of powder mixture impacted on the bottom of the mixer vessel, this amount was discarded.

7.2. ACI

7.2.1. Low shear mixer

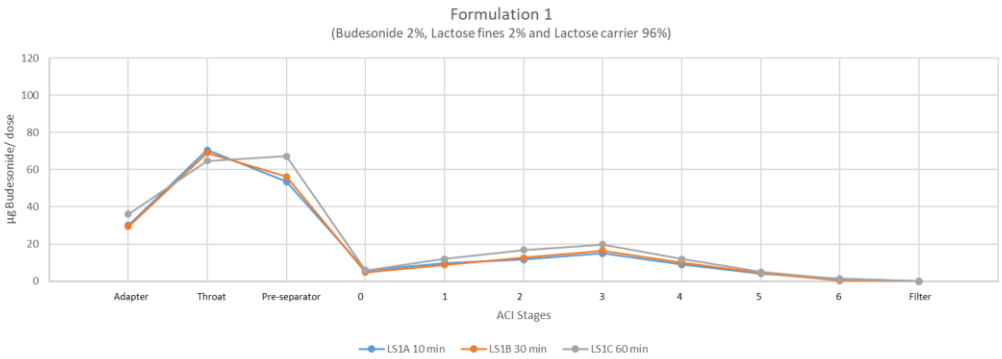


Figure 36 ACI Formulation 1 aerodynamic size distribution profile for low shear mixer.

Figure 36, Formulation 1 presents considerable deposition of the API on the first ACI components adapter, throat, and pre-separator for all mixing times. Stage 3 presents the highest deposition for the collection plates stages for all mixing times. Where LS1C 60 min (gray) had the highest deposit of API. The values are the average of at least two replicates.

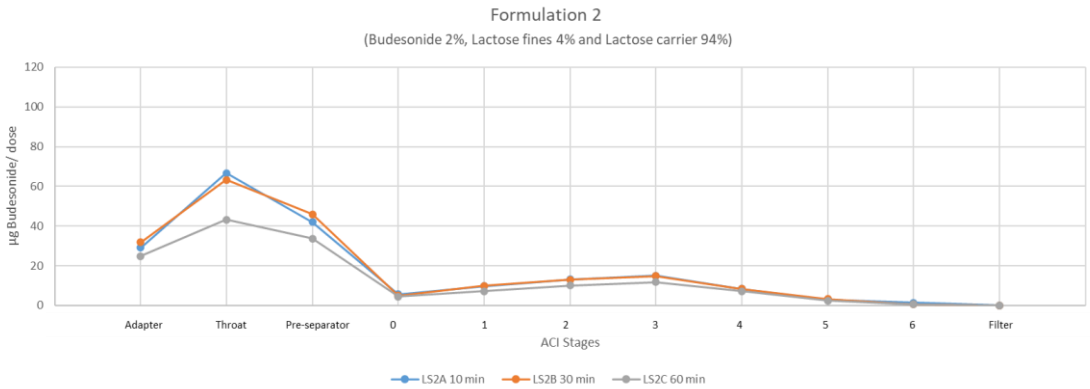


Figure 37 ACI Formulation 2 aerodynamic size distribution profile for low shear mixer.

Figure 37, Formulation 2 presents considerable deposition of the API on the first ACI components adapter, throat, and pre-separator for all mixing times. Stage 3 presents the highest deposition for the rest of the collection plates stages for all mixing times. Where LS2A (blue) and LS2B (orange) had a similar distribution profile. The values are the average of at least two replicates.

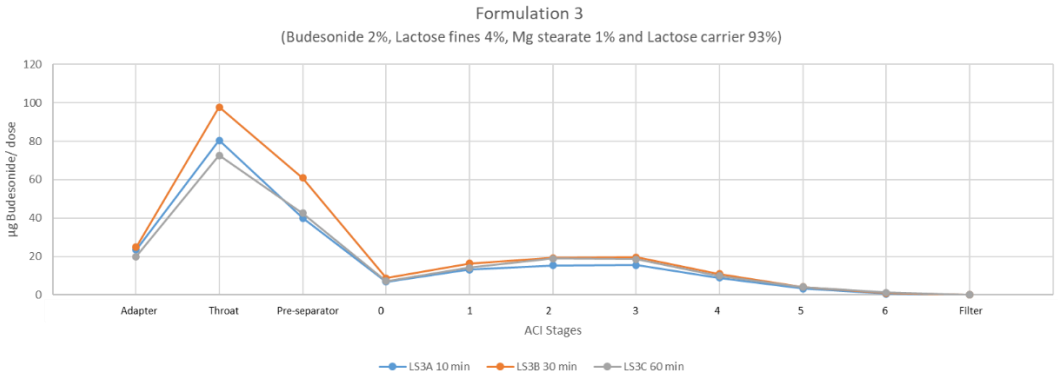


Figure 38 ACI Formulation 3 aerodynamic size distribution profile for low shear mixer.

Figure 38, Formulation 3 presents considerable deposition of the API on the first ACI components adapter, throat and pre-separator for all mixing times and compared to other formulations (1 and 2). Stage 3 presents the highest deposition for the collection plates stages for all mixing times. Where LS3A and LS3B had a similar distribution profile. The values are the average of at least two replicates.

Table 9 ACI Low shear aerodynamic size distribution summary

ACI Low shear summary									
80L/min, 6 doses/ACI, coating Brij/glycerol									
Formulation	**1**			**2**			**3**		
Batch	**LS1A**	**LS1B**	**LS1C**	**LS2A**	**LS2B**	**LS2C**	**LS3A**	**LS3B**	**LS3C**
Device	**Novolizer**								
Mixing time (10 min)	**10**	**30**	**60**	**10**	**30**	**60**	**10**	**30**	**60**
ACI Flow	**80**	**80**	**80**	**80**	**80**	**80**	**80**	**80**	**80**
Time (sec)	**44**	**44**	**44**	**44**	**44**	**44**	**44**	**44**	**44**
µg Bude/ dose									
Inlet+adapter+Presept	154.2	154.6	168.0	137.8	141.0	101.7	143.9	183.7	135.1

Stage 0	5.82	4.74	5.82	5.71	4.96	4.48	6.82	8.63	7.22
Stage 1	9.79	8.76	12.01	9.73	9.98	7.15	13.06	16.29	14.10
Stage 2	11.62	12.64	16.70	13.15	12.88	10.14	15.28	19.31	18.92
Stage 3	14.96	16.48	19.71	14.99	14.84	11.75	15.55	19.66	18.56
Stage 4	9.03	10.17	12.01	8.36	8.41	7.16	8.93	10.95	9.94
Stage 5	4.15	4.43	4.98	2.92	3.34	2.44	3.29	4.12	4.12
Stage 6	1.24	0.38	1.01	1.40	0.60	0.47	0.61	0.88	1.21
Filter	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
SUM in ACI (=DD)	**210.83**	**212.2**	**240.2**	**194.0**	**196.0**	**145.3**	**207.4**	**263.5**	**209.2**
FPD<5µm µg/dose	49.27	51.50	64.57	49.04	48.50	37.99	54.69	68.69	64.68
FPF<5µm % of Sum	23.37	24.24	26.87	25.26	24.75	26.21	26.18	26.05	31.01
MMAD µm	2.57	2.55	2.61	2.70	2.71	2.64	2.85	2.86	2.85
GSD	1.75	1.68	1.71	1.72	1.70	1.66	1.73	1.73	1.77
R-value	0.99	0.996	1.00	0.99	1.00	1.00	1.00	1.00	0.99

7.2.2. High shear mixer (700 rpm)

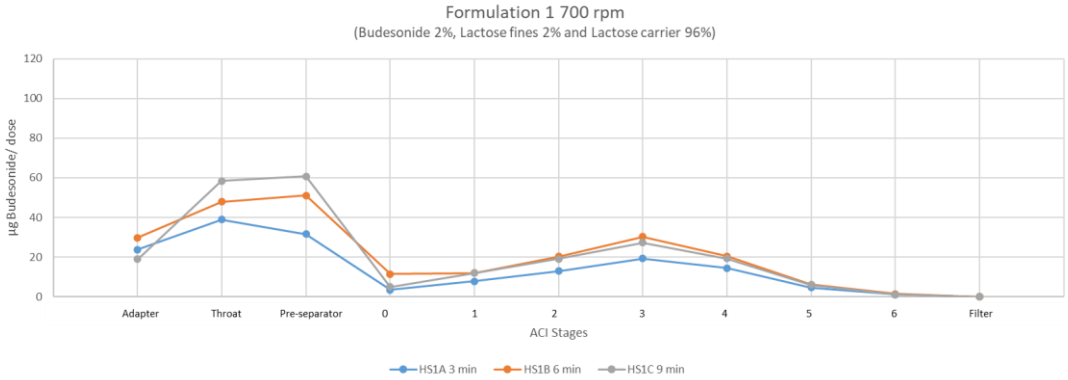


Figure 39 ACI Formulation 1 aerodynamic size distribution profile for high shear mixer at 700 rpm.

Figure 39, There is deposition of the API on the first ACI components Adapter, Throat and Pre-separator for all the batches, but it is higher for HS1C 9 min. Stage 3 presents the highest deposition for the collection plates stages for all samples. Where HS1B 6 min (orange) had the highest deposit of API. The values are the average of at least two replicates.

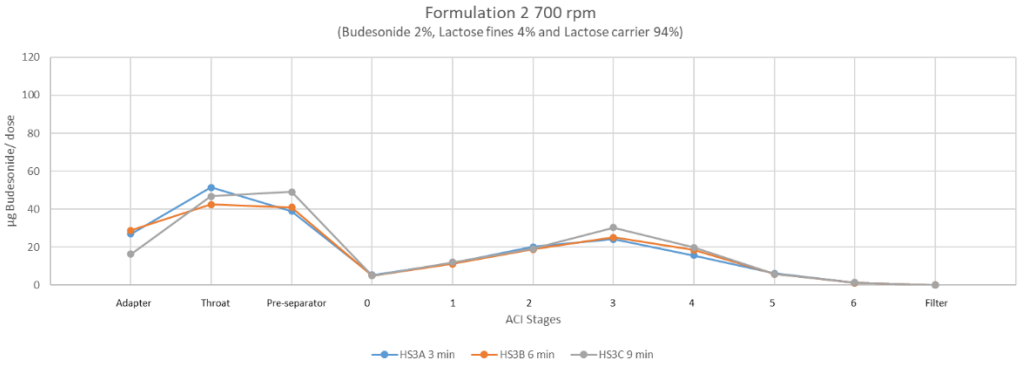


Figure 40 ACI formulation 2 aerodynamic size distribution profile for high shear mixer at 700 rpm.

Figure 40, There is deposition of the API on the first ACI components adapter, throat,

and pre-separator the tendency is similar for all the samples. Stage 3 presents the highest deposition for the collection plates stages for all mixing times. Where HS3C 9 min (gray) had the highest deposit of API. The values are the average of at least two replicates.

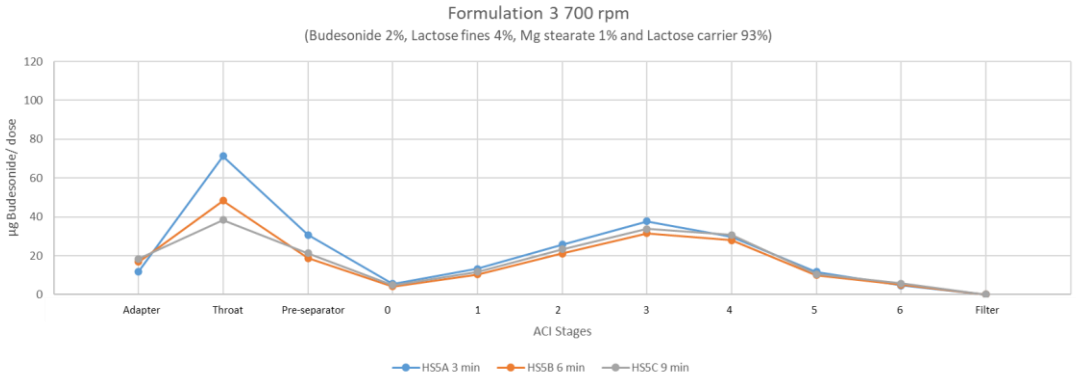


Figure 41 ACI Formulation 3 aerodynamic size distribution profile for high shear mixer at 700 rpm.

Figure 41, There is deposition of the API on the first ACI components adapter, throat, and pre-separator for samples, HS5A 3 min (blue) had a peak value at the "throat". Stage 3 presents the highest deposition for the collection plates stages for all mixing times. Where HS5A 3 min (blue) had slightly the maximum deposit of API. The values are the average of at least two replicates.

Table 10 ACI High shear aerodynamic size distribution summary (700 rpm)

ACI High shear summary									
Mixing speed	**700 rpm**								
Batch	**HS1A**	**HS1B**	**HS1C**	**HS3A**	**HS3B**	**HS3C**	**HS5A**	**HS5B**	**HS5C**
Device	**Novolizer**								
Mixing time (10 min)	**3**	**6**	**9**	**3**	**6**	**9**	**3**	**6**	**9**
ACI Flow	**80**	**80**	**80**	**80**	**80**	**80**	**80**	**80**	**80**
Time (sec)	**44**	**44**	**44**	**44**	**44**	**44**	**44**	**44**	**44**
µg Bude/ dose									
Inlet+adapter+Presept	94.29	128.8	137.9	117.5	112.4	112.4	114.0	83.99	78.15
Stage 0	3.42	11.51	4.95	5.33	4.97	5.06	5.54	4.24	4.91
Stage 1	7.82	11.92	11.91	11.48	11.16	12.00	13.28	10.27	11.68
Stage 2	13.01	20.28	19.17	20.24	18.85	19.22	25.81	21.08	23.30
Stage 3	19.31	30.19	27.31	24.19	25.13	30.42	37.71	31.53	33.89
Stage 4	14.52	20.46	19.22	15.68	18.48	19.86	29.90	28.07	30.65
Stage 5	4.61	6.14	5.91	6.26	5.84	5.86	11.65	10.08	10.54
Stage 6	1.18	1.46	1.16	1.24	1.16	1.46	4.72	5.10	5.66
Filter	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
SUM in ACI (=DD)	**158.15**	**230.7**	**227.6**	**201.9**	**197.9**	**206.3**	**242.6**	**194.3**	**198.8**
FPD<5µm µg/dose	59.23	88.61	82.85	77.31	78.88	86.95	121.00	104.53	113.91
FPF<5µm % of Sum	37.66	38.37	36.37	38.29	39.96	42.15	49.92	53.96	57.22
MMAD µm	2.35	2.39	2.42	2.51	2.42	2.39	2.23	2.16	2.18
GSD	1.60	1.59	1.60	1.68	1.61	1.58	1.67	1.66	1.66
R-value	1.00	0.998	1.00	1.00	0.999	1.00	1.00	0.999	1.00

7.2.3. High shear mixer (1000 rpm)

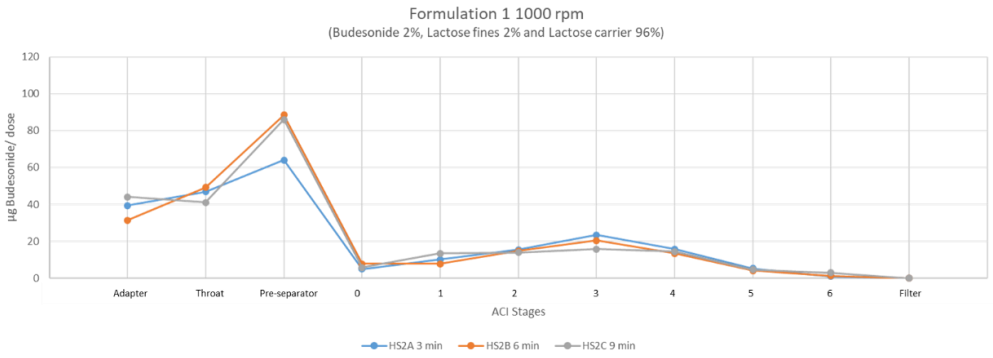


Figure 42 ACI Formulation 1 aerodynamic size distribution profile for high shear mixer at 1000 rpm.

Figure 42, there is deposition of the API on the first ACI components adapter, throat and pre-separator for all the batches, there is a peak at the pre-separator, the three samples had the same deposition pattern. Stage 3 presents the highest deposition for the collection plates stages for all samples. Where HS2A 3 min (blue) had slightly the highest deposit of API. The values are the average of at least two replicates.

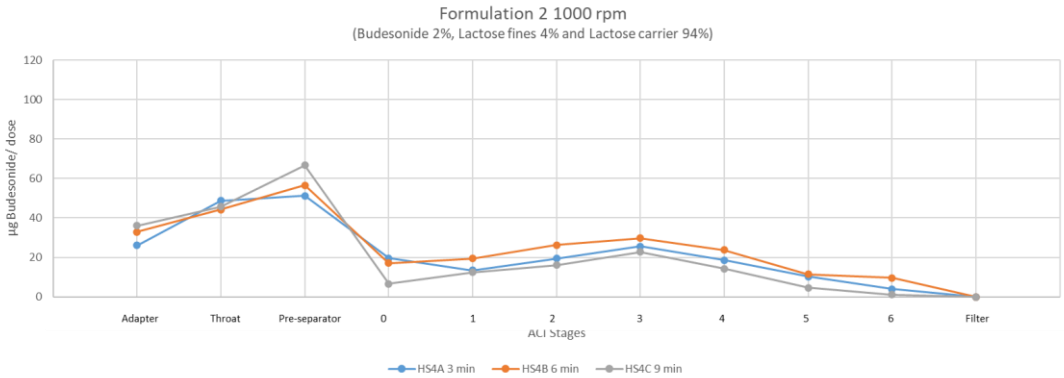


Figure 43 ACI Formulation 2 aerodynamic size distribution profile for high shear mixer at 1000 rpm.

Figure 43, There is deposition of the API on the first ACI components adapter, throat and Pre-separator, the tendency is similar for all the samples. Stage 3 presents the highest deposition for the collection plates stages for all samples. Where HS4B 3 min (orange) had the highest deposit of API. The values are the average of at least two replicates.

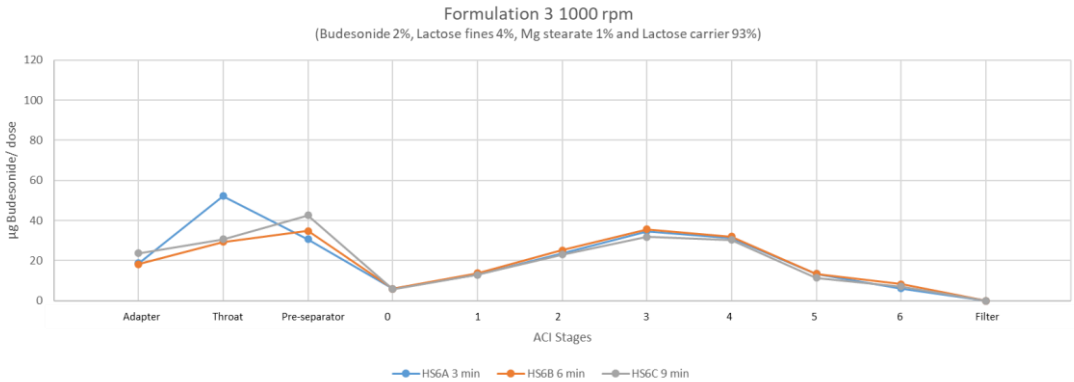


Figure 44 ACI Formulation 3 aerodynamic size distribution profile for high shear mixer at 1000 rpm.

Figure 44, there is deposition of the API on the first ACI components adapter, throat and pre-separator for samples, HS6A 3 min (blue) had a peak value at the "throat". Stage 3 presents the highest deposition for the collection plates stages for all mixing times. The values are the average of at least two replicates.

Table 11 ACI High shear aerodynamic size distribution summary (1000 rpm)

ACI High shear summary									
Mixing speed	**1000 RPM**								
Batch	**HS2A**	**HS2B**	**HS2C**	**HS4A**	**HS4B**	**HS4C**	**HS6A**	**HS6B**	**HS6C**
Device	**Novolizer**								
Mixing time (10 min)	**3**	**6**	**9**	**3**	**6**	**9**	**3**	**6**	**9**
ACI Flow	**80**	**80**	**80**	**80**	**80**	**80**	**80**	**80**	**80**
Time (sec)	**44**	**44**	**44**	**44**	**44**	**44**	**44**	**44**	**44**
µg Bude/ dose									
Inlet+adapter+Presept	150.46	169.1	171.0	126.1	133.8	148.6	101.6	82.29	96.75
Stage 0	4.99	7.84	5.87	19.56	17.16	6.54	5.92	5.94	5.72
Stage 1	10.06	7.89	13.48	13.39	19.40	12.49	13.05	13.76	12.89
Stage 2	15.41	14.79	13.90	19.36	26.28	16.07	23.52	25.09	23.03
Stage 3	23.42	20.47	15.77	25.62	29.79	22.82	34.68	35.70	31.86
Stage 4	15.72	13.50	14.52	18.62	23.68	14.32	31.13	31.99	30.33
Stage 5	5.28	4.22	4.65	10.28	11.37	4.64	13.45	13.33	11.38
Stage 6	0.95	1.25	3.02	3.99	9.68	1.08	6.04	8.29	7.17
Filter	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
SUM in ACI (=DD)	**226.29**	**239.11**	**242.25**	**236.91**	**271.15**	**226.61**	**229.35**	**216.39**	**219.13**
FPD<5µm µg/dose	69.28	60.89	63.26	89.19	117.20	69.48	119.84	126.02	114.66
FPF<5µm % of Sum	30.59	25.47	26.11	37.66	43.22	30.65	52.25	58.24	52.31
MMAD µm	2.40	2.42	2.49	2.32	2.34	2.52	2.15	2.14	2.15
GSD	1.60	1.61	1.80	1.81	1.92	1.63	1.70	1.73	1.71
R-value	1.00	0.997	1.00	1.00	0.996	1.00	1.00	0.998	1.00

7.3.NGI

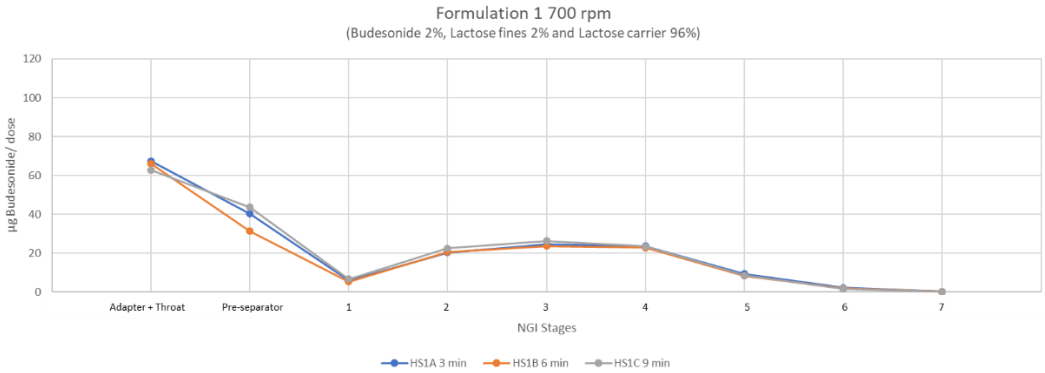


Figure 45 NGI Formulation 1 aerodynamic size distribution profile for high shear mixer at 700 rpm.

Figure 45, there is deposition of the API on the first ACI components adapter + throat and pre-separator for all samples. Stage 3 presents the highest deposition for the collection plates stages for all samples. Where HS1C 9 min (gray) had a slightly highest deposit of API. The values are the average of at least two replicates.

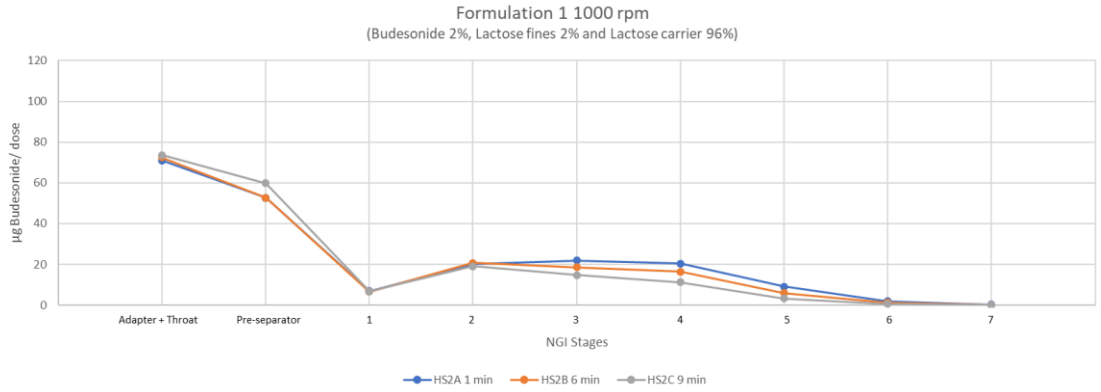


Figure 46 NGI Formulation 1 aerodynamic size distribution profile for high shear mixer at 1000 rpm.

Figure 46, there is deposition of the API on the first ACI components adapter + throat and pre-separator for all samples. Stage 3 presents the highest deposition for the collection plates stages for all samples. HS2C 9 min (gray) had the highest value at the adapter + throat and pre-separator and the lowest at the collection plates stages.

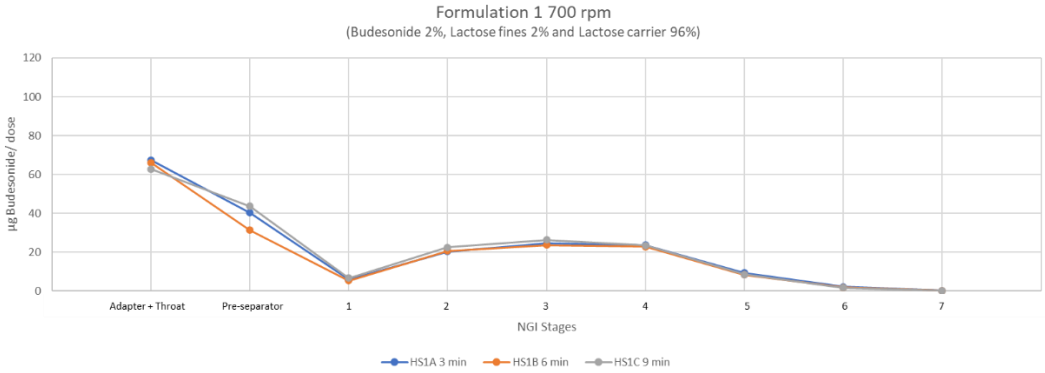


Figure 47 NGI Formulation 1 aerodynamic size distribution profile for high shear mixer at 700 rpm.

Figure 47, there is deposition of the API on the first ACI components adapter + throat and pre-separator for all samples. Stage 3 presents the highest deposition for the collection plates stages for all samples. Where HS1C 9 min (gray) had a slightly highest deposit of API. The values are the average of at least two replicates.

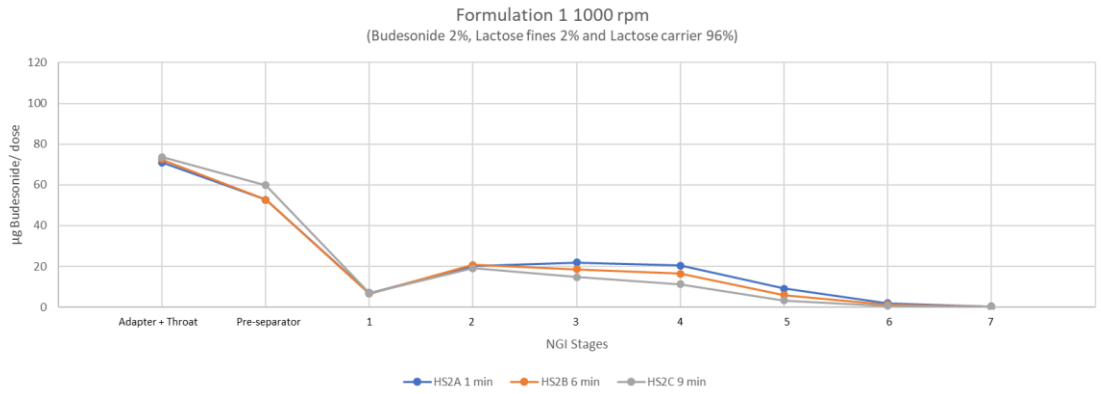


Figure 48 NGI Formulation 1 aerodynamic size distribution profile for high shear mixer at 1000 rpm.

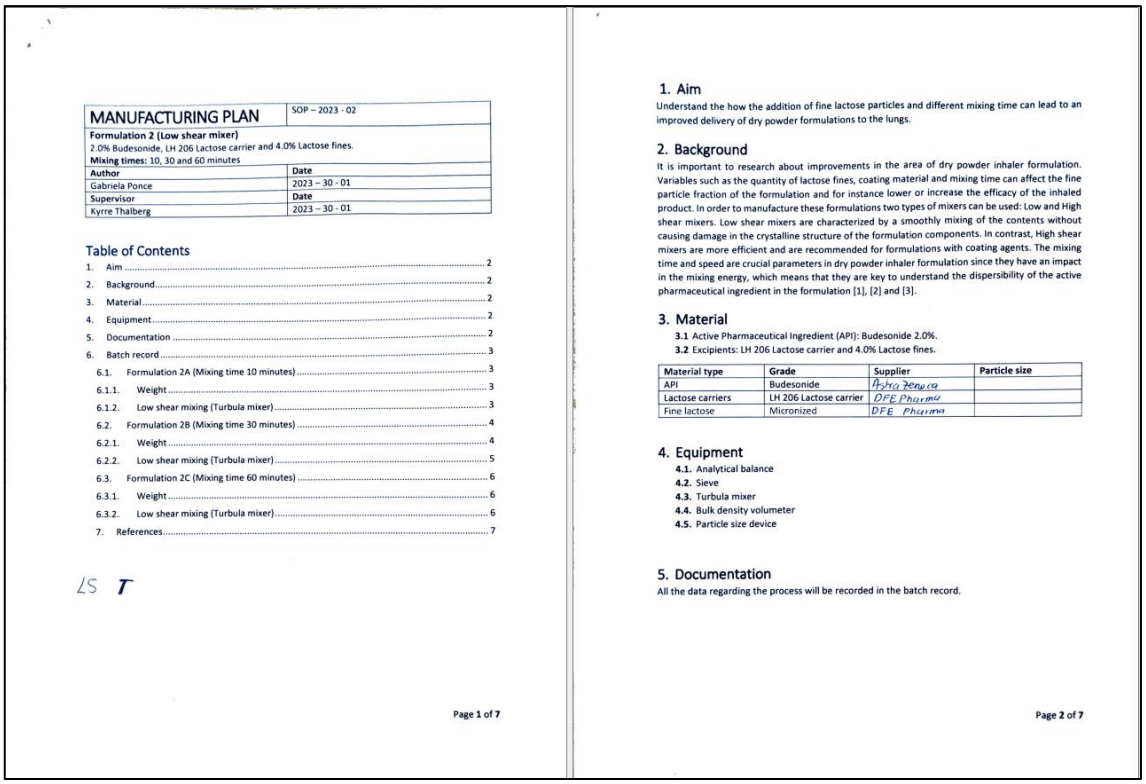
Figure 48, There is deposition of the API on the first ACI components adapter + throat and pre-separator for all samples. Stage 3 presents the highest deposition for the collection plates stages for all samples. HS2C 9 min (gray) had the highest value at the Adapter + Throat and Pre-separator and the lowest at the collection plates stages.

Table 12 NGI Formulation 1 aerodynamic size distribution profile for high shear mixer summary table at 700 and 1000 rpm

NGI summary formulation 1 high shear													
Batch	**HS1C**	**HS1C**	**HS1A**	**HS1A**	**HS1B**	**HS1B**	**HS2A**	**HS2A**	**HS2B**	**HS2B**	**HS2C**	**HS2C**	**HS1A**
Device	**Novolizer**												
NGI No	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
NGI Flow	**80**	**80**	**80**	**80**	**80**	**80**	**80**	**80**	**80**	**80**	**80**	**80**	**80**
Time (sec)	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**
µg Bude/ dose													
Inlet+adapter	58.8	66.9	62.9	63.5	58.3	74.1	71.9	70.0	74.2	70.8	75.2	72.2	76.2
Presep	41.6	45.6	33.0	45.9	28.1	34.5	44.8	60.7	46.8	58.5	52.1	67.6	42.1
Stage 1	6.7	6.7	5.2	6.5	4.7	6.2	6.3	7.4	6.0	7.1	6.8	6.7	6.2
Stage 2	22.6	22.6	19.7	20.3	18.1	23.2	19.7	20.5	19.6	21.7	19.8	18.4	21.3
Stage 3	25.8	26.8	24.8	24.9	21.3	26.3	23.0	20.8	18.6	18.7	15.7	13.9	23.9
Stage 4	25.2	21.8	25.6	23.2	22.0	23.7	21.1	19.8	16.2	16.6	12.5	10.0	22.1
Stage 5	9.2	8.0	11.1	8.4	8.3	8.5	10.8	7.2	5.5	6.3	3.9	2.5	8.9
Stage 6	2.0	1.4	2.8	1.9	2.1	1.7	2.2	1.6	1.3	1.2	0.8	0.4	2.1
Stage 7	0.2	0.1	0.2	0.2	0.2	0.1	0.3	0.2	0.1	0.1	0.1	0.0	0.2
MOC	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Filter	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
SUM in NGI (=DD)	**192.3**	**199.9**	**185.4**	**194.9**	**163.1**	**198.3**	**200.1**	**208.2**	**188.4**	**201.0**	**186.9**	**191.7**	**202.9**
FPD<5µm µg/dose	72.71	68.30	73.47	67.76	62.03	70.72	66.23	58.76	50.56	52.67	41.95	35.08	66.77
FPF<5µm % of Sum	37.81	34.18	39.63	34.77	38.04	35.66	33.10	28.22	26.84	26.21	22.44	18.31	32.91
FPF<3µm % of Sum	25.19	21.79	27.54	23.09	25.92	23.18	22.41	18.35	16.77	16.26	13.08	10.05	21.76
FPF<1µm % of Sum	2.93	2.24	3.81	2.63	3.26	2.49	3.21	2.13	1.82	1.81	1.22	0.71	2.73
MMAD µm	2.88	3.00	2.67	2.88	2.77	2.94	2.80	3.04	3.16	3.25	3.44	3.65	2.89
GSD	1.82	1.80	1.84	1.80	1.82	1.81	1.93	1.87	1.86	1.92	1.80	1.77	1.86

7.4.Low shear (Turbula®) Batch record

7.4.1. Uncoated formulation



MANUFACTURING PLAN	SOP – 2023 - 02
Formulation 2 (Low shear mixer) 2.0% Budesonide, LH 206 Lactose carrier and 4.0% Lactose fines. **Mixing times:** 10, 30 and 60 minutes	
Author	**Date**
Gabriela Ponce	2023 – 30 - 01
Supervisor	**Date**
Kyrre Thalberg	2023 – 30 - 01

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LS T

1. Aim

Understand the how the addition of fine lactose particles and different mixing time can lead to an improved delivery of dry powder formulations to the lungs.

2. Background

It is important to research about improvements in the area of dry powder inhaler formulation. Variables such as the quantity of lactose fines, coating material and mixing time can affect the fine particle fraction of the formulation and for instance lower or increase the efficacy of the inhaled product. In order to manufacture these formulations two types of mixers can be used: Low and High shear mixers. Low shear mixers are characterized by a smoothly mixing of the contents without causing damage in the crystalline structure of the formulation components. In contrast, High shear mixers are more efficient and are recommended for formulations with coating agents. The mixing time and speed are crucial parameters in dry powder inhaler formulation since they have an impact in the mixing energy, which means that they are key to understand the dispersibility of the active pharmaceutical ingredient in the formulation [1], [2] and [3].

3. Material

3.1 Active Pharmaceutical Ingredient (API): Budesonide 2.0%.
3.2 Excipients: LH 206 Lactose carrier and 4.0% Lactose fines.

Material type	Grade	Supplier	Particle size
API	Budesonide	Astra Zeneca	
Lactose carriers	LH 206 Lactose carrier	DFE Pharma	
Fine lactose	Micronized	DFE Pharma	

4. Equipment

4.1. Analytical balance
4.2. Sieve
4.3. Turbula mixer
4.4. Bulk density volumeter
4.5. Particle size device

5. Documentation

All the data regarding the process will be recorded in the batch record.

6. Batch record

6.1. Formulation 2A (Mixing time 10 minutes)

Batch size	Formulation name:	Mixing time	Fabrication date
80 g	**Formulation 2A:** (2.0% Budesonide, LH 206 Lactose carrier and 4.0% Lactose fines).	**10 minutes**	03 - Feb - 2023

6.1.1. Weight

Material	Batch number	Expiration date
Budesonide	4211059 - 01	
Lactose carrier (LH 206)	600365	17 - NOV - 2013
Lactose fines	1089C67	13 - Feb - 2022

Step	Description	Sign	Notes
1	Check that the balance is clean, zeroed and that the laboratory's doors are closed.	GP	Today is raining
2	Label a container (250 mL) and record the tara weight: 220.89 g	GP	
3	Weight **75.2 g** of the **Lactose carrier (LH 206)** in an adequate container. Experimental weight: 75.22 g	GP	
4	Weight **1.6 g** of the **Budesonide** in an adequate container. Experimental weight: 1.6072 g	GP	
5	Weight **3.2 g** of the **Lactose fines** in an adequate container. Experimental weight: 3.2049 g	GP	

6.1.2. Low shear mixing (Turbula mixer)

Step	Description	Sign	Notes
1	Check that the Turbula mixer is clean and ready to use	GP	
2	Check that the laboratory sieves are clean and ready to use	GP	
3	Add approximately half of the previously weighted **Lactose carrier (LH 206)** into the mixing vessel 250 mL.	GP	
4	Add the whole content of the previously weighted **Budesonide** into the mixing vessel.	GP	
5	Add the whole content of the previously weighted **Lactose fines** into the mixing vessel.	GP	
6	Add the rest of the previously weighted **Lactose carrier (LH 206)** into the mixing vessel.	GP	
7	Close the mixing vessel and seal the lead with parafilm	GP	
8	Place the container inside the Turbula mixer and hold the machine with two extra straps.	GP	
9	Start mixing for **5 minutes.** Initial time: 10:35 Final time: 10:40 Speed: 68 rpm	GP	
10	Sieve the powder mixture. Sieve mesh: 0.710 milimeter.	GP	

11	Note if aggregates are present and take a picture	GP	
12	Put the powder back into the container and close and seal the container.	GP	
13	Start mixing for **5 minutes.** Initial time: 10:53 Final time: 10:58 Speed: 68 rpm	GP	
14	Weight the container Weight 300.84 g	GP	
15	**Calculate yield.** $Yield = \left(\frac{grams\ of\ formulation\ produced}{grams\ of\ formulation\ planned}\right) x\ 100 = \frac{79.95}{80} x\ 100 = 99.9375$ Production yield: 99.9375 % Production loss: 0.0625 %	GP	
16	Storage in an airtight container at room temperature and add parafilm to the lid.	GP	

6.2. Formulation 2B (Mixing time 30 minutes)

Batch size	Formulation name:	Mixing time	Fabrication date
80 g	**Formulation 2B:** (2.0% Budesonide, LH 206 Lactose carrier and 4.0% Lactose fines).	**30 minutes**	03 - Feb - 2023

6.2.1. Weight

Material	Batch number	Expiration date
Budesonide	4211059 - 01	
Lactose carrier (LH 206)	600365	17 - NOV - 2013
Lactose fines	1089C67	13 - Feb - 2022

Step	Description	Sign	Notes
1	Check that the balance is clean, zeroed and that the laboratory's doors are closed.	GP	
2	Label a container (250 mL) and record the tara weight: 221.18g	GP	
3	Weight **75.2 g** of the **Lactose carrier (LH 206)** in an adequate container. Experimental weight: 75.24 g	GP	
4	Weight **1.6 g** of the **Budesonide** in an adequate container. Experimental weight: 1.6007 g	GP	
5	Weight **3.2 g** of the **Lactose fines** in an adequate container. Experimental weight: 3.2019 g	GP	

6.2.2. Low shear mixing (Turbula mixer)

Step	Description	Sign	Notes
1	Check that the Turbula mixer is clean and ready to use	GP	
2	Check that the laboratory sieves are clean and ready to use	GP	
3	Add approximately half of the previously weighted **Lactose carrier (LH 206)** into the mixing vessel 250 mL.	GP	
4	Add the whole content of the previously weighted **Budesonide** into the mixing vessel.	GP	
5	Add the whole content of the previously weighted **Lactose fines** into the mixing vessel.	GP	
6	Add the rest of the previously weighted **Lactose carrier (LH 206)** into the mixing vessel.	GP	
7	Close the mixing vessel and seal the lead with parafilm	GP	
8	Place the container inside the Turbula mixer and hold the machine with two extra straps.	GP	
9	Start mixing for **15 minutes.** Initial time: 11:42 Final time: 11:57 Speed: 68 rpm	GP	
10	Sieve the powder mixture. Sieve mesh: 0.710 milimeter.	GP	
11	Note if aggregates are present and take a picture	GP	YES
12	Put the powder back into the container and close and seal the container.	GP	
13	Start mixing for **15 minutes.** Initial time: 12:09 Final time: 12:24 Speed: 68 rpm	GP	
14	Weight the container Weight 351.21 GP 301.03 g	GP	
15	**Calculate yield.** $Yield = \left(\frac{grams\ of\ formulation\ produced}{grams\ of\ formulation\ planned}\right) x\ 100 =$ $\frac{79.85}{80}$ Production yield: 99.8125 % Production loss: 0.1875 %	GP	
16	Storage in an airtight container at room temperature and add parafilm to the lid.	GP	

6.3. Formulation 2C (Mixing time 60 minutes)

Batch size	Formulation name:	Mixing time	Fabrication date
80 g	Formulation 2C: (2.0% Budesonide, LH 206 Lactose carrier and 4.0% Lactose fines).	60 minutes	03 - Feb - 2023

6.3.1. Weight

Material	Batch number	Expiration date
Budesonide	421/0659-01	
Lactose carrier (LH 206)	6003605	17-Nov-2023
Lactose fines	10836067	15-FEB-2022

Step	Description	Sign	Notes
1	Check that the balance is clean, zeroed and that the laboratory's doors are closed.	GP	
2	Label a container (250 mL) and record the tara weight: 220.594	GP	
3	Weight **75.2 g** of the **Lactose carrier (LH 206)** in an adequate container. Experimental weight: 75.26	GP	
4	Weight **1.6 g** of the **Budesonide** in an adequate container. Experimental weight: 1.60378 GP 43	GP	
5	Weight **3.2 g** of the **Lactose fines** in an adequate container. Experimental weight: 3.20354	GP	

6.3.2. Low shear mixing (Turbula mixer)

Step	Description	Sign	Notes
1	Check that the Turbula mixer is clean and ready to use	GP	
2	Check that the laboratory sieves are clean and ready to use	GP	
3	Add approximately half of the previously weighted **Lactose carrier (LH 206)** into the mixing vessel 250 mL.	GP	
4	Add the whole content of the previously weighted **Budesonide** into the mixing vessel.	GP	
5	Add the whole content of the previously weighted **Lactose fines** into the mixing vessel.	GP	
6	Add the rest of the previously weighted **Lactose carrier (LH 206)** into the mixing vessel.	GP	
7	Close the mixing vessel and seal the lead with parafilm	GP	
8	Place the container inside the Turbula mixer and hold the machine with two extra straps.	GP	
9	Start mixing for **30 minutes.** Initial time: 14:35 Final time: 15:05 Speed: 68 rpm	GP	
10	Sieve the powder mixture. Sieve mesh: 0.710 milimeter.	GP	
11	Note if aggregates are present and take a picture	GP	YES

12	Put the powder back into the container and close and seal the container.	GP	
13	Start mixing for **30 minutes.** Initial time: 15:16 Final time: 15:47 Speed: 68 rpm	GP	
14	Weight the container Weight 300.62 g	GP	
15	**Calculate yield.** $Yield = \left(\frac{grams\ of\ formulation\ produced}{grams\ of\ formulation\ planned}\right) x\ 100 =$ $\frac{80.03}{80}$ GP 100.0375 Production yield: 80.03 % Production loss: 0 %	GP	
16	Storage in an airtight container at room temperature and add parafilm to the lid.	GP	

7. References

[1] K. Thalberg, F. Papathanasiou, M. Fransson and M. Nicholas, "Controlling the performance of adhesive mixtures for inhalation using mixing energy," *International Journal of Pharmaceutics*, vol. 592, pp. 1-14, 2021.

[2] M. Aulton and K. Taylor, Aulton's Pharmaceutics: The Design and Manufacture of Medicines, USA: Elsevier Health Sciences, 2013.

[3] K. Thalberg, "Formulation development of adhesive mixtures for inhalation - A multi-factorial optimization challenge: Paart 1," *Inhalation*, pp. 1-7, 2022.

7.4.2. Coated formulation

MANUFACTURING PLAN	SOP – 2023 - 03
Formulation 3 (Low shear mixer) 2.0% Budesonide, LH 206 Lactose carrier, Magnesium stearate 1.0% and 4.0% Lactose fines LH 300. **Mixing times:** 10, 30 and 60 minutes	
Author	**Date**
Gabriela Ponce	2023 – 06 - 02
Supervisor	**Date**
Kyrre Thalberg	2023 – 06 - 02

Table of Contents

1. Aim

Understand the how the addition of fine lactose particles and different mixing time can lead to an improved delivery of dry powder formulations to the lungs.

2. Background

It is important to research about improvements in the area of dry powder inhaler formulation. Variables such as the quantity of lactose fines, coating material and mixing time can affect the fine particle fraction of the formulation and for instance lower or increase the efficacy of the inhaled product. In order to manufacture these formulations two types of mixers can be used: Low and High shear mixers. Low shear mixers are characterized by a smoothly mixing of the contents without causing damage in the crystalline structure of the formulation components. In contrast, High shear mixers are more efficient and are recommended for formulations with coating agents. The mixing time and speed are crucial parameters in dry powder inhaler formulation since they have an impact in the mixing energy, which means that they are key to understand the dispersibility of the active pharmaceutical ingredient in the formulation [1], [2] and [3].

3. Material

3.1 Active Pharmaceutical Ingredient (API): Budesonide 2.0%.
3.2 Excipients: Magnesium stearate, LH 206 Lactose carrier and 4.0% Lactose fines LH 300.

Material type	Grade	Supplier	Particle size
API	Budesonide	AstraZeneca	—
Lactose carriers	LH 206 Lactose carrier	DFE Pharma	—
Lactose fines	LH 300 Micronized	DFE Pharma	—
Coating agent	Magnesium stearate	Peter Greven	—

4. Equipment

4.1. Analytical balance
4.2. Sieve
4.3. Turbula mixer
4.4. Bulk density volumeter
4.5. Particle size device

5. Documentation

All the data regarding the process will be recorded in the batch record.

6. Batch record

6.1. Formulation LS 3A (Mixing time 10 minutes)

Batch size	Formulation name:	Final mixing time	Fabrication date
80 g	**Formulation LS 3A:** (2.0% Budesonide, LH 206 Lactose carrier, Magnesium stearate 1.0% and 4.0% Lactose fines LH300).	10 minutes	06-Feb-23

6.1.1. Weight

Material	Batch number	Expiration date
Budesonide	4211059-01	-
Lactose carrier (LH 206)	600365	17-NOV-2013
Lactose fines (LH 300)	1083C67	13-FEB-2022
Magnesium stearate	C723845	-

Step	Description	Sign	Notes
1	Check that the balance is clean, zeroed and that the laboratory's doors are closed.	GP	
2	Label a container (250 mL) and record the tara weight: 220.84	GP	
3	Weight **74.4 g** of the **Lactose carrier (LH 206)** in an adequate container. Experimental weight: 74.44	GP	
4	Weight **3.2 g** of the **Lactose fines (LH 300)** in an adequate container. Experimental weight: 3.2018	GP	
5	Weight **0.8 g** of the **Magnesium stearate** in an adequate container. Experimental weight: 0.8031	GP	
6	Weight **1.6 g** of the **Budesonide** in an adequate container. Experimental weight: 1.6023	GP	

6.1.2. Low shear mixing (Turbula mixer)

Step	Description	Sign	Notes
1	Check that the Turbula mixer is clean and ready to use	GP	
2	Check that the laboratory sieves are clean and ready to use	GP	
3	Add approximately half of the previously weighted **Lactose carrier (LH 206)** into the mixing vessel 250 mL.	GP	
4	Add the whole content of the previously weighted **Magnesium stearate** into the mixing vessel.	GP	
5	Add the rest of the previously weighted **Lactose carrier (LH 206)** into the mixing vessel.	GP	
7	Close the mixing vessel and seal the lead with parafilm	GP	
8	Place the container inside the Turbula mixer and hold the machine with two extra straps.	GP	
9	Start mixing for 10 minutes. Initial time: 16:04 Final time: 16:19 Speed: 68 rpm	GP	

10	Sieve the powder mixture. Sieve mesh: 0.710 milimeter.	GP	
11	Note if aggregates are present and take a picture	GP	NO
12	Put the powder back into the container and close and seal the container.	GP	
13	Start mixing for 15 minutes. Initial time: 16:26 Final time: 16:43 Speed: 68 rpm	GP	
14	Remove the parafilm from the container	GP	
15	Weight the container Weight 295.68 g	GP	
16	**Calculate yield for the coating process.** $Yield = \left(\frac{74.79\ g\ of\ formulation\ produced}{75.2\ g\ of\ formulation\ planned}\right) x\ 100 =$ Production yield: 99.45 % Production loss: 0.54 %	GP	
17	Take out half of the coated carrier	GP	
18	Add the whole content of the previously weighted **Lactose fines (LH 300)** into the mixing vessel.	GP	
19	Add the whole content of the previously weighted **Budesonide** into the mixing vessel.	GP	
20	Add the rest of the coated carrier with rinsing.	GP	
21	Close the mixing vessel and seal the lead with parafilm	GP	
22	Place the container inside the Turbula mixer and hold the machine with two extra straps.	GP	
23	Start mixing for **5 minutes.** Initial time: 16:51 Final time: 16:56 Speed: 68 rpm	GP	
24	Sieve the powder mixture. Sieve mesh: 0.710 milimeter.	GP	
25	Note if aggregates are present and take a picture	GP	YES, big one
26	Put the powder back into the container and close and seal the container.	GP	
27	Close the mixing vessel and seal the lead with parafilm	GP	
28	Place the container inside the Turbula mixer and hold the machine with two extra straps.	GP	
29	Start mixing for **5 minutes.** Initial time: 17:08 Final time: 17:13 Speed: 68 rpm	GP	
30	Remove the parafilm	GP	
31	Weight the container Weight 300.20 g	GP	
32	**Calculate yield.** $Yield = \left(\frac{79.31\ grams\ of\ formulation\ produced}{80\ grams\ of\ formulation\ planned}\right) x\ 100 =$ Production yield: 99.1375 % Production loss: 0.8625 %	GP	

33	Storage in an airtight container at room temperature and add parafilm to the lid.	GP	

6.2. Formulation LS 3B (Mixing time 30 minutes)

Batch size	Formulation name:	Mixing time	Fabrication date
80 g	**Formulation LS 3B:** (2.0% Budesonide, LH 206 Lactose carrier, Magnesium stearate 1.0% and 4.0% Lactose fines (LH 300)).	**30 minutes**	07-Feb-23

6.2.1. Weight

Material	Batch number	Expiration date
Budesonide	4211059-01	-
Lactose carrier (LH 206)	600365	17-NOV-2013
Lactose fines (LH 300)	1083C67	13-FEB-2022
Magnesium stearate	C723845	-

Step	Description	Sign	Notes
1	Check that the balance is clean, zeroed and that the laboratory's doors are closed.	GP	
2	Label a container (250 mL) and record the tara weight: 221.09g	GP	
3	Weight **74.4 g** of the **Lactose carrier (LH 206)** in an adequate container. Experimental weight: 74.40g	GP	
4	Weight **3.2 g** of the **Lactose fines (LH 300)** in an adequate container. Experimental weight: 3.2052	GP	
5	Weight **0.8 g** of the **Magnesium stearate** in an adequate container. Experimental weight: 0.8003g	GP	
6	Weight **1.6 g** of the **Budesonide** in an adequate container. Experimental weight: 1.6069 g	GP	

6.2.2. Low shear mixing (Turbula mixer)

Step	Description	Sign	Notes
1	Check that the Turbula mixer is clean and ready to use	GP	
2	Check that the laboratory sieves are clean and ready to use	GP	
3	Add approximately half of the previously weighted **Lactose carrier (LH 206)** into the mixing vessel 250 mL.	GP	
4	Add the whole content of the previously weighted **Magnesium stearate** into the mixing vessel.	GP	
5	Add the rest of the previously weighted **Lactose carrier (LH 206)** into the mixing vessel.	GP	
7	Close the mixing vessel and seal the lead with parafilm	GP	

8	Place the container inside the Turbula mixer and hold the machine with two extra straps.	GP	
9	Start mixing for **15 minutes.** Initial time: 13:13 Final time: 13:29 Speed: 68 rpm	GP	
10	Sieve the powder mixture. Sieve mesh: 0.710 milimeter.	GP	
11	Note if aggregates are present and take a picture	GP	NO
12	Put the powder back into the container and close and seal the container.	GP	
13	Start mixing for **15 minutes.** Initial time: 13:36 Final time: 13:51 Speed: 68 rpm	GP	
14	Remove the parafilm from the container	GP	
15	Weight the container Weight 295.68 g	GP	
16	**Calculate yield for the coating process.** $Yield = \left(\frac{74.59\ g\ of\ formulation\ produced}{75.2\ g\ of\ formulation\ planned}\right) x\ 100 =$ Production yield: 99.18 % Production loss: 0.8111 %	GP	
17	Take out half of the coated carrier	GP	
18	Add the whole content of the previously weighted **Lactose fines (LH 300)** into the mixing vessel.	GP	
19	Add the whole content of the previously weighted **Budesonide** into the mixing vessel.	GP	
20	Add the rest of the coated carrier with rinsing.	GP	
21	Close the mixing vessel and seal the lead with parafilm	GP	
22	Place the container inside the Turbula mixer and hold the machine with two extra straps.	GP	
23	Start mixing for **15 minutes.** Initial time: 13:59 Final time: 14:14 Speed: 68 rpm	GP	
24	Sieve the powder mixture. Sieve mesh: 0.710 milimeter.	GP	
25	Note if aggregates are present and take a picture	GP	YES
26	Put the powder back into the container and close and seal the container.	GP	
27	Close the mixing vessel and seal the lead with parafilm	GP	
28	Place the container inside the Turbula mixer and hold the machine with two extra straps.	GP	
29	Start mixing for **15 minutes.** Initial time: 14:25 Final time: 14:40 Speed: 68 rpm	GP	
30	Remove the parafilm	GP	
31	Weight the container Weight 300.16 g	GP	

32	**Calculate yield** $Yield = \left(\frac{74.61\ grams\ of\ formulation\ produced}{80\ grams\ of\ formulation\ planned}\right) x\ 100 =$ Production yield: 98.8315 % Production loss: 1.1685 %	GP	
33	Storage in an airtight container at room temperature and add parafilm to the lid.	GP	

6.3. Formulation LS 3C (Mixing time 60 minutes)

Batch size	Formulation name:	Mixing time	Fabrication date
80 g	**Formulation LS 3C:** (2.0% Budesonide, LH 206 Lactose carrier, Magnesium stearate 1.0% and 4.0% Lactose fines (LH 300)).	**60 minutes**	09-Feb-2023

6.3.1. Weight

Material	Batch number	Expiration date
Budesonide	4211059-01	-
Lactose carrier (LH 206)	600365	17-NOV-2013
Lactose fines (LH 300)	1083C67	13-FEB-2022
Magnesium stearate	C723845	-

Step	Description	Sign	Notes
1	Check that the balance is clean, zeroed and that the laboratory's doors are closed.	GP	
2	Label a container (250 mL) and record the tara weight: 220.35 g	GP	
3	Weight **74.4 g** of the **Lactose carrier (LH 206)** in an adequate container. Experimental weight: 74.41 g	GP	
4	Weight **3.2 g** of the **Lactose fines (LH 300)** in an adequate container. Experimental weight: 3.2000 g	GP	
5	Weight **0.8 g** of the **Magnesium stearate** in an adequate container. Experimental weight: 0.8010 g	GP	
6	Weight **1.6 g** of the **Budesonide** in an adequate container. Experimental weight: 1.6041g	GP	

6.3.2. Low shear mixing (Turbula mixer)

Step	Description	Sign	Notes
1	Check that the Turbula mixer is clean and ready to use	GP	
2	Check that the laboratory sieves are clean and ready to use	GP	
3	Add approximately half of the previously weighted **Lactose carrier (LH 206)** into the mixing vessel 250 mL.	GP	

4	Add the whole content of the previously weighted **Magnesium stearate** into the mixing vessel.	GP	
5	Add the rest of the previously weighted **Lactose carrier (LH 206)** into the mixing vessel.	GP	
7	Close the mixing vessel and seal the lead with parafilm	GP	
8	Place the container inside the Turbula mixer and hold the machine with two extra straps.	GP	
9	Start mixing for **15 minutes.** Initial time: 11:00 Final time: 11:15 Speed: 68 rpm	GP	
10	Sieve the powder mixture. Sieve mesh: 0.710 milimeter.	GP	
11	Note if aggregates are present and take a picture	GP	NO
12	Put the powder back into the container and close and seal the container.	GP	
13	Start mixing for **15 minutes.** Initial time: 11:25 Final time: 11:40 Speed: 68 rpm	GP	
14	Remove the parafilm from the container	GP	
15	Weight the container Weight 295.57 g	GP	
16	**Calculate yield for the coating process.** $Yield = \left(\frac{74.82\ g\ of\ formulation\ produced}{75.2\ g\ of\ formulation\ planned}\right) x\ 100 =$ Production yield: 99.49 % Production loss: 0.5053 %	GP	
17	Take out half of the coated carrier	GP	
18	Add the whole content of the previously weighted **Lactose fines (LH 300)** into the mixing vessel.	GP	
19	Add the whole content of the previously weighted **Budesonide** into the mixing vessel.	GP	
20	Add the rest of the coated carrier with rinsing.	GP	
21	Close the mixing vessel and seal the lead with parafilm	GP	
22	Place the container inside the Turbula mixer and hold the machine with two extra straps.	GP	
23	Start mixing for **30 minutes.** Initial time: 14:18 Final time: 14:48 Speed: 68 rpm	GP	
24	Sieve the powder mixture. Sieve mesh: 0.710 milimeter.	GP	
25	Note if aggregates are present and take a picture	GP	YES
26	Put the powder back into the container and close and seal the container.	GP	
27	Close the mixing vessel and seal the lead with parafilm	GP	
28	Place the container inside the Turbula mixer and hold the machine with two extra straps.	GP	
29	Start mixing for **30 minutes.** Initial time: 15:00 Final time: 15:30 Speed: 68 rpm	GP	

30	Remove the parafilm	GP	
31	Weight the container Weight 80.04 g	GP	
32	**Calculate yield.** $Yield = \left(\frac{79.99 \ grams\ of\ formulation\ produced}{80 \ grams\ of\ formulation\ planned}\right) x\ 100 =$ Production yield: 99.1125 % Production loss: 0.8875 %	GP	
33	Storage in an airtight container at room temperature and add parafilm to the lid.	GP	

7. References

[1] K. Thalberg, F. Papathanasiou, M. Fransson and M. Nicholas, "Controlling the performance of adhesive mixtures for inhalation using mixing energy," *International Journal of Pharmaceutics*, vol. 592, pp. 1-14, 2021.

[2] M. Aulton and K. Taylor, Aulton's Pharmaceutics: The Design and Manufacture of Medicines, USA: Elsevier Health Sciences, 2013.

[3] K. Thalberg, "Formulation development of adhesive mixtures for inhalation - A multi-factorial optimization challenge: Paart 1," *Inhalation*, pp. 1-7, 2022.

7.5.High shear (Diosna®) Batch record

7.5.1. Uncoated formulation

GALENICA — Technical Batch Record

Title: Manufacturing plan of budesonide dry powder formulation for inhalation Formulation 2 High Shear (700 rpm)	Date: 2022-13-02	Page: 1 (4)
Author: Gabriela Ponce	Batch number: HS 3	Batch size: 250 g

1 STUDY DESIGN

The aim of this study is to research how the mixing time and speed are crucial parameters in dry powder inhaler formulation and understand how they can impact the dispersibility of the active pharmaceutical ingredient in the formulation. Three formulations (250g each batch) with different compositions will be produced at two different speeds (700 and 1000 rpm). Three samples (40-50 g) will be taken at 3, 6 and 9 minutes. Temperature after mixing will be measured.

2 BATCH FORMULA AND DISPENSING

2.1 Complete composition

Raw Material	Amount (%)
Budesonide	2.0
Lactose fines LH300	4.0
Lactose carrier LH206	94.0

2.2 Batch formula

Prepare 0.250 kg batch size of the powder formulation.

Raw materials	Batch No	Target Amount (g)	Dispensed Amount (g)	Balance No.
Budesonide	4211059-01	5.0	5.018	Process 3
Lactose fines LH300	1083C67	10.0	10.010	Process 3
Lactose carrier LH206	600365	235.0	235.07	Process 1

3 EQUIPMENT AND UTENSILS

Equipment	Inventory No.	Comment
Diosna Mixer P1-6	F445	1 L vessel
Scale	F445 (3/2023)	Type = PR2002 Process 1
Testo 610 Temp and Humidity meter	F531 (6/2023)	
Sieve 1 mm	130027 22	S/N
Testo Termometer IR	P420 (11/2023)	
Bulk density meter	LTH	LTH
Timer	A164	
Analytical scale	Process 3	

4 PACKAGING

Table 1. Packaging.

Material	Trade name	Supplier	Batch no	Description
Plastic		DUMA		Plastic container

GALENICA — Technical Batch Record

Title: Manufacturing plan of budesonide dry powder formulation for inhalation Formulation 2 High Shear (700 rpm)	Date: 2022-13-02	Page: 2 (4)
Author: Gabriela Ponce	Batch number: HS 3	Batch size: 250 g

5 MANUFACTURING

5.1 Preparation

Check

5.1.1 Label a plastic container (300 mL) *"HS 3 A 3 min 700 rpm"* and record the tara weight: 35.94 g. GP

5.1.2 Label a plastic container (300 mL) *"HS 3 B 6 min 700 rpm"* and record the tara weight: 35.57 g. GP

5.1.3 Label a plastic container (300 mL) *"HS 3 C 9 min 700 rpm"* and record the tara weight: 35.91 g. GP

5.2 Mixing

Date 13-feb-23 Humidity 27.3 %RH 21.5 °C

Check

5.2.1 Weigh 235.0 g of the Lactose carrier LH206 and add half of the amount to the Diosna 1 L vessel. GP

5.2.2 Weigh 10.0 g of Lactose fines LH300 and add evenly over the bed to the Diosna vessel. GP

5.2.3 Weigh 5.0 g of Budesonide and add evenly over the bed to the Diosna vessel. GP

5.2.4 Add the rest of the Lactose carrier LH206 to the Diosna vessel. GP

5.2.5 Attach the lid to the Diosna vessel. GP

5.2.6 Premixing at 150 rpm for 1 minute. GP

5.2.7 Increase the mixing speed to **700 rpm** without stopping for **3 minutes**. GP

5.2.8 Stop the mixer, wait **1 minute**, open the lid, and measure the temperature. Temperature 24.6 °C GP

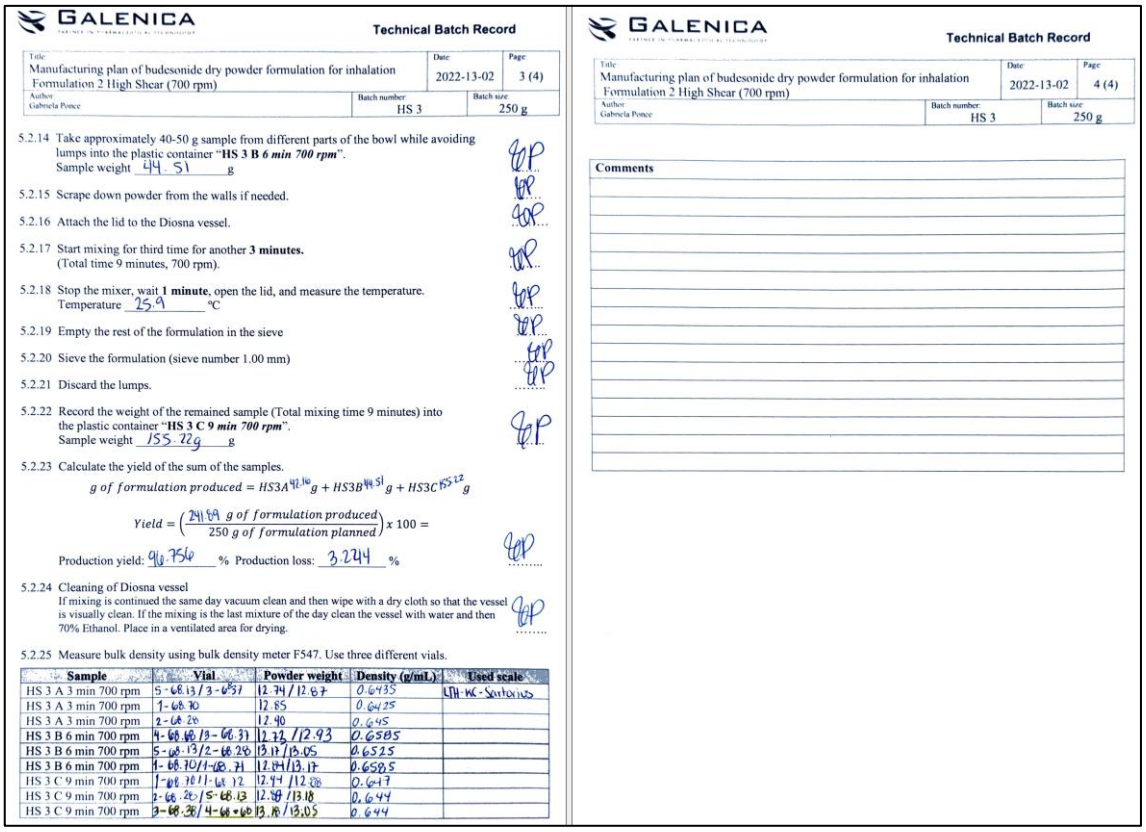
5.2.9 Take approximately 40-50 g sample from different parts of the bowl while avoiding lumps into the plastic container **"HS 3 A *3 min 700 rpm*"**. Sample weight 42.16 g GP

5.2.10 Scrape down powder from the walls if needed. GP

5.2.11 Attach the lid to the Diosna vessel. GP

5.2.12 Start mixing for second time for another **3 minutes**. (Total time 6 minutes, 700 rpm). GP

5.2.13 Stop the mixer, wait **1 minute**, open the lid, and measure the temperature. Temperature 25.5 °C GP



GALENICA

Technical Batch Record

Title	Date	Page
Manufacturing plan of budesonide dry powder formulation for inhalation Formulation 2 High Shear (700 rpm)	2022-13-02	3 (4)
Author: Gabriela Ponce	Batch number: HS 3	Batch size: 250 g

5.2.14 Take approximately 40-50 g sample from different parts of the bowl while avoiding lumps into the plastic container "**HS 3 B *6 min 700 rpm***". Sample weight 44.51 g

5.2.15 Scrape down powder from the walls if needed.

5.2.16 Attach the lid to the Diosna vessel.

5.2.17 Start mixing for third time for another **3 minutes.** (Total time 9 minutes, 700 rpm).

5.2.18 Stop the mixer, wait **1 minute**, open the lid, and measure the temperature. Temperature 25.9 °C

5.2.19 Empty the rest of the formulation in the sieve

5.2.20 Sieve the formulation (sieve number 1.00 mm)

5.2.21 Discard the lumps.

5.2.22 Record the weight of the remained sample (Total mixing time 9 minutes) into the plastic container "**HS 3 C 9 *min 700 rpm***". Sample weight 155.22g g

5.2.23 Calculate the yield of the sum of the samples.

$$g\ of\ formulation\ produced = HS3A^{92.16}g + HS3B^{44.51}g + HS3C^{155.22}g$$

$$Yield = \left(\frac{291.89\ g\ of\ formulation\ produced}{250\ g\ of\ formulation\ planned}\right) x\ 100 =$$

Production yield: 98.756 % Production loss: 3.244 %

5.2.24 Cleaning of Diosna vessel
If mixing is continued the same day vacuum clean and then wipe with a dry cloth so that the vessel is visually clean. If the mixing is the last mixture of the day clean the vessel with water and then 70% Ethanol. Place in a ventilated area for drying.

5.2.25 Measure bulk density using bulk density meter F547. Use three different vials.

Sample	Vial	Powder weight	Density (g/mL)	Used scale
HS 3 A 3 min 700 rpm	5 - 68.13 / 3 - 6.31	12.74 / 12.87	0.6435	LTH-KC - Sartorius
HS 3 A 3 min 700 rpm	1 - 68.30	12.85	0.6425	
HS 3 A 3 min 700 rpm	2 - 68.26	12.90	0.645	
HS 3 B 6 min 700 rpm	4 - 68.66 / 3 - 66.37	12.72 / 12.93	0.6585	
HS 3 B 6 min 700 rpm	5 - 68.13 / 2 - 68.28	13.17 / 13.05	0.6525	
HS 3 B 6 min 700 rpm	1 - 68.30 / 1 - 68.31	12.84 / 13.17	0.6585	
HS 3 C 9 min 700 rpm	1 - 68.30 / 1 - 68.32	12.94 / 12.28	0.647	
HS 3 C 9 min 700 rpm	2 - 68.25 / 5 - 68.13	12.89 / 13.18	0.644	
HS 3 C 9 min 700 rpm	3 - 68.36 / 4 - 66.60	13.16 / 13.05	0.644	

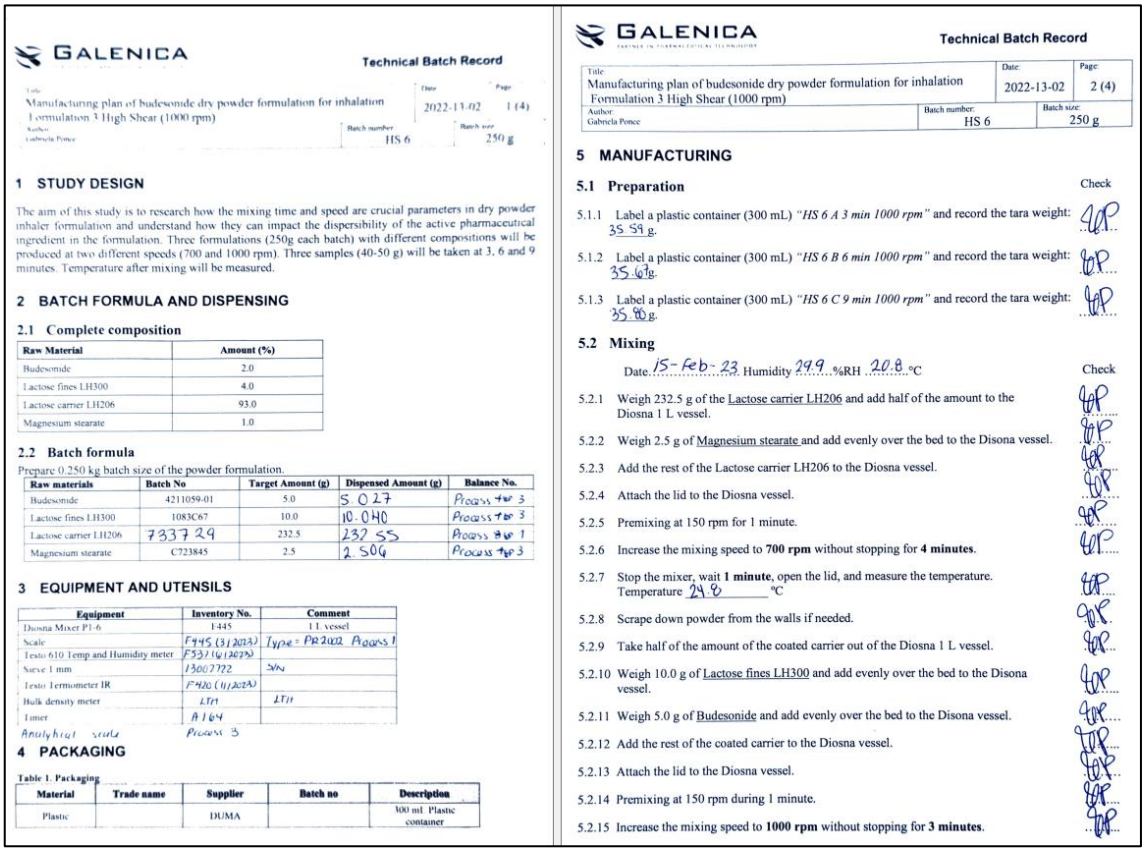
GALENICA

Technical Batch Record

Title	Date	Page
Manufacturing plan of budesonide dry powder formulation for inhalation Formulation 2 High Shear (700 rpm)	2022-13-02	4 (4)
Author: Gabriela Ponce	Batch number: HS 3	Batch size: 250 g

Comments

7.5.2. Coated formulation



GALENICA

Technical Batch Record

Title	Date	Page
Manufacturing plan of budesonide dry powder formulation for inhalation Formulation 3 High Shear (1000 rpm)	2022-13-02	1 (4)
Author: Gabriela Ponce	Batch number: HS 6	Batch size: 250 g

1 STUDY DESIGN

The aim of this study is to research how the mixing time and speed are crucial parameters in dry powder inhaler formulation and understand how they can impact the dispersibility of the active pharmaceutical ingredient in the formulation. Three formulations (250g each batch) with different compositions will be produced at two different speeds (700 and 1000 rpm). Three samples (40-50 g) will be taken at 3, 6 and 9 minutes. Temperature after mixing will be measured.

2 BATCH FORMULA AND DISPENSING

2.1 Complete composition

Raw Material	Amount (%)
Budesonide	2.0
Lactose fines LH300	4.0
Lactose carrier LH206	93.0
Magnesium stearate	1.0

2.2 Batch formula

Prepare 0.250 kg batch size of the powder formulation.

Raw materials	Batch No	Target Amount (g)	Dispensed Amount (g)	Balance No.
Budesonide	4211059-01	5.0	5.027	Process Bal 3
Lactose fines LH300	1083C67	10.0	10.040	Process Bal 3
Lactose carrier LH206	7337 29	232.5	232.55	Process Bal 1
Magnesium stearate	C723845	2.5	2.506	Process Bal 3

3 EQUIPMENT AND UTENSILS

Equipment	Inventory No.	Comment
Diosna Mixer P1-6	1445	1 L vessel
Scale	F945 (31/2023)	Type: PR2022 Process 1
Testo 610 Temp and Humidity meter	F531 (6/2023)	
Sieve 1 mm	13007722	3/4
Testo Termometer IR	F420 (11/2023)	
Bulk density meter	LTH	LTH
Timer	A164	

Analytical scale Process 3

4 PACKAGING

Table 1. Packaging

Material	Trade name	Supplier	Batch no	Description
Plastic		DUMA		300 ml Plastic container

GALENICA

Technical Batch Record

Title	Date	Page
Manufacturing plan of budesonide dry powder formulation for inhalation Formulation 3 High Shear (1000 rpm)	2022-13-02	2 (4)
Author: Gabriela Ponce	Batch number: HS 6	Batch size: 250 g

5 MANUFACTURING

5.1 Preparation

Check

5.1.1 Label a plastic container (300 mL) *"HS 6 A 3 min 1000 rpm"* and record the tara weight: 35.59 g.

5.1.2 Label a plastic container (300 mL) *"HS 6 B 6 min 1000 rpm"* and record the tara weight: 35.67g.

5.1.3 Label a plastic container (300 mL) *"HS 6 C 9 min 1000 rpm"* and record the tara weight: 35.80 g.

5.2 Mixing

Date 15-Feb-23 Humidity 29.9 %RH 20.8 °C

Check

5.2.1 Weigh 232.5 g of the Lactose carrier LH206 and add half of the amount to the Diosna 1 L vessel.

5.2.2 Weigh 2.5 g of Magnesium stearate and add evenly over the bed to the Diosna vessel.

5.2.3 Add the rest of the Lactose carrier LH206 to the Diosna vessel.

5.2.4 Attach the lid to the Diosna vessel.

5.2.5 Premixing at 150 rpm for 1 minute.

5.2.6 Increase the mixing speed to **700 rpm** without stopping for **4 minutes**.

5.2.7 Stop the mixer, wait **1 minute**, open the lid, and measure the temperature. Temperature 29.8 °C

5.2.8 Scrape down powder from the walls if needed.

5.2.9 Take half of the amount of the coated carrier out of the Diosna 1 L vessel.

5.2.10 Weigh 10.0 g of Lactose fines LH300 and add evenly over the bed to the Diosna vessel.

5.2.11 Weigh 5.0 g of Budesonide and add evenly over the bed to the Diosna vessel.

5.2.12 Add the rest of the coated carrier to the Diosna vessel.

5.2.13 Attach the lid to the Diosna vessel.

5.2.14 Premixing at 150 rpm during 1 minute.

5.2.15 Increase the mixing speed to **1000 rpm** without stopping for **3 minutes**.

GALENICA

Technical Batch Record

Title: Manufacturing plan of budesonide dry powder formulation for inhalation Formulation 3 High Shear (1000 rpm)	Date: 2022-13-02	Page: 3 (4)
Author: Gabriela Ponce	Batch number: HS 6	Batch size: 250 g

5.2.16 Stop the mixer, wait **1 minute**, open the lid, and measure the temperature.
Temperature 26.3 °C

5.2.17 Take approximately 40-50 g sample from different parts of the bowl while avoiding lumps into the plastic container **"HS 6 A *3 min 1000 rpm*".**
Sample weight 64.06 g

5.2.18 Scrape down powder from the walls if needed.

5.2.19 Attach the lid to the Diosna vessel.

5.2.20 Start mixing for second time for another **3 minutes**.
(Total time 6 minutes, 1000 rpm).

5.2.21 Stop the mixer, wait **1 minute**, open the lid, and measure the temperature.
Temperature 27.7 °C

5.2.22 Take approximately 40-50 g sample from different parts of the bowl while avoiding lumps into the plastic container "**HS 6 B *6 min 1000 rpm***".
Sample weight 43.46 g

5.2.23 Scrape down powder from the walls if needed.

5.2.24 Attach the lid to the Diosna vessel.

5.2.25 Start mixing for third time for another **3 minutes.**
(Total time 9 minutes, 1000 rpm).

5.2.26 Stop the mixer, wait **1 minute**, open the lid, and measure the temperature.
Temperature 28.4 °C

5.2.27 Empty the rest of the formulation in the sieve

5.2.28 Sieve the formulation (sieve number 1.00 mm)

5.2.29 Discard the lumps.

5.2.30 Record the weight of the remained sample (Total mixing time 9 minutes) into the plastic container "**HS 6 C *9 min 1000 rpm***".
Sample weight 154.89 g (substract tara) = 119.09g

5.2.31 Calculate the yield of the sum of the samples.

$g\ of\ formulation\ produced = HS6A\ \overset{64.06}{\ }\ g + HS6B\ \overset{43.46}{\ }\ g + HS6C\ \overset{119.09}{\ }\ g$

$$Yield = \left(\frac{226.61 g\ of\ formulation\ produced}{250\ g\ of\ formulation\ planned}\right) x\ 100 =$$

Production yield: 90.652 %

Production loss: 9.348 %

GALENICA

Technical Batch Record

Title: Manufacturing plan of budesonide dry powder formulation for inhalation Formulation 3 High Shear (1000 rpm)	Date: 2022-13-02	Page: 4 (4)
Author: Gabriela Ponce	Batch number: HS 6	Batch size: 250 g

5.2.1 Cleaning of Diosna vessel
If mixing is continued the same day vacuum clean and then wipe with a dry cloth so that the vessel is visually clean. If the mixing is the last mixture of the day clean the vessel with water and then 70% Ethanol. Place in a ventilated area for drying.

5.2.2 Measure bulk density using bulk density meter F547. Use three different vials.

Sample	Vial	Powder weight	Density (g/mL)	Used scale
HS 2 A 3 min 1000 rpm	1-68.69	15.67	0.7835	
HS 2 A 3 min 1000 rpm	2-68.36	15.60	0.78	
HS 2 A 3 min 1000 rpm	3-68.36	15.60	0.78	
HS 2 B 6 min 1000 rpm	1-68.69	15.46	0.7730	
HS 2 B 6 min 1000 rpm	2-68.29	15.47	0.7735	
HS 2 B 6 min 1000 rpm	3-68.36	15.40	0.7700	
HS 2 C 9 min 1000 rpm	1-68.68	15.29	0.7645	
HS 2 C 9 min 1000 rpm	2-68.29/4-68.68	15.42/15.30	0.7656	
HS 2 C 9 min 1000 rpm	3-68.40/5-68.14	15.17/15.26	0.7630	

Comments