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 nonactive 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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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.

Table of Contents

L	IST OF A	BREVIATIONS	
1.	. INTR	ODUCTION	9
2.	. MAT	ERIALS AND METHODS	
	2.1.	Manufacturing	
	2.2.	Filling	
	2.3.	Analytical investigations	
	2.3.1	Mixing homogeneity and drug content assay	
	2.3.3	Andersen Cascade Impactor (ACI)	
	2.3.4	Next Generation Impactor (NGI)	
	2.3.5	Particle size	
	2.3.6	. Calculations	
3.	RESU	JLTS AND DISCUSSION	
	3.1.	Particle size	
	3.2.	Manufacturing	
	3.3.	Budesonide content assay and Mixing homogeneity	
	3.4.	Bulk density	
	3.5.	ACI	
	3.5.1	. Low shear mixer batches	
	3.5.2	. High shear mixer batches (700 rpm)	
	3.5.3	. High shear mixer batches (1000 rpm)	
	3.6.	NGI	
	3.7.	Mixing energy analysis	
	3.8.	Comparison of low (Turbula®) and high (Diosna®) mixers	
4.	. CON	CLUSIONS	
5.	. FUTI	URE DIRECTIONS	
6.	. REFI	BRENCES	
7.	. APPI	ENDIX	
	7.1.	Manufacturing	
	7.2.	ACI	
	7.2.1	. Low shear mixer	
	7.2.2	. High shear mixer (700 rpm)	
	7.2.3	. High shear mixer (1000 rpm)	
	7.3.	NGI	
	7.4.	Low shear (Turbula [®]) Batch record	
	7.4.1	. Uncoated formulation	
	7.4.2	. Coated formulation	
	7.5.	High shear (Diosna®) Batch record	50
	7.5.1	. Uncoated formulation	50
	7.5.2	Coated formulation	

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
1	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 μ m 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 μ m) will deposit in the oropharynx, and smaller particles (<0.5 μ m) 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 μ m) per loaded dose is defined by the Fine Particle Fraction (FPF) [8], [9]. However, micronized particles (1 - 5 μ m) 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)*.

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

Table 1 Raw materials used to manufacture the formulations.

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

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

Table 2 Formulation composition.

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.

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

Table 3 Low shear mixer batch names.

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.

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

Table 4 High shear mixer batches names.

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.

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

Table 5 Mixing homogeneity and drug content assay analyzed batches.

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*:

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

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*:

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

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.

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 6 Production yield for Low shear mixer batches

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 %.

Mixing speed					700 rpn	ı			
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	

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

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 %.

Mixing speed					1000 rpn	n				
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		

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

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 $<5 \ \mu m$ [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 $<5 \mu m$ [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 $<5 \ \mu m$ [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 $<5 \mu m$ [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.

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			

Table 0 ACI	I and also an	a ana di		ai- a	diamilantion	~~~~~
I UDIE 9 ACI	Low sneur	aeroa	ynamic	size	aismounon	summary

Stage 0	5.82	1 71	5.82	5 71	1.96	1 18	6.82	8 63	7 22
Stage 0	5.62	7./7	5.62	5.71	ч .70	 -0	0.02	0.05	1.22
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.

	ACI High shear summary													
Mixing speed					700 rpm									
Batch	HS1A	HS1B	HS1C	HS3A	HS3B	HS3C	HS5A	HS5B	HS5C					
Device				Ν	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 Bu	de/ 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					

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

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.

	ACI High shear summary													
Mixing speed				1	000 RPM	[
Batch	HS2A	HS2B	HS2C	HS4A	HS4B	HS4C	HS6A	HS6B	HS6C					
Device				Ν	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 Bι	ıde/ 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	239.1 1	242.2 5	236.9 1	271.1 5	226.6 1	229.3 5	216.3 9	219.1 3					
FPD<5µm µg/dose	69.28	60.89	63.26	89.19	117.2 0	69.48	119.8 4	126.0 2	114.6 6					
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					

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

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 i	formulatio	on 1 high s	hear					
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
					με	g Bude/ dos	e						
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

Г

Formulation 2 (Low snear mixer) 20% Budgenode, 1x266 Lactose criter and 4.0% Lactose fines. Mining times: 10.30 and 60 minutes Mining times: 10.30 and 60 minutes Cable and conduct and for instance lower or increase the efficiency of the formulation and for instance lower or increase the efficiency of the formulation and for instance lower or increase the efficiency of the formulation structure these formulations two types of mixers can be shear mixers, save other mixers are characterized by a smoothly mixing of the casuing damage in the crystalline structure of the formulation structure the foremulation structure the formulation structure the formul	inhaler formulai e can affect the icacy of the inh- iused: Low and i e contents with contrast, High sl i agents. The mi sibility of the ac
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Table of Contents a bear mixers. Low shear mixers are characterized by a smoothly mixing of the causing damage in the crystalline structure of the formulation components. In cause of the cause of the formulation components. In cause of the cause of	he contents with contrast, High sl ; agents. The mi they have an im sibility of the ac
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1. Alm 2 1. Alm 2 2. Background 2 3. Material 2 3. Material 2 3. Material 2 5. Documentation 2 5. Documentation 2 6. Batch record 3 6.1. Formulation 2A (Mixing time 10 minutes) 3 6.1. Weight 3 6.1.1. Weight 3	they have an im sibility of the ac
2. Background 2 3. Material 2 3. Material 2 4. Equipment 2 5. Documentation 2 6. Batch record 3 6.1. Fourier 10 minutes) 3 6.1. Weight 3	sibility of the at
3. Material 2 4. Equipment 2 5. Documentation 2 6. Batch record 3 6.1. Formulation 2A (Mking time 10 minutes) 3 6.1. Weight 3	
4. Equipment 2 5. Documentation 2 6. Documentation 2 7. Bothereord 3 8. In Formulation 2A (Mixing time 10 minutes) 3 6.1. Formulation 2A (Mixing time 10 minutes) 3 6.1. In Weight 3 6.1. In Weight 3	
5. Documentation 3.1 Active remandactures an ignoremut (v/r) sources once Z/v/s. 6. Batch record 3.2 Exclipents: UH 206 Lactose carrier and 4.0% Lactose fines. 6.1. Formulation 2A (Mixing time 10 minutes) 3 6.1. Weight 3 6.1. Weight 3	
6.1 Formulation 2A (Mixing time 10 minutes)	
6.1.1. Weight	ticle size
Lactose carriers Lh 200 Lactose carrier DFE Phayme	
6.1.2. Low shear mixing (Turbula mixer)	
6.2. Formulation 28 (Mixing time 30 minutes)	
62.1. Weight 4 . Equipment	
b.2. Low mean many (violate mark) 6 4.1. Analytical balance	
42. Sieve 42. Sieve 42. Sieve	
6.3.2. Low shear mixing (Turbula mixer)	
7. References	
All the data regarding the process will be recorded in the batch record.	
Page 1 of 7	Page 2
6. Batch record 11 Note if aggregates are present and take a picture 40° 6.1. Formulation 2A (Mixing time 10 minutes) 12 Put the powder back into the container and dose and seal the Gypt 40° 13 Start nize formulation name: 10 minutes 10 minutes 40° 80 g Formulation 2A (Mixing time 10 minutes) 13 Start nize for a failed time:	>
6.1.1. Weight Material Batch number Experimental and the submatrix and the sub	ication date - Feb - 2023 5 0 22 Notes > >
6.1.1. Weight Material Batch number Material Batch number 13 Calculate yield. 14 100 = 000000000000000000000000000000000	rication date - Feb - 2023 5 0.22 Notes > >
6.1.1. Weight Material Batch number Explication date Material Batch number Explication date Lactose carrier (IL 2006) (2003.65) (7 - MOV - 20/5) Lactose carrier (IL 2006) (2003.65) (7 - MOV - 20/5) Lactose carrier (IL 2006) (2003.65) (7 - MOV - 20/5) Lactose carrier (IL 2006) (2003.65) (7 - MOV - 20/5) Lactose frees 10.673.620 (2003.65) (7 - MOV - 20/5) Lactose carrier (IL 2006) (2003.65) (7 - MOV - 20/5) (2003.65) (2003.65) 2 Label a container (200 mL) and record the tara weight: (200.86) (200.86) (200.86) (200.86) 3 Weight 75.7 g of the Lactose carrier (IL 2006) in an adequate container. (200.86) (200.86) (210.80) (200.86) (210.80) (200.86) (210.80) (200.86) (210.80) (210.80) (210.80) (210.80) (200.86) (210.80) (210.80) (210.80) (210.80) (210.80) (210.80) (210.80) (210.80) (210.80) (210.80) (210.80) (210.80) (210.80) (210.80) (210.80) (210.80)	rication date - Feb - 2023 - 2023 Notes - 2023 - 2025 - 2025 - 2025 - 2025 -
6.1.1. Weight Material Stch number Expiration date Material Stch number Expiration date Startos fines (2015) (2015) Lactos carrier (LH 206) (2015) (2015) Lactos fines (2015) (2015) Step Description (2015) (2015) 1 Check that the balance is clean, zeroed and that the laboratory's (2017) 2 Label a container (250 mL) and record the tara weight (2017) 3 Weight 73.2 g of the Lactose carrier (LH 206) in an adequate (2017) 4 Weight 73.2 g of the Lactose container. (2017) 5 Weight 73.2 g of the Lactose container. (2017) 4 Weight 73.2 g of the Lactose container. (2017) 5 Weight 73.2 g of the Lactose container. (2017) 6 1.1.1. Check that the lactose fines in an adequate container. (2017) 5 Weight 73.2 g of the Lactose container (250 mL) and sequate container. (2017) 6 1.1.1. Check that the lactose fines in an adequate container. (2017) 5 Weight 73.2 g of the Lactose container (101 ME) (2017) <	rication date - Feb - 2023 - Solution - Feb - 2023 - Solution -
6.1.1. Weight Material Batch number Expiration date Material Batch number Expiration date Stations for arring (11 200) (2003,65) (27 - AGV - 20/5) Lactose carrier (11 200) (2003,65) (27 - AGV - 20/5) Lactose carrier (11 200) (2003,65) (27 - AGV - 20/5) Lactose carrier (11 200) (2003,65) (27 - AGV - 20/5) Statose fines 1/0,633,6,62 (27 - AGV - 20/5) Lactose carrier (11 200) (2003,65) (27 - AGV - 20/5) Lactose carrier (12 200,100) (20 - 200) (20 - 200) 2 Label a container (250 mL) and record the tara weight: (20 - 200) 3 Weight 75.2 g of the Lactose carrier (101 200) in an adequate container. (20 - 200) 5 Experimental weight: 3, 20/3, g (20 - 200) 5.1.1. Cow shear mixing (Turbula mixer) (27 - AGV - 20) 5.2. Check that the lactose fines in an adequate container. (27 - AGV - 20) 1 Check that the lactose and ready to use (21 - AGV - 20) 1 Check that the lactose and ready to use (21 - AGV - 20) 2 Check that the lactose and ready to use (21 - AGV - 2	- reation date - reb - 2023
6.1.1. Weight 94 A 5 Material Batch number Expiration date Material Batch number Expiration date Lactose arrise (U1 206) (L0 20 5 G 5) // - AUV - 20/5 Lactose arrise (U1 206) (L0 20 5 G 5) // - AUV - 20/5 Step Description 10 8 3 C G 2 // - AUV - 20/5 Cock that the balance is clean, zened and that the laboratory's by Today on Taxino the field Total (Mixing time 20 minutes) 2 Label a container (120 mi) and record the tara weight the container. Description Description 20 (L0 20 G G G G) 3 Weight 75.2 g of the Lactose carrier (14 206) in an adequate container. Description Description 20 (L0 20 G G G G G) 6.2.1. Weight Description Step Description 20 (L0 20 G G G G G G) Divention 20 (L0 20 G G G G G G G G G G G G G G G G G G	rication date - Feb - 2023 - 22 Notes
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by More and the second se		6.2.2. Low shear mixing (Turbula mixer)		6.3	Formulation 2C (Mis	xing time 60 minutes)		
 	Step 1	Description Sign Check that the Turbula mixer is clean and ready to use 940	Notes	Batch 80 m	size Formulation nar	me: Mixing ti : (2.0% Budesonide, LH 206 60 minut	ne Fabri	cation date
<form></form>	2	Check that the laboratory sieves are clean and ready to use		ovg	Lactose carrier a	and 4.0% Lactose fines).	03-	Feb - 2023
	3	Add approximately half of the previously weighted Lactose carrier (LH 206) into the mixing vessel 250 mL.			pere arrow.			
 And the device current of the proceeding weighted tables of the device current bias of the de	4	Add the whole content of the previously weighted Budesonide into the mixing vessel.		Mater	6.3.1. Weight	Batch number Expir	tion date	
	5	Add the whole content of the previously weighted Lactose fines		Budes	onide	4211059-01	Atri - 70	14
 	6	Add the rest of the previously weighted Lactose carrier (LH 206)		Lactos	e fines	1083667 13	FEB - 20	22
a Part of the contract rank the final data is also be the matter data is all the final data is also data of the data is all the final data is all the	7	into the mixing vessel. Close the mixing vessel and seal the lead with parafilm 40P						
¹ / ₁ 1/ ₁ ¹ / ₁ <td< td=""><td>8</td><td>Place the container inside the Turbula mixer and hold the machine</td><td></td><td>Step 1</td><td>Description Check that the balance</td><td>e is clean, zeroed and that the laborator</td><td>IS CAN</td><td>Notes</td></td<>	8	Place the container inside the Turbula mixer and hold the machine		Step 1	Description Check that the balance	e is clean, zeroed and that the laborator	IS CAN	Notes
Apple of the product water and the product of the product	9	Start mixing for 15 minutes.		2	doors are closed.	250 ml) and record the tara weig	til ano	
¹ / ₁ we served ¹ / ₁ we served ¹ / ₁ we serve ¹ /	10	Sieve the powder mixture.		-	220 599	Lastres series (IN 206) is an adapt	WP -	
121 In the growth tak its the container and does and used the <u>GP</u> is the growth tak its the container and does and used the <u>GP</u> is the growth tak its the container and does and used the <u>GP</u> is the growth tak its the container and <u>GP</u> is the growth tak its the <u>GP</u> is the <u>GP</u>	11	Sieve mesh: 0.710 milimeter. U1 Note if aggregates are present and take a picture GPP	Yes	3	container.	75 2/	8P	
A provide the product of the second set	12	Put the powder back into the container and close and seal the UP container.		4	Experimental weight: Weight 1.6 g of the Bud	desonide in an adequate container.	0,0	
1 Topological and the contrainer and close and seal the close control (1) and close control of the provide vertice the close control (1) and close control of the provide vertice the close control (1) and close control of the provide vertice the close control (1) and close control of the provide vertice the close control (1) and close control of the provide vertice the close control (1) and close control of the close control (1) and close control of the close control (1) and c	13	Start mixing for 15 minutes.		5	Experimental weight: Weight 3.2 g of the Lact	1. 60373° 43 tose fines in an adequate container.	100	
¹ Contract and the contract of the contencont of the contract of the contract of the	14	Weight the container 42 21 speed of spin 4			Experimental weight:	3. 20359	UP	
If the degreener of a mutation production graduation grad	15	Weight <u>301-21-4 bP 301-03 g</u> (// Calculate yield. 79,95			6.3.2. Low shear mi	ixing (Turbula mixer)		
Imposite the product pr		$Yield = \left(\frac{grams \ of \ formulation \ produced}{arams \ of \ formulation \ planmed}\right) x \ 100 = 0.00$		Step	Description	mixer is clean and ready to use	Sign	Notes
¹ Contaction from the statistic contaction of the periodic variable and the peri		Production vield: 99.8125 % 80		2	Check that the laborato	ory sieves are clean and ready to use	4P	
10 box get m is arright counter at foon temperature and and with the factor of the provide weighted Lattices fine with the maning result. 2 bit is provider back into the container and close and seal the with the seal with partition. 2 bit is provider back into the container and close and seal the with with the seal with partition. 2 bit is provider back into the container and close and seal the with with the seal with partition. 2 bit is provider back into the container and close and seal the with with the seal with partition. 3 bit is provider back into the container and close and seal the with with with the seal with partition. 2 bit is provider back into the container and close and seal the with with with with with with with the seal with partition. 3 bit is provider back into the container and close and seal the with with with with with with with with		Production loss: 0.1875 %		3	(LH 206) into the mixing	g vessel 250 mL.	en fol	
2 Act the show content of the previously weighted Lattone first in the name sets in the the name sets in the the name sets in the	16	Storage in an airtight container at room temperature and add good parafilm to the lid.		4	Add the whole content the mixing vessel.	of the previously weighted Budesonide in	900 at	
2 Pat the gowder back into the container and doue and seal the given the second seco				5	Add the whole content	t of the previously weighted Lactose fit	es 9%	
2 In the poole has into the continent and close and seal the transmit of transmi				6	Add the rest of the pre	eviously weighted Lactose carrier (LH 2)	6) Gar	
8 Plue the container inside the Turbula mixer and hold the maker of the make				7	Close the mixing vessel.	and seal the lead with parafilm	200	
Page 5 of 7 Page 5 of 7 Page 5 of 7 Page 5 of 7 Page 5 of 7 Page 5 of 7 Page 5 of 7 Page 5 of 7 Page 5 of 7 Page 5 of 7 Page 5 of 7 Page 5 of 7 Page 5 of 7 Page 5 of 7 Page 5 of 7 Page 5 of 7 Page 5 of 7 Page 5 of 7 Page 5 of 7 Page 5 of 7 Page 5 of 7 Page 5 of 7 Page 5 of 7 Page 5 of 7 Page 5 of 7 Page 5 of 7 Page 5 of 7 Page 5 of 7 Page 5 of 7 Page 5 of 7 Page 5 of 7 Page 5 of 7 Page 5 of 7 Page 5 of 7 Page 5 of 7 Page 5 of 7 Page 5 of 7 Page 5 of 7 Page 5 of 7 Page 5 of 7 Page 5 of 7 Page 5 of 7 Page 5 of 7 Page 5 of 7 Page 5 of 7 Page 5 of 7 Page 5 of 7 Page 5 of 7 Page 5 of 7 Page 5 of 7 Page 5 of 7 Page 5 of 7 Page 5 of 7				8	Place the container insi with two extra straps.	ide the Turbula mixer and hold the mach	ne MP	
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	2 3 4 5 6 6 8 8 8 8 8 8 9 8 9 8 9 8 9 8 9 8 9 8	Put the powder back into the container and close and seal the container. Start mining for 50 minutes . Initial time: [5:42. Speed: 68 rpm 4/2 Weight the container Weight the container Weight the container Weight the container of grams of formulation planned Yield (G) (grams of formulation planned) x 100 = Production size _ % Storage in an airlight container at room temperature and add gramatim to he id. Erences Particle mixtures for inhalation sung mising energy," International Journal of P 592, pp. 1-14, 2021. Aution and K. Taylor, Aution's Pharmaceutics: The Design and Manufacture Elsevier Health Sciences, 2013. Halberg, "Formulation development of adhesive mixtures for inhalation - A imization challenge: Paart 1," Inholotion, pp. 1-7, 2022.	Page 5 of 7					
	2 3 4 5 5 16 16 18 18 18 18 10 10 10 10 10 10 10 10 10 10 10 10 10	Put the powder back into the container and close and seal the container. Container. Start mining for 3D minutes . Initiatium: [5:42_Speed:68 rpm for the container were for a search of the container were for the container were for an and the container were for a search of the container produced and the formulation the formulation of the formul	Page 5 of 7					
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	2 3 4 4 5 16 8 1 K. Tr adh vol. 2 1 M. J USA 3 3 1 K. Tr opti	Put the powder back into the container and close and seal the container. Sart mining for Bormburger Initial times. <u>15. U.</u> Final time: <u>15.47</u> . Speed: 68 rpm Weight the container Weight the container Weight by Container of formulation produced <i>Yield</i> grans of formulation produced <i>Yield</i> grants of <i>Yield</i> grants of <i>Yield</i> grants <i>Yield</i> grants of <i>Yield</i> grants of <i>Yield</i> grants of the <i>Yield</i> grants of the <i>Yield</i> grants of the <i>Yield</i> grants of <i>Yield</i> g	Page 5 of 7					
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	2 3 4 5 16 1] K. Ti adhi vol. J USA 3] K. T opti	Put the powder back into the container and close and seal the container.	Page 5 of 7					

7.4.2. Coated formulation

rmula	ation 3 (Low shear mixed	r)						tand the now	the addition of fine lactor	se particles and different	t mixing time c	
0% Bud	desonide, LH 206 Lactose	carrier, Magn	esium stearate 1.0	.0% and 4.0%	6 Lactos	se fines LH	improv	ed delivery of	dry powder formulations	to the lungs.		
ixing ti	imes: 10, 30 and 60 minute	es					2. Ba	ckground				
thor	Booce		Date				It is im	portant to res	search about improveme	nts in the area of dry po	owder inhaler	formulation.
pervis	ior		Date				particle	es such as the fraction of th	quantity of lactose fines, ne formulation and for in:	stance lower or increase	the efficacy o	f the inhaled
rre Th	alberg		2023 - 06 - 02		1		produc shear r	t. In order to m nixers. Low sh	nanufacture these formula near mixers are character	ations two types of mixers ized by a smoothly mixin	s can be used: I ng of the cont	Low and High ents without
ble c	of Contents						causing mixers	g damage in th are more effic	e crystalline structure of t cient and are recommend	he formulation compone ed for formulations with	ents. In contrast coating agents	st, High shear s. The mixing
Aim .						2	time ar	nd speed are cr	rucial parameters in dry po	owder inhaler formulation	n since they ha e dispersibility	of the active
Back	ground					2	pharm	aceutical ingre	dient in the formulation [1], [2] and [3].		
Fauit	erial					2	2 14	atorial				
Docu	mentation						3.1	Active Pharm	aceutical Ingredient (API)	Budesonide 2.0%.		
Batc	h record						3.2	Excipients: M	lagnesium stearate, LH 20	6 Lactose carrier and 4.09	% Lactose fines	LH 300.
5.1.	Formulation LS 3A (Mixing	g time 10 minu	ites)				Mate	rial type	Grade	Supplier	Particle siz	e
5.1.1.	Weight						Lacto	se carriers	LH 206 Lactose carrie	Pr DFE Pharma	-	
5.1.2.	Low shear mixing (Turb	ula mixer)					Lacto	se fines	LH 300 Micronized	DFE Pharma Peter Greven	-	
5.2.	Formulation LS 3B (Mixing	g time 30 minu	tes)			5	Loati	of agent	I magnesium steafate	Peter Greven		
.2.1.	Weight	ula mixor)				5 c	4 5	uipmont				
6.3.	Formulation LS 3C (Mixing	time 60 minur	tes)				4. EC	L. Analytical ba	alance			
5.3.1.	Weight						4.3	. Sieve				
5.3.2.	Low shear mixing (Turb	ula mixer)				7	4.3	 Turbula mixe Bulk density 	volumeter			
. Re	eferences					9	4.5	5. Particle size	device			
							3. 0	ocumenta		ded to the batch second		
						-						
						Page 1 of 9						Page 2 of 9
						Page 1 of 9						Page 2 of 9
						Page 1 of 9						Page 2 of 9
. 0-						Page 1 of 9	10	Sieve the po	owder mixture.		10	Page 2 of 9
i. Ba	itch record	living time 10	0 minutes)			Page 1 of 9	10	Sieve the po Sieve mesh: Note if agen	owder mixture. 0.710 milimeter. ceates are necessnt and ta	ke a picture	A	Page 2 of 9
6.1 Batch	itch record L. Formulation LS 3A (M size Formulation name:	lixing time 10	0 minutes) Final m	nixing time	Fab	Page 1 of 9	10 11 12	Sieve the po Sieve mesh: Note if aggr Put the po	owder mixture, 0.710 milimeter. egates are present and ta wder back into the conta	ke a picture iner and close and seal	I the Lap	Page 2 of 9
6. Ba 6.1 Batch 80 g	tch record L. Formulation L5 3A (M Formulation L5 3A:	lixing time 1(0 minutes) Final m pnide, H 30 min	nixing time	Fab	Page 1 of 9	10 11 12 13	Sieve the po Sieve mesh: Note if aggr Put the po container. Start mixing	owder mixture. 0.710 milimeter. egates are present and ta wder back into the conta tor 15 mizeter	ke a picture iner and close and seal	I the GP	Page 2 of 9
5. Ba 6.1 Batch 80 g	tch record L. Formulation LS 3A (M Size [Formulation LS 3A: Formulation LS 3A: 206 Lactose carrier 1.0% and 4.0% Lact	lixing time 1(: : (2.0% Budeso r, Magnesium ; Ose fines LH30	0 minutes) Final m nide, LH 30 min stearate 0).	nixing time nutes	Fab.	Page 1 of 9 rication date	10 11 12 13	Sieve the po Sieve mesh: Note if aggr Put the poo container. Start mixing Initial time:	weder mixture. 0.710 milimeter. ogates are present and ta weder back into the conta is for 15 missure $16 \cdot 12$. Final time: 1	ke a picture iner and close and seal (: 43 Speed: 68 rpm	I the GP	Page 2 of 9
6. Ba 6.1 Batch 80 g	tch record . Formulation LS 3A (M size Formulation LS 3A: Formulation LS 3A: 206 Lactose carrier 1.0% and 4.0% Lactor	lixing time 1(: : (2.0% Budeso r, Magnesium cose fines LH30	D minutes) Final min stearate 00).	nixing time nutes	Fab 06 -	Page 1 of 9 rication date	10 11 12 13 14 15	Sieve the po Sieve mesh: Note if aggr Put the po container. Start mixing Initial time; Remove the Weight the	by der mixture. 0.710 milimeter. egates are present and ta wder back into the conta if or the instances ($f_1 \in X_0$ — Final time: <u>1</u> parafilm from the contail container	ke a picture iner and close and seal (4: 47) Speed: 68 rpm ner	I the GP	NO
. Ba 6.1 Batch 80 g	Itch record Formulation LS 3A (M Formulation S 3A: 206 Lactose carrier 1.0% and 4.0% Lacto 6.1.1. Weight	lixing time 10 : (2.0% Budeso r, Magnesium lose fines LH30	0 minutes) Final m Inide, LH 20 min stearate 00).	nixing time nutes	Fab.	Page 1 of 9 rication date	10 11 12 13 14 15	Sieve the po Sieve mesh: Note if aggr Put the po container. Start mixing Initial time: Remove the Weight the Weight	weder mixture. 0.710 milimeter. egates are present and ta weder back into the contai for $\frac{15}{52}$ minutes $\frac{15}{52}$ Final time: <u>1</u> parafilm from the contail container $\frac{2}{3}$ 45 · 60	ke a picture iner and close and seal (g. 47) Speed: 68 rpm ner 6	I the GP GP GP GP GP	Page 2 of 9
6.1 6.1 Batch 80 g Mater	tch record Formulation LS 3A (M Formulation LS 3A: 206 Lackse carrier 1.0% and 4.0% Lack 6.1.1. Weight rial	lixing time 1(; ; (2.0% Budeso ;, Magnesium ose fines LH30 Batch numbe ; (2211055-01	O minutes) Final m Inide, LH 20 min stearate 0).	nixing time nutes Expiration	Fabi 06 -	Page 1 of 9	10 11 12 13 14 15 16	Sieve the po Sieve mesh: Note if aggr Put the pox- container. Start mixing Initial time; Remove the Weighthe Weighthe Calculate yi	weder mixture. 0.710 milimeter. egates are present and ta wder back into the contai for <u>S minimum</u> [$(z + 2b - Final time:]$ parafilm from the contail container: 2 + 3 - E + b eld for the coating process	ke a picture iner and close and seal (g. <u>47</u>) Speed: 68 rpm ner <u>8</u> .	I the GP UP UP	Page 2 of 9
. Ba 6.1 Batch 80 g Mater Budes Lacto:	tch record Formulation LS 3A (M Formulation LS 3A: 206 Latose carrier 1.0% and 4.0% Lator 6.1.1. Weight rial isonide se carrier (LH 206)	lixing time 10 (2.0% Budeso r, Magnesium ose fines LH30 Batch numble 4211059-01 600365	0 minutes) Final m Inide, LH 20 min stearate IO).	nixing time nutes Expiration - 17-NOV-20	Fab 06 - date	Page 1 of 9	10 11 12 13 14 15 16	Sieve the po Sieve mesh: Note if aggr Put the pox container. Start mixing initial time; Remove the Weighthe Weighthe Weighthe Calculate yi Yield =	bowder mixture. 0.710 milimeter. cgates are present and ta wder back into the contain the container. 16:20 Final time: 1 19:245 Final time: 1 245.60 leid for the coating process $(71.742 g of formula 75.2 \text{ or for form$	ke a picture iner and close and seal (g. 4/3) Speed: 68 rpm ner s. iton produced) x 100 =	I the GP GP GP GP = Cav	Page 2 of 9
6. Ba 6.1 Batch Bades Lactor Lactor	tch record . Formulation LS 3A (M size Formulation LS 3A: 206 Lactose carrier 10% and 4.0% Lactor 6.1.1. Weight rial sonide se carrier (LH 206) se fines (LH 300) estimes (LH 300)	lixing time 10 2 (20% Budeso 7, Magnesium ose fines LH30 4211059-01 600365 1083667 (7273845	0 minutes) Inide, LH Somin stearate 00).	Expiration - 17-NOV-2(13-FEB-20	Fab 06 - date D13 22	Page 1 of 9 rication date	10 11 12 13 14 15 16	Sieve the po Sieve mesh: Note if aggn Put the pox container. Start mixing initial time; Remove the Weight Calculate yi Yield =	bowder mixture. 0.710 milimeter. egates are present and ta wder back into the contain (16:20. Final time: 1 parafilm from the contail container 2.45.46 eld for the coating process eld for the coating process = $\left(\frac{74.34}{74.9} g o f formula 75.2 g o f formula$	ke a picture iner and close and seal iner and close and seal is speed: 68 rpm rer s. tion produced x 100 = tion planned	the GP UP UP UP	Page 2 of 9
6.1 Batch 80 g Matee Budes Lactor Lactor Magn	tch record L Formulation LS 3A (M Size [Formulation LS 3A: Formulation LS 3A: 206 Lactose carrier 1.0% and 4.0% Lactor 6.1.1. Weight rial sonide se carrier (H 206) se carrier (H 206) se times (LH 200) esium stearate	tixing time 10 (2.0% Budeso (2.0% Budeso (3.0% Budeso (3.	0 minutes) Final m stearate 00).	Expiration - 17-NOV-2(13-FEB-20 -	Fabr 06 -	Page 1 of 9 rication date	10 11 12 13 14 15 16	Sieve the po Sieve mesh: Note if aggr Put the po container. Start mixing Initial time: Remove the Weight Calculate yi Yield = Production Production	bwder mixture. 0.710 milimeter. cgates are present and ta wder back into the contai- for ta manadal $16 \cdot 20$ Final time: 1 parafilm from the contai- container $2.45 \cdot 4b$ delf for the coating procei- elf for the coating procei- $(\frac{74.34}{75.2} g \text{ of formula}$ 75.2 g of formula 75.2 g of formula	ke a picture iner and close and seal is and close and seal is speed: 68 rpm rer <u>8</u> is. tion produced ation planned) x 100 =	I the GP UP UP UP	Page 2 of 9
6.1 Batch Batch Budes Lactor Lactor Magn Step	tch record Formulation LS 3A (M size Formulation LS 3A:	tixing time 10 (2.0% Budeso , Magnesium ose fines LH30 Batch numbe 4211059-01 600365 1083C67 C723845	0 minutes) Final m stearate 00).	Expiration 17-NOV-20 13-FEB-20	Fabric 606 -	Page 1 of 9 rication date Feb-23 Notes	10 11 12 13 14 15 16	Sieve the po Sieve mesh: Note if agg Put the pov container. Start mixing Initial time; Remove the Weighth Calculate yi Yield = Production Production	by der mixture. 0.710 milimeter. cgates are present and ta wider back into the contain the 'LC - Final time: $\frac{1}{12}$ or $\frac{1}{12}$ of formula vield: $\frac{21}{12}$ of formula $\frac{21}{12}$ of formula $\frac{21}{12}$ of formula $\frac{21}{12}$ of formula $\frac{21}{12}$ $\frac{21}{12}$ $\frac{5}{12}$ $\frac{8}{10}$ loss: $\frac{21}{10}$ $\frac{54}{10}$ $\frac{8}{10}$ for cast carrier	ke a picture iner and close and seal (147) Speed: 68 rpm ner ss. ss. tion produced ation planned) x 100 =	I the UP UP UP UP UP UP	Page 2 of 9
. Ba 6.1 Batch Bog Mater Budes Lactor Magn Step 1	tch record . Formulation LS 3A (M size Formulation LS 3A (M size Formulation S 3A: 206 Lactose carrier 1.0% and 4.0% Lacto 6.1.1. Weight fail sonide se carrier (LH 206) se fines (LH 206) sestims stearate Description Check that the balance dons are discussed	lixing time 1(2 (20% Budesor r, Magnesium ose fines LH30 Batch numbe 4211059-01 1083(67 C723845 is clean, zeroe	O minutes) inide, LH stearate NO). er d and that the lab	Expiration - 17-NOV-20 13-FEB-20 -	Fabi 06 - 06 - 013 22 Sign	Page 1 of 9 rication date Feb-23 Notes	10 11 12 13 14 15 16 16	Sieve the po Sieve mesh: Note if aggn Put the pov container. Start mixing Initial time; Remove the Weighth Calculate yi Yield = Production Production Take outh add the wh Add the wh	bowder mixture. 0.710 milimeter. egates are present and ta wder back into the contail ($r_1 = 20$ Final time: $\int_1^1 (2 \cdot 20 - Final time: \int_1^1 (2 \cdot 20 - Final time: \int_1^1 (2 \cdot 20 - Final time: \int_1^1 (2 \cdot 20 - Final time) (2 \cdot 20 - Fina$	ke a picture iner and close and seal (4: 47) Speed: 68 rpm ner 5. 5. 5. 5. 5. 5. 5. 5. 5. 5.	I the GP GP GP GP GP GP GP GP GP GP GP GP GP G	Page 2 of 9 No
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. Ba 6.1 Batch Budes Lacto: Magn 1 1 2 3	tch record . Formulation LS 3A (M size Formulation LS 3A: Formulation LS 3A: 206 Lactose carrier 10% and 4.0% Lactor 6.1.1. Weight rial sonide se carrier (LH 206) se fines (LH 206) se fines (LH 206) check that the balance i doors are closed. Label a container (25 220 84) Weight 74.4 e of the 1	lixing time 10 2.0% Budeso r, Magnesium ose fines LH30 Batch numbe 4211059-01 600365 1083C67 C723845 is clean, zeroei is clean, zeroei io mL) and actose carrier	0 minutes) Final m stearate 00). or d and that the lab record the tara	Expiration - 17-NOV-20 - - boratory's a weight: adequate	Fabr 06 - 013 22 Sign UP UP	Page 1 of 9 rication date Fab-23 Notes	10 11 12 13 14 15 16 17 18 19 20	Sieve the po Sieve mesh: Note if aggr Put the pox Start mixing Remove the Weight Start mixing Yield = Production Production Take out ha Add the wh the mixing Add the vice	bowder mixture. 0.710 milimeter. cgates are present and ta wder back into the contai tor b microsoft [16] 2.40 Final time:] 16] 2.40 Final time:] 2.45 ± 0.0 16] 6 for the coating process 16] 6 for the coating process 17.52 g of formula 7.52 g of formula 17.52 g of formula 17.52 g of formula 17.52 g of formula 17.52 g of formula 18.52 g of formula 19.52 g of formul	ke a picture iner and close and seal (2.47) Speed: 68 rpm ner 	I the GP GP GP GP GP GP GP GP SLH GP SLH GP GP GP GP GP GP GP GP GP GP GP GP GP	Page 2 of 9
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5. Ba 6.1 Batch 80 g Matee Budes Lacto: Lacto: Magn 1 2 3 4	tch record L Formulation LS 3A (M size [Formulation LS 3A: Formulation LS 3A: 206 Lactose carrier 1.0% and 4.0% Lacto 6.1.1. Weight rial conide se carrier (LH 206) se fines (LH 300) esium stearate Description Check that the balance i doors are closed. Label a container (DS 2 2 0 8/2 Weight 374.4 g of the Lacto Experimental weight: 7	tixing time 1(2.0% Budesor, 7, Magnesium ose fines LH30 Batch numbe 4211059-01 600365 1083667 C723845 is clean, zeroe: 50 mL) and .actose carrier 141 - 444 se fines (LH 30	0 minutes) Final m stearate 0). r d and that the lab record the tara r (LH 206) in an 0) in an adequate c	Expiration 	Fabric 06- date 22 Sign 20 20 20 20 20 20 20 20 20 20 20 20 20	Page 1 of 9 rication date Feb-23 Notes	10 11 12 13 14 15 16 17 18 19 20 21 22	Sieve the po Sieve mesh: Note if aggr Put the pox container. Start mixing initial time; Weight the Weight the Model of the Production Take out ha Add the wh the mixing Add the res Close the m Place the co With two es	bwder mixture. 0.710 milimeter. gates are present and ta wder back into the contai ($r_1 = r_1 = r_2 = r_1 = r_2 = $	ke a picture iner and close and seal (g. 43) Speed: 68 rpm ner <u>8</u> sis. tion produced ation planned) x 100 = siy weighted Budesonide h rinsing. a mixer and hold the mac	I the GP UP UP UP UP UP UP UP UP SUH UP SUH UP SUH UP SUH UP	Page 2 of 9
5. Ba 6.1 Batch 80 g Matees Budess Lacto: Lacto: Magn 1 2 3 3	tch record L Formulation LS 3A (M size [Formulation LS 3A (M Size [Formulation LS 3A: 206 Lactose carrier 1.0% and 4.0% Lacto 6.1.1. Weight final fina	tixing time 1((2.0% Budeso, r, Magnesium ose fines LH30 Batch numbe 4211059-01 1083667 (723845 is clean, zeroe io mL) and actose carrier LH, HH as fines (LH30 2, 22.0%	0 minutes) Final m stearate 00). Pr d and that the lab record the tara r (LH 206) in an . 0) in an adequate co	Expiration - - 17-NOV-2(13-FEB-20 - boratory's { a weight: adequate { container. -	Fabric 06- 06- 013 22 Sign UP UP UP	Page 1 of 9 rication date Fab- 23 Notes	10 11 12 13 14 15 16 17 18 19 20 21 22 23	Sieve the po Sieve mesh: Note if aggn Put the pov container. Start mixing Initial time; Weighthe Calculate yi Yield = Production Production Production Add the wh Add the wh Add the res Close the m Place the cd with two es Start mixing	bowder mixture. 0.710 millimeter. cgates are present and ta wider back into the contain to the container 1.45 $\pm b$ elel for the container 7.52 g of formula 75.2 g of formula 75.2 g of formula 75.2 g of formula 16 of the coating process elel for the coating process elel for the coating process elel for the coating process (1.52 $\pm b$) elel for the coating process elel for the coating process (1.52 $\pm b$) elel for the coating process elel for the coating process (1.52 $\pm b$) elel for the coating process elel for the coating process (1.52 $\pm b$) (1.52 $\pm b$) (1.53 $\pm b$) (1.54 $\pm b$) (1.55 $\pm b$)	ke a picture iner and close and seal (2.43) Speed: 68 rpm ner 	I the UP UP UP UP SLU SLU SLU SLU SLU SLU SLU SLU SLU SLU	Page 2 of 9
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5. Ba 6.1 Batch 80 g Matee Budes Lacto: Magn 2 3 4 5 6 5 6 5 6 1 2	tch record Formulation LS 3A (M size Formulation LS 3A 206 Lactose carrier Formulation LS 3A 206 Lactose carrier 206 Lactose carrier 206 Lactose carrier 206 Lactose carrier 108 and 4.0% Lacto 6.1.1. Weight 118 108 and 4.0% Lacto 6.1.1. Weight 118 108 and 4.0% Lacto 6.1.1. Weight 118 108 and 4.0% Lacto 108	Tixing time 10 (2.0% Budeso r, Magnesium ose fines LH30 Batch numbe 4211059-01 600365 1083667 (723845 is clean, zeroe: io mL) and actose carrier 14/, -44/ sefines (LH30) 5, 2018 (02) ing (Turbula <i>i</i> nixer is clean ar y sizes ar cd	0 minutes) Final m stearate 0). r d and that the lab record the tara r (LH 206) in an . 0) in an adequate co te in an adequate container mixer) nd ready to use tara and ready to use	nixing time nutes Expiration - - 17-NOV-20 - 13-FEB-20 - boratory's a weight: adequate (container. container. - - - - - - - - - - - - -	Fabi 06- 013 22 Sign UP UP UP UP	Page 1 of 9 rication date Fab-23 Notes Notes	10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 26 27 27 28 26 27 27 29 20	Sieve the po Sieve mesh: Note if aggr. Put the pox container. Start mixing Calculate yi Yield = Production Production Production Take out ha Add the wh the mixing Add the yield Add the wh the mixing Add the yield add the white Sieve the po- Sieve mesh Note if aggr. Place the container Sieve the po- Sieve mesh Note if aggr. Put the po- container. Close the mesh Sieve the po- Sieve mesh Note if aggr. Place the container.	bowder mixture. 0.710 milimeter. cgates are present and ta wder back into the contai- for 5 -minatemini- [$[4]: \lambda \Delta$ Final time:] parafilm from the contai- container $\frac{7}{125.2}$ g of formula 75 : 2g of formula 75 : 2g of formula ($\frac{71+74}{19}$ g of formula 75 : 2g of formula ($\frac{71+74}{19}$ g of formula ($\frac{71+75}{19}$ g of formula ($\frac{71+75}{19}$ g of commula ($71+75$	ke a picture iner and close and seal iner and close and seal iner and close and seal is. icon produced ation produced) x 100 = isly weighted Lactose finer sly weighted Budesonide h rinsing. a mixer and hold the mac iner and close and seal iner and close and seal iner and close and seal iner and hold the mac	I the GP GP GP GP GP GP GP GP GP GP	Page 2 of 9 N _C γξ3, bg σφ)
A Batch Batch 80 g Matee Budes Lacto: Magn 2 3 4 5 6 5 6 5 6 5 6 5 5 6	tch record . Formulation LS 3A (M size Formulation LS 3A (M Size Formulation LS 3A: 206 Lactose carrie formulation bescription Check that the blance i formental weight: 1 6.1.2. Low shear mills for the Bude Experimental weight: 1 6.1.2. Low shear mills for the B	tixing time 10 2.0% Budeso r, Magnesium ose fines LH30 Batch numble 4211059-01 600365 1083C67 C723845 1083C67 C723845 is clean, zeroes is clean, z	0 minutes) onide, LH stearate 00). or d and that the lab record the tara r (LH 206) in an a of in an adequate container mixer) nd ready to use en and ready to use sen and ready to use sen and ready to use sen and ready to use the man adequate targets on the set of the se	Expiration Expiration T7-NOV-20 13-FEB-20 - boratory's a weight: adequate (container. r, r, sse sse carrier C	Fabr 06- 013 22 Sign &P &P &P &P &P &P &P &P &P &P &P &P &P	Page 1 of 9 rication date Fab-23 Notes Notes	10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29	Sieve the po Sieve mesh: Note if aggr Put the pox Start mixing Initial time; Remove the Weight Me Weight Calculate yi Yield = Production Production Take out ha Add the wh 300 into th Add the wh 300 into th Add the wh the mixing Add the who sieve mesh Note if aggr Put the po Sieve mesh Note if aggr Put the pot Sieve the of Sieve	wider mixture. 0.710 millimeter. gates are present and ta wider back into the contai for b minutesi $[[\underline{b}, 2\Delta]$ Final time:] $\underline{b}, 2\Delta$ Final time:] $\underline{b}, 2\Delta$ Final time:] $\underline{c}, 2\Delta$ Final time:]	ke a picture inier and close and seal (2.43) Speed: 68 rpm ner 	I the GP GP GP GP GP GP GP GP GP SILH GP SILH GP GP GP GP GP GP GP GP GP GP GP GP GP	Page 2 of 9 No
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A Batch Batch Budes Lacto: Magn Step 1 2 3 4 5 6 5 6 5 5 5	tch record I. Formulation LS 3A (M size [Formulation IS 3A: Formulation IS 3A: 206 Lactose carrier 1.0% and 4.0% Lact 6.1.1. Weight rial conide secarrier (LH 206) se fines (LH 300) esium stearate Description Check that the balance i doors are closed. Label a container (DS 2 2 C 0 3'f) Weight 24, g of the Lacto Experimental weight: 1 6.1.2. Low shear mixi Description Check that the laboratory Add pervoluted weight: 1 Add the whole content stearate into the mixing Add the mest of the proceeded	tixing time 10 (2.0% Budesor, Magnesium cose fines LH30 Batch number 4211059-01 600365 1083667 C723845 is clean, zeroe- io mL) and actose carrier 14] -44 -94 -550 mL actose carrier 14] -44 -93 - 320 mS - 100	0 minutes) Final m nide, LH stearate 00). rr d and that the lab record the tara r (LH 206) in an a quarter of the tara r (LH 206) in an a dequate container mixer) nd ready to use the nan adequate of dequate container mixer) nd ready to use the nan adequate of the tara output the tara r (LH 206) in an a dequate container mixer) nd ready to use the nan adequate of the tara dequate container mixer)	nixing time Expiration - 17-NOV-2(13-FEB-20) - boratory's (a weight: adequate (container. container. r. Sise carrier (lagnesium (r (LH 206) ()	Fabr 06- 06- 06- 06- 07- 08- 09-	Page 1 of 9 rication date F@-23 Notes Notes Notes	10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32	Sieve the po Sieve mesh: Note if aggr Put the pox container. Start mixing Calculate yi Yield = Production Production Take out ha Add the whit Add the whit Add the whit Add the whit Add the whit Sieve the pilace the co Sieve the pilace the co with two ex Start mixing Initial time: Sieve the pilace the co start mixing Initial time: Sieve the pilace the co Start mixing Initial time: Sieve the pilace the co Start mixing Initial time: Sea the start mixing Initial time: Start mixin	wider mixture. 0.710 milimeter. cgates are present and ta wider back into the contai- for 15 milimeter. [16:220 Final time:] 19:230 final time:] 19:230 formula 75.2 g of formula 75.2 g of formula 75.2 g of formula (17:24 g of formula 75.2 g of formula (17:25 g of formula 19:25 g of some (17:25 g of formula 19:25 g of some (17:25 g of formula 19:25 g of some 19:25 g of so	ke a picture iner and close and seal iner and close and seal iner and close and seal in produced st. iton produced x 100 = sty weighted Lactose finer sly weighted Budesonide h rinsing. ad witer parafilm a witer and hold the mac p: Sto Speed: 68 rpm ke a picture ainer and close and seal a wite parafilm a mixer and hold the mac 1/12 Speed: 68 rpm 8 ulation produced.	I the WP UP UP UP UP UP UP UP UP UP U	Page 2 of 9 N/C N/C
6. Ba 61 Batch Batch Budes Lacto: Lacto: Magn Magn 5 5 6 6 5 5 6 5 5 7 8	tch record Formulation LS 3A (M size Formulation LS 3A (M Size Formulation LS 3A (M Constraint) Solution Formulation LS 3A (20 Constraint) Solution Constraint (20 Constraint) Solution Solution Constraint (20 Constraint) Solution Constraint Co	Tixing time 10 (2.0% Budeso r, Magnesium ose fines LH30 Batch numbe 4211059-01 600365 1083667 (723845 108367 (723845 109367 (723845 109367 (723845 109367 (723845 (723845 10967 (723845 (7238	D minutes) Final m Stearate 0). ar d and that the lab record the tara r (LH 206) in an a of (LH 206) in an a dequate container mixer) nd ready to use an and ready to use usiy weighted Lactor usiy weighted Mit actions carrier ad with parafilm mixer and hold the	nixing time Expiration - - 17-NOV-20 - boratory's a weight: adequate (container. container. r. - - - - - - - - - - - - -	Fabi 06- 113 22 Sign UP UP UP UP	Page 1 of 9 rication date Fab-23 Notes Notes	10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32	Sieve the po Sieve mesh: Note if aggn Put the pox container. Start mixing Remove the Weight Calculate yi Yield = Production Production Production Production Add the whi Add the whi Add the whi Add the whi Add the whi Add the whi and the start mixing Note if aggn Put the po container. Close the m Place the co start mixing Initial time: Sieve the po Sieve mesh Note if aggn Put the po container. Cos the m Sieve the po Sieve mesh Note if aggn Start mixing Container. Cos the m Sieve the po Sieve the po Sieve the po Sieve mesh Note if aggn Start mixing Container. Cos the m Sieve the po Sieve mesh Note if aggn Start mixing Container. Cos the m Sieve the po Sieve the	by der mixture. 0.710 milimeter. cgates are present and ta wder back into the contai- for 5 -minated [16:120 Final time:] 19:230 Final time:] 19:250 formula 245.60 eld for the coating process- 19:250 formula 245.60 eld for the coated carrier 245.60 eld for the coated carrier 19:250 formula 245.60 eld content of the previou vessel. 10:50 formulations: 10:50 formul	ke a picture iner and close and seal (4.43 Speed: 68 rpm ner 5.5 s. s. s. s. s. s. s. s. s. s.	I the GP GP GP GP GP GP GP GP GP GP	No χψι, bg σφι
5. Ba 6.1 Batch 80 g Mate Budes Lacto: Magn 1 2 3 4 5 6 6 5 5 6 7 7 8 8	tch record . Formulation LS 3A (M size Formulation LS 3A (M Size Formulation LS 3A: 206 Lactose carrie formulation serial bescription Check that the balance i doors are closed. Label a container (25 220 84) Weight 12.4 g of the Laber container. 220 84) Weight 12.4 g of the Bude Experimental weight: _1 40.12. Low shear milk for the mixing check that the Turbulam Add approximately half Race the mixing vessel. Close the m	tixing time 10 2.0% Budeso r, Magnesium ose fines LH30 Batch numble 4211059-01 600365 1083C67 C723845 1083C67 C723845 is clean, zeroes is clean	0 minutes) inde, LH stearate 00). ar d and that the lab record the tara r (LH 206) in an a dequate container mixer) in an adequate container mixer and ready to us is weighted Lactor is weighted Mi is d Lactose carrier is d with parafilm mixer and hold the	nixing time Expiration - 17-NOV-21 13-FEB-20 - boratory's (a weight: adequate (container. r. 5 sse carrier (sse carrier (sse carrier (r (H 206) (e machine ()	Fabi 06- 06- 113 22 55gn &P &P &P &P &P &P &P &P &P &P &P &P &P	Page 1 of 9 rication date Fab-23 Notes Notes	10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 1 32	Sieve the po Sieve mesh Note if aggn Put the pox Start mixing Remove the Weight the Weight Calculate by Yield = Production Production Take out ha Add the wh 300 into th Add the wh 300 into th Add the wh 300 into th Add the wh 300 into th Add the wh 300 into th 300 into	wider mixture. 0.710 millimeter. cgates are present and ta wider back into the container 10 20 Final time: 1 12 20 Final time: 1 245 ψ 245 ψ 25	ke a picture inier and close and seal (14) Speed: 68 rpm ner 	I the GP GP GP GP GP GP GP GP SILH SILH SILH SILH SILH SILH SILH SILH	Page 2 of 5

parafilm	n to the lid	ontainer at room temperat	ure and add	WY			wi	ith two extra straps.	XX	
parailin						9	St	tart mixing for 15 minutes,	Sap	
						10	Ini	eve the powder mixture	41	-
6.2. Form	ulation LS 3B (M	Aixing time 30 minutes)				10	Sie	ieve mesh: 0.710 milimeter.	20P	
tch size	Formulation nam	ie:	Mixing time	Fabri	ication date	11	No	lote if aggregates are present and take a picture	80	NO
g	Lactose carrier	Magnesium stearate 1.0%	po minutes	07-H	6b-23	12	PL	ut the powder back into the container and close and seal the	409	
	and 4.0% Lactose	fines (LH 300)).				13	St	tart mixing for 15 minutes	4.0	-
							In	hitial time: 13 34 Final time: 13:5) Speed: 68 rpm	DR	
6.2.1	Weight					14	Re	emove the parafilm from the container	400	
aterial		Batch number	Expiratio	on date		15	W	Veight the container	90P	
desonide		4211059-01	-	2045		16	C	Calculate yield for the coating process.	wi	
ctose carrie	r (LH 206)	600365	17-NOV-	2013						
agnesium st	(LH 300) tearate	C723845	-	.022				$Yield = \left(\frac{74.51 \text{ g of formulation produced}}{75.9 \text{ formulation produced}}\right) x \ 100 =$		
0								(75.2 g of formulation plannea)	00	
ep Descrip	ption			Sign	Notes		P	Production yield: 99-18 %	UR	
Check	that the balance	is clean, zeroed and that the	laboratory's	900		17	P	Production loss: 0.911 %	9.0	-
doors a	are closed.	o mil) and record the	tara weight:	2.0	-	18	A	Add the whole content of the previously weighted Lactose fines (LH	0.0	
221	099	so me) and record the r	tala weight.	OP			3	100) into the mixing vessel.	AI	
Weight	t 74.4 g of the l	Lactose carrier (LH 206) in	an adequate			19	A	Add the whole content of the previously weighted Budesonide into	AOP	
contain	ner. mental weight:	24.400		bP		20	A	Add the rest of the coated carrier with rinsing.	get	-
Weight	t 3.2 g of the Lacto	se fines (LH 300) in an adequa	te container.	an		21	C	Close the mixing vessel and seal the lead with parafilm	ter	
Experin	mental weight:	3. 2052		QY		22	P	Place the container inside the Turbula mixer and hold the machine	TOP	
Weight	t U.8 g of the Mag	nesium stearate in an adequa 0. හරාපිය	ite container.	40P		23	St	itart mixing for 15 minutes.	An	
Weight	t 1.6 g of the Bud	esonide in an adequate conta	iner.	90				13:59	YAP	
Experin	mental weight:	1. 6069 g		WI			In	nitial time: 12:01 Final time: 17:14 Speed: 68 rpm	W1	
6.9.5	Lawakaraa	ing (Turbula mina)				24	S	lieve mesh: 0.710 milimeter.	ter	-
6.2.2.	Low shear mix	ing (Turbula mixer)				25	N	Note if aggregates are present and take a picture	tip	yes
					1	26	P	Put the powder back into the container and close and seal the	SOP	
p Descrip	ption	niver is clean and ready to		Sign	Notes	27	0	Close the mixing vessel and seal the lead with parafilm	Top	
Check	that the laborator	y sieves are clean and ready to us	o use	GP		28	P	Place the container inside the Turbula mixer and hold the machine	900	
Add ap	proximately half	of the previously weighted La	ctose carrier	900			w	vith two extra straps.	WI	
(LH 20	6) into the mixing	vessel 250 mL.	Magnesium	WI		29	St	tart mixing for 15 minutes.	90D	
stearat	te into the mixing	vessel.	magnesium	HOP			In	nitial time: 14:25 Final time: 14:40 Speed: 68 rpm	W1	
Add th	e rest of the pre	viously weighted Lactose car	rier (LH 206)	Nor	2	30	R	temove the parafilm	WP	
into th	e mixing vessel.	and seal the lead with parafile	n	900		31	M	Veight 300. 10 g	WP	
					Page 5 of					rage
Calud					Page 5 of					rage
Calculat	te yield . (79_0} gram	ss of formulation produce	rd) x 100 =		Page 5 of	4	A	idd the whole content of the previously weighted Magnesium	4P	Page
Calculat Yield	te yield. = $\left(\frac{\frac{74}{0}}{80} gram\right)$	is of formulation produce is of formulation planne	$\left(\frac{d}{d}\right) \times 100 =$	9.V	Page 5 of	4	Ac st Ac	dd the whole content of the previously weighted Magnesium tearate into the mixing vessel. dd the rest of the previously weighted Lactose carrier (LH 206)	4P 40F	rage
Calculat Yield	ie yield, = $\left(\frac{\frac{79}{0}}{80} \text{ gram}\right)$	ss of formulation produce ss of formulation planned 3/5 %	$\left(\frac{d}{d}\right) \times 100 =$	- Ar	Page 5 of	4	Ac st in	dd the whole content of the previously weighted Magnesium tearate into the mixing vessel. dd the rest of the previously weighted Lactose carrier (LH 206) to the mixing vessel.	UP UP	rage
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32	Colculate yield. Yield = $\left(\frac{74}{80} \frac{y}{grams of formulation produced}}{80 grams of formulation planned}\right) x 100 =$ Production yield: $\frac{94}{125} \frac{y}{55}$	2P	
33	Storage in an airtight container at room temperature and ad parafilm to the lid.	* 90P	
[1] K a v [2] N U [3] K o	. Thalberg, F, Pagathanasiou, M. Fransson and M. Nicholas, "Contro dhesive mixtures for inhalation using mixing energy," <i>International J</i> . ol. 592, pp. 1-14, 2021. 4. Aulton and K. Taylor, Aulton's Pharmaceutics: The Design and Ma SA: Elsevier Health Sciences, 2013. . Thalberg, "Formulation development of adhesive mixtures for inha ptimization challenge: Paart 1," <i>Inhalation</i> , pp. 1-7, 2022.	ling the performa	ance of eeutics,

7.5.High shear (Diosna®) Batch record

7.5.1. Uncoated formulation

View Mass and the state of the powder formulation for inhalation Date: 2021-13:02 1 (4) Address more Wate humber 1 (4) Address more His 3 (4) 1 (4) Address more 1 (4) 1 (4) Address mo	22-13-02 2 1 21-3-02 2 1 Batch size: 250 g Cheven a weight: Affinition a weight: A
Address Bach surfer	Bach size 250 g Chee a weight: 4 weight: 1 weight:
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STUDY DESIGNThe aim of this study is to research how the mixing time and speed are crucial parameters in dry powder hadre formulation. Three formulations (250g each batch) with different compositions will be roduced 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.5.1 Preparation2.1 Complete composition5.1 Cable a plastic container (300 mL) "HS 3 A 3 min 700 rpm" and record the tar $35 \cdot 94 \cdot g$.2.1 Complete composition5.1 Label a plastic container (300 mL) "HS 3 C 9 min 700 rpm" and record the tar $35 \cdot 54 \cdot g$.2.2 Batch formula2.0 Lactose fines L13002.2 Batch formula2.0 Lactose fines L13002.2 Batch formula2.0 Lactose fines L13002.3 Batch formula2.0 Lactose fines L13002.4 Batch NoTerget Anomat (9) $5.0 \cdot 5.0 \cdot 16$ $4.5 \cdot 0.16$ $10.0 \cdot 10.0 \cdot 10.0$	Chee a weight: Lef a weight: Lef a weight: Lef
The aim of this study is to research how the mixing time and speed are crucial parameters in dry powder halter formulation and understand how they can impact the dispersibility of the active pharmaceutical produced at two different speeds (700 and 1000 rpm). Three samples (40-50 g) will be taken at 3, 6 and 9 intrutes. Temperature after mixing will be measured. 2 BATCH FORMULA AND DISPENSING 2.1 Complete composition Raw Material Anousat (%) Budeomide 2.0 Lactore fines L1300 4.0 Lactore fines L1300 4.0 Lactore fines L1300 4.0 1.1 Label a plastic container (300 mL) " <i>HS 3 B 6 min 700 rpm</i> " and record the tar $\frac{555f_B}{255f_B}$. 5.2 Mixing 5.1 Merganation 5.1 Dereganation 5.2 Mixing 5.3 Here and the second s	a weight: GF a weight: GF 1 weight: GF
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Sequipment AND UTENSILS 5.2.6 Premixing at 150 rpm for 1 minute. Equipment Inventory No. Comment 5.2.7 Increase the mixing speed to 700 rpm without stopping for 3 minutes. Disess Mixer P1-6 F445 1.1.vessel 5.2.8 Stop the mixer, wait 1 minute, open the lid, and measure the temperature. Temperature Fundary (Storpo): Non-Portuge Pages of 1 or or	U
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Diosan Mixer PI-6 P445 L L Vessel Diosan Mixer PI-6 P445 L L Vessel Common Mixer PI-6 P445 L L Vessel Diosan Mixer PI-6 P445 C L Vessel Diosan	9.0
	UT.
Calc Tests 610 Temp and Humidity meter $F531$ (G/1075)	
Sieve 1 mm 130027 22 S//V 5.2.9 Take approximately 40-50 g sample from different parts of the bowl while avo	ding
Testo Termometer IR / #420 (U1/2022)	10
Bulk density meter LTH LTH Sample weight 47.1 W g	
Timer 0 164 5.2.10 Scrape down powder from the walls if needed.	YOK.
Analytical scale process 3	Qal
PACKAGING S.2.11 Attach the lid to the Diosna vessel.	
5.2.12 Start mixing for second time for another 3 minutes.	-Ure
able 1. Packaging. (Total time 6 minutes, 700 rpm).	Cino
Material Tracename Suppuer Batch no Description 24	LOR.
russic uumin uumite, open the lid, and measure the temperature. Temperature 25.5 °C °C	WR.

GALENIEA	Technica	al Batch Re	cord	S GALENICA	Technica	I Batch Reco	ord
Tote Manufacturing plan of budesonide dry powder formulation for Formulation 2 High Shear (700 rpm)	inhalation	Dute 2022-13-0	Page 2 3 (4)	Tute Manufacturing plan of budesonide dry p	owder formulation for inhalation	Date 2022-13-02	Psgc 4 (4)
Authory Gabriela Ponce	Batch number HS 3	Batc	250 g	Author Gabriela Ponce	Batch number: HS 3	Batch si.	250 g
5.2.14 Take approximately 40-50 g sample from different parts, lumps into the plastic container "HS 3 B 6 min 700 rpm" Sample weight $\underline{-4/4} - 51$ 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 Temperature $\underline{-2.5} - \underline{2}$ °C 5.2.19 Empty the rest of the formulation in the sieve 5.2.20 Sizeve 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 the plastic container "HS 3 C 9 min 700 rpm". Sample weight $\underline{-155} \cdot 322 - \underline{g}$ 5.2.23 Calculate the yield of the sum of the samples. $g \ of \ formulation produced = HS3A^{4L/6}g + H$ $Yield = (\underline{-24/5} - g \ of \ formulation rm 25.2.24 Cleaning of Diosna vessel If mixing is contained the same day use under of the day de 70% Ethanol. Place in a ventilated area for drying. 5.2.25 Measure bulk density using bulk density meter F547. Use \underline{S} \ A \ Diopn \ T - 64 \ (3 / 3 - 6^{27}) \ Diomn \ 24.5 \ (2 - 3 / 1.24 / 1/2.92 - 1.5 \ (3 - 3 / 1.24 / 1/2.92 - 1.5 \ (3 - 3 / 1.24 / 1/2.92 - 1.5 \ (3 - 3 / 1.24 / 1/2.92 - 1.5 \ (3 - 3 / 1.24 / 1/2.92 - 1.5 \ (3 - 3 / 1.24 / 1/2.92 - 1.5 \ (3 - 3 / 1.24 / 1/2.92 - 1.5 \ (3 - 3 / 1.24 / 1/2.92 - 1.5 \ (3 - 3 / 1.25 - 1.24 / 1$	f the bowl whil of the bowl while the temperature time 9 minutes) $S3B^{ijk}S^{j}g + HS$ $duced_{anned}$ x 100 - 214 x 100 - 21	into $3C f^{5} L^{2}g$ = h so that the ve h water and the vials. L $L = L^{1} L^{1} L^{1} L^{1}$	Grandes	Comments			



	ENVE						S GALEN	NICA	Technic	al Batch Reco	ord
Manufacturing p Lormulation 31 Rathur Lathur Dime	plan of budesor high Shear (10	nde dry powder 00 rpm)	formulation for	Tech	nical Batcl	Page 11.02 1 (4) Batch titer 250 gt	Title Manufacturing plan o Formulation 3 High 5 Author Gabricla Ponce	f budesonide dry powder formula Shear (1000 rpm)	ation for inhalation Batch number: HS (Date: 2022-13-02 Batch si	Page: 2 (4) ize: 250 g
				1	10.0		5 MANUFACTUR	RING			
1 STUDY DE	SIGN						5.1 Preparation				Check
The aim of this sti inhaler formulatio ingredient in the f	udy is to resear in and understa formulation. Th	rch how the mixi and how they can hree formulations	ng time and spe n impact the dis s (250g each ba	eed are cruc spersibility tch) with di	ial paramete of the activitifferent com	rs in dry powder e pharmaceutical positions will be ken at 3, 6 and 9	5.1.1 Label a plastic c 3 <u>5.59 g</u> .	container (300 mL) "HS 6 A 3 min	a 1000 rpm " and record	the tara weight:	: 4p
produced at two d minutes. Tempera	ture after mixir	(700 and 1000 r ng will be measu	red.	pies (40-50	g) will be ta	Ken at 5, 0 and 7	5.1.2 Label a plastic c 35.67g.	container (300 mL) "HS 6 B 6 min	a 1000 rpm" and record	the tara weight:	EP.
2 BATCH FO	ORMULA A	ND DISPENS	SING				5.1.3 Label a plastic c 35.00 g.	container (300 mL) "HS 6 C 9 min	n 1000 rpm" and record	the tara weight:	: tP
2.1 Complete	composition	n					5.2 Mixing				
Raw Material		Amount	(%)				15-6	h- 12	109		C1 - 1
Budesonide	0	2.0					Date.	Humidity 27.7.%RH .	°C		Check
Lactose times LH300	ne .	4.0					5.2.1 Weigh 232.5 g o	of the Lactose carrier LH206 and a	add half of the amount 1	to the	JAP
Lactose carrier LH2	08	93.0					Diosna 1 L vess	el.			
2.2 Batch for Prepare 0.250 kg	mula batch size of th	e powder formul	ation.				5.2.2 Weigh 2.5 g of] 5.2.3 Add the rest of t	Magnesium stearate and add even the Lactose carrier LH206 to the I	ly over the bed to the D Diosna vessel.	isona vessel.	YOR
Raw materials	Batch N	No Ta	rget Amount (g)	Dispensed	Amount (g)	Balance No.	5.2.4 Attach the lid to	the Digens vessel			YOK
Budesonide	42	11059-01	5.0	5.01+		Process the 3	5.2.4 Pattach the hd to	The Diosna vessel.			OnP
Lactose fines LH3	00 10	7 2 0	10.0	10.040		Processing	5.2.5 Premixing at 15	0 rpm for 1 minute.			T
Lactose carrier L1	1206 733	723845	232.5	1 506	>	Process the 3	5.2.6 Increase the mix	king speed to 700 rpm without sto	opping for 4 minutes.		401
3 EQUIPME	NT AND UT	TENSILS		1.004			5.2.7 Stop the mixer, Temperature 2	wait 1 minute, open the lid, and r ↓.℃	measure the temperature	в.	tap.
Equip	ment	Inventory No.	Comm	ent	1		5.2.8 Scrape down po	wder from the walls if needed.			908
Diosna Mixer P1-6 Scale		F445 F445 (312013)	Type = PR200	n Process	1		5.2.9 Take half of the	amount of the coated carrier out of	of the Diosna 1 L vesse	l.	Sof.
Sieve 1 mm	a Humidity meter	13002722	NN				5 3 10 W 1 1 10 0	CL and and add and add and	and a sum the bad to the	Disease	0.0
Testo Termometer I	R	F420 (11/2022)					5.2.10 Weigh 10.0 g of vessel	Lactose fines LH300 and add eve	enty over the bea to the	Disona	YON
Hulk density meter		LTM	LTH				vessel.				And
Limer		A164			_		5.2.11 Weigh 5.0 g of]	Budesonide and add evenly over t	the bed to the Disona ve	essel.	
Analyhiat su	ula	Process 3					5.2.12 Add the rest of t	the coated carrier to the Diosna ve	essel		TTP
4 PACKAGI	NG						5.2.13 Attach the lid to	the Diosna vessel.			Sap
Table 1. Packaging Material	Trade name	Supplier	Batch no		Description			0 1 1 1 1 1 1 1			SAP
Plantes		INUMA			300 ml. Plast	c	5.2.14 Premixing at 15	0 rpm during 1 minute.			20
Plastic		DUMA			container		5.2.15 Increase the mix	king speed to 1000 rpm without s	topping for 3 minutes.		TA

-	PERTNER IN PROPERTIES AL TECHNOLOGY	Technica	I Daten Kee	oru	~			LE PROVINCE		Technical	Batch Reco	ord
Take: Manufacturing plan of budesonide dry powder formulation for inhalation Formulation 3 High Shear (1000 rpm)		Date: 2022-13-02	Page: 3 (4)	Tale Manufacturing plan of budesonide dry powder formulati Formulation 3 High Shear (1000 mm)				er formulation for i	inhalation	Date 2022-13-02	Page 4 (
Author: Gabriela	Ponce	Batch number: HS 6	Batch	size: 250 g	Author Gabrie	la Ponce	girone	ar (1000 ipin)		Batch number HS 6	Batch se	250 g
2.16	Stop the mixer, wait Lminute, open the lid, and measure th Temperature <u>10</u> , <u>5</u> , <u>c</u> Take approximately 40-50 g sample from different parts of lumps into the plastic container "HS 6 A 3 min 1000 rpm". Sample weight <u>GPL_00_g</u>	the bowl while	avoiding	4P 4P	5.2.1	Cleaning of I If mixing is cc is visually clea 70% Ethanol. Measure bulk	Diosna ontinued an. If th Place in k densit	vessel I the same day vacuus e mixing is the last m n a ventilated area for ty using bulk densit	m clean and then wip ixture of the day clea drying. y meter F547. Use	e with a dry cloth in the vessel with y three different via	so that the vess water and then als.	sel
.2.18	Scrape down powder from the walls if needed.			44	LIC 2	Sample		Vial	Powder weight	Density (g/mL) Used s	scale
2.19	Attach the lid to the Diosna vessel.			YOX	HS 2	A 3 min 1000	rpm	1-68.64	15.61	0.1055		
				0.0	HS 2	A 3 min 1000) rpm	3-68.35	15.60	0.76		
2.20	Start mixing for second time for another 3 minutes.			YOP	HS 2	B 6 min 1000	rpm	1-68.69	15.46	0.7730		
	(10tai time 6 minutes, 1000 rpm).			4.1.	HS 2	B 6 min 1000	pm	2-68.29	15.47	0.7735		
2.21	Stop the mixer, wait 1 minute, open the lid, and measure th	e temperature.		Jop	HS 2	B 6 min 1000) rpm	3-68.36	15.40	0.7700		
	Temperature 27.7 °C	224		U/I	HS 2	C 9 min 1000) rpm	1-68.68	15.29	0. 7645		
			11		HS 2	C 9 min 1000) rpm	2-68.29 14-68.68	15.42/15.30	0.7656	-	
2.22	Take approximately 40-50 g sample from different parts of lumps into the plastic container "HS 6 B 6 min 1000 rpm". Sample weight <u>43, 40 g</u>	the bowl while	avoiding	ger .	HS 2	C 9 min 1000) rpm [3-66.4015-66.14	15.17/15.26	0, 1630		
2.23	Scrape down powder from the walls if needed.			WY .	Com	iments						
2.24	Attach the lid to the Diosna vessel.			HOY								
.2.25	Start mixing for third time for another 3 minutes. (Total time 9 minutes, 1000 rpm).			MR.								
2.26	Stop the mixer, wait 1 minute, open the lid, and measure the Temperature 284 °C	e temperature.		9ep								
2.27	Empty the rest of the formulation in the sieve			40								
2.28	Sieve the formulation (sieve number 1.00 mm)			000								
2.29	Discard the lumps.			ur								
2.30	Record the weight of the remained sample (Total mixing tin the plastic container "HS 6 C 9 min 1000 rpm". Sample weight <u>154.89</u> g (substract tara)	ne 9 minutes) = 9 09g	into	for								
.2.31	Calculate the yield of the sum of the samples. $g \text{ of } formulation \ produced = HS6A \qquad g + HS6A$	$\frac{43.48}{g} + HS$	119-09 6 <i>C g</i>									
	$Yield = \left(\frac{2\mathcal{U}_{d} \cdot \mathcal{U}_{g} \text{ of formulation prod}}{250 \text{ g of formulation plan}}\right)$	$\left(\frac{uced}{uned}\right) x \ 100 =$										
	Production yield: 90.652 %			1.0								
				YAV	11							