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EVALUATION OF FLUID BED TECHNOLOGY FOR THE PREPARATION OF SOLID DISPERSIONS INTENDED FOR IMMEDIATE DRUG RELEASE SYSTEMS

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EVALUATION OF FLUID BED TECHNOLOGY FOR THE PREPARATION OF SOLID DISPERSIONS INTENDED FOR IMMEDIATE DRUG RELEASE SYSTEMS

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LIST OF ABBREVIATIONS

A

Al:	Aluminium
ASD:	Amorphous Solid Dispersion
AUC:	Area under the curve
a_w:	Water activity

B

BA:	Bioavailability
BET:	Brunauer, Emmer, and Teller
BCS:	Biopharmaceutics Classification System

C

C_{max}:	Peak plasma concentration
CMAs:	Critical Material Attributes
CPPs:	Critical Process Parameters
CQAs:	Critical Quality Attributes

D

DCM:	Dichloromethane
dm:	Change in mass
DMF:	Dimethyl Formamide
DMSO:	Dimethyl Sulfoxide
DP:	Drug product
DS:	Drug substance
DVS:	Dynamic vapour sorption
3D:	Three-dimensional

E

EPAS:	Evaporative precipitation into aqueous solution
EC:	Ethyl Cellulose
EtOH:	Ethanol
EU:	European

G

GC-FID:	Gas chromatography with a flame ionization detector
GI:	Gastrointestinal
GMP:	Good Manufacturing Practice

H

HME:	Hot-melt extrusion
HPC:	Hydroxypropyl cellulose
HPLC:	High Performance Liquid Chromatography
HPMC:	Hydroxypropyl methylcellulose
HPMCAS:	Hydroxypropyl methylcellulose acetate succinate
HPMCP:	Hydroxypropyl methylcellulose phthalate

I

ICH:	International Council for Harmonisation
ICL:	Initial container load
IPA:	Isopropanol
IPCs:	In-Process Controls

L

LOD:	Loss on drying
Log P:	Logarithm of octanol - water partition coefficient
IPCs:	In-Process Controls

M

MBP:	Micropreciptated bulk powder

MCC: Microcrystalline cellulose
MDSC: Modulated Differential Scanning Calorimetry
MeOH: Methanol

O

oPA: Oriented Polyamide

P

PE: Polyethylene
PEG: Polyethylene Glycol
PK: Pharmacokinetic
PSD: Particle Size Distribution
PVA: Polyvinyl Alcohol
PVAP: Polyvinyl Acetate Phthalate
PVC: Polyvinylchloride
PVdC: Polyvinylidenchloride
PVP: Polyvinylpyrrolidone
PVP/VA: Polyvinylpyrrolidone Vinyl Acetate

Q

QAs: Quality Attributes
QbD: Quality by Design
QC: Quality Control
QTPP: Quality Target Product Profile

R

RA: Risk Assessment
RH: Relative Humidity
RLD: Reference Listed Drug

S

SDD: Spray Dried Dispersion
SEM: Scanning Electron Microscopy
SGD: Spray Granulated Dispersion
SGF: Simulated Gastric Fluid
SLS: Sodium Lauryl Sulfate
SSA: Specific Surface Area

T

T_g: Glass transition temperature
T_m: Melting temperature
T_{max}: Time to reach maximum concentration in plasma
TPGS: Tocopheryl Polyethylene Glycol Succinate
T/R: Test/Reference

U

UDU: Uniformity of Dosage Units
UV: Ultraviolet

V

V_0: Untapped bulk volume
$V_{10,\ 500,\ 1250}$: Tapped bulk volume at different time (in minutes)
V_f: Final tapped bulk volume
v/v: Volume/volume

W

w/w: Weight/weight

X

XRPD: X-Ray Powder Diffraction

ÍNDICE/
TABLE OF CONTENTS

TABLE OF CONTENTS

RESUMEN/ RESUMO/ SUMMARY


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SUMMARY

In the pharmaceutical industry, achieving drug solubilization is a critical aspect in ensuring the efficacy and bioavailability of orally administrated solid dosage forms. The ability of a drug to dissolve in water or other physiological fluids directly affects its absorption and subsequent therapeutic effects. However, a significant percentage of drugs, both currently marketed and under development, faces challenges due to poor water solubility. According to literature, approximately 40% of drugs on the market and up to 90% of those in development exhibit poor water solubility, which are drugs categorized by the Biopharmaceutics Classification System (BCS) as class II (low solubility and high permeability) and class IV (low solubility and low permeability).

The formulation of amorphous solid dispersions (ASDs) serves as a potent strategy for enhancing the dissolution and solubility of poorly soluble drugs. They involve the dispersion of drug molecules within a carrier(s) matrix in an amorphous state, which enhances dissolution rates and overall bioavailability compared to crystalline forms.

While spray drying stands out as one of the most common manufacturing methods for the production of ASDs, it presents challenges such as the production of powders with low bulk density and poor flow properties, as well as high investment costs which can particularly affect generic pharmaceutical companies. An alternative technique to prepare solid dispersions involves the utilization of fluid bed technology, where a solution of the drug and carrier(s) is sprayed onto an inert substrate, which could be sugar pellets or traditional fillers like microcrystalline cellulose (MCC) or lactose. This method has been successfully employed for the production of itraconazole solid dispersions with hydroxypropyl methylcellulose (HPMC), which are marketed as drug-layered sugar pellets in capsules under the brand name Sporanox®. However, the number of marketed ASD-products produced with fluid bed is notably lower compared to those produced by spray drying and hot melt extrusion. Nonetheless, fluid bed is widely available in pharmaceutical companies specialized in solid dosage forms and offers a promising alternative due to its potential to address challenges related to powder properties and production costs.

ASDs produced using different technologies can differ notably in chemical and physical stability, as well as *in vitro* and *in vivo* performance. Therefore, a comprehensive assessment of conventional pharmaceutical technologies like fluid bed for the industrial production of ASDs as an alternative to spray drying holds significant value for the pharmaceutical industry.

At the same time, the polymeric carrier(s) used to produce an ASD are key for the stabilization of the drug substance (DS) amorphous state and enhancement of its dissolution by sustaining the drug in a supersaturated state. Numerous polymers have been reported in literature including but not limited to cellulose derivatives such as HPMC, hydroxypropyl methylcellulose acetate succinate (HPMCAS), hydroxypropyl methylcellulose phthalate (HPMCP), hydroxypropyl cellulose (HPC); and vinyl polymers such as polyvinylpyrrolidone (PVP), polyvinyl alcohol (PVA), polyvinylpyrrolidone vinyl acetate (PVP/VA). The selection of the polymer type in ASDs is a critical aspect of formulation development, as it can profoundly influence the stability, release kinetic, and overall performance of the drug product (DP). Hence, exploring the viability of using an alternative polymeric carrier is of interest not only from scientific standpoint but also for generic companies. Using alternative key formulation components offers opportunities for innovation, cost savings, regulatory advantages, and market differentiation in the competitive landscape of generic drug development.

This doctoral thesis explores the potential of fluid bed top-spray granulation as an alternative to spray drying for the production of ASDs intended for immediate release film-coated tablets. A BCS class II drug substance, referred as LM2, was used throughout this work. Comparative analysis of ASDs physical properties, stability, and dissolution profiles obtained by either spray drying or FB top-spray granulation were conducted. Additionally, HPMCP HP-55 was evaluated as alternative polymer to HPMCAS-MG, both exhibiting enteric properties. In this study, three ASD-based prototypes produced via fluid bed top-spray system and different polymeric carriers (HPMCAS-MG and HPMCP HP-55) were developed followed by an *in vivo* pilot bioavailability (BA) study comparing their pharmacokinetic (PK) behaviour with a marketed spray dried formulation. A Quality by Design (QbD) approach was followed for development studies, beginning with the definition of the quality target product profile (QTPP), followed by the definition of the critical quality attributes (CQAs), and subsequently performing a risk assessment for the formulation components. Before conducting the *in vivo* pilot BA study, a control strategy was established, including material attributes, equipment operating conditions, and in-process controls (IPCs) to ensure consistent performance and product quality. Additionally, the formulation risk assessment was updated to capture the reduced level of risk and identify the residual risks.

This doctoral thesis is organized in a literature review and four primary sections.

In the **introduction** of this thesis, an overview of the most relevant literature related to fundamental concepts regarding ASDs is compiled, prevalent methods used for their preparation, and predominant polymers and techniques employed in marketed ASD-based products. Additionally, a review of the principals of spray drying and fluid bed technologies, along with an evaluation of their respective advantages and limitations in ASD production, is compiled. Concluding this section, a summary of the most commonly used excipients in ASDs is provided.

In the first section, **preformulation studies** are focused on the characterization of LM2 drug substance and the reference listed drug (RLD), and the comprehension of the RLD formulation. As aforementioned, LM2 drug substance belongs to the BCS class II category. Throughout this study, the crystalline form A of LM2 was used. The RLD consists of an immediate release film-coated tablet containing a spray dried ASD of LM2 and HPMCAS, using acetone as a solvent. Considering the LM2 and HPMCAS solubility in several organic solvents, the solvent toxicity, and the available information of the RLD, acetone was selected as a solvent for this investigation. The grade and exact quantity of HPMCAS used by the RLD are uncertain. Therefore, studies were conducted to design a spray dried ASD formulation to mimic the RLD and use as a benchmark for subsequent studies using fluid bed technology. Various weight ratios of LM2 to HPMCAS-MG were assessed in terms of their ability of producing a homogeneous ASD and achieving a similar dissolution and level of supersaturation to the RLD. X-Ray Powder Diffraction (XRPD), Modulated Differential Scanning Calorimetry (MDSC), and a two-step dissolution analysis were used for this evaluation. A non-sink *in vitro* dissolution method was designed with two-steps to simulate the transition from stomach to intestine. This involved subjecting the formulations to 30 minutes in 300 mL of pH 1.2 medium followed by a shift to 900 mL of pH 6.8 medium.

The second section explores the **feasibility** of the fluid bed top-spray technology for the production of an ASD of LM2 and HPMCAS-MG in the weight ratio of 1:5, assessing physicochemical properties, dissolution, and stability, and comparing them to those obtained by spray drying. Fluid bed in top-spray configuration was selected with the aim to simulate the spray drying system and to promote the agglomeration of particles. In the fluid bed top-spray granulation, it is essential to incorporate an inert excipient into the container, known as the substrate. This substrate serves as the base onto which the solution containing the drug substance and polymer is sprayed. In this investigation, MCC was selected as the substrate, the same filler used during the preformulation studies to further process the spray dried dispersion (SDD) into tablet form. Given the substantial proportion of solids to be sprayed onto the substrate, accounting for 73.9% of the total tablet weight, the entire quantity of MCC in the formulation was utilized as the substrate for the ASD. Despite the high percentage of ASD (composed of LM2 and HPMCAS-MG) in the total tablet weight (73.9% w/w), XRPD and MDSC analysis demonstrated the feasibility of achieving a homogeneous and stable ASD could be obtained via fluid bed top-spray granulation. Both spray drying and fluid bed granulation processes yielded ASDs with a high glass transition temperature (T_g), ranging from 105 to 108ºC, which significantly exceeded storage temperatures according to International Council for Harmonisation (ICH) guidelines, indicating minimal risk of crystallization during storage. Dynamic vapour sorption (DVS) analysis were carried out to compare the hygroscopicity of the spray granulated dispersion (SGD) obtained in fluid bed with the SDD obtained in spray dryer. Comparable water uptake levels were obtained in both cases, categorizing them as moderately hygroscopic materials. Furthermore, stability studies conducted over 6 months at 40ºC/75%RH confirmed the stability of drug products formulated with either SGD and SDD material in terms of amorphous state, dissolution profile, assay, and impurities, indicating their suitability for long-term storage.

The characterization of the physical properties of the obtained SGD and SDD materials were conducted, assessing the appearance, loss on drying, bulk and tapped densities, and flow properties. Additionally, the morphology and particle size was assessed using Scanning Electron Microscopy (SEM). The results obtained revealed that fluid bed top-spray granulation produced a powder with increased density and enhanced flow characteristics compared to those of the SDD powder. This was attributed to the agglomeration of ASD and substrate (MCC) particles during top-spray granulation, resulting in favourable compression properties and avoiding the need for a dry granulation step prior to tableting. On the other hand, SDD powder required a dry granulation in roller compaction prior to tableting in order to enhance product flow characteristics. Although a similar level of supersaturation was achieved in both cases, tablets formulated with SGD powder exhibited a slower dissolution profile than those formulated with SDD material.

From a manufacturing process standpoint, fluid bed top-spray granulation demonstrated significantly shorter processing times and greater outputs compared to spray drying at a laboratory scale. The higher efficiency of top-spray granulation was attributed to faster average feed rates and the feasibility of working with higher concentration of solids in solution. Moreover, fluid bed technology effectively reduced the solvent (acetone) content below ICH limits within a reasonable timeframe, demonstrating its capability for effective solvent evaporation. Nonetheless, certain challenges were noted, such as the need to control initial and final container loads to prevent excessive loads and ensure process feasibility. Adjustments to process parameters, including inlet air flow, feed rate, and atomization air pressure, were required throughout the spraying process to maintain optimal conditions. Therefore, careful consideration of process parameters and scale-up challenges is necessary for successful implementation in large-scale manufacturing.

Based on this study, fluid bed top-spray was deemed viable for the production of homogeneous and stable LM2 ASD with HPMCAS-MG in ratio 1:5. Nevertheless, before proceeding with an *in vivo* pilot BA study, formulation studies were conducted to enhance the dissolution profile. The third section corresponds to the **development** of ASD-based film-coated tablets prototypes via fluid top-spray granulation, evaluating various formulation variables and HPMCP HP-55 as an alternative polymer to HPMCAS-MG.

For the development studies, a QbD approach was adopted. Initially, a QTPP was established taking into consideration the drug substance properties, the characterization of the RLD, and the RLD label and target patient population. Subsequently, the quality attributes (QAs) necessary for the final product were listed, and CQAs were determined based on the potential influence on patient safety and efficacy in case of any failure to meet these QAs. This investigation primarily focused on those CQAs susceptible to be affected by changes in the drug product formulation process. For LM2 drug product, these CQAs included appearance, solid state form, assay, uniformity of dosage units (UDU), hardness, disintegration time, dissolution profile, residual solvents, WC, and degradation impurities.

Variables of the formulation based on HPMCAS-MG were assessed guided by a formulation risk assessment (RA). Key high-risk variables affecting the dissolution profile included disintegrant percentage, substrate amount and type, and surfactant addition as part of the ASD. The addition of disintegrant in the intragranular phase (4 – 8% w/w of croscarmellose sodium) and 1.5% w/w of poloxamer 188 (surfactant) significantly enhanced the drug product dissolution profile. However, varying substrate amount (ranging from 8.7 to 34.0% w/w of MCC) or type (MCC or mannitol) did not significantly affect dissolution. Furthermore, the influence of the SGD particle size was evaluated through the milling step. Although no significant influence on the dissolution profile was observed, a more vigorous milling was required to increase SGD density and achieve the target tablet weight with the desired punches design. Based on *in vitro* studies, a fluid bed ASD-formulation of LM2 and HPMCAS-MG in the weight ratio of 1:5, along with 4% of intragranular croscarmellose sodium and 1.5% of poloxamer 188, emerged as promising for further assessment in an *in vivo* pilot BA study.

This section also describes the evaluation of HPMCP HP-55 as alternative polymeric carrier to HPMCAS-MG for the production of ASD with LM2 drug substance. HPMCP HP-55 and HPMCAS-MG are both cellulose derivatives polymers with enteric properties, but differ in substituent groups, which can influence solubility and pH sensitivity. HPMCP HP-55 starts to dissolve at pH 5.5, while HPMCAS-MG starts to dissolve at pH 6.0. Experiments conducted with fluid bed top-spray demonstrated the feasibility to produce homogenous and stable ASDs of LM2 and HPMCP HP-55 in weight ratios of 1:4 and 1:5, exhibiting a high T_g of approximately 125ºC, as confirmed by XRPD and MDSC analysis. Furthermore, faster dissolution profiles than those obtained with HPMCAS-MG were obtained. These findings suggest that HPMCP HP-55 could serve as a potential alternative to HPMCAS-MG in enhancing LM2 solubility and dissolution profile. Hence, these formulations were considered promising for further assessment in an *in vivo* pilot BA study.

Stability studies of all three formulations selected for further *in vivo* assessment are presented to confirm their stability at accelerated (40ºC/75%RH) and long-term (25ºC/60%RH) conditions. Results after 6 months confirmed the stability of all three formulations in terms of amorphous state, dissolution profile, WC, assay, and impurities, suggesting a shelf-life of at least 12 months.

In this section, it is also provided the manufacturing process flow diagram followed for the production of batches tested in an *in vivo* pilot BA study. Following the QbD approach, each manufacturing step is detailed, highlighting the critical material attributes and process parameters that influence intermediate and finished product quality attributes. A control strategy for all three prototypes was established, including excipients material attributes, equipment operating conditions, and IPCs to ensure consistent performance and product quality. This control strategy ensured adherence to Good Manufacturing Practice (GMP) standards for human use. One batch of each prototype of LM2 film-coated tablets was manufactured under GMP conditions. All release tests performed on film-coated tablets showed to be within the specifications, including appearance, weight, hardness, solid state form, disintegration time, dissolution profile, WC, assay, UDU, impurities, and residual acetone content. After this development work, an updated risk assessment of the formulation is provided to capture the reduced level of risk and identify the residual risks before proceeding with the *in vivo* pilot BA study.

Finally, in the fourth section, an ***in vivo* pilot BA study** compares prototypes developed in fluid bed to the RLD spray dried formulation. This study provides insight into the effect of polymer type and percentage on the pharmacokinetics of the drug, as well as the feasibility of achieving a bioequivalent product using fluid bed technology instead of spray drying. The three selected prototypes were compared to the RLD under fasting conditions, deemed more sensitive than fed conditions. A parallel study with 60 healthy male volunteers was conducted, administering film-coated tablets with water and analysing LM2 blood samples solely for the parent compound concentration.

In conclusion, this doctoral thesis has addressed the potential of fluid bed technology for ASD production as an alternative to spray drying, offering comparable *in vivo* performance with the added advantage of improved flow properties and good compression properties. Furthermore, it provides valuable insights into the formulation, characterization, and evaluation of ASDs produced by fluid bed top-spray granulation, emphasizing the importance of careful formulation design and process optimization. While *in vitro* studies laid the groundwork for formulation selection, *in vivo* BA studies were crucial for assessing the potential bioequivalence of different formulations with the RLD, highlighting the complex interplay between formulation and physiological factors. Overall, this work contributes to advancing pharmaceutical development and emphasizes the significance of exploring manufacturing technologies for ASDs production. Future research may focus on refining formulation and addressing challenges in scaling up of ASDs in fluid bed for commercial production.

RESUMEN

En la industria farmacéutica, lograr la solubilización de fármacos es un aspecto crítico para garantizar la eficacia y la biodisponibilidad de las formas de dosificación sólidas administradas por vía oral. La capacidad de un fármaco para disolverse en agua u otros fluidos fisiológicos afecta directamente en su absorción y en sus efectos terapéuticos posteriores. Sin embargo, un porcentaje significativo de fármacos, tanto los comercializados actualmente como los que se encuentran en vía de desarrollo, presenta dificultados debido a la baja solubilidad en agua. Según bibliografía, aproximadamente el 40% de los fármacos en el mercado y hasta el 90% de los que están en desarrollo presentan una baja solubilidad en agua y son clasificados por el Sistema de Clasificación Biofarmacéutica (BCS) como clase II (baja solubilidad y alta permeabilidad) y clase IV (baja solubilidad y baja permeabilidad).

La formulación de dispersiones sólidas amorfas (ASDs) es una estrategia empleada para mejorar la disolución y la solubilidad de fármacos poco solubles. Estas ASDs implican la dispersión a nivel molecular del principio activo dentro de una matriz portadora en estado amorfo, lo que aumenta la solubilidad y velocidad de disolución y, por ende, la biodisponibilidad en comparación con las formas cristalinas del principio activo.

Si bien la tecnología *spray drying* destaca como uno de los métodos de fabricación más comunes para la producción de ASDs, esta presenta desafíos como la producción de productos pulverulentos con baja densidad aparente y propiedades de flujo pobres, así como altos costos de inversión que pueden afectar particularmente a las empresas farmacéuticas de genéricos. Un método alternativo para preparar dispersiones sólidas implica la utilización de la tecnología de lecho fluido, donde una solución del principio activo y portador/es se pulveriza sobre un sustrato inerte, el cual podría tratarse de esferas de azúcar o diluyentes comúnmente utilizados como la celulosa microcristalina (MCC) o la lactosa. Este método se ha empleado con éxito para la producción de dispersiones sólidas de itraconazol con hidroxipropilmetilcelulosa (HPMC), que se comercializan como esferas de azúcar recubiertas con el principio activo y dosificadas en cápsulas con el nombre Sporanox®. Sin embargo, el número de productos comercializados con ASDs producidas con el lecho fluido es notablemente menor en comparación con las producidas por *spray drying* e extrusión por fusión (*hot melt extrusion*). No obstante, el lecho fluido es una tecnología muy utilizada y disponible en la mayoría de empresas farmacéuticas especializadas en formas de dosificación sólidas y ofrece una alternativa prometedora debido a su potencial para abordar desafíos relacionados con las propiedades del polvo y los costos de producción.

Las ASDs producidas utilizando diferentes tecnologías pueden diferir notablemente en su estabilidad química y física, así como en el comportamiento *in vitro* e *in vivo*. Por lo tanto,

la evaluación exhaustiva de tecnologías convencionales como el lecho fluido para la producción industrial de ASDs como alternativa al spray drying, es de gran valor para la industria farmacéutica.

Al mismo tiempo, los portadores poliméricos utilizados para la producción de ASDs son clave para la estabilización del estado amorfo del principio activo y para mejorar su disolución al mantener el principio activo en un estado de sobresaturación. Numerosos polímeros han sido reportados en bibliografía para este propósito, incluyendo, entre otros, derivados de celulosa como la hidroxipropilmetilcelulosa (HPMC), el acetato-succinato de hidroxipropilmetilcelulosa (HPMCAS), el ftalato de hidroxipropilmetilcelulosa (HPMCP) y la hidroxipropilcelulosa (HPC); y polímeros vinílicos como la polivinilpirrolidona (PVP), el alcohol polivinílico (PVA) y el copolímero polivinilpirrolidona-acetato de vinilo (PVP/VA). La selección del tipo y cantidad de polímero en las ASDs es un aspecto crítico en el desarrollo de formulaciones, ya que puede influir significativamente en la estabilidad, la cinética de liberación y el comportamiento *in vivo* del producto. Por lo tanto, explorar la viabilidad de utilizar un portador polimérico alternativo es de interés no solo desde un punto de vista científico, sino también para las empresas genéricas. El uso de componentes de la formulación clave alternativos ofrece oportunidades para la innovación, el ahorro de costes, ventajas regulatorias y diferenciación en el panorama competitivo del desarrollo de productos genéricos.

Esta tesis doctoral explora el potencial de la granulación en lecho fluido como alternativa a la tecnología *spray drying* para la producción de ASDs posteriormente formuladas en comprimidos recubiertos de liberación inmediata. Para ello, se utilizó un principio activo BCS clase II, referido como LM2. Se llevó a cabo un análisis comparativo de las propiedades físicas, la estabilidad y los perfiles de disolución de las ASDs obtenidas mediante *spray drying* o granulación en el lecho fluido (configuración *top-spray*). Además, se evaluó el HPMCP HP-55 como polímero alternativo al HPMCAS-MG, ambos con propiedades entéricas. En esta investigación, se desarrollaron tres prototipos basados en ASDs producidas mediante granulación en el lecho fluido y diferentes polímeros (HPMCAS-MG y HPMCP HP-55), seguidos de un estudio piloto de biodisponibilidad (BA) *in vivo* comparando su perfil farmacocinético con una formulación comercializada obtenida por *spray drying*. Los estudios de desarrollo se realizaron siguiendo un enfoque basado en Calidad por diseño (QbD), empezando con el diseño del perfil de calidad del producto (QTPP), seguido por la definición de los atributos críticos de calidad (CQAs) y posteriormente realizando una evaluación de riesgos de las variables de formulación. Antes de llevar a cabo el estudio piloto de BA *in vivo*, se estableció una estrategia de control, la cual incluyó los atributos de los materiales, los parámetros de cada etapa del proceso y los controles en proceso (IPCs) para garantizar una ejecución y una calidad del producto consistentes. Además, se realizó una actualización de la evaluación de riesgos de la formulación para registrar la reducción del nivel de riesgo e identificar los riesgos residuales.

Esta tesis doctoral está organizada en una revisión bibliográfica y cuatro secciones principales.

En la **introducción** de esta tesis, se realiza una recopilación bibliográfica de los conceptos fundamentales sobre las ASDs, sobre los métodos más utilizados para su preparación y los polímeros y técnicas más empleados en productos comerciales basados en ASDs. Además, se realiza una revisión de los principios de *spray drying* y la granulación en lecho fluido, junto con una evaluación de sus respectivas ventajas y desventajas en la producción de ASDs. Para concluir con esta sección, se proporciona un resumen de los excipientes más comúnmente utilizados en las ASDs.

En la primera sección se presentan los estudios de **preformulación**, los cuales se centran en la caracterización del principio activo LM2 y del producto de referencia (RLD), así como la comprensión de la formulación del RLD. Como se mencionó anteriormente, el principio activo LM2 pertenece a la categoría BCS clase II. A lo largo de este estudio, se utilizó la forma cristalina A del LM2. El RLD consiste en un comprimido recubierto de liberación inmediata que contiene una ASD de LM2 y HPMCAS obtenida por *spray drying*, utilizando acetona como solvente. Considerando la solubilidad del principio activo LM2 y HPMCAS en varios solventes orgánicos, la toxicidad de los solventes y la información disponible del RLD, se seleccionó la acetona como solvente para esta investigación. Dado que el grado y la cantidad de HPMCAS utilizados por el RLD son inciertas, se llevaron a cabo estudios para desarrollar una formulación mediante *spray drying* que presentara resultados similares al RLD, con el fin de utilizarla como punto de referencia para investigaciones posteriores utilizando el lecho fluido. Se evaluaron diversas proporciones de LM2 y HPMCAS-MG con el objetivo de determinar su capacidad para generar una ASD uniforme y alcanzar un perfil de disolución y un nivel de sobresaturación comparables al RLD. Para esta evaluación se utilizaron difracción de rayos X (XRPD), calorimetría diferencial de barrido modulada (MDSC) y un método de disolución en dos etapas. Se diseñó un método de disolución *in vitro* con condiciones *non-sink* con dos etapas para simular la transición del estómago al intestino. Esto implicó someter las formulaciones durante 30 minutos en 300 mL de medio a pH 1.2, seguido de un cambio a 900 mL de medio a pH 6.8.

En la segunda sección, se explora la **viabilidad** de la tecnología de lecho fluido con la configuración *top-spray* para la producción de una ASD de LM2 y HPMCAS-MG en un ratio 1:5, evaluando propiedades fisicoquímicas, disolución y estabilidad, y comparándolas con las obtenidas por *spray drying*. Se seleccionó el lecho fluido con la configuración *top-spray* con el objetivo de simular el proceso de *spray drying* y promover la aglomeración de partículas. En la granulación en lecho fluido, es esencial incorporar un excipiente inerte en el contenedor, denominado sustrato. Este sustrato sirve como base sobre la cual se pulveriza la solución que contiene el principio activo y el polímero. Para este estudio, se eligió la MCC como sustrato, el mismo excipiente utilizado como diluyente durante los estudios de preformulación para procesar la SDD obtenida en comprimidos. Dada la elevada proporción de sólidos que se deben pulverizar sobre el sustrato, representando el 73.9% del peso total de los comprimidos, se utilizó toda la cantidad de MCC en la formulación como sustrato de la ASD. A pesar del alto porcentaje de ASD (LM2 y HPMCAS-MG) respecto al peso total del comprimido (73.9% p/p), los análisis de XRPD y MDSC demostraron que se podía obtener una ASD homogénea y estable por granulación en lecho fluido. Tanto los procesos de *spray drying* como granulación en lecho fluido produjeron ASDs con una temperatura de transición vítrea (T_g) alta, que oscilaba entre 105 y 108ºC, significativamente superior a las temperaturas de almacenamiento según las directrices de la ICH, indicando un riesgo mínimo de cristalización durante el almacenamiento. Adicionalmente, se llevaron a cabo análisis de Sorción Dinámica de Vapor (DVS) para comparar la higroscopicidad de las ASDs obtenidas por granulación en lecho fluido (SGD) o por *spray drying* (SDD). Los resultados mostraron unos niveles de absorción de agua comparables en ambos casos, categorizándolos como materiales moderadamente higroscópicos. Además, los estudios de estabilidad realizados durante 6 meses a 40ºC/75%HR confirmaron la estabilidad de ambos productos en términos de estado amorfo, perfil de disolución, contenido de principio activo e impurezas, indicando su idoneidad para el almacenamiento a largo plazo.

Se realizó la caracterización de las propiedades física de los materiales SGD y SDD obtenidos, evaluando el aspecto, la pérdida por secado, las densidades aparentes y compactadas y las propiedades de flujo. Además, se evaluó la morfología y el tamaño de partícula utilizando microscopio electrónica de barrido (SEM). Los resultados obtenidos revelaron que la SGD obtenida por granulación en lecho fluido presenta una densidad mayor y unas características de flujo mejoradas en comparación con la SDD obtenida por *spray drying*. Este resultado se atribuyó a la aglomeración de partículas de ASD y sustrato (MCC) durante la granulación en lecho fluido, lo que resultó en propiedades de compresión favorables y evitó la necesidad de realizar una granulación vía seca previa a la compresión. Por otro lado, la SDD obtenida requirió una granulación por vía seca mediante compactación por rodillos, previa a la compresión, para mejorar las características de flujo del producto. Aunque se logró un nivel de sobresaturación similar en ambos casos, los comprimidos formulados con la SGD mostraron un perfil de disolución más lento comparado con aquellos formulados con la SDD.

Desde un punto de vista de proceso de fabricación a escala de laboratorio, la granulación en lecho fluido mostró tiempos de procesamiento significativamente más cortos y mayores rendimientos en comparación con el *spray drying*. La mayor eficiencia del lecho fluido se atribuyó a la posibilidad de aplicar una velocidad de alimentación mayor y a la viabilidad de trabajar con concentraciones más altas de sólidos en solución. Además, la tecnología de lecho fluido redujo de manera eficiente el contenido de solvente (acetona) por debajo de los límites de la ICH en un período de tiempo razonable, demostrando su capacidad para una evaporación efectiva de solventes. No obstante, se observaron ciertos desafíos, como la necesidad de controlar las cargas iniciales y finales del contenedor para evitar cargas excesivas y garantizar la viabilidad del proceso. Debido al cambio de carga a lo largo del proceso, se requirieron ajustes en los parámetros de proceso a lo largo del proceso de pulverización para mantener las condiciones óptimas, incluido el flujo de aire de entrada, la velocidad de alimentación y la presión de atomización. Por este motivo, resulta fundamental considerar detenidamente los parámetros del proceso y los desafíos de escalado para lograr una implementación exitosa en la fabricación a gran escala.

Basándonos en este estudio, la granulación en lecho fluido se consideró viable para la producción de una ASD homogénea y estable de LM2 y HPMCAS-MG en un ratio 1:5. Sin embargo, antes de proceder a la realización de un estudio piloto de BA *in vivo*, se llevaron a cabo estudios de formulación para mejorar el perfil de disolución. La tercera sección de los resultados presentados corresponde al **desarrollo** de prototipos de comprimidos recubiertos basados en ASD producidas por granulación en lecho fluido, evaluando diversas variables de formulación y el HPMCP HP-55 como polímero alternativo al HPMCAS-MG.

Para los estudios de desarrollo, se adoptó un enfoque basado en QbD. Inicialmente, se estableció un QTPP considerando las propiedades del principio activo, la caracterización del RLD, la ficha técnica del RLD y la población de pacientes objetivo. Posteriormente, se enumeraron los atributos de calidad (QAs) necesarios para el producto final y se identificaron los CQAs en función de la influencia potencial en la seguridad y eficacia del paciente en caso de cualquier falla para cumplir con estos QAs. Esta investigación se centró principalmente en aquellos CQAs susceptibles de ser afectados por cambios en la formulación del producto. Para el principio activo LM2, estos CQAs incluyeron apariencia, polimorfismo, contenido de principio activo, uniformidad de contenido (UDU), dureza, tiempo de disgregación, perfil de disolución, solventes residuales, contenido de agua e impurezas de degradación.

Las variables de la formulación basada en HPMCAS-MG se evaluaron siguiendo la evaluación de riesgos (RA) de formulación. Las variables consideradas con alto riesgo de afectación al perfil de disolución incluyeron el porcentaje de disgregante, la cantidad y tipo de sustrato y la adición de un tensioactivo como parte de la ASD. La adición de un disgregante intragranular (4 – 8% p/p de croscarmelosa sódica) y 1.5% p/p de poloxámero 188 (tensioactivo) mejoró significativamente el perfil de disolución del producto. Por lo contrario, variaciones en la cantidad (de 8.7 a 34.0% p/p de MCC) y tipo (MCC o manitol) de sustrato no mostró un efecto significativo en el perfil de disolución. Además, también se evaluó la influencia del tamaño de partícula de la SGD, evaluado a través del proceso de tamización. Aunque no se observó una influencia significativa en el perfil de disolución, se requirió una molienda más agresiva para aumentar la densidad de la SGD y lograr el peso objetivo del comprimido con el diseño de punzones deseado. Basado en estos estudios *in vitro*, una formulación con una ASD de LM2 y HPMCAS-MG en ratio 1:5 producida por granulación en lecho fluido junto con un 1.5% de poloxámero 188 y un 4% de disgregante intragranular, se consideró prometedora para ser evaluada en un estudio piloto de BA *in vivo*.

Esta sección también describe la evaluación del HPMCP HP-55 como polímero alternativo al HPMCAS-MG para la producción de una ASD con el principio activo LM2. Ambos polímeros son derivados de celulosa con propiedades entéricas, pero difieren en los grupos sustituyentes, los que puede influir en la solubilidad y la sensibilidad al pH. El HPMCP HP-55 empieza a disolverse a pH 5.5, mientras que el HPMCAS-MG lo hace a pH 6.0. Los experimentos realizaos por granulación en el lecho fluido mostraron la viabilidad de la obtención de ASD homogéneas y estables de LM2 y HPMCP HP-55 en ratios 1:4 y 1:5, mostrando una alta T_g de aproximadamente 125ºC, como lo demostraron los análisis de XRPD y MDSC. Adicionalmente, se obtuvieron perfiles de disolución más rápidos que los obtenidos con HPMCAS-MG. Estos hallazgos sugieren que el HPMCP HP-55 podría servir como una alternativa potencial al HPMCAS-MG para mejorar la solubilidad y el perfil de disolución del LM2. Es por esto que estas formulaciones fueron consideradas prometedoras para ser evaluadas en un estudio piloto de BA *in vivo*.

Finalmente, se presentan estudios de estabilidad de las tres formulaciones seleccionadas para confirmar su estabilidad en condiciones aceleradas (40ºC/75%HR) y a largo plazo (25ºC/60%HR). Los resultados después de 6 meses de almacenamiento confirmaron la estabilidad de las tres formulaciones en términos de estado amorfo, perfil de disolución, contenido de agua, contenido de principio activo e impurezas, sugiriendo una vida útil de al menos 12 meses.

En esta sección, también se proporciona el diagrama de flujo del proceso de fabricación seguido para la producción de los lotes testeados en un estudio piloto de BA *in vivo*. Siguiendo el enfoque de QbD, se detalla cada etapa del proceso, resaltando los atributos críticos de los materiales y los parámetros de proceso que influyen en los atributos de calidad de los intermedios y del producto acabado. Se estableció una estrategia de control para los tres prototipos, que incluía los atributos de los materiales, los parámetros de cada etapa del proceso y los IPCs para garantizar una ejecución y calidad del producto consistentes. Esta estrategia de control aseguró el cumplimiento de los estándares de Buenas Prácticas de Manufactura (GMP) para uso humano. Se fabricó un lote de cada prototipo de comprimidos recubiertos de LM2 bajo condiciones GMP. Todos los análisis de liberación realizados en comprimidos recubiertos mostraron estar dentro de las especificaciones, las cuales incluían la apariencia, el peso, la dureza, el polimorfismo, el tiempo de disgregación, el perfil de disolución, el contenido de agua, el contenido del principio activo, la UDU, las impurezas y el contenido de acetona residual. A continuación, se proporciona la actualización de la evaluación de riesgos de la formulación para plasmar la reducción de los riesgos e identificar los riesgos residuales antes de proceder con el estudio piloto de BA *in vivo*.

Finalmente, en la cuarta sección, se presenta un **estudio piloto de BA *in vivo*** que compara los prototipos desarrollados en el lecho fluido con el RLD fabricado por *spray drying*. Este estudio proporciona información sobre el efecto del tipo y porcentaje de polímero en la farmacocinética del medicamento, así como la viabilidad de conseguir un producto bioequivalente utilizando la tecnología de lecho fluido en lugar de *spray drying* para la preparación de ASDs. Los tres prototipos seleccionados fueron comparados con el RLD en condiciones de ayuno, consideradas más sensibles que en condiciones posprandiales. Se llevó a cabo un estudio paralelo con 60 voluntarios sanos, administrando los comprimidos recubiertos con agua y analizando muestras de sangre únicamente para la concentración del compuesto principal (LM2).

En conclusión, esta tesis doctoral ha abordado el potencial de la tecnología de lecho fluido para la producción de ASDs como una alternativa al *spray drying*, ofreciendo un comportamiento *in vivo* comparable y con la ventaja adicional de obtener un producto con mejores propiedades de flujo y buenas propiedades de compresión. Además, ofrece valiosos conocimientos sobre la formulación, caracterización y evaluación de ASDs producidas mediante granulación en lecho fluido, haciendo hincapié en la importancia de un cuidadoso diseño de la formulación y la optimización del proceso. Si bien los estudios *in vitro* sentaron las bases para la selección de la formulación, los estudios *in vivo* de BA fueron cruciales para evaluar la posible bioequivalencia de diferentes formulaciones con el RLD, destacando la compleja interacción entre la formulación y los factores fisiológicos. En general, este trabajo contribuye al avance del desarrollo farmacéutico y enfatiza la importancia de explorar tecnologías de fabricación para la producción de ASDs. Las investigaciones futuras pueden centrarse en perfeccionar la formulación y abordar los desafíos en la escalabilidad de las ASDs en lecho fluido para su producción comercial.

RESUMO

Na industria farmacéutica, lograr a solubilización de fármacos é un aspecto crítico para garantir a eficacia e a biodisponibilidade das formas de dosificación sólidas administradas por vía oral. A capacidade dun fármaco para disolverse en auga ou outros fluídos fisiolóxicos afecta directamente a súa absorción e os seus efectos terapéuticos posteriores. Non obstante, un porcentaxe significativo de fármacos, tanto dos comercializados actualmente como dos que se atopan en vía de desenvolvemento, presenta dificultades debido á baixa solubilidade en auga. Segundo bibliografía, aproximadamente un 40% dos fármacos no mercado e ata o 90% dos que están en desenvolvemento presentan a súa baixa solubilidade en auga e son clasificados polo Sistema de Clasificación Biofarmacéutica (BCS) como clase II (baixa solubilidade e alta permeabilidade) ou clase IV (baixa solubilidade e baixa permeabilidade).

A formulación de dispersións sólidas amorfas (ASDs) é unha estratexia empregada para mellorar a disolución e a solubilidade de fármacos pouco solubles. Estas ASDs implican a dispersión a nivel molecular do principio activo dentro dunha matriz portadora en estado amorfo, o que aumenta a solubilidade e velocidade de disolución e, en consecuencia, a biodisponibilidade en comparación coas formas cristalinas do principio activo.

Aínda que a tecnoloxía de *spray drying* destaca como un dos métodos de fabricación máis comúns para a produción de ASDs, esta presenta desafíos como a produción de produtos pulverulentos con baixa densidade aparente e propiedades de fluxo pobres, así como altos custos de investimento que poden afectar particularmente ás empresas farmacéuticas de xenéricos. Un método alternativo para preparar dispersións sólidas implica a utilización da tecnoloxía de leito fluído, onde unha solución do principio activo e portador/es se pulveriza sobre un substrato inerte, o cal poderían ser esferas de azucre ou diluíntes comunmente utilizados como a celulosa microcristalina (MCC) ou a lactosa. Este método empregouse con éxito para a produción de dispersións sólidas de itraconazol con hidroxipropilmetilcelulosa (HPMC), que se comercializan como esferas de azucre recubertas co principio activo e dosificadas en cápsulas co nome Sporanox®. Porén, o número de produtos comercializados con ASDs producidas co leito fluído é notablemente menor en comparación coas producidas por *spray drying* e extrusión por fusión (*hot melt extrusion*). Non obstante, o leito fluido é unha tecnoloxía moi utilizada e dispoñible na maioría de empresas farmacéuticas especializadas en formas de dosificación sólidas e ofrece unha alternativa prometedora debido ao seu potencial para abordar desafíos relacionados coas propiedades do po e os custos de produción.

As ASDs producidas utilizando diferentes tecnoloxías poden diferir notablemente na súa estabilidade química e física, así como no comportamento *in vitro* e *in vivo*. Polo tanto, a

avaliación exhaustiva de tecnoloxías convencionais como o leito fluído para a produción industrial de ASDs como alternativa ao secado por pulverización, ten un gran valor para a industria farmacéutica.

Ao mesmo tempo, os portadores poliméricos utilizados para a produción de ASDs son clave para a estabilización do estado amorfo do principio activo e para mellorar a súa disolución ao manter o principio activo nun estado de sobresaturación. Numerosos polímeros foron reportados na bibliografía para este propósito, incluíndo, entre outros, derivados de celulosa como a hidroxipropilmetilcelulosa (HPMC), o acetato-succinato de hidroxipropilmetilcelulosa (HPMCAS), o ftalato de hidroxipropilmetilcelulosa (HPMCP) e a hidroxipropilcelulosa (HPC); e polímeros vinílicos como a polivinilpirrolidona (PVP), o alcohol polivinílico (PVA) e o copolímero polivinilpirrolidona-acetato de vinilo (PVP/VA). A selección do tipo e cantidade de polímero nas ASDs é un aspecto crítico no desenvolvemento de formulacións, xa que pode influír significativamente na estabilidade, na cinética de liberación e no comportamento *in vivo* do produto. Polo tanto, explorar a viabilidade de utilizar un portador polimérico alternativo é de interese non só dende un punto de vista científico, senón tamén para as empresas xenéricas. O uso de compoñentes da formulación clave alternativos ofrece oportunidades para a innovación, o aforro de custos, vantaxes regulatorias e diferenciación no panorama competitivo do desenvolvemento de produtos xenéricos.

Esta tese de doutoramento explora o potencial da granulación en leito fluído como alternativa á tecnoloxía de *spray drying* para a produción de ASDs posteriormente formuladas en comprimidos recubertos de liberación inmediata. Para iso, utilizouse un principio activo BCS clase II, referido como LM2. Levouse a cabo un análise comparativo das propiedades físicas, a estabilidade e os perfís de disolución das ASDs obtidas mediante secado por *spray drying* ou granulación en leito fluído (configuración *top-spray*). Ademais, avaliouse o HPMCP HP-55 como polímero alternativo ao HPMCAS-MG, ambos con propiedades entéricas. Nesta investigación, desenvolvéronse tres prototipos baseados en ASDs producidas mediante granulación en leito fluído e diferentes polímeros (HPMCAS-MG e HPMCP HP-55), seguidos dun estudo piloto de biodispoñibilidade (BA) *in vivo* comparando o seu perfil farmacocinético cunha formulación comercializada obtida por *spray drying*. Os estudos de desenvolvemento realizáronse seguindo un enfoque baseado na Calidade por Deseño (QbD), comezando co deseño do perfil de calidade do produto (QTPP), seguido pola definición dos atributos críticos de calidade (CQAs) e posteriormente realizando unha avaliación de riscos das variables de formulación. Antes de levar a cabo o estudo piloto de BA *in vivo*, estableceuse unha estratexia de control, a cal incluíu os atributos dos materiais, os parámetros de cada etapa do proceso e os controis en proceso (IPCs) para garantir unha execución e calidade do produto consistentes. Ademais, realizouse unha actualización da avaliación de riscos da formulación para rexistrar a redución do nivel de risco e identificar os riscos residuais.

Esta tese de doutoramento está organizada nunha revisión bibliográfica e catro seccións principais.

Na **introdución** desta tese, faise unha recompilación bibliográfica dos conceptos fundamentais sobre as ASDs, sobre os métodos máis utilizados para a súa preparación e os polímeros e técnicas máis empregados en produtos comerciais baseados en ASDs. Ademais, faise unha revisión dos principios do *spray drying* e da granulación en leito fluído, xunto cunha avaliación das súas respectivas vantaxes e desvantaxes na produción de ASDs. Para concluír con esta sección, proporciónase un resumo dos excipientes máis comunmente utilizados nas ASDs.

Na primeira sección preséntanse os estudos de **preformulación**, os cales se centran na caracterización do principio activo LM2 e do produto de referencia (RLD), así como na comprensión da formulación do RLD. Como se mencionou anteriormente, o principio activo LM2 pertence á categoría BCS clase II. Ao longo deste estudo, utilizouse a forma cristalina A do LM2. O RLD consiste nun comprimido recuberto de liberación inmediata que contén unha ASD de LM2 e HPMCAS obtida por *spray drying*, utilizando acetona como solvente. Considerando a solubilidade do principio activo LM2 e HPMCAS en varios solventes orgánicos, a toxicidade dos solventes e a información dispoñible do RLD, seleccionouse a acetona como solvente para esta investigación. Dado que o grao e a cantidade de HPMCAS utilizados polo RLD son incertos, leváronse a cabo estudos para desenvolver unha formulación mediante *spray drying* que presentase resultados similares ao RLD, co fin de utilizala como punto de referencia para investigacións posteriores utilizando o leito fluído. Avaliáronse diversas proporcións de LM2 e HPMCAS-MG co obxectivo de determinar a súa capacidade para xerar unha ASD uniforme e acadar un perfil de disolución e un nivel de sobresaturación comparables ao RLD. Para esta avaliación utilizáronse difracción de raios X (XRPD), calorimetría diferencial de barrido modulada (MDSC) e un método de disolución en dúas etapas. Desenvolveuse un método de disolución *in vitro* con condicións *non-sink* con dúas etapas para simular a transición do estómago ao intestino. Isto implicou someter as formulacións durante 30 minutos en 300 mL de medio a pH 1.2, seguido dun cambio a 900 mL de medio a pH 6.8.

Na segunda sección, explórase a **viabilidade** da tecnoloxía de leito fluído coa configuración *top-spray* para a produción dunha ASD de LM2 e HPMCAS-MG nunha proporción de 1:5, avaliando propiedades fisicoquímicas, disolución e estabilidade, e comparándoas coas obtidas por *spray drying*. Seleccionouse o leito fluído coa configuración *top-spray* co obxectivo de simular o proceso de *spray drying* e promover a aglomeración de partículas. Na granulación en leito fluído, é esencial incorporar un excipiente inerte no contedor, denominado substrato. Este substrato serve como base sobre a cal se pulveriza a solución que contén o principio activo e o polímero. Para este estudo, elixiuse a MCC como substrato, o mesmo excipiente utilizado como diluínte durante os estudos de preformulación para procesar a SDD obtida en comprimidos. Dada a elevada proporción de sólidos que se deben pulverizar sobre o substrato, representando o 73.9% do peso total dos comprimidos, utilizouse toda a cantidade de MCC na formulación como substrato da ASD. A pesar do alto porcentaxe de ASD (LM2 e HPMCAS-MG) respecto ao peso total do comprimido (73.9% p/p), os análises de XRPD e MDSC demostraron que se podía obter unha ASD homoxénea e estable por granulación en leito fluído. Tanto os procesos de *spray drying* como granulación en leito fluído produciron ASDs cunha temperatura de transición vítrea (Tg) alta, que oscilaba entre 105 e 108ºC, significativamente superior ás temperaturas de almacenamento segundo as directrices da ICH, indicando un risco mínimo de cristalización durante o almacenamento. Ademais, leváronse a cabo análises de Sorción Dinámica de Vapor (DVS) para comparar a higroscopicidade das ASDs obtidas por granulación en leito fluído (SGD) ou por *spray drying* (SDD). Os resultados mostraron uns niveis de absorción de auga comparables en ambos casos, categorizándoos como materiais moderadamente higroscópicos. Ademais, os estudos de estabilidade realizados durante 6 meses a 40ºC/75%HR confirmaron a estabilidade de ambos produtos en termos de estado amorfo, perfil de disolución, contido de principio activo e impurezas, indicando a súa idoneidade para o almacenamento a longo prazo.

Realizouse a caracterización das propiedades físicas dos materiais SGD e SDD obtidos, avaliando o aspecto, a perda por secado, as densidades aparentes e compactadas e as propiedades de fluxo. Ademais, avaliouse a morfoloxía e o tamaño de partícula utilizando microscopio electrónico de barrido (SEM). Os resultados obtidos revelaron que a SGD obtida por granulación en leito fluído presenta unha densidade maior e características de fluxo melloradas en comparación coa SDD obtida por *spray drying*. Este resultado atribuíuse á aglomeración de partículas de ASD e substrato (MCC) durante a granulación en leito fluído, o que resultou en propiedades de compresión favorables e evitou a necesidade de realizar unha granulación vía seca previa á compresión. Por outra banda, a SDD obtida requiriu unha granulación por vía seca mediante compactación por rodetes, previa á compresión, para mellorar as características de fluxo do produto. Con todo, aínda que se logrou un nivel de sobresaturación similar en ambos casos, os comprimidos formulados coa SGD mostraron un perfil de disolución máis lento en comparación cos formulados coa SDD.

Dende un punto de vista do proceso de fabricación a escala de laboratorio, a granulación en leito fluído mostrou tempos de procesamento significativamente máis curtos e maiores rendementos en comparación co *spray drying*. A maior eficiencia do leito fluído atribuíuse á posibilidade de aplicar unha velocidade de alimentación maior e á viabilidade de traballar con concentracións máis altas de sólidos en solución. Ademais, a tecnoloxía de leito fluído reduciu de forma eficiente o contido de solvente (acetona) por baixo dos límites da ICH nun período de tempo razoable, demostrando a súa capacidade para unha evaporación efectiva de solventes. Non obstante, observáronse certos desafíos, como a necesidade de controlar as cargas iniciais e finais do contedor para evitar cargas excesivas e garantir a viabilidade do proceso. Debido ao cambio de carga ao longo do proceso, requiríronse axustes nos parámetros do proceso ao longo do proceso de pulverización para manter as condicións óptimas, incluído o fluxo de aire de entrada, a velocidade de alimentación e a presión de atomización. Por este motivo, resulta fundamental considerar detidamente os parámetros do proceso e dos desafíos de escalado para lograr unha implantación exitosa da fabricación a gran escala.

Baseándonos neste estudo, a granulación en leito fluído considerouse viable para a produción dunha ASD homoxénea e estable de LM2 e HPMCAS-MG nunha proporción de 1:5. Así e todo, antes de proceder á realización dun estudo piloto de BA *in vivo*, leváronse a cabo estudos de formulación para mellorar o perfil de disolución. A terceira sección dos resultados presentados corresponde ao **desenvolvemento** de prototipos de comprimidos recubertos baseados en ASD producidas por granulación en leito fluído, avaliando diversas variables de formulación e o HPMCP HP-55 como polímero alternativo ao HPMCAS-MG.
Para os estudos de desenvolvemento, adoptouse un enfoque baseado en QbD. Inicialmente, deseñouse o QTPP considerando as propiedades do principio activo, a caracterización do RLD, a ficha técnica do RLD e a poboación de pacientes obxectivo. Posteriormente, enumeráronse os atributos de calidade (QAs) necesarios para o produto final e identificáronse os CQAs en función da influencia potencial na seguridade e eficacia do paciente no caso de calquera erro para cumprir con estes QAs. Esta investigación centrouse principalmente naqueles CQAs susceptibles de verse afectados por un cambio na formulación do produto. Para o principio activo LM2, estes CQAs incluíron aparencia, polimorfismo, contido de principio activo, uniformidade de contido (UDU), dureza, tempo de desagregación, perfil de disolución, solventes residuais, contido de auga e impurezas de degradación.
As variables da formulación baseada en HPMCAS-MG avaliáronse seguindo a avaliación de riscos (RA) de formulación. As variables consideradas con alto risco de afectar ao perfil de disolución incluíron o porcentaxe de disgregante, a cantidade e tipo de substrato e a adición dun tensioactivo como parte da ASD. A adición dun disgregante intragranular (4 - 8% p/p de croscarmelosa sódica) e 1.5% p/p de poloxámero 188 (tensioactivo) mellorou significativamente o perfil de disolución do produto. Polo contrario, variacións na cantidade (de 8.7 a 34.0% p/p de MCC) e tipo (MCC ou manitol) de substrato non mostraron un efecto significativo no perfil de disolución. Ademais, tamén se avaliou a influencia do tamaño de partícula da SGD a través do proceso de tamización. Aínda que non se observou unha influencia significativa no perfil de disolución, requiriuse unha moenda máis agresiva para aumentar a densidade da SGD e lograr o peso obxectivo do comprimido co deseño de

punzóns desexado. Baseado nestes estudos *in vitro*, unha formulación cunha ASD de LM2 e HPMCAS-MG nun ratio de 1:5 producida por granulación en leito fluído xunto cun un 1.5% de poloxámero 188 e un 4% de disgregante intragranular, considerouse prometedora para ser avaliada nun estudo piloto de BA *in vivo*.

Esta sección tamén describe a avaliación do HPMCP HP-55 como polímero alternativo ao HPMCAS-MG para a produción dun ASD co principio activo LM2. Ambos polímeros son derivados de celulosa con propiedades entéricas, pero difiren nos grupos substituíntes, o que pode influír na solubilidade e na sensibilidade ao pH. O HPMCP HP-55 comeza a disolverse a un pH de 5.5, mentres que o HPMCAS-MG o fai a un pH de 6.0. Os experimentos realizados por granulación no leito fluído mostraron a viabilidade da obtención de ASD homoxéneas e estables de LM2 e HPMCP HP-55 en proporcións de 1:4 e 1:5 cunha T_g alta (ao redor de 125ºC), como demostraron as análises de XRPD e MDSC. Ademais, obtivéronse perfís de disolución máis rápidos que os obtidos con HPMCAS-MG. Estes achados suxiren que o HPMCP HP-55 podería servir como unha alternativa potencial ao HPMCAS-MG para mellorar a solubilidade e o perfil de disolución do LM2. É por iso que estas formulacións foron consideradas prometedoras para seren avaliadas nun estudo piloto de BA *in vivo*.

Finalmente, preséntanse estudos de estabilidade das tres formulacións seleccionadas para confirmar a súa estabilidade en condicións aceleradas (40ºC/75%HR) e a longo prazo (25ºC/60%HR). Os resultados despois de 6 meses de almacenamento confirmaron a estabilidade das tres formulacións en termos de estado amorfo, perfil de disolución, contido de auga, contido de principio activo e impurezas, o que suxire unha vida útil de polo menos 12 meses.

Nesta sección, tamén se proporciona o diagrama de fluxo do proceso de fabricación seguido para a produción dos lotes testados nun estudo piloto de BA *in vivo*. Seguindo o enfoque de QbD, detállase cada etapa do proceso, salientando os atributos críticos dos materiais e os parámetros do proceso que inflúen nos atributos de calidade dos intermedios e do produto rematado. Estableceuse unha estratexia de control para os tres prototipos, que incluía os atributos dos materiais, os parámetros de cada etapa do proceso e IPCs para garantir unha execución e calidade do produto consistentes. Esta estratexia de control asegurou o cumprimento dos estándares de Boas Prácticas de Manufactura (GMP) para uso humano. Fabricouse un lote de cada prototipo de comprimidos recubertos de LM2 baixo condicións GMP. Todos os análises de liberación realizados en comprimidos recubertos mostraron estar dentro das especificacións, as cales incluían a aparencia, o peso, a dureza, o polimorfismo, o tempo de disgregación, o perfil de disolución, o contido de auga, o contido do principio activo, a UDU, as impurezas e o contido de acetona residual. A continuación, proporciónase a actualización da avaliación dos riscos da formulación para plasmar a redución dos riscos e identificar os riscos residuais antes de proceder co estudo piloto de BA *in vivo*.

Finalmente, na cuarta sección, preséntase un **estudio piloto de BA *in vivo*** que compara os prototipos desenvolvidos no leito fluído co RLD fabricado por *spray drying*. Este estudo proporciona información sobre o efecto do tipo e porcentaxe de polímero na farmacocinética do medicamento, así como a viabilidade de conseguir un produto bioequivalente utilizando a tecnoloxía do leito fluído en lugar de *spray drying* para a preparación de ASDs. Os tres prototipos seleccionados foron comparados co RLD en condicións de xaxún, consideradas máis sensibles que en condicións posprandiais. Levouse a cabo un estudo paralelo con 60 voluntarios sans, administrando os comprimidos recubertos con auga e analizando mostras de sangue unicamente para a concentración do composto principal (LM2).

En conclusión, esta tese doutoral abordou o potencial da tecnoloxía de leito fluido para a produción de ASDs como unha alternativa ao *spray drying*, ofrecendo un comportamento *in vivo* comparable e coa vantaxe adicional de obter un produto con mellores propiedades de fluxo e boas propiedades de compresión. Ademais, ofrece coñecementos valiosos sobre a formulación, caracterización e avaliación de ASDs producidas mediante granulación en leito fluído, facendo fincapé na importancia dun coidadoso deseño da formulación e na optimización do proceso. Aínda que os estudos *in vitro* sentaron as bases para a selección da formulación, os estudos *in vivo* de BA foron cruciais para avaliar a posible bioequivalencia de diferentes formulacións co RLD, destacando a complexa interacción entre a formulación e os factores fisiolóxicos. En xeral, este traballo contribúe ao avance do desenvolvemento farmacéutico e salienta a importancia de explorar tecnoloxías de fabricación para a produción de ASDs. As investigacións futuras poden centrarse en perfeccionar a formulación e abordar os desafíos na escalabilidade das ASDs en leito fluído para a súa produción comercial.

OBJECTIVES AND ORGANIZATION

1. OBJECTIVES AND ORGANIZATION

1.1. STATEMENT OF THE PROBLEM

Over the last decade, there has been an increase in the discovery of medicinal compounds that possess significant therapeutic benefits but exhibit limited solubility in water and a slow dissolution rate. This presents one of the major challenges in developing them into oral medications, hindering their clinical utilization and commercial success due to their poor dissolution and bioavailability.

Several strategies have been investigated to overcome these limitations, among which the preparation of ASDs is considered one of the most successful for improving the dissolution and/or apparent solubility of these types of molecules and, subsequently, the bioavailability. However, the technologies or processes most frequently used for the preparation of ASDs (i.e., spray drying and hot melt extrusion) present a number of difficulties for the pharmaceutical industry limiting the commercial applications, especially in the generic industry, since they often involve high investments. Therefore, the thorough evaluation of conventional technologies for the preparation of solid dispersions would be of great value to the pharmaceutical industry. It is for that reason that the main objective of this thesis is the assessment of the fluid bed technology, a well-known and conventional technology for the pharmaceutical industry, for the preparation of solid dispersions intended for immediate drug release systems.

The fluid bed is a conventional technology, well-known by the pharmaceutical industry and available in most pharmaceutical companies of solid dosage forms. The successful preparation of ASDs with coating of pellets or sugar spheres in fluid bed is described in several research studies. However, the number of marketed products are limited. Therefore, more in-depth investigation of fluid bed technology will bring clear advantages to the pharmaceutical industry.

Furthermore, one of the hurdles encountered in the development of generic products involves engineering around formulation patents. These patents often cover key components essential for the production of a certain ASDs, including specific polymeric carriers. Consequently, generic manufacturers must engineer around these patents to develop alternative formulations. This necessity underscores the importance of exploring alternative components. Moreover, the investigation of alternative polymers fosters innovation and drives advancements in ASD technology.

1.2. OBJECTIVES

Taking these factors into account, the overarching goal of this thesis is to assess the viability of fluid bed technology in the production of ASDs intended for immediate drug release systems instead of spray dryer technology.

In particular, the goals of the present thesis can be summarized in the following points:

1. Characterize of the drug substance (LM2).
2. Characterize of the RLD.
3. Investigate the formulation of the RLD using spray drying and design of a spray drying formulation to serve as a reference for this work.
4. Compare fluid bed top-spray and spray dryer technologies for the production of ASDs, assessing manufacturability, physicochemical properties, and stability of the resulting ASDs.
5. Develop prototypes of film-coated tablets formulated with ASDs produced by fluid bed top-spray, using different polymeric carriers, and following a QbD approach.
6. Assess the *in vivo* performance of the developed drug product prototypes in comparison to the RLD.

For this work, a BCS class II drug substance was used, named as LM2, which is currently marketed into an ASD-based immediate release film-coated tablets produced by spray drying.

1.3. ORGANIZATON

This doctoral thesis has been structured in accordance with the guidelines set by the International Doctorate School at the University of Santiago de Compostela (Spain), encompassing considerations related to thesis structure, languages, as well as ethical and intellectual properties. Based on the formulated objectives, this thesis is organized in a literature review and four primary sections.

In the first section, **preformulation studies** were conducted with the aim to comprehend the formulation of the RLD and to design an ASD formulation by spray drying to mimic the RLD. This formulation was intended as a benchmark for subsequent studies using fluid bed technology. With this objective, the RLD and DS used (LM2) were characterized and the influence of the percentage of the HPMCAS, the polymeric carrier used by the RLD to produce the ASD, was evaluated on the amorphous LM2 production and its dissolution enhancement.

The second section focusses on the assess the **feasibility** of using fluid bed as an alternative to spray dryer for the production of an ASD of LM2 and HPMCAS-MG in ratio 1:5, assessing the manufacturability, the physicochemical properties, dissolution, and stability of ASDs obtained via both techniques.

The third section corresponds to the **development** of different prototypes of ASD based film-coated tablets prepared by fluid top-spray granulation technique. Several formulation variables and their influence on drug product CQAs are assessed. This sections also comprises the evaluation of HPMCP HP-55 as alternative polymer to HPMCAS-MG.

The fourth section comprises an ***in vivo* pilot BA clinical study** designed to evaluate the pharmacokinetic behaviour of different prototypes developed using top-spray fluid bed. These prototypes incorporate either HPMCAS-MG or HPMCP HP-55 polymers and are compared with the RLD formulated with HPMCAS and produced by spray drying. This study aims to assess the potential bioequivalence of three different formulations containing an ASDs of LM20 and produced by fluid bed top-spray granulation as an alternative to spray drying. Furthermore, it investigates the effect of polymer type (HPMCAS-MG vs. HPMCP HP-55) and HPMCP HP-55 percentage on *in vivo* pharmacokinetic parameters.

INTRODUCTION

2. INTRODUCTION

2.1. GENERAL CONCEPTS OF THE ASDs

In the pharmaceutical field, achieving drug solubilization is a crucial prerequisite for facilitating systemic absorption of orally administered solid dosage forms. Around 40% of marketed drugs and up to 90% of those under development are reported to exhibit poor water solubility (1), which are compounds categorized by the BCS as class II and IV. Hence, exploring methods to enhance drug solubility, dissolution, and consequently bioavailability is paramount. As shown in Figure 1, several approaches have emerged to tackle the solubility and/or dissolution challenges associated with these drugs, including physical and chemical methods.

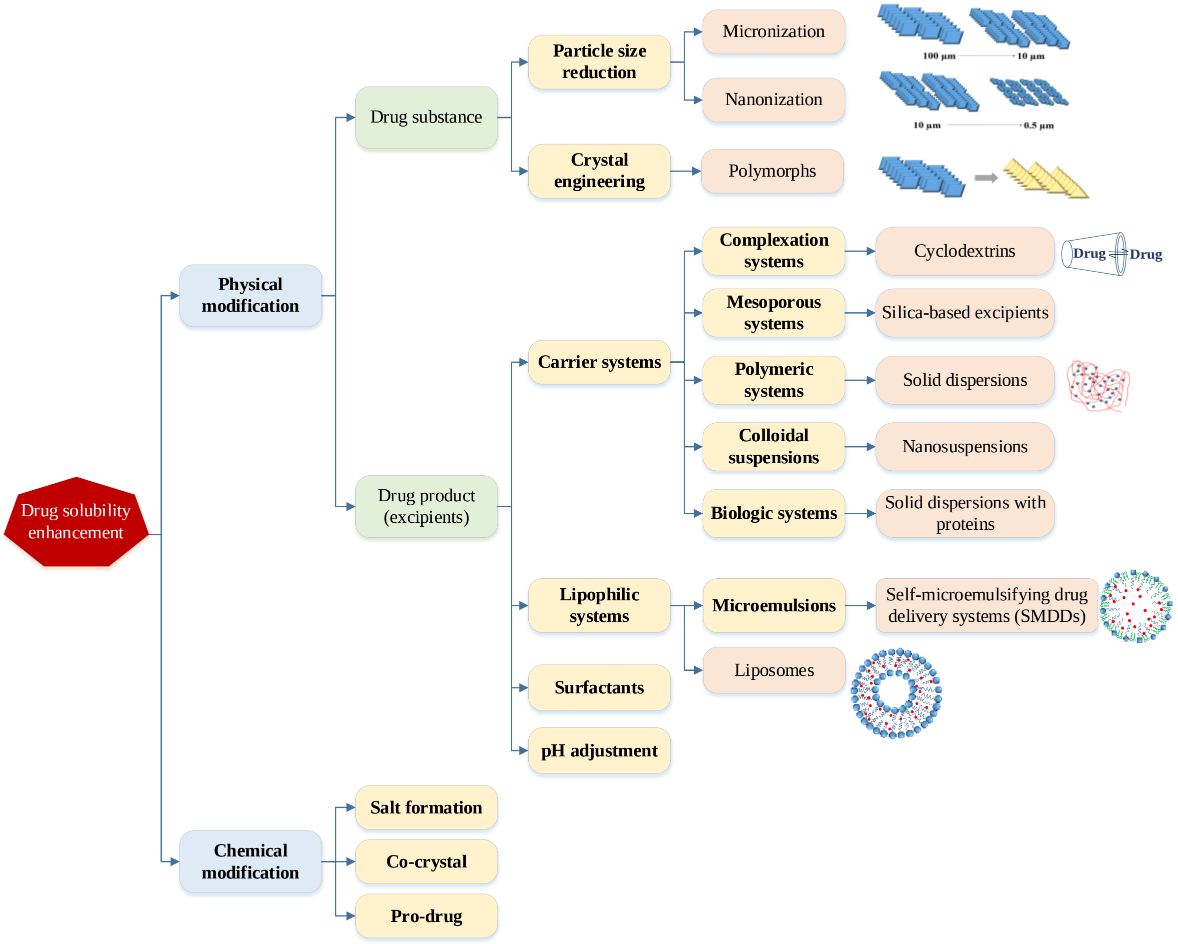
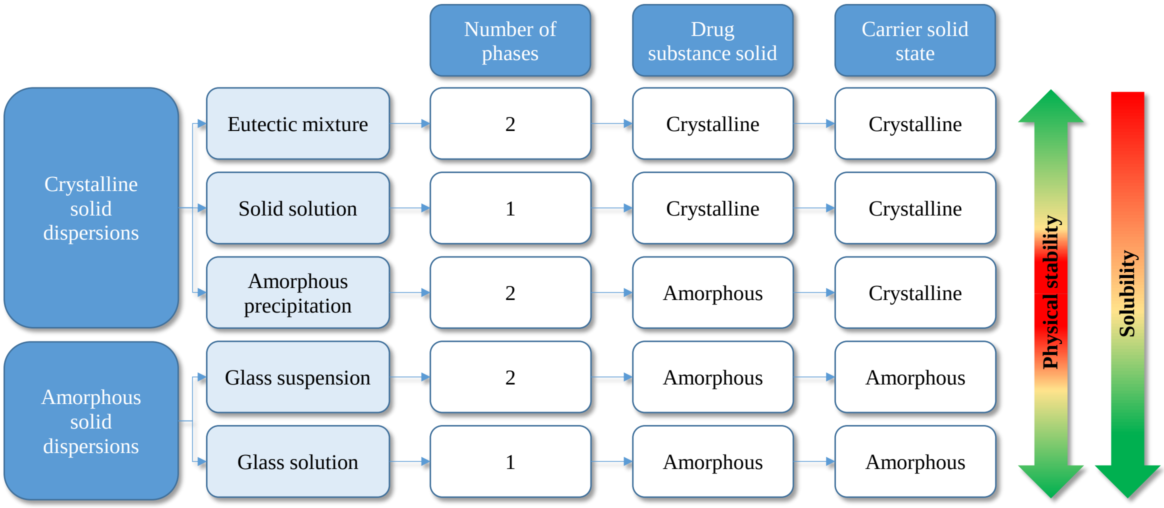


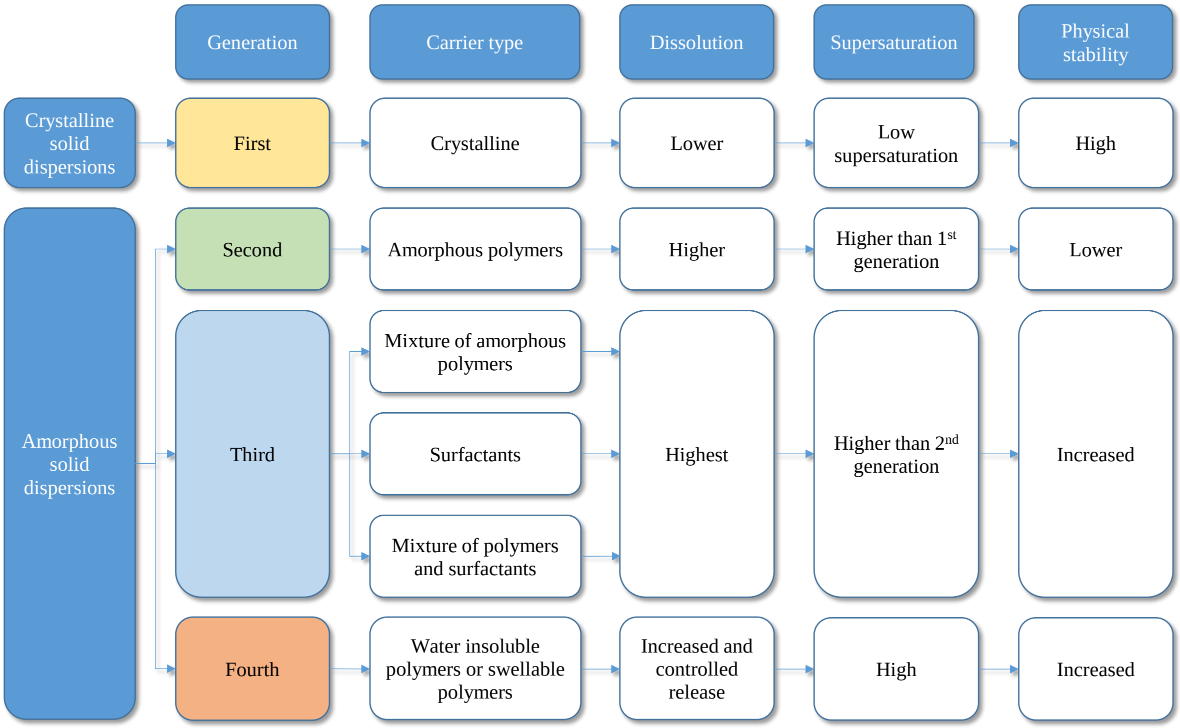
Figure 1. Approaches to improve the solubility and dissolution of poorly soluble drugs (2–7).

Among these methods, solid dispersions have gained significant attention for their effectiveness in improving drug solubility. The concept of “solid dispersion” was first introduced by Chiou and Riegelmann in 1971. They defined solid dispersions as “a dispersion of one or more active ingredients in an inert carrier in solid state, prepared by either the melting, the solvent or the melting solvent method” (8). The number of components in solid dispersions is not limited to two; however, they usually are binary systems in which the drug substance and carrier can exist in different arrangements. Based on the physical state and the molecular arrangement, solid dispersions are typically classified into five types (Figure 2). Solid dispersions are also classified in four generations based on the carrier type and complexity of the system (Figure 3).



		Number of phases	Drug substance solid	Carrier solid state
Crystalline solid dispersions	Eutectic mixture	2	Crystalline	Crystalline
	Solid solution	1	Crystalline	Crystalline
	Amorphous precipitation	2	Amorphous	Crystalline
Amorphous solid dispersions	Glass suspension	2	Amorphous	Amorphous
	Glass solution	1	Amorphous	Amorphous

Figure 2. Solid dispersions classification based on the physical state and molecular arrangement of the drug substance and carrier in the produced dispersion (6,8–11).



	Generation	Carrier type	Dissolution	Supersaturation	Physical stability
Crystalline solid dispersions	First	Crystalline	Lower	Low supersaturation	High
Amorphous solid dispersions	Second	Amorphous polymers	Higher	Higher than 1st generation	Lower
	Third	Mixture of amorphous polymers Surfactants Mixture of polymers and surfactants	Highest	Higher than 2nd generation	Increased
	Fourth	Water insoluble polymers or swellable polymers	Increased and controlled release	High	Increased

Figure 3. Solid dispersions classification based on the carrier type and complexity of the system (1,8,10–12).

Poorly water-soluble drug substance molecularly dispersed in a carrier, whether amorphous or crystalline, frequently results in enhanced dissolution rate, drug supersaturation upon exposure to water, and bioavailability. This enhancement is attributed to various factors, including enhanced wettability of the drug substance by the carrier, increased porosity and reduced particle size of the drug substance (even down to molecular level), reduced lattice energy, separation of individual drug particles by carrier particles, and subsequent prevention of drug precipitation when exposed to water (6,8,10,12,13).

Amorphous solids are characterized by the lack of long-range order symmetry operators (translational, orientational, and conformational order) found in their crystalline counterpart. This is attributed to the randomly orientation of individual molecules to one another and existence in various conformational states (14). Amorphous is typically manifested by the lack of X-ray diffraction peaks found in crystalline solid, and “halo” is observed instead (see Figure 4). Furthermore, amorphous has no distinct melting point but typically exhibits a T_g when analysed by MDSC (see Figure 5) (15).

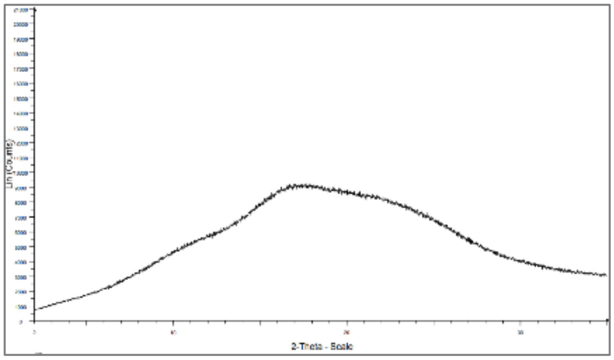


Figure 4. XRPD pattern of an amorphous solid.

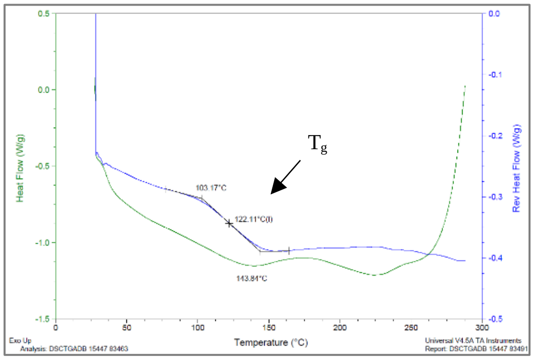


Figure 5. MDSC curve of an amorphous solid.

The crystalline form of a drug provides high physical and chemical stability, but the lattice energy barrier hinders its dissolution. In contrast, amorphous drugs present a disordered structure with higher enthalpy, entropy and free energy, leading to increased apparent solubility, dissolution rate, and oral absorption (4). Despite these advantages, pure amorphous drugs encounter stability and dissolution challenges. They tend to convert into a more stable crystalline form during storage. Moreover, amorphous drugs usually undergo rapid dissolution resulting in a supersaturated drug solution (16,17), where the drug concentration exceeds the thermodynamic equilibrium solubility (18). Supersaturation is a thermodynamically metastable state that prompts drug precipitation towards its equilibrium solubility, which is a more energetically favourable state (19). This phenomenon, known as the “spring effect” (4), can occur *in vivo* prior to drug absorption and thus compromise the bioavailability (20). To harness the amorphous solubility benefits and overcome the challenges associated, ASDs, characterized by the dispersion of an amorphous drug substance within an amorphous polymeric carrier, have been established as a prevalent pharmaceutical strategy to produce stable amorphous systems of poorly water soluble compounds with enhanced solubility and inhibiting or retarding drug precipitation from supersaturated solution (1,2,4,5). The spring effect is also observed in ASD with polymers, but the subsequent drop in drug concentration may be slower, known as “parachute effect” or even completely inhibited (8,17). The spring and parachute effects are depicted in Figure 6. Lately, more attention is being placed on the main mechanisms of the polymer to maintain supersaturation, considering both concentration and duration aspects (refer to sections 2.1.2 and 2.1.3). Maintaining concentrations dissolved above the thermodynamic solubility for a long period is associated with an increased absorption. Hence, the carrier’s capability to maintain supersaturation is a crucial consideration in carrier selection (21). Further discussion on the polymer mechanisms for ASDs stabilization is provided in section 2.1.3.

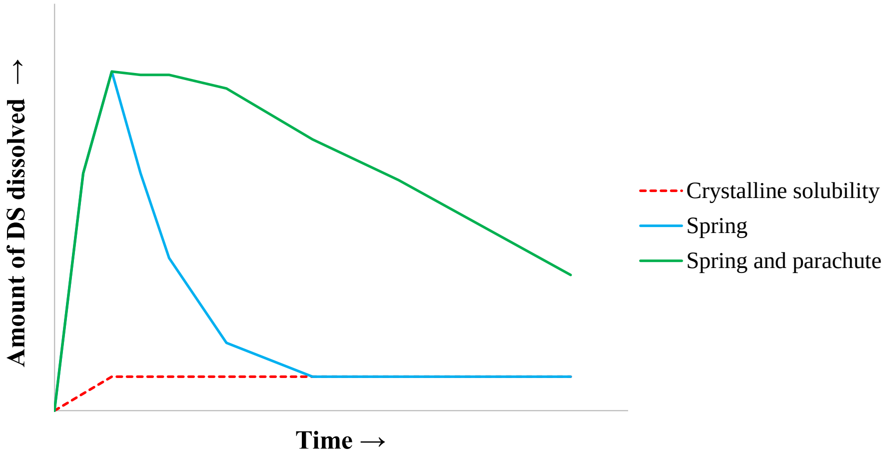


Figure 6. Spring and parachute effects of supersaturated solutions.

As shown in Figure 2, ASD can be further categorized into glass solution and glass suspension, differentiated by the molecular dispersion of the drug substance in the carrier. In the former system, both the drug and carrier are homogeneously and molecularly dispersed within a single phase, resulting in a single T_g when analysed by MDSC. In contrast, the latter system contains the drug in partially miscible state with the carrier, leading to the presence of two distinct phases (6). Consequently, MDSC analysis reveals the presence of two T_g values, one corresponding to the amorphous drug and the other to the amorphous polymer.

Glass suspensions can initially enhance drug solubility but are more susceptible to undergo drug crystallization during storage (see section 2.1.1 for more details). On the other hand, glass solution is the best system for achieving solubility enhancement with good thermal and physical stability. The term ASD is currently widely adopted to denote these “glass solution” systems and will be consistently used throughout this work.

Over the last decade, there has been a rise in the number of ASDs under development and marketed (1). Comprehensive understanding of ASDs aspects – including carrier attributes, preparation methods, characterization techniques, and the pharmaceutical mechanism governing matrix formulation and drug release – is crucial to ensure the production of an effective and marketable ASD (12).

2.1.1. Factors affecting the physical stability of ASDs

The molecular dispersion of a drug in a polymer matrix avoid or retard the crystallization of the drug by altering the thermodynamics and kinetics of the system (22). The amorphous physical instability of ASDs are related to amorphous-amorphous phase separation and/or the crystallization, both of which diminish the solubility advantage of ASDs. Amorphous-amorphous phase separation occurs when the initially homogeneous ASD of drug and polymer separates into distinct drug-rich and polymer-rich phases within the solid matrix. This separation can lead to physical instability in the ASD, as the drug-rich regions may be more prone to crystallization due to reduced polymer inhibition effect. As a result, amorphous-amorphous phase separation can compromise the intended solubility enhancement and stability of the ASD formulation (1).

The ease of drug crystallization from its amorphous state relies on the driving force for crystallization, determined by the difference in free energy between the amorphous and crystalline states, as well as molecular interactions (4). Generally, crystallization comprises two primary stages: nucleation and crystal growth. In the nucleation stage, drug molecules gather into clusters within the carrier matrix. Then, these clusters continue to grow, moving to the crystal growth stage where the molecules arrange themselves in a periodic manner, ultimately forming the crystal structure (17). Nucleation prevails near and at the T_g, whereas crystal growth dominates at higher temperatures close to melting temperature (T_m). Consequently, the maximum rate of crystallization is reached at a temperature between the T_g and T_m (14). The crystallization mechanism of a binary ASD is illustrated in Figure 7 and Table 1 summarizes several factors that can affect the solid state physical stability of ASDs.

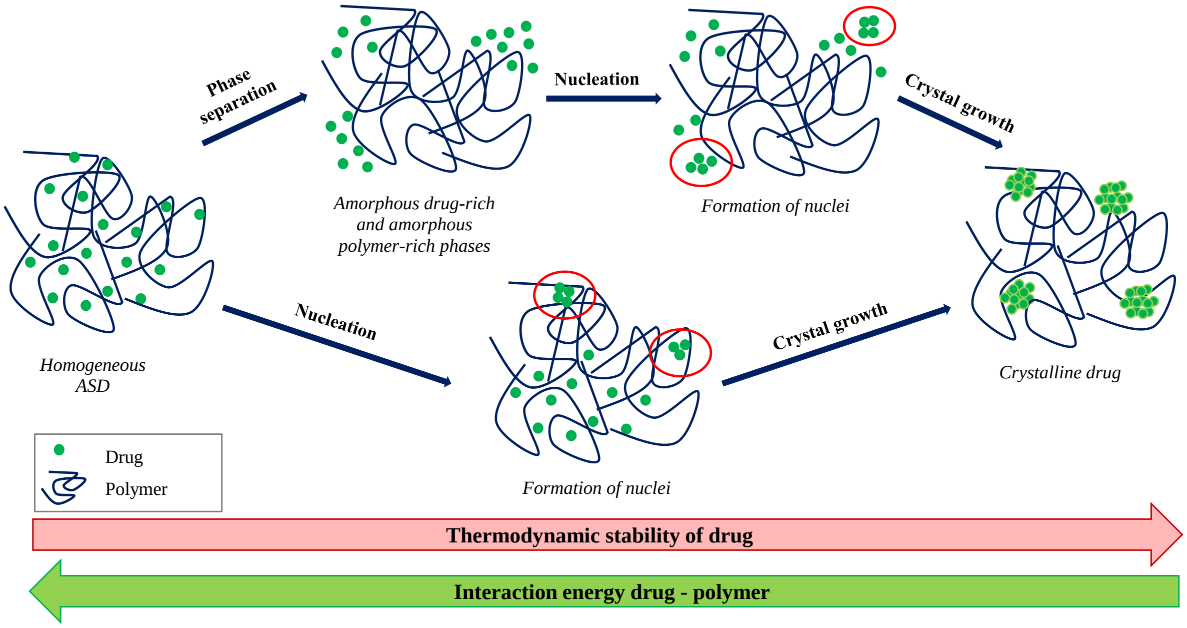


Figure 7. Crystallization mechanism of a binary ASD. Adapted from (23).

Table 1. Variables influencing the physical stability of ASDs (4).

↑ **Factor**	**Stability**	**Cause**
Structural relaxation/ molecular mobility	↓	Structural relaxation and molecular mobility is the responsible for drug recrystallization.
Glass transition temperature	↑	A higher T_g reduces the molecular mobility and improves the stability. Polymers with high T_g functions as an antiplasticizer, restricting the molecular mobility and improving stability. This is the primary reason for the 'T_g – 50ºC' rule, which lies in the fundamental observation that the molecular mobility of an amorphous solid becomes negligible 50ºC below its T_g (1).
Configurational entropy	↑	High configurational entropy favours amorphous stability. This can be explained by the lower thermodynamic driving force for crystallization.
Configurational enthalpy	↓	Higher configurational enthalpy causes higher thermodynamic driving force for crystallization.
Gibbs free energy	↓	Systems having higher Gibbs free energy are generally less stable.
Molecular-level chemical interactions	↑	Functional groups with hydrogen bond donors or acceptors can lead to energetically favourable intermolecular interactions between drug and polymer. This combined with high entropy results in a lower chemical potential of the drug in an ASD system compared to that of a pure amorphous drug. This decreased drug chemical potential reduces the thermodynamic driving force for the drug to crystallize. (1)
Temperature, humidity, and mechanical stress	↓	High temperature promotes structural relaxation and molecular mobility, responsible for drug recrystallization. Moisture may plasticize the material by lowering the T_g, decreasing the crystallization temperature and so increasing the crystallization rate. Additionally, absorbed water can also potentially disrupt the drug-polymer interactions by competing with hydrophilic polymers for hydrogen bond formation (1). Mechanical stress can also cause a higher crystallization tendency.
Preparation method and conditions	↑↓	Different preparation methods (such as fusion or solvent evaporation method, freeze drying, supercritical fluid technology) or preparation conditions (like cooling rate, processing temperature, and time) result in diverse thermal histories and mechanical stresses, influencing the degree of drug-polymer mixing and drug mobility within the dispersion. Consequently, the ASD may exhibit different solid state stability.

Friesen et al. (24) found that the T_m/T_g ratio (ºK/ºK) of the drug substance serves as an indication of the compound's likelihood to crystallize. Compounds with higher T_m values exhibit a strong tendency to crystallize owing to the large thermodynamic driving forces. Compounds with low T_g values also exhibit a tendency to crystallize as they encounter a reduced kinetic barrier for molecular diffusion. Consequently, the T_m/T_g ratio amalgamates both thermodynamic (T_m) and kinetic (T_g) parameter. They divide the compounds in four groups considering the T_m/T_g ratio and log *P* value (a standard measure of the lipophilicity of a compound). As illustrated in Figure 8, they divide the compounds in four groups based on the T_m/T_g ratio and log *P*:

- Group 1: ASD drug loading may be high due to the high T_g of the drug.
- Group 2: ASD drug loading within the typical range.
- Group 3: ASD drug loading may be limited by its propensity to crystallize.
- Group 4: ASD drug loading may be limited by its low solubility.

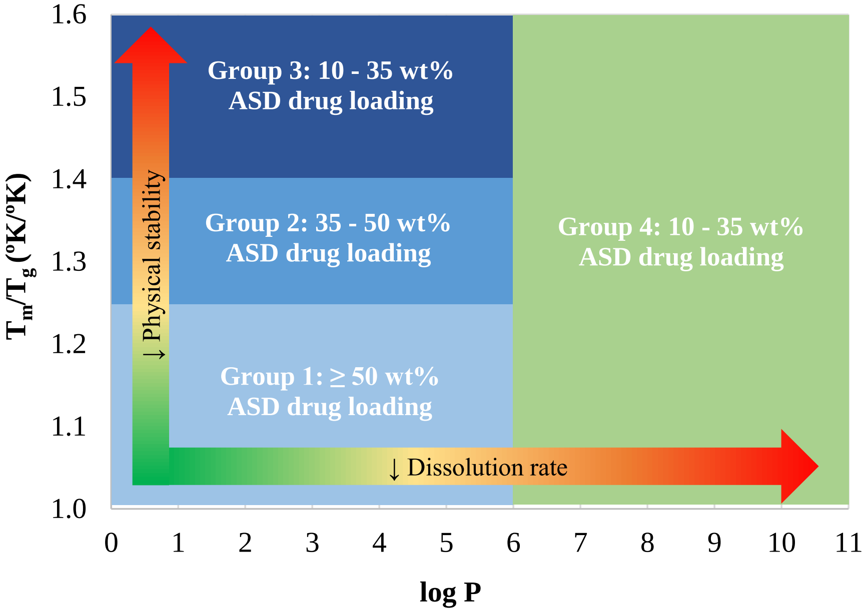


Figure 8. Groups of compounds based on their T_m/T_g ratio and log *P* and formulated as ASDs. Adapted from (24).

2.1.2. Precipitation inhibition mechanisms of polymers in ASDs

One crucial aspect in the development of ASDs is the precipitation inhibition mechanism, which plays a pivotal role in maintaining drug stability in solution, thereby enhancing drug bioavailability (25). Drug precipitation (or crystallization) consist of two stages: nucleation and crystal growth. The inhibition of this process depends on various factors, including the properties of the inhibitor, the drug itself, and the surrounding medium (17). The optimal type and concentration of drug precipitation inhibitor varies depending on the formulation.

When polymers are used as inhibitors of drug precipitation, they may disrupt crystal nucleation and/or growth by interacting with drug groups or modifying the characteristics of the medium. The following precipitation inhibition mechanisms are described in literature:

- *Polymer and drug molecule interactions:*
  Commonly present more than one type of interaction, such as hydrogen bonding, hydrophobic/hydrophilic, aromatic, dipolar intermolecular forces (26). Several studies have showcased the significance of drug-polymer miscibility and interactions in precipitation inhibition of various drugs (27–29).
- *Polymer molecular weight and steric hindrance:*
  Several studies have described that polymers with higher molecular weight are more efficient in maintaining the supersaturated state than lower molecular weight polymers. This is often attributed to the greater number of functional groups available on the polymer chain, which enhance interactions with crystal surfaces, and/or the increase in solution viscosity (17). For instance, Knopp et al. (30) demonstrated that the *in vitro* and *in vivo* behaviour of celecoxib:PVP ASD was notably influenced by the molecular weight of the polymer. Nonetheless, it is noteworthy that the polymer with the highest molecular weight may not always exert the strongest inhibitory effect, as steric hindrance can also be a contributing factor (17).
- *Ternary ASDs:*
  Combination of polymers or polymer-surfactant ternary ASDs have been explored and revealed their potential in inhibiting drug precipitation both *in vitro* and *in vivo* (31,32).

Overall, the field of precipitation inhibition mechanisms of ASDs is constantly evolving, with a focus on enhancing drug stability, solubility, and bioavailability through the strategic incorporation of polymeric precipitation inhibitors and understanding the drug-polymer interactions.

2.1.3. Critical polymeric carriers attributes on dissolution and stability of ASDs

The polymer carriers play a crucial role in enhancing the dissolution and physical stability of ASDs, the main challenges associated to the development of these systems. As already mentioned, these polymeric excipients possess the capability to inhibit the crystallization of the amorphous drug and to sustain the drug in a supersaturated state within the gastrointestinal (GI) tract after dissolution in GI fluids. This attribute makes them more desirable than other solubilizing strategies (26). The critical polymer attributes and their influence on ASD dissolution and physical stability are summarized in Figure 9.

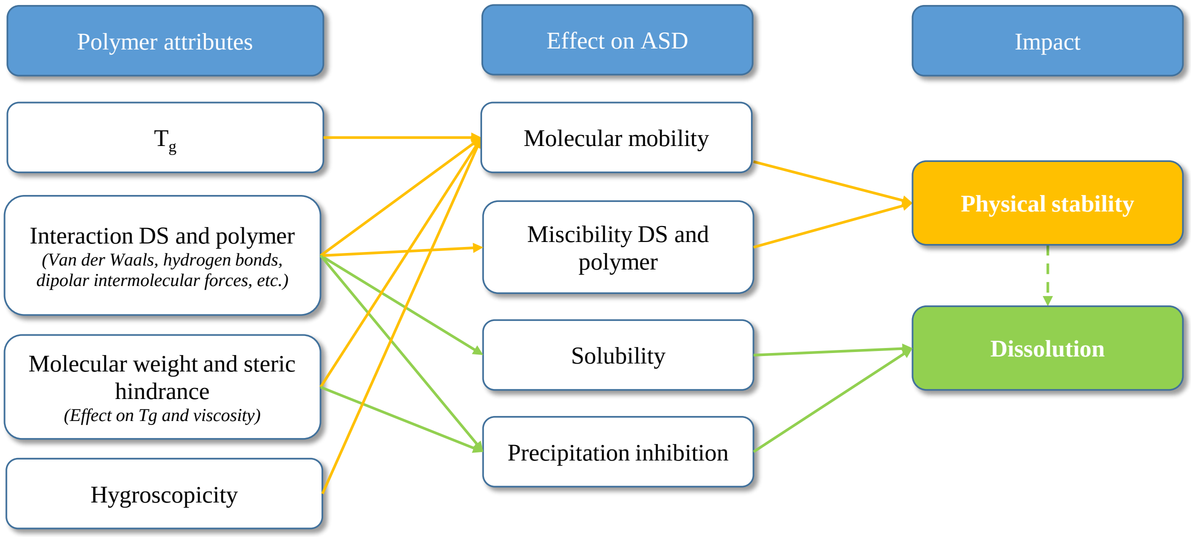


Figure 9. Influence of polymer attributes on ASD physical stability and dissolution (1,14,33,34).

2.2. INDUSTRIALIZATION OF ASDs: MOST FREQUENTLY USED TECHNOLOGIES

Four primary methods are described for preparing solid dispersions: solvent-based, fusion-based, fusion-solvent-based, and co-grinding methods. A brief summary of these methods is given in Table 2.

Table 2. Primary methods for solid dispersions preparation (10).

Method	Description
Solvent-based method	The drug and the carrier are solubilized in a common solvent, which is then removed yielding a solid powder.
Fusion-based method	The drug and the carrier are heated together to the lowest temperature above the melting points of both components, or the drug is incorporated into the melted carrier. The mixture is kept under heating until a homogeneous solution is obtained, after which it is swiftly cooled.
Fusion-solvent based method	It combines elements from both the fusion and the solvent methods. The carrier is heated above its melting point and the drug is dissolved in an appropriate solvent. The drug solution is added into the melted carrier under stirring, removing the solvent. Then, cooling and solidification of the mixture is carried out.
Co-grinding method	Mechanical energy is applied to physically break down coarse particles into finer ones. Once the particle size reduction reaches a critical threshold – beyond which further comminution becomes challenging even with prolonged grinding – the continued application of mechanical energy to the drug can induce partial or complete amorphization. The co-grinding of drugs with carriers is beneficial to reduce drug particles agglomeration and recrystallization.

Among these methods, solvent-based and fusion-based are the most prevalent, with manufacturing processes available for industrial application (10,35). The different processing technologies available are shown in Table 3.

Table 3. Processing methods in the manufacture of ASDs (1,11,14,35–37).

Solvent-based methods	
Spray drying	Rapid removal of the solvent in a controlled environment (temperature and pressure) that is accelerated by generating high surface area.
Fluid bed granulation/ layering/ film coating	Removal of solvent in various conventional pharmaceutical equipment.
Co-precipitation	The drug and carrier(s) are dissolved in a solvent and stirred until a homogeneous mixture is obtained. Then, water is added dropwise to induce precipitation. The precipitate is filtered and dried. Examples of solvent-controlled precipitation technologies are microprecipitated bulk powder (MBP), evaporative precipitation into aqueous solution (EPAS), Nanomorph, flash precipitation, etc.
Supercritical fluids	Involves utilizing supercritical fluids as solvents or carriers to create homogeneous mixtures of drug and polymer. Supercritical fluids are gases that under certain pressure and temperature present simultaneously gaseous and liquid state properties. Liquid properties are advantageous for solubilisation, and gaseous features favour drug and carrier(s) diffusion and solvent removal.
Cryogenic processing	E.g., spray freeze drying and thin film freezing. In freeze drying/ lyophilisation, a solution/suspension of drug and carrier(s) is frozen followed by a reduction of the surrounding pressure to allow water and solvents in the sample to undergo solid-gas transition (sublimation). The manufacture of solid dispersion by freeze-drying is limited to drugs with some water solubility, inorganic solvents miscible water, or very limited number of organic solvents.
Electrospinning	Drawing nanofibers from solution or molten material under high electrostatic voltage.
Electrospraying	Electrical forces atomize the feed solution of drug and carrier(s) into small droplets in the range of few nanometres to micrometres.
Rotating jet spinning	Combination of centrifugation and pinning to produce nanofibers.
Fusion-based methods	
Hot-melt extrusion (HME)	The drug and carrier(s) melt under high temperature and is further forced through a die with the help of one or two conveyor screws in a barrel, resulting in a product of uniform shape.
Melt granulation	A molten mass of drug and carrier(s) id added to the powdered excipients of the formulation as a granulation liquid.
KinetiSol®	Rapid melting of drug and carrier(s) blend exerting high shear and friction force without external heat input.
Fluid bed hot-melt coating	Molten drug and carrier(s) are sprayed onto powdered excipients in a fluid bed coater.
Three-dimensional (3D) printing	Relatively innovative technology that can transform 3D computer models into physical objects by additive manufacturing.

From industrial standpoint, spray drying and hot-melt extrusion are the two technologies with more commercial success (4,14). Additionally, co-precipitation, freeze-drying, and fluid bed technologies have also proven to be effective for preparing solid dispersions in commercial production (5,35,38). In recent times, progress in supercritical fluid and cryogenic freezing technologies has demonstrated potential in producing finely powders of ASDs (39).

The selection of the preparation method is crucial, as it greatly affects the physicochemical properties such as amorphization, enthalpic relaxation, and recrystallization of the resulting solid dispersion (23). The choice of the preparation method encompasses several key factors (39):

- Solubility in organic solvents of both the drug substance and the carrier.
- Thermal stability of both the compound and the carrier.
- Extent of improvement in bioavailability.
- Selection of the stabilizing polymer and other processing aids.
- Formulation complexity and ability to achieve highest drug loading.
- Availability of equipment scaling, spanning from laboratory to commercial scale.
- Robustness of the product (processability, amorphous stability, and dissolution performance)

Figure 10 provides a decision tree for selecting the optimal preparation method at the industrial scale.

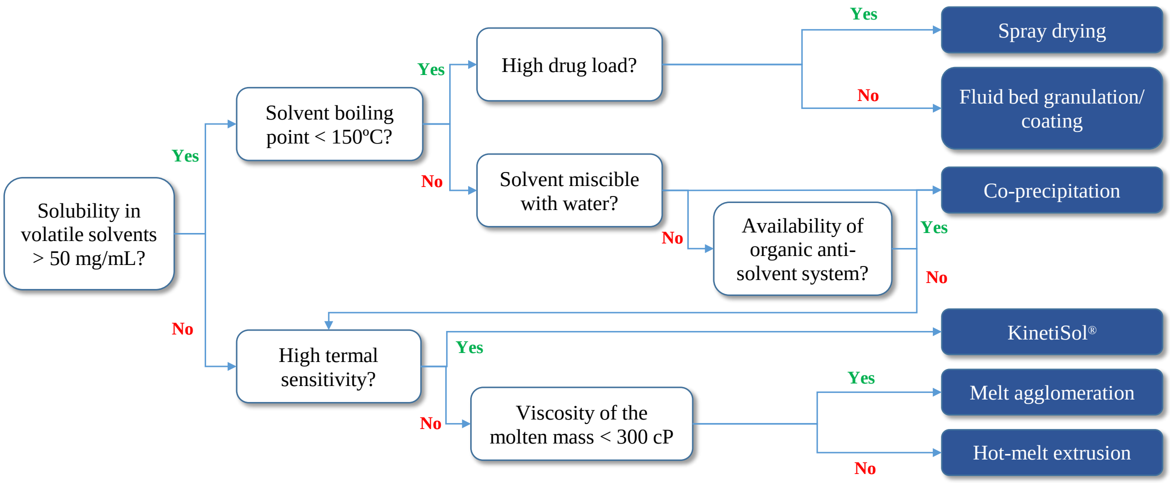


Figure 10. Decision tree of the preparation method selection with the commonly used manufacturing processes for preparing ASDs. Adapted from (1).

2.3. COMMERCIAL PRODUCTS CONTAINING SOLID DISPERSIONS

There has been a significant increase in the number of approved solid dispersion based formulations. Table 4 provides a summary of ASD-based products currently available in the market and Figure 11 illustrates the upward trend in ASD-based products approved over the last twenty years.

Table 4. List of marketed ASD-based products (1,2,4,5,7,11,22,35,40–43).

Product name	Drug substance	Carrier	Solid dispersion preparation method	Dosage form	Year of FDA approval
Cesamet®	Nabilone	PVP	Solvent evaporation	Capsule	1985
Nivadil®	Nilvadipine	HPMC	HME	Tablet	1989
Sporanox®	Itraconazole	HPMC	Fluid bed coating on sugar beads	Capsule	1992
Prograf®	Tacrolimus	HPMC	Kneading, drying	Capsule	1994
Rezulin®	Troglitazone	PVP	HME	Tablet	1997
Crestor®	Rosuvastatin	HPMC	Spray drying	Tablet	2002
Kaletra®	Lopinavir + Ritonavir	PVP/VA	HME	Tablet	2005
Eucreas®	Vildagliptin + Metformin HCl	HPC	HME	Tablet	2007
Intelence®	Etravirine	HPMC	Spray drying	Tablet	2008
Modigraf®	Tacrolimus	HPMC	Spray drying	Granules for oral suspension	2009
Samsca®	Tolvaptan	HPC	Spray drying	Tablet	2009
Zortress®	Everolimus	HPMC	Spray drying	Tablet	2010
Norvir®	Ritonavir	PVP/VA	HME	Tablet	2010
Onmel®	Itraconazole	HPMC	HME	Tablet	2010
Incivek®	Telaprevir	HPMCAS	Spray drying	Tablet	2011
Zelboraf®	Vemurafenib	HPMCAS	Co-precipitation	Tablet	2011
Kalydeco®	Ivacaftor	HPMCAS/ SLS	Spray drying	Tablet	2012
Lozanoc®	Itraconazole	HPMCP	Spray drying	Capsule	2012
Astagraf XL®	Tacrolimus	HPMC/ EC	Solvent method	Capsule	2013
Noxafil®	Posaconazole	HPMCAS	HME	Tablet	2013
Belsomra®	Suvorexant	PVP/VA	HME	Tablet	2014
Harvoni®	Ledipasvir + Sofosbuvir	PVP/VA	Spray drying (Ledipasvir)	Tablet	2014
Viekira XR®	Dasabuvir + Ombitasvir + Paritaprevir + Ritonavir	PVP/VA/ HPMC	HME	Tablet	2014

Product name	Drug substance	Carrier	Solid dispersion preparation method	Dosage form	Year of FDA approval
Orkambi®	Lumacaftor/ Ivacaftor	HPMCAS/ SLS	Spray drying (Ivacaftor)	Tablet Granules	2015 2018
Epclusa®	Sofosbuvir + Velpatasvir	PVP/VA	Spray drying	Tablet	2016
Venclexta®	Venetoclax	PVP/VA	HME	Tablet	2016
Zepatier®	Elbasvir/ Grazoprevir	TPGS/ PVP/VA/ HPMC	Spray drying	Tablet	2016
Mavyret®	Glecaprevir + Pibrentasvir	PVP/VA/ TGPS	HME	Tablet	2017
Vosvei®	Sofosbuvir + Velpatasvir + Voxilaprevir	PVP/VA	HME	Tablet	2017
Delstrigo®	Doravirine + Lamivudine + Tenofovir disoproxil fumarate	HPMCAS	Spray drying	Tablet	2018
Erleada®	Apalutamide	HPMCAS	Spray drying	Tablet	2018
Symdeko®	Tezacaftor + Ivacaftor	HPMCAS	Spray drying	Tablet	2018
Braftovi®	Encorafenib	PVP/VA	HME	Capsule	2018
Trikafta™	Elexacaftor + Ivacaftor + Tezacaftor	HPMCAS	Spray drying	Tablet	2019
Tukysa™	Tucatinib	PVP/VA	Spray drying	Tablet	2020
Xtandi®	Enzalutamide	HPMCAS	Spray drying	Tablet	2020

PVP – Poly(vinylpyrrolidone); HPMC – Hydroxypropyl methylcellulose; PVP/VA – Poly(1-vinylpyrrolidone-co-vinyl acetate); HPC – Hydroxypropylcellulose; HPMCAS – Hydroxypropyl methylcellulose acetate succinate; SLS – Sodium lauryl sulfate; HPMCP – Hydroxypropyl methylcellulose phthalate; EC – Ethyl cellulose; TPGS - tocopheryl polyethylene glycol succinate.

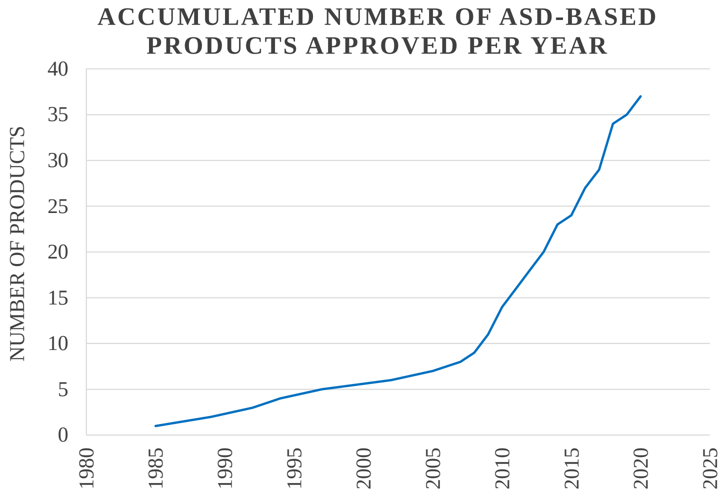


Figure 11. Accumulated number of ASD-based products approved by the FDA per year.

It is also worth noting that, as illustrated in Figure 12, the predominant technologies used in marketed products are spray drying and hot-melt extrusion. Additionally, the primary polymers employed are PVP/VA, HPMCAS, and HPMC.

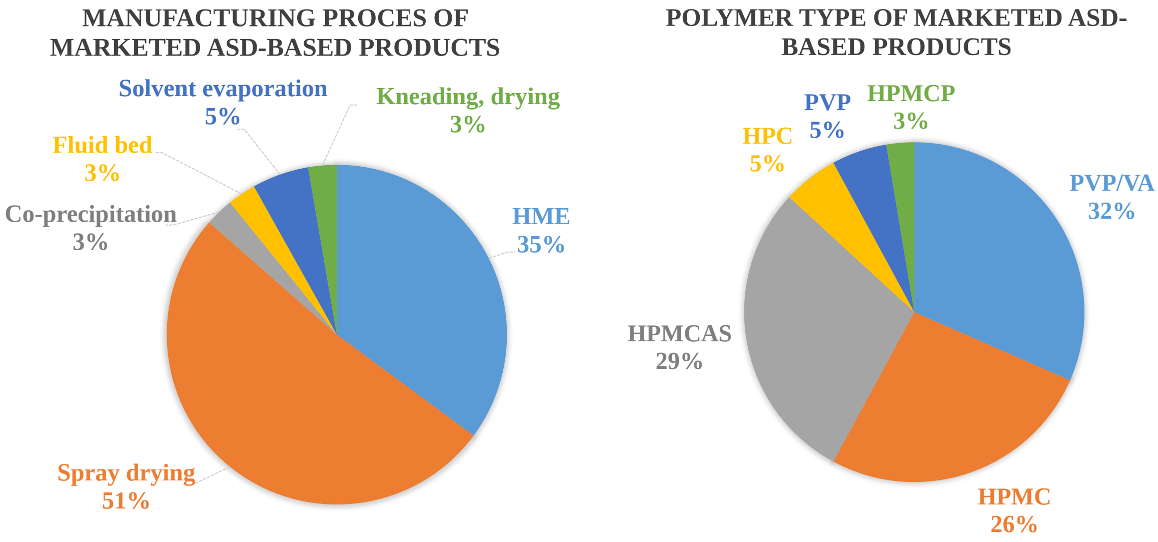


Figure 12. Manufacturing process and polymer type of marketed ASD-based products.

2.4. SPRAY DRYER TECHNOLOGY FOR ASDs PREPARATION

Spray drying is widely used in pharmaceutical industry to prepare ASD due to the possibility of continuous manufacturing, the ease of scalability, and the cost-effectiveness at large scales (12). Furthermore, spray drying can be conducted across all scales ranging from laboratory to commercial (39).

The spray drying process is used to convert a solution or suspension of a drug and carrier(s) into a dry powder. It involves the rapid evaporation (within milliseconds) of solvent from an atomized solution of drug and carrier(s) by mixing the spray with a drying hot gas. As depicted in Figure 13, spray drying process for the preparation of ASD constitutes four main steps (44):

1. **Feed solution preparation**:
   The drug substance and carrier(s) are dissolved in an appropriate volatile solvent and stirred until a solution or homogeneous suspension is obtained.
2. **Atomization:**
   The feed solution/suspension is pumped and atomized into the drying chamber through a spray-nozzle. The selection of the feed pump depends on both the feed solution viscosity and the type of atomizer system used (21). Different kind of energy can be used to disperse the liquid into fine particles. Table 5 gives a brief summary of the most commonly used bi-fluid nozzles for spray drying of ASD. The selection of nozzle type depends on the properties and quantity of feed solution, as well as the desired characteristics of the final dried product.
3. **Drying:**
   The droplets are rapidly dried within seconds with the drying hot fluid circulating inside the drying chamber. The feed solution/suspension is sprayed in the same direction as the flow of the drying fluid, known as co-current flow. While air can be used as the drying fluid, nitrogen is often used for ASD applications as organic solvents are typically used.
4. **Isolation of solid particles:**
   The dried material is isolated from the drying gas using a cyclone and is collected in a collection vessel.

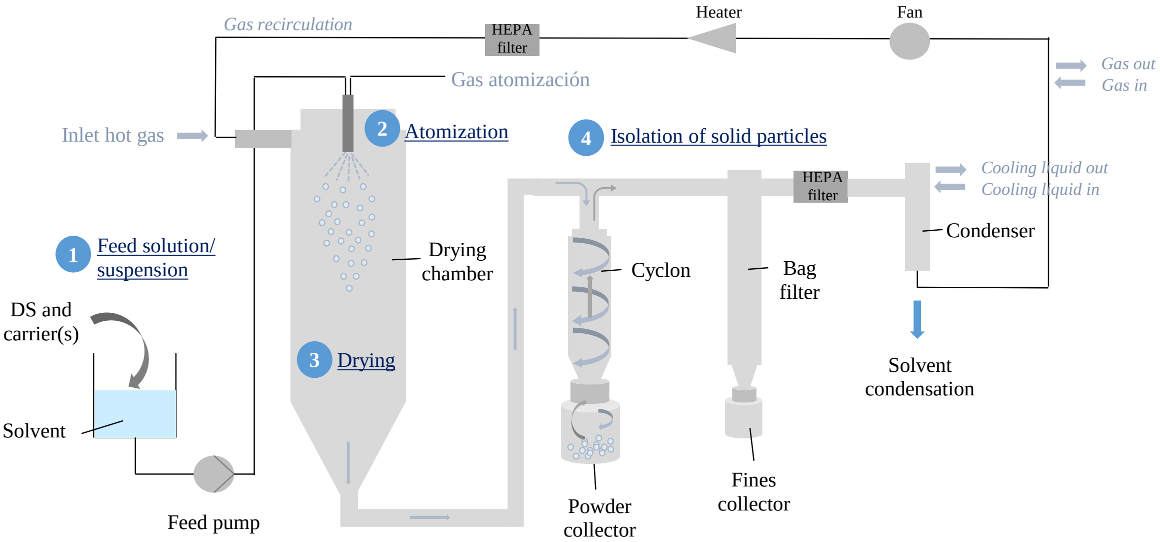
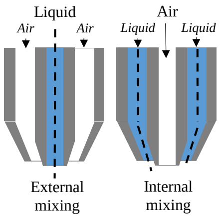
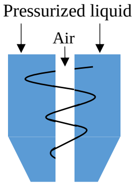
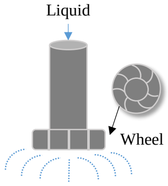
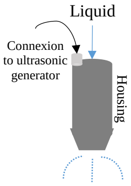


Figure 13. Schematic representation of a closed-loop spray dryer and main process steps.

Table 5. Spray-nozzle used for spray drying (1,39).

Nozzle	Energy type	Energy source	Solution viscosity	Droplet range size	Main application
Two-fluid 	Kinetic	Gas	Low to high	3 – 200 µm *(wide distribution)*	Laboratory and pilot scale. Limited use in industrial scale due to high gas consumption
Pressure 	Pressure	Feed liquid pressure	Low	20 – 500 µm *(narrow distribution)*	Industrial
Rotary 	Centrifugal	Disk or wheel rotating at high speed (10000 – 50000 rpm)	Slurries or high viscous solutions/ suspensions	20 – 200 µm	Industrial
Ultrasonic 	Acoustic	High-frequency sound waves	Low to high	20 – 100 µm *(narrow distribution)*	Laboratory and pilot scale, due to the low throughput

Spray drying offers great control of the powder characteristics (4), as they can be fine-tuned and well controlled by spray drying process parameters. Figure 14 shows the main manufacturing variables affecting the characteristics of the obtained powder.

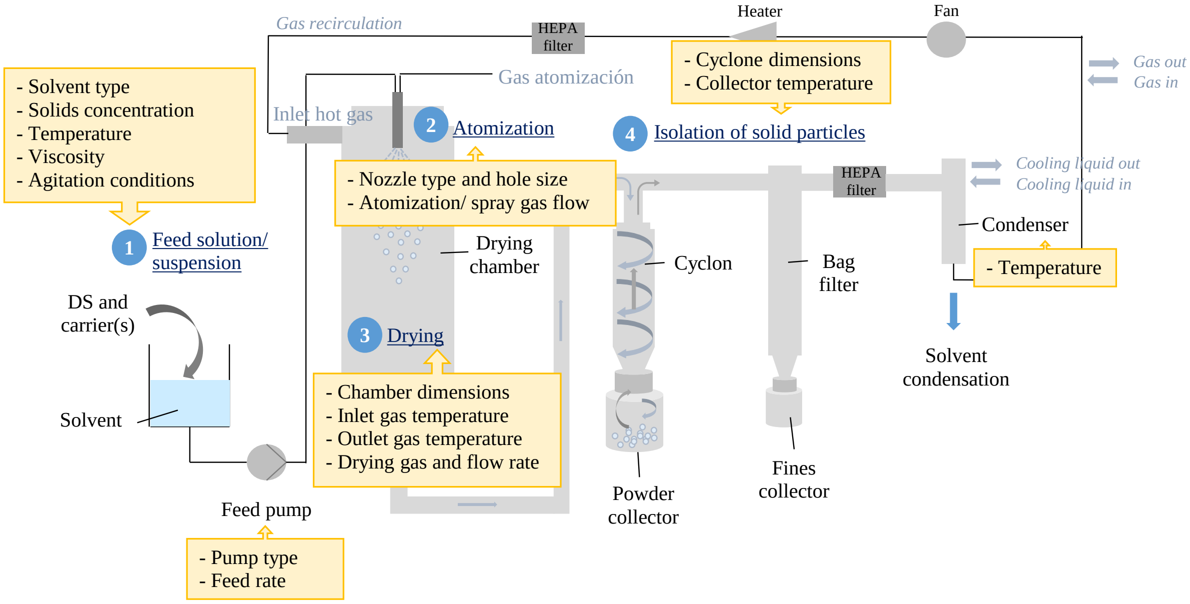


Figure 14. Spray drying process parameters.

The influence of the main process parameters on the particle size and residual solvents of the obtained ASD, and on the process yield is discussed in Table 6.

Table 6. Influence of spray drying process parameters on particle size, residual solvents, and process yield (6,21,44,45).

Process parameter ↑	ASD particle size	ASD residual solvents	Process yield
Organic solvent instead of water	↓ Due to the lower surface tension	↑ Due to the use of organic solvents	↑ When low boiling point solvents are used
Solids concentration/ Solution viscosity	↑ More solids in a drop	↓ Decrease of partial pressure of solvent in the gas	↑↓ Produce bigger particles, which are easier to isolate. However, high viscosity can cause sticking of the droplets on the drying chamber walls
Feed rate	↑ Increase of droplet size as more liquid has to be dispersed	↑ More liquid to evaporate per second	↑↓ Optimal feed rate should be sought

Process parameter ⇧	**ASD particle size**	**ASD residual solvents**	**Process yield**
Atomization/ spray gas flow	⇩ Smaller droplets produced	⇓ Smaller droplets, easier to dry	↑↓ Optimal spray gas flow should be sought
Chamber dimensions	⇧ Larger chambers can produce larger particles due to the higher residence time	▬	⇑ Process yield is generally higher at larger scale
Inlet gas temperature	▬	⇓ Increase heat transfer into the drying droplet	↑ Generally leads to dryer product, which is less sticky
Difference inlet and outlet gas temperature	⇩ Due to the slower feed rate	⇩ Smaller droplets, easier to dry	↑↓ Optimal parameters should be sought
Drying gas flow rate	▬	⇓ More drying energy	⇑ Higher degree of separation in the cyclone
Condenser temperature	↑ Recycled drying gas can contain significant solvent vapour, resulting in slower droplet drying rate	⇑ Poor condensation of solvents, leading to less vapour uptake capability in the gas stream	↓ Moist particles can adhere to the spray dryer walls

⇧ High influence; ⇑ Moderate influence; ↑ Minor influence; ▬ No direct influence

The primary function of the solvent is to dissolve the drug and carrier(s). Hence, choosing an appropriate solvent is crucial, as it can influence the solute precipitation, as well as the physical and chemical characteristics, the formation process of the ASD, and the drug release profile (45). Solution temperature and agitation conditions are also important to ensure the dissolution of both the drug and carrier(s) and to avoid precipitation throughout the overall manufacturing process. Some of the major criteria in selecting the solvent type are the good solubility of drug and carrier(s), good chemical compatibility with feed components, low boiling point, low viscosity, and low toxicity according to ICH classification, favouring Class III over Class II solvents, and avoiding Class I solvents (45). Dielectric constant of solvent is also important since the solubility of the solute in the solvent is dependent on it, which is defined as the energy required to separate two opposite charged bodies is inversely proportional to the dielectric constant of the solvent (6). The most commonly used solvents for spray drying technology are listed in Table 7.

Table 7. Commonly used solvents for spray drying (1,6).

Solvent	Boiling point (°C)	Dielectric constant	Viscosity	Solubility in water	ICH class and limit (ppm)
Ethanol (EtOH)	78.5	24.6	1.04	Miscible	III – 5000
Methanol (MeOH)	64.6	32.6	0.543	Miscible	II – 3000
Isopropanol (IPA)	82.6	18.2	1.96	Miscible	III – 5000
Acetone	56.2	20.7	0.295	Miscible	III – 5000
Ethyl acetate	77	6	0.428	8.7	III – 5000
Butanone	79.6	18.51	0.4	29	III – 5000
DCM	39.8	9.08	0.413	1.32	II – 600
Chloroform	61.7	4.81	0.536	0.795	II – 60
Tetrahydrofuran	66	7.52	0.48	Miscible	II – 720
Butyl acetate	126.1	5.07	0.685	0.68	III – 5000
Dimethyl sulfoxide (DMSO)	189	47	1.987	25.3	III – 5000
Dimethyl formamide (DMF)	153	36.7	0.97	Miscible	II – 880
Water	100	78.54	1	-	-

2.5. FLUID BED TECHNOLOGY FOR ASDs PREPARATION

While spray drying remains the foremost well-understood and established process for ASD production, alternative methods are also commonly employed. One such alternative is fluid bed technology, which is well known in the pharmaceutical industry as a one-step method for different applications such as granulation/agglomeration (fluid bed granulator), layering/coating of particles (fluid bed coater), and drying (fluid bed dryer) (1). Although fluid bed technology is recognized as a method for preparing ASD, only a limited number of ASD-based products are marketed using this approach (see Figure 12 in section 2.3).

Fluid bed technology operates on the principle of air suspension. Hot air is introduced at high pressure onto the bed of solid particles, suspending the particles in an air stream and creating a fluidized state (45). The method for the preparation of ASD in fluid bed involves spraying a solution containing the drug and carrier(s) onto the surface of inert excipients or beads, referred as substrate. The solvent removal and deposition of ASD onto the substrate occur simultaneously. This process yields either ASD-granules suitable for tableting or ASD-layered pellets for encapsulation (46).

Fluid bed granulation or coating for ASD preparation consists of four main steps:

1. **Feed solution preparation:**
   The drug substance and carrier(s) are dissolved in an appropriate volatile solvent and stirred until a solution or suspension is obtained.

2. **Blending and warm-up:**
   The substrate is fluidized by hot inlet air for blending and warm-up.
3. **Spraying:**
   Feed solution/suspension is pumped and atomized through a spray-nozzle onto the substrate. In most fluid bed equipment, two-fluid nozzle is commonly used (see Table 5 in section 2.4) (47). Nevertheless, other nozzle types such as pressure, rotating, and airless spray are also described as spray systems for fluid bed granulation (48).
4. **Drying:**
   Once the feed solution is completely sprayed, drying begins for a sufficient time to reduce the residual solvents content below the acceptable limits.

Three fluid bed technologies are well-established in the pharmaceutical industry, including top-spray, bottom-spray (Wurster), and tangential-spray (rotary) (49). A schematic representation of these three technologies is given in Figure 15. Fluid bed top-spray technology is frequently employed for granulation, typically resulting in highly porous particles with enhanced flowability and compressibility, ideal for tableting. Bottom-spray configuration is more commonly used for layering of drug substance and coating to modify drug release, resulting in pellets with excellent film formation suitable for encapsulation. Tangential-spray configuration is frequently used for both granulation and coating. The resulting granules tend to be larger, denser, less friable, less porous, and more spherical compared to those produced via top-spraying. Due to the surface morphology of the granules, they are suitable for further coating in the same equipment (50).

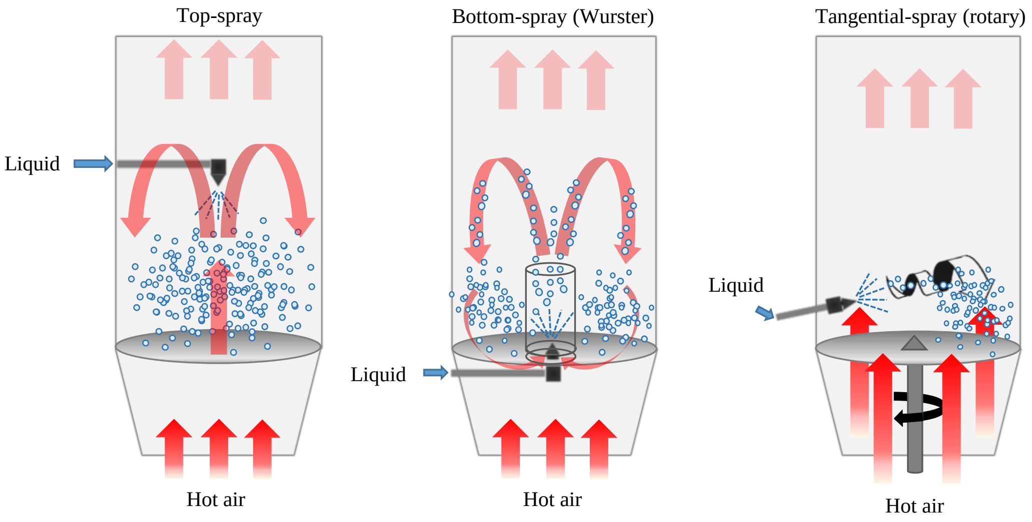


Figure 15. Schematic representation of fluid bed configurations. Adapted from (49).

In addition to the aforementioned standard and well-stablished technologies, more recent advanced and innovative fluid bed technologies are available which could serve for the production of either ASD-granules or ASD-layered pellets without requiring any starter substrate. These technologies include CPS (complex perfect spheres), MicroPx, and ProCell, being the latter two continuous manufacturing processes (50). All these technologies operate on the principals of spray granulation, wherein granules or pellets are formed from a solution without requiring a substrate. The process itself generates the particles necessary to build up the granulate or pellet. While continuous fluid bed equipment find applications in the chemical and food sectors, they utilization in the pharmaceutical industry is notably infrequent (49). Studies carried out by Tanaka et al. (51), confirmed the feasibility of a continuous-spray granulator for the production of ASD.

Among the commercially available ASD-based products listed in Table 4, only Sporanox® (Itraconazole oral capsules) explicitly states its preparation using fluid bed technology with bottom-spray (Wurster) configuration. This involves layering a solution of drug and HPMC, dissolved in an organic solvent mixture of dichloromethane and ethanol, onto sugar spheres (52). Then, a seal-coating layer of polyethylene glycol (PEG) is performed to prevent sticking of the beads (38).

Furthermore, various publications describe the preparation of ASD using either fluid bed granulation (53–56) or fluid bed coating (57–67) techniques. Table 8 provides a summary of these studies.

Table 8. Published studies on ASD prepared by fluid bed technology.

Drug substance	Polymer	Solvent	Substrate	Dosage form	Findings	Reference
Fluid bed top-spray						
Celecoxib	Cremophor RH40	Water	MCC + Lactose + Crospovidone	Tablets	Enhanced dissolution compared with Celecoxib drug substance and commercial product Celebrex® with crystalline DS	(53)
Raloxifene HCl	HPC	EtOH + acetone	Lactose + Crospovidone	Tablets	Enhanced stability of amorphous Raloxifene HCl with similar dissolution profile to the commercial product Evista® with crystalline drug substance	(54)
Curcumin	Cremophor RH40 *(solubilizer)* + Ryoto sugar ester L-1695 *(absorption enhancer)* + PVP *(polymeric carrier)*	Water at 60ºC	MCC + Crospovidone	Granules	Enhanced solubility and intestinal absorption of Curcumin ASD, reflected by the high blood concentration in rats compared to native Curcumin.	(55)
Paclitaxel	PVP-K30	EtOH:Water in ratio 7:3	Croscarmellose sodium	Tablets	Superior *in vitro* dissolution and enhanced BA in beagle dogs *in vivo*. Additionally, dissolution rate and extend of Paclitaxel ASD prepared by fluid bed was excellent and superior compared the one prepared by spray drying	(56)
Fluid bed bottom-spray (Wurster)						
Nifedipine	HPMC	Acetone: Water in ratio 7:3	Sugar spheres (0.71 – 0.85 mm)	Pellets	Enhanced dissolution of Nifedipine as more HPMC was added to the ASD	(57)
Dipyridamole	Eudragit® L 100-55, L & S	EtOH:DCM in ratio 1:1	Neutral pellets	Pellets	Similar *in vitro* dissolution profiles than those obtained from coevaporates prepared by solvent-evaporation method	(58)
Silymarin	PVP	EtOH	Sugar spheres (710 – 850 µm)	Pellets in capsules	Significant enhancement in dissolution rate, advantageous properties for easy formulation into capsules, and increased bioavailability in beagle dogs	(60,61)

Drug substance	Polymer	Solvent	Substrate	Dosage form	Findings	Refe-rence
Fenofibrate	PEG 6000	EtOH	Sugar spheres (710 – 850 µm)	Pellets in capsules	Enhanced performance of ASD pellets compared to the micronized Fenofibrate formulation (Lipanthyl®)	(62)
Lansoprazole	PVP	Acetone: EtOH in ratio 2:8	Sugar spheres (710 – 850 µm)	Pellets in capsules	Significant improvement in dissolution	(63)
Tanshinone II A	PVP + Poloxamer 188	EtOH + Ethyl acetate	Sugar pellets (0.75-0.85 µm)	Pellets in capsules	Significant improvement of absorption and oral bioavailability of Tanshinone II A in rabbits	(64)
Ezetimibe + Lovastatin	Soluplus® + Enteric coating layer of Eudragit L100® or L100-55® and triethyl citrate	EtOH	Sucrose beads of 300 – 450 µm or 710 – 850 µm	Pellets	Both compounds were molecularly dispersed in Soluplus®. Smaller beads tend to agglomerate and release was jeopardized in acidic conditions. Eudragit L100-55® provided lower drug release	(65)
Itraconazole + Posaconazole	Eudragit® L100-55	EtOH: DCM in ratio 35:36	Tartaric acid (functional) or MCC (inert) spheres	Pellets	Uniforme ASD were achieved in both cases, but the use of tartaric acid instead of MCC resulting in a faster release but subsequent precipitation of posaconazole, attributed to the weaker interactions between drug and tartaric acid	(66)
Indomethacin	PVP + controlled release top layer of Eudragit RL® or ethyl cellulose	EtOH	Sucrose spheres (710 – 850 µm)	Pellets	The underlying ASD layer remains amorphous after coating of the rate controlling membrane, whether formed from an EtOH solution or an aqueous dispersion	(67)
Ketoconazole + Loratadine	HPMCAS or Eudragit L100-55®	EtOH 96%	MCC pellets (1.0 – 1.4 mm)	Pellets	ASD prepared either by fluid bed or spray drying were compared. ASD-pellets exhibited improved properties than spray dried material for capsule filling or tableting. Both products exhibited similar dissolution performance and high physical stability	(59)
Glipizide	PVAP + HPMC	DCM: MeOH in ratio 1:1	Sucrose spheres (710 – 850 µm)	Pellets	Increase in apparent solubility of the Glipizide, high T_g and acceptable chemical and physical stability	(26)

PVAP: Polyvinyl acetate phthalate

Fluid bed top-spray technology bears close resemblance to the spray dryer system and is presented as a potential alternative to spray drying process. Fluid bed top-spraying typically yields granules of larger size, exhibiting superior flowability and compressibility, conducive to tablet formulation (49). The resulting granules generally exhibit a porous surface and an interstitial void space, leading to enhanced liquid absorption into the granules and improved disintegration and dispersibility (47). Among the different steps involved in fluid bed granulation of ASD (feed solution preparation, blending and warm-up, spraying, and drying), spraying step is considered the most critical. The processing and equipment-related process parameters of the spraying step are presented in Table 9 together with their influence on the particle size and residual solvents of the obtained SGD, and on the process yield.

Table 9. Influence of fluid bed top-spray granulation process parameters on SGD particle size, residual solvents, and process yield (49,50,68).

Process parameter ↑	**SGD particle size**	**SGD residual solvents**	**Process yield**
Organic solvent instead of water	↓ Due to the lower surface tension	↑ Due to the use of organic solvents	↓ Smaller particles, leading to higher loss on filters, may be obtained due to the lower surface tension and higher vapour pressure of the organic solvent.
Solids concentration/ Solution viscosity	↑ More solids in a drop	↓ Decrease of partial pressure of solvent in the gas	↑↓ Produce bigger particles leading to less loss on filters. However, high viscosity can cause sticking of the droplets on the container walls
Feed rate	↑ Increase of droplet size as more liquid has to be dispersed	↑ More liquid to evaporate per second	↑↓ Optimal feed rate should be sought
Atomization air pressure	↓ Smaller droplets produced	↓ Smaller droplets, easier to dry	↑↓ Optimal spray gas flow should be sought
Nozzle size	↑ Increase of droplet size	↑ More liquid to evaporate per second	↑↓ Optimal nozzle size should be sought
Container size	—	—	↑ Larger batch size generally results in higher yields

Process parameter ⬆	**SGD particle size**	**SGD residual solvents**	**Process yield**
Inlet air temperature	⬇ Reduces the wettability and permeability of the material, reducing the cohesion and agglomeration between particles	⬇ Faster evaporation due to increased heat transfer into the drying droplet	↑↓ Excessive drying can promote the formation of fines and increase losses in filters. On the contrary, too low drying could cause sticking of the droplets on the container walls
Product temperature			
Inlet air flow	↓	⬇	
Inlet air humidity	⇧ More liquid bridges are formed, increasing the contact surface area between particles	↓ Molecular replacement of solvents by water through hydrogen bonding interactions	↓ Moist particles can adhere to the spray dryer walls

⬆ High influence; ⇧ Moderate influence; ↑ Minor influence; ▭ No direct influence

The atomization air pressure, liquid feed rate, and inlet air temperature are considered the most critical process parameters (50). Nonetheless, good control over all the process parameters is crucial to mitigate batch-to-batch variation during production.

It is noteworthy that during the initial stages of SGD preparation in fluid bed, the initial container load is typically lower than the final load, particularly when the total percentage of drug substance and carrier(s) is high compared to the substrate. Therefore, at the beginning of the spraying process, it is essential to maintain a low solution feed rate to facilitate particle agglomeration with the substrate. As the amount of fluidized material increases, the rate of liquid addition can be increased, owing to the synergistic effects of particle agglomeration and the concurrent layering or spray drying of the liquid (50).

Similar to the spray drying technique, choosing an appropriate solvent is crucial. The criteria in selecting the solvent type are the same as the ones described in section 2.4 for spray drying. The most commonly used solvents for fluid bed technology are dichloromethane, acetone, methanol, ethanol, isopropanol, and water (47). Their characteristics are described in Table 7 in section 2.4.

In the process of preparing SGD using fluid bed with top-spray method, a substrate is required to spray the drug and carrier(s) solution onto. Commonly used fillers and disintegrants could be used for this purpose. As shown in Table 8, the substrates employed in published studies include microcrystalline cellulose, lactose, crospovidone, and croscarmellose sodium.

2.6. SPRAY DRYING VS. FLUID BED TOP-SPRAY GRANULATION: PROS AND CONS

Spray drying and fluid bed top-spray granulation methods for ASD preparation rely on the same principle. In both methods, the solution of drug and carrier(s) is atomized into a chamber of hot gas or air to promote solvent evaporation. The advantages and disadvantages of spray drying and fluid bed top-spray granulation for ASD preparation are outlined in Table 10 and Table 11, respectively.

Table 10. Pros and cons of spray drying technology for ASD preparation.

Pros
Continuous manufacturing (12) and flexibility to accommodate the desired throughput or batch size (69).
Scalable from lab-scale to industrial-scale production, offering flexibility in manufacturing (12,69).
Cost-effectiveness at large scales (12).
Fast drying kinetics, spray solution droplets are evaporated in milliseconds.
Application of broad spectrum of compounds including heat-sensitive substances as they are exposed to heat for a very short period of time (70).
Compatible with water and with a large number of organic solvents (see Table 7).
Precise control over the particle size of the dried powder and high reproducibility (70).
Cons
Powder obtained exhibits low bulk density and poor flow, requiring additional downstream processing prior tabletting or encapsulation.
A secondary drying is usually required in another equipment to reduce the residual solvent content to acceptable levels from toxicological and/or stability standpoint (36). The most commonly used unit operations are convection tray dryers, agitated vacuum dryers, biconical rotating vacuum dryers, or fluid bed can be used for this purpose (69).
Fine particles may be lost during the drying process, reducing overall yield and increasing production costs (71).
Require large investments costs for infrastructure development in pharmaceutical companies.
High-energy consumption due to the high energy input for both heating, atomization, and condensation of solvents. This contributes to higher operating costs and environmental footprint.
Requirement for skilled operators.

Table 11. Pros and cons of fluid bed top-spray technology for ASD preparation.

Pros
ASD granules or pellets obtained exhibited improved density, flow, and compression properties. Direct tableting or encapsulation can be performed without additional downstream processing (12). Thus, reducing the manufacturing operations (51) and the risk of phase separation associated with multiple step manufacturing approaches.
Generally, the granules obtained require low pressure to compress into tablets (49).
Less fine particles, reducing the dust for operator and environmental safety.
In the top-spray process, a large air volume can be applied and liquid can be dried in the chamber at an inlet air temperature much lower than that used for traditional spray-drying (50). This is especially beneficial for heat-sensitive products.
If required, further drying is carried out in the same equipment to reduce the residual solvent content to acceptable levels from toxicological and/or stability standpoint.
Fluid bed technology is commonly accessible in the majority of pharmaceutical companies.
Cons
Not continuous manufacturing.
Batch size is limited to container occupancy.
Although the process is scalable from lab-scale to industrial-scale production, offering flexibility in manufacturing, it presents difficulty in scaling (72).
A substrate is required to spray the solution of drug and carrier(s) onto, which can be a limitation for high drug load.
Lower number of organic solvents than spray drying are suitable (see section 2.5).
Product is exposed to heat during the entire process.

2.7. MOST COMMONLY USED EXCIPIENTS IN ASDs

As highlighted in section 2.1.3, polymer carriers are generally used for the preparation of ASDs to stabilize the amorphous solid state of the drug and to prevent its precipitation from supersaturated solution. Nevertheless, other excipients such as sugar glasses (trehalose, sucrose, inulin) or surfactants are also used (21).

Over the last decades, surfactants have also found application in ASDs, either alone or in combination with a polymeric carrier, forming ternary solid dispersions. Incorporating surfactant(s) into ASDs can enhance drug-polymer miscibility, reduce recrystallization, and enhance the wettability of ASDs. This leads to an enhanced dissolution and improved physical stability of the ASD. Numerous studies have been published exploring this avenue (73–78). Nevertheless, careful consideration is required when selecting the surfactant, as they may interact with polymers, potentially increasing drug crystallization (79).

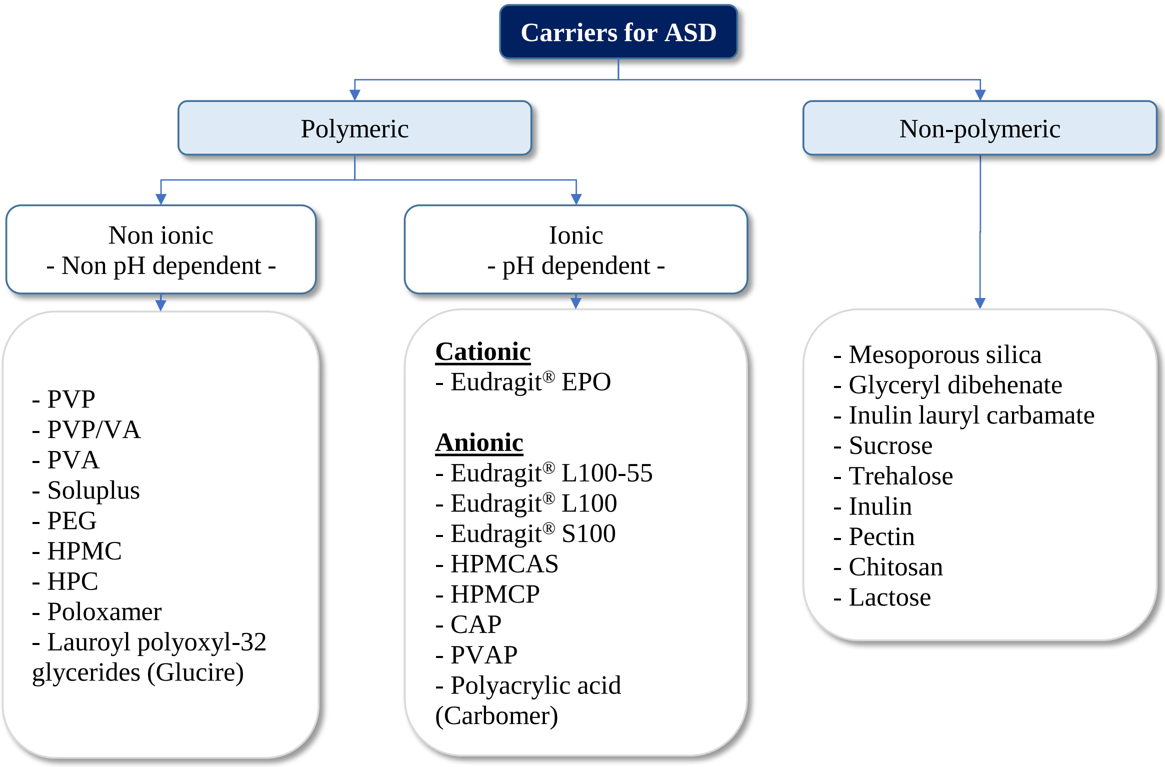


Figure 16. Polymeric carriers used in ASD formulations (2,11,21,33,34,40).

Examining the ASD-based products available in the market as listed in Table 4, HPMCAS emerges as the predominant polymer utilized for spray drying, while PVP/VA is more frequently used for HME, as depicted in Figure 17.

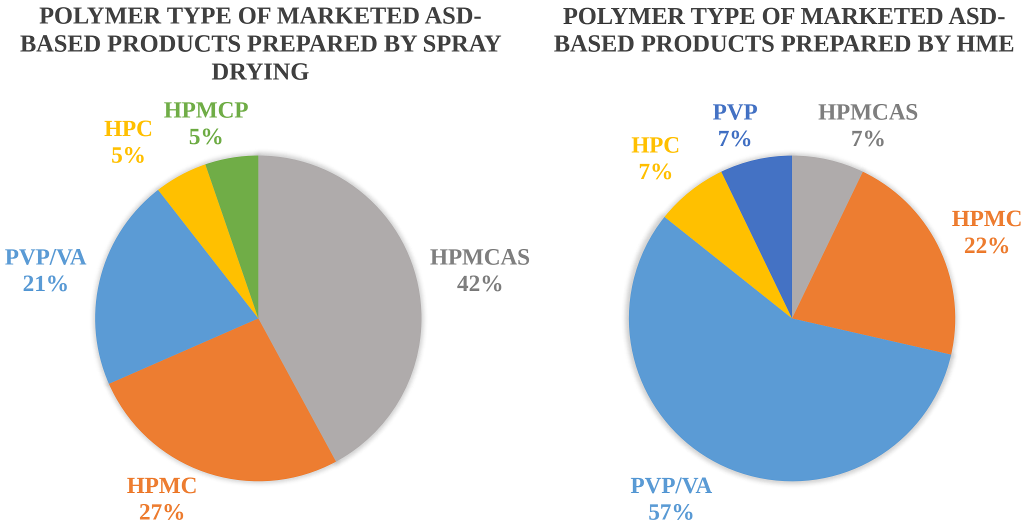


Figure 17. Polymer type of marketed ASD-based products classified by the manufacturing process used, either spray drying or HME.

MATERIALS AND METHODS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3. MATERIALS

3.1. DRUG SUBSTANCE

LM2 drug substance is a white to off-white powder, and non-hygroscopic. A single polymorphic form has been observed which is consistently produced by the manufacturing process. Four other solvates have been observed but are not produced from the manufacturing process. It has log *P* (octanol-water) < 6 and it is practically insoluble in aqueous media between pH 1 – 11. It appears to be a high permeable compound that crosses Caco-2 cell monolayers by passive diffusion and it is not substrate for P-glycoprotein. Based on the low aqueous solubility and high permeability, LM2 is categorized as a BCS class II drug substance. LM2 drug substance falls within group 2 ASD drug loading (refer to Figure 8 in section 2.1.1), indicating that a ASD drug loading within 35 – 50 wt% may be feasible from stability and dissolution perspective.

LM2 drug substance was purchased from Aurisco Pharmaceutical Co., Ltd., Laurus Labs Limited, and Synthon s.r.o.

3.2. HYPROMELLOSE ACETATE SUCCINATE

HPMCAS (cellulose, 2-hydroxypropyl methyl ether, acetate hydrogen butanedioate; CAS registry number 71138-97-1) is a mixture of acetic acid and monosuccinic acid esters of HPMC. The chemical structure in given in Figure 18.

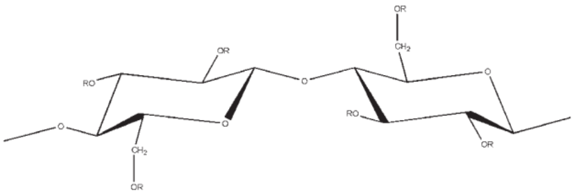


Figure 18. Chemical structure of HPMCAS where –OR represents one of the following functional groups: hydroxyl, methoxyl, 2-hydroxypropoxyl, acetyl, or succinoyl (80).

HPMCAS is an amorphous amphiphilic derivate of cellulose widely used as a polymer in ASDs to enhance the bioavailability of poorly soluble compounds.

HPMCAS (AQOAT®) was purchased from Shin-Etsu Chemical Co., Ltd. AQOAT® is available in six grades suitable for different applications (refer to Table 12). They differ in the degree of substitution, mainly involving acetyl and succinoyl groups, the pH threshold for dissolution initiation (low, L; medium, M; and high, H), and their predominant particle size (micronized grade, F; and granular grade, G). The acetyl and succinoyl substitutions on the HPMC backbone dictate the pH-solubility characteristics of the polymer.

Table 12. Grades of AQOAT® (81).

AQOAT® grade		Acetyl (%)	Succinoyl (%)	Dissolving pH	Mean particle size	Main application
Micronized	AS-LF	8	15	≥ 5.5	5 µm	Enteric/delayed coating (aqueous suspension and dry)
	AS-MF	9	11	≥ 6.0		
	AS-HF	12	7	≥ 6.5		
Granular	AS-LG	8	15	≥ 5.5	1000 µm	Enteric/delayed coating (aqueous or solvent-based solution) and ASDs by spray drying
	AS-MG	9	11	≥ 6.0		
	AS-HG	12	7	≥ 6.5		

The reported solubility of the different HPMCAS grades in several solvents is summarized in Table 13.

Table 13. Solubility of AQOAT® grades in several solvents (80,81).

Solvent	AQOAT®		
	LF & LG	MF & MG	HF & HG
Purified water	I	I	I
Acetone	S	S	S
Acetone/ Water (1:1 weight ratio)	P	P	P
Methanol	S	S	S
Methanol/ Water 1:1 weight ratio)	P	P	P
Ethanol	P	P	P
Ethanol/ Water (4:1)	S	S	S
Ethanol/ Water (1:1)	S	S	S
Ethanol/ Water (4:6)	I	I	I
Isopropyl alcohol	P	P	P
Isopropyl alcohol/ Water (4:1)	S	S	S
Isopropyl alcohol/ Water (1:1)	S	S	S
Dichloromethane	P	P	S
Dichloromethane/ Methanol (1:1)	S	S	S
Dichloromethane/ Ethanol (1:1)	S	S	S
Dichloromethane/ Isopropyl alcohol (1:1)	S	S	S
Tetrahydrofuran	S	S	S
Methyl acetate	S	S	S
Ethyl acetate	S	S	S
Diethyl ether	I	I	I

S = Soluble (solution may be slightly opaque); P = Partly soluble or swelling; I = Insoluble

3.3. HYPROMELLOSE PHTHALATE

HPMCP (cellulose phthalate hydroxypropyl methyl ether; CAS registry number 9050-31-1) is a cellulose in which some of the hydroxyl groups are replaced with methyl ethers, 2-hydroxyproypl ethers, or phthalyl esters. HPMCP exhibits a T_g of approximately 145ºC (81). The chemical structure is given in Figure 19.

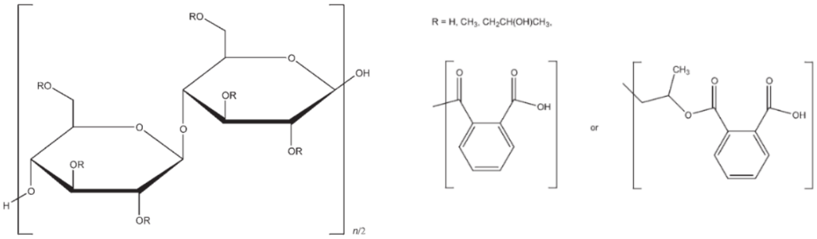


Figure 19. Chemical structure of HPMCP (80).

HPMCP HP-55 were acquired from Shin-Etsu Chemical Co., Ltd. It is available in three different grades (refer to Table 14), which vary in the viscosity, nominal phthalyl content, and the pH at which they start to dissolve.

Table 14. HPMCP grades and applications (82).

HPMCP grade	Labelled viscosity (cSt)	Nominal Phthalyl content (%)	Mean particle size (µm)	Dissolving pH	Application
HP-55	40	31	1000	≥ 5.5	Regular grade
HP-55S	170				Greater film strength
HP-50	55	24		≥ 5.0	Soluble at lower pH

The reported solubility of the different HPMCP HP-55 grades in several solvents is summarized in Table 15.

Table 15. Solubility of HPMCP grades in several solvents (80,82).

Solvent	HPMCP	
	HP-50	HP-55 and HP-55S
Purified water	I	I
Acetone	I	S
Acetone/ Water (95:5 weight ratio)	S	S
Acetone/ Water (1:1 weight ratio)	P	P
Acetone/ Ethanol (1:1 weight ratio)	P	P
Methanol	I	P
Methanol/ Water (1:1 weight ratio)	P	P
Ethanol	I	P
Ethanol/ Water (4:1)	CS	CS

Solvent	HPMCP	
	HP-50	HP-55 and HP-55S
Ethanol/ Water (1:1)	P	P
Ethanol/ Water (4:6)	P	P
Isopropyl alcohol	I	I
Isopropyl alcohol/ Water (4:1)	CS	S
Isopropyl alcohol/ Water (1:1)	P	P
Dichloromethane	P	P
Dichloromethane/ Methanol (1:1)	CS	CS
Dichloromethane/ Ethanol (1:1)	CS	CS
Dichloromethane/ IPA (1:1)	CS	CS
Tetrahydrofuran	CS	CS
Methyl acetate	I	S
Ethyl acetate	I	P
Diethyl ether	I	I

CS = Clearly soluble (solution may be slightly opaque)
S = Soluble (haze)
P = Partly soluble or swelling
I = Insoluble

3.4. OTHER EXCIPIENTS

Poloxamer 188 (Kolliphor P188) was purchased from BASF Corporation. Vivapur 101® (microcrystalline cellulose) was purchased from JRS Pharma, Ac-Di-Sol® (croscarmellose sodium) from DuPont, Aerosil 200 VV Pharma® (anhydrous colloidal silica) from Evonik Operations GmBH, Ligamed MF-2-V-MB® (magnesium stearate) from Peter Greven, and Opadry® yellow 03F220119 from Colorcon Limited Dartford (England).

3.5. PACKAGING MATERIAL

Aluminium blisters (Al/Al) were purchased from Amcor Flexibles (Germany). Triplex 180 blisters [polyvinylchloride (PVC) 250/ polyethylene (PE) 25/ polyvinylidenchloride (PVdC) 180/ Al] was purchased from Perlen Converting AG (Switzerland), marketed under the trade name Perlalux® - Tristar Ultra 250.25.180. The characteristics of each packaging materials are detailed below.

Aluminium blisters consist of the following materials:

1. Aluminium blister cold forming foil composition:
    - Oriented polyamide (oPA) of 25 µm (adhesive/ primer outer layer)
    - Aluminium of 45 – 47 µm
    - PVC of 60 µm (adhesive inner layer in contact with the drug product)
2. Aluminium lidding foil consists of the following layers (from the inner layer in contact with drug product to the outer layer):

- Heat seal lacquer
- Aluminium of 20 µm
- Primer

Triplex 180 blisters consist of the following materials:

1. Blister foil of three layers (from the inner to the outer layer):
    - PVdC with a coating weight of 180 g/m^2 (170 – 190 g/m^2)
    - PE of 25 µm (20 – 30 µm)
    - PVC of 250 µm (238 – 263 µm)
2. Aluminium lidding foil consists of the following layers (from the inner to the outer layer):
    - Heat seal lacquer
    - Aluminium of 20 µm
    - Primer

4. METHODS

4.1. MANUFACTURING PROCESSES

4.1.1. Manufacturing of ASD by spray drying

4.1.1.1. Preformulation studies

The procedure described below was adhered to for the studies aimed at comprehending the RLD formulation in the spray dryer.

SDDs with different weight ratios of LM2 and HPMCAS-MG were prepared by spray drying using the Büchi mini spray dryer B-290 equipped with Inert Loop B-295. LM2 and HPMCAS-MG were dissolved in an appropriate amount of acetone to achieve a concentration of solids in solution of 12.0% w/w. The mixtures were stirred at room temperature until turbid yellowish solutions without undissolved particles were obtained. The resulting turbidity of the mixture was due to the properties of HPMCAS, which forms a sort of colloidal solution. The resulting homogeneous solutions were sprayed into the drying chamber of the spray dryer, using a two-fluid spray nozzle system and a peristaltic pump, with a constant hot nitrogen to rapidly evaporate the solvent and yield the SDD powder. The established process parameters are presented Table 16.

Table 16. Spray drying process parameters set in Büchi mini spray dryer B-290.

Process parameters	Value set
Feed solution temperature (ºC)	Room temperature
Nozzle hole size (mm)	0.7
Feed rate (g/min)	4.1 ± 0.3
Spray gas flow (L/h)	414 – 536
Drying gas flow rate (m^3/h)	35
Inlet temperature (ºC)	72 ± 2ºC
Outlet temperature (ºC)	59 ± 2ºC

The SDDs powder obtained were subjected to additional secondary drying in a vacuum drying oven (Memmert Ule 4000) for 60 minutes at 50ºC under vacuum conditions to remove the excess of solvent.

4.1.2. Manufacturing of ASD by fluid bed

The procedure described below was followed for feasibility and prototypes development studies using fluid bed equipment (refer to results in sections 5.1 and 5.2).

SGDs were prepared via fluid bed using top-spray configuration in a Glatt GPCG-2 LabSystem fluid bed granulator. In the formulations containing HPMCAS-MG as the polymeric carrier, LM2 and HPMCAS-MG, in a weight ratio of 1:5, were dissolved in an appropriate amount of acetone to achieve a concentration of solids in solution of 15.0% w/w, with a viscosity of approximately 95 mPa·s. The mixtures were stirred at room temperature until turbid yellowish solutions without undissolved particles were obtained. When applicable, an aqueous solution of poloxamer 188 (10% w/w solids concentration) was incorporated to the previous solution.

In formulations with HPMCP HP-55 as the polymeric carrier, LM2 and HPMCP HP-55, in a weight ratio of either 1:5 o 1:4, were dissolved in an appropriate amount of a mixture of acetone and purified water in ratio 95:5 (w/w) to achieve a concentration of polymer in solution of 13.0% w/w, with a viscosity of approximately 80 Cp. The mixtures were stirred at room temperature until homogeneous yellowish solutions, free of undissolved particles, were obtained.

The homogeneous solutions obtained were sprayed onto the preheated fluidized substrate (MCC alone, MCC and croscarmellose sodium, or mannitol and croscarmellose sodium) using a two-fluid spray nozzle system and a peristaltic pump. Concurrently, a constant flow of hot air was maintained to facilitate solvent evaporation. The operating conditions are detailed in Table 17 for batch size of 0.60 – 2.50 kg.

Table 17. Fluid bed top-spray granulation process parameters.

Process parameters	**Values range**		
	0.60 – 0.65 kg batch size[2]	**1.00 kg batch size[2]**	**2.00 - 2.50 kg batch size[2]**
Drying chamber dimensions (L)	3	6	12
Nozzle hole size (mm)	1.0	1.0	1.2
Average feed rate (g/min) [1]	20 – 21	25	33 – 34
Atomization pressure (bar) [1]	2.0 – 2.2	2.0 – 2.5	2.0 – 2.8
Air flow (m^3/h) [1]	25 – 60	40 – 70	45 – 100
Inlet temperature (ºC) [1]	55 – 75	60 – 77	56 – 79
Product temperature (ºC)	43 ± 3ºC	43 ± 3ºC	43 ± 3ºC

[1] At the beginning of the process, lower feed rate, atomization pressure, and air flow were set due to the lower amount of substrate in the fluid bed chamber. It was steadily increased in correlation with the increasing amount of substrate. Inlet air temperature was adjusted accordingly to maintain the desired product temperature.

[2] Final blend batch size.

After the complete spraying of the solutions, the SGDs obtained were dried further within the same fluid bed equipment for 30 minutes at a product temperature of 50ºC to reduce the residual acetone levels.

4.1.3. Manufacturing of uncoated tablets by slugging

The procedure described below was adhered to for the studies aimed at comprehending the RLD formulation in the spray dryer.

The SDDs produced according to the procedure described in section 4.1.1.1 were blended in a diffusion mixer (Turbula® T2 F) with the de-agglomerated MCC, anhydrous colloidal silica, and croscarmellose sodium for 10 minutes at 72 rpm. Then, they were further blended with magnesium stearate for 3 minutes at 72 rpm. The resulting blends were dry granulated by slugging in an eccentric tablet press equipped with a 20 mm round punch, targeting a tablet height of 3.4 ± 0.3 mm and a tablet hardness of approximately 110 N. The tablets obtained were crushed using a double roll crusher (Erweka TG 2000) and manually sieved through a 1.4 mm mesh size, followed by either 0.5, 0.8 or 1.0 mm to obtain a homogeneous granulate. The granules were then blended in a diffusion mixer (Turbula® T2 F) with the de-agglomerated MCC, anhydrous colloidal silica, and croscarmellose sodium for 10 minutes at 72 rpm. Then, they were further blended with magnesium stearate for 3 minutes at 72 rpm. The resulting blend was tableted into tablets using an eccentric tablet press (Korsch EK-0) equipped with an oval biconcave punch of 18 x 10 mm and applying the required compression force to achieve a tablet tensile strength of approximately 1.8 MPa. Tensile strength was used instead of hardness value, as different punches dimensions were used throughout development work.

4.1.4. Manufacturing of SDD-based uncoated tablets by roller compaction

The procedure described below was followed for the production of ASD via spray drying in the comparative study between spray drying and fluid bed technologies (refer to results in section 5.1).

Around 1.1 kg of the SDD was blended in a diffusion mixer (LM40, L.B. Bohle) with the de-agglomerated intragranular MCC, anhydrous colloidal silica, and croscarmellose sodium for 15 minutes at 20 rpm. Then, it was further blended with magnesium stearate for 3 minutes at 20 rpm. The resulting blend was subjected to dry granulation using a roller compactor with integrated milling (WP120 Pharma roller compactor, Alexanderwerk), with a compaction force of 4.0 kN/cm, a gap width of 2.0 mm, and using a pre-granulator mesh of 1.6 mm and a fine-granulator mesh of 0.8 mm.

The granules obtained were blended in a diffusion mixer (LM40, L.B. Bohle) with the de-agglomerated MCC, anhydrous colloidal silica, and croscarmellose sodium for 10 minutes at 20 rpm. Then, it was further blended with magnesium stearate for 3 minutes at 20 rpm.

The resulting blend was tableted into tablets usin a rotary tablet press (Korsch XL100) equipped with biconcave punches of 17 x 9 mm, applying a compression force of 20 kN to achieve a tablet tensile strength of 1.8 MPa.

4.1.5. Manufacturing of SGD-based uncoated tablets by direct compression

The procedure described below was followed for feasibility and prototypes development studies using fluid bed equipment (refer to results in sections 5.1 and 5.2).

The SGDs produced via fluid bed top-spray granulation, following the procedure described in section 4.1.2, did not require a dry granulation, given the good powder flow properties suitable for tableting process. SGDs were subjected to either manual de-agglomeration using a 0.8 mm mesh size or milling using a hammer mill (Fitz-Mill, Fitzpatrick) operating at 4000 rpm speed and equipped with either 1.0 mm or 0.5 mm mesh size. Subsequently, they were blended in a diffusion mixer (LM40, L.B. Bohle) with the de-agglomerated croscarmellose sodium and anhydrous colloidal silica for 10 minutes at 20 rpm. They were then further blended with magnesium stearate for 3 minutes at 20 rpm.

The resulting blends were tableted into tablets using a rotary tablet press (Korsch XL 100 or GEA Courtoy Modul P), equipped with biconcave punches of either 19 x 11mm, 18 x 10 mm, or 17 x 9 mm, and applying the required compression force to achieve a tablet tensile strength between 1.4 – 1.8 MPa.

4.1.6. Tablets film-coating

Film-coating of uncoated tablets was carried out using a perforated pan coater (O’Hara Labcoat M) with an aqueous suspension of Opadry® 03F220119 yellow at a solids concentration of 15.0% (w/w). The product temperature during coating process was kept within 42 – 44ºC. A 3.0% of tablet weight increase was applied.

4.2. CHARACTERIZATION OF SOLID POWDERS (DS, ASD, GRANULES, AND FINAL BLEND)

4.2.1. Scanning Electron Microscopy (SEM)

SEM was used to study the morphology and particle size of drug substance and ASDs (either SDDs or SGDs). Analysis were carried out at Synthon s.r.o (Blansko, Czech Republic) using a JCM-6000 microscope (JEOL) or TESCAN VEGA LMu. Samples were sputtered using alloy of 80% gold and 20% palladium to provide conductive coating.

4.2.2. Specific Surface Area (SSA)

Analysis of the drug substance SSA were carried out at INFARMADE, S.L. (Sevilla, Spain) using an Accelerated Surface Area and Porosimetry System (Micrometics ASAP

2420 V2.06) and Kripton gas as the adsorbate. Samples were degassed at 90ºC for 720 minutes. The amount of gas adsorbed at a given temperature, for different relative pressures (adsorption isotherm), was registered and from these data the specific surface area was calculated with the Brunauer, Emmer, and Teller (BET) method.

4.2.3. X-Ray Powder Diffraction (XRPD)

XRPD measurements were carried out at Synthon s.r.o (Blansko, Czech Republic) to determine the DS solid state form. Bruker and Empyrean diffractometer with Data Collector from Malvern Panalytical was used. Samples of less than 0.5 g were equally spread across a Cling film or another appropriate foil and stretched, resulting in a sample layer thickness of approximately 0.1 – 1 mm. Samples were spun in the plane at 30 rpm (1 per 2 s) to minimize crystal orientation effects. The X-ray source (Cu) was operated at 40 kV and 40 mA. Data for each sample were collected from 2° to 35° on the 2θ scale. Parameters set for each diffractometer and sample are summarized in Table 18.

Table 18. Parameters set for Bruker and Empyrean diffractometers.

Parameter	**Bruker diffractometer**		**Empyrean diffractometer**	
	Drug substance	**Drug product**	**Drug substance**	**Drug product**
Time	1 hour	3 hours	6 min	12 min
Step size	0.016º	0.016º	0.026º	0.026º
Time per step	1.5 s	0.7 s	-	-
Scan speed	-	-	0.0955º/s	0.0515º/s

4.2.4. Modulated Differential Scanning Calorimetry

MDSC measurements were carried out at Synthon s.r.o. (Blansko, Czech Republic), using a DSC Q2000 V24.11 Build 124 (TA Instruments). Indium standard were used to calibrate the MDSC temperature and enthalpy scale. Samples of 1.0 – 5.0 mg were sealed into aluminium pans. Inert atmosphere was maintained by purging nitrogen gas at a flow rate of 50 mL/min. Samples were heated from 0ºC to 300ºC at a constant heating rate of 10ºC/min with a modulation of ±1ºC amplitude in a period of 30 s.

The differential total heat flow (in W/g) to the sample and an inert reference (empty pan) was recorded as a function of temperature and represented in green in the MDSC curves. The total heat flow signal was calculated from the average value of the measured modulated heat flow signal. Simultaneously, the MDSC can obtain the reversing heat flow signal (in W/g) that corresponds to the specific heat capacity and is represented in blue in the MDSC curves.

Melting temperature was measured at the peak onset in the total heat flow, whereas glass transition temperatures were measured at half height of decrease in the reversing heat flow. Data were treated mathematically using Universal Analysis software (version 4.5A, TA Instruments).

4.2.5. Loss on drying (LOD)

LOD measurements were carried out using a HG63 moisture analyser (Mettler Toledo). Approximately 2 g of powder were placed in a pan that was inserted into the analyser. Samples was heated up to 105ºC and switch-off criterion 3 was set (1 mg of mean weight loss per 50 s).

4.2.6. Gas chromatography

The residual acetone content in SDD, SGD, and tablets was quantified using gas chromatography equipped with a flame ionization detector (GC-FID) with headspace injection. Amount equivalent to one film-coated tablet was accurately weight and dissolved in DMF to liberate the solvent contained in the solid. An Agilent A7890 Series GC System with an Agilent G1888 headspace sampler was used. The column used was Rtx-1301 series 16085 (Restek) of 30.0 m of length, 530 µm of diameter, and 3.0 µm film thickness. Peaks were quantified and compared with a standard curve of known concentrations.

4.2.7. Dynamic Vapour Sorption

DVS was used to determine the hygroscopicity of SDD and SGD samples. Analysis were carried out at Synthon s.r.o. (Blansko, Czech Republic) using a water vapour sorption analyser SPSx-1µ-Advance. Sample of 100 – 200 mg of SDD and SGD were first dried and then exposed to increasing relative humidity (RH) from 0% to 90%. First sorption and desorption cycle was carried out at 25ºC and second cycle at 40ºC. The weight changes were measured by an ultra-microbalance. The equilibrium criterion was 0.05% w/w change within 30 minutes. The equilibrium mass values at the end of each humidity step was used to calculate the water sorption isotherms.

4.2.8. Particle size distribution (PSD)

PSD of SGD samples was measured by mass-based sieve analysis. A vibratory sieve shaker AS 200 Digit CA (Retsch) was employed for this purpose. The apparatus was equipped with nine sieves of 100 mm of diameter with different mesh screens: 710, 500, 355, 250, 180, 125, 90, 63, and 45 µm.

Prior to initiating the analysis, each sieve was accurately weighed. The sieves were stack in descending order of mesh size, positioning the finest sieve at the bottom and the coarsest at the top. A representative sample of approximately 20 g was weighed and placed onto the top sieve with a mesh size of 710 µm. The stack of sieves was covered and secured in the sieve shaker. Then, the sieve shaker was operated for 10 minutes. After sieving, each sieve was removed from the sack and weighed.

The mass retained on each sieve was determined by subtracting the initial weight of the sieve from its final weight. The mass fraction of the sample retained on each sieve was then calculated dividing the mass retained on each sieve by the total initial sample amount. Subsequently, the cumulative distribution was calculated by summing up the percentage of particles retained in each sieve and the ones below, starting with the smallest fraction. The resulting data was expressed as a percentage of particles retained in each sieve and the cumulative percentage of particles below each sieve.

4.2.9. Bulk and tapped density

Bulk and tapped density of powder samples were measured in a graduated cylinder using the apparatus Pharmatest PT-TD in compliance with the current USP <616> as well as with EP <2.9.34> method 2.

The test sample was poured into a dry 250 mL graduated glass cylinder (readable to 2 mL and a mass of 220 ± 44 g) avoiding any significant compacting stress. The required amount of test sample (m) to reach an untapped bulk volume of 150 – 250 mL was used. The untapped bulk volume (V_0) was read to the nearest graduated unit.

The 250 mL graduated glass cylinder was assembled into the holder of a tapping apparatus capable of producing 250 taps per minute of a fixed height of 3 ± 0.2 mm. The sample was tapped 10, 500 and 1250 times, and the volumes of the tapped sample at each time (V_{10}, V_{500}, and V_{1250}) were read to the nearest graduated unit. If the difference between V_{500} and V_{1250} was less than or equal to 2 mL, V_{1250} was the final tapped bulk volume (V_f). If the difference between V_{500} and V_{1250} was more than 2 mL, the sample was tapped for 1250 times more until the difference between successive measurements was less than or equal to 2 mL. The bulk and tapped densities are expressed in g/mL and are calculated as follows:

- Bulk density = $\frac{m}{V_0}$
- Tapped density = $\frac{m}{V_f}$

4.2.10. Hausner Ratio and Compressibility Index

Hausner Ratio and Compressibility Index, also called Carr Index, are popular methods of predicting powder flow characteristics. They are determined according to EP <2.9.36>. The basic procedure is to measure the V_0 and the final V_f of the same powder sample after tapping the powder until no further volume changes occur. The Hausner Ratio and Carr Index are calculated as follows:

- Hausner Ratio = $\frac{V_0}{V_f}$
- Carr Index = 100 x $\frac{V_0\text{-}V_f}{V_0}$

According to the EP <2.9.36>, a commonly reported relative ranking of flow by Hausner ratio and Carr Index is given in Table 19.

Table 19. Relative ranking of flow by Hausner ratio and Carr Index according to EP <2.9.36>.

Hausner ratio	Flow property	Carr Index (%)
1.00 - 1.11	Excellent	1 - 10
1.12 - 1.18	Good	11 - 15
1.19 - 1.25	Fair	16 - 20
1.26 - 1.34	Passable	21 - 25
1.35 - 1.45	Poor	26 - 31
1.46 - 1.59	Very poor	32 - 37
> 1.60	Very, very poor	> 38

4.3. SOLUBILITY OF LM2, HPMCAS-MG, AND HPMCP HP-55 IN ORGANIC SOLVENTS

Solubility of LM2 was tested in several organic solvents using a Crystalline (Avantium) parallel reactor with turbidimetry sensor. Different amounts of LM2 were added to 1 ml of the solvent and the mixture was warmed up from 23ºC to 46ºC in the Crystalline instrument with a magnetic stirring. Clear point was detected by turbidimetry sensor indicating complete dissolution of solute.

Solubility of LM2 and HPMCAS-MG was also tested in several organic solvents by adding the solvent steadily onto 5 g of solid, either LM2 or HPMCAS-MG, until solids were completely dissolved. DS was considered dissolved in the solvent when a clear solution without precipitated solids was visually observed. HPMCAS-MG was considered dissolved when no precipitated or undissolved particles were visually observed, although turbid solutions were obtained in all cases due to the HPMCAS properties.

Solubility of HPMCP HP-55 and LM2 in acetone and a mixture of acetone:water 95:5 was determined by adding the solvent steadily onto 2.5 g of solid polymer until clear yellowish solution without undissolved particles was visually observed.

4.4. CHARACTERIZATION OF TABLETS

4.4.1. X-Ray Powder Diffraction

See section 4.2.3.

4.4.2. Modulated Differential Scanning Calorimetry

See section 4.2.4.

4.4.3. Weight, dimensions, and hardness

The weight, thickness (or height), diameter (or length), and hardness of the tablets were measured automatically using a Pharmatest WHT 4 (Pharma Test, Germany), which offers the four test parameters of the same sample. Results were registered with WHT32 software program. The measurements were carried out from samples consisted of 5 tablets for each preparation. The hardness was measured applying a linear force of 20 N/s.

4.4.4. Tensile strength

The tensile strength of the tablets was calculated with the Equation 1 generated by Pitt et al. (83) for a convex-faced elongated tablet, where σ_t is the tensile strength, P is the fracture load, D is the length of the short axis, t is the overall thickness, and W is the wall height of the tablet.

$$\sigma_t = \frac{2}{3}\left(\frac{10P}{\pi D^2 (2.84\frac{t}{D} - 0.126\frac{t}{w} + 3.15\frac{w}{D} + 0.01)}\right)$$

Equation 1. Tensile strength for convex-faced elongated tablet.

4.4.5. Friability

Friability of uncoated tablets was measured according to Ph. Eur. 2.9.7, using a friability tester (Pharmatest PTF 20E, Pharma Test, Germany) equipped with double drum. Samples of whole uncoated tablets corresponding as near as possible to 6.5 g were taken. The tablets were dedusted prior testing and the initial mass of the sample was recorded accurately. The tablets were placed in the drum of the friability tester which was rotated 100 times at 25 revolutions per minute. After the test, the tablets were removed from the drum and were carefully weighed to determine the amount of mass loss. The difference between the initial mass (m_0) and the final mass (m_f) was calculated. The friability was expressed as a percentage of mass loss and was calculated using the following equation:

$$Friability\ (\%) = \frac{(m_0 - m_f)\ x\ 100}{m_0}$$

4.4.6. Disintegration time

The disintegration time of tablets was determined in a disintegration tester Pharmatest PTZ-Auto 2 with Apparatus A consisting of a basket-rack assembly with disk. The disintegration medium consisted of 800 mL of distilled water, maintained at 37ºC ± 1ºC. The tablets were considered disintegrated when no residue of the units were tested and the time taken to complete the disintegration was recorded.

4.4.7. Dissolution profile

4.4.7.1. Different pHs

The dissolution tests at different pH levels were performed using a dissolution apparatus (Vankel 7000) equipped with an automatic sampling unit (VK 8000). The dissolution procedure was performed with the USP Paddle (apparatus II) method, maintaining a paddle speed of 50 rpm for 60 minutes. Afterwards, the paddle speed was increased to up to 250 rpm for additional 15 minutes to detect any potential artefacts, such as conning. Different dissolution media were tested: simulated gastric fluid (SGF) pH 1.2, acetate buffer pH 4.5, and phosphate buffer pH 6.8. All with a volume of 900 mL and maintained at 37.0 ± 0.5ºC. The concentration of LM2 was quantified with a ultraviolet (UV) spectrophotometer (Lambda 25), using stoppered quartz cuvettes of 2 mm (for the higher strength) and 5 mm (for the lower strength), at a wavelength of 235 nm with a reference range of 500 - 550 nm, and compared to the calibration curve of LM2 in the same media. Samples of approximately 10 mL were taken from the dissolution vessels at different time points (5, 10, 15, 30, 45, 60, and 75 minutes).

4.4.7.2. Two-step dissolution method

The dissolution tests in two-steps were performed using a dissolution apparatus (Vankel 7000) equipped with an automatic sampling unit (VK 8000). The dissolution procedure was performed with the USP Paddle (apparatus II) method, maintaining a paddle speed of 50 rpm for 180 minutes. Afterwards, the speed was increased to up to 250 rpm for additional 15 minutes to detect any potential artefacts, such as conning. 300 mL of a medium of hydrochloric acid 0.03N (pH 1.2) at 37 ± 0.5ºC was used for 30 minutes and then shifted to phosphate buffer pH 6.8 medium by adding concentrated higher pH media in the same vessel to reach a final volume of 900 mL. The concentration of LM2 was quantified with a UV spectrophotometer (Lambda 25), using stoppered quartz cuvettes of 2 mm (for the higher strength) and 5 mm (for the lower strength), at a wavelength of 235 nm with a reference range of 500 - 550 nm, and compared to the calibration curve of LM2 in the same mediums. Samples of approximately 10 mL were taken from the dissolution vessels at different time points (5, 15, 30, 45, 60, 75, 90, 120, 150, 180, and 195 minutes).

4.4.7.3. Quality control (QC) dissolution method

The dissolution tests were performed using a dissolution apparatus (Vankel 7000) equipped with an automatic sampling unit (VK 8000). The dissolution procedure was performed with the USP Paddle (apparatus II) method, maintaining a paddle speed of 50 rpm for 60 minutes. Afterwards, the paddle speed was increased to up to 250 rpm for additional 15 minutes to detect any potential artefacts, such as conning. Dissolution medium was 900 mL of phosphate buffer pH 6.8 + 0.15% of SLS, maintained at 37.0 ± 0.5ºC. The concentration of LM2 was quantified with a UV spectrophotometer (Lambda 25), using stoppered quartz cuvettes of 2 mm (for the higher strength) and 5 mm (for the lower strength), at a wavelength of 239 nm with a reference wavelength of 500 – 550 µm, and compared to the calibration curve of LM2 in the same medium. Samples of approximately 10 mL were taken from the dissolution vessels at different time points (5, 10, 15, 30, 45, 60, and 75 minutes).

4.4.8. Assay and purity

The enzalutamide content in film-coated tablets was determined with High Performance Liquid Chromatography (HPLC) with column heater and temperature controlled autosampler, using a series of dilutions of enzalutamide in a mixture of methanol and purified water in ratio 60:40 (volume/volume, v/v). Experiments were carried out in duplicate. HPLC analysis were performed with a HPLC Agilent, UV detector, autosampler, and analytical column Inertsil ODS-3 or Prodigy ODS-3 (100 x 4.6 mm, 3 µm). 10 mM Ammonium acetate buffer pH 4.0/Acetonitrile was used as a mobile phase at a flow rate of 1.0 mL/min. Elution was programmed in gradient mode. All solvents used were HPLC grade. The injection volume was 20 µl and UV detection was used at a wavelength of 254 nm (bandwidth 4 nm).

The assay results were reported with one decimal place. The total (un)specified impurities was determined by summing up the content of single impurities greater than the reporting threshold of 0.10%. In cases where no impurity exceeded this threshold, the total (un)impurities content was reported as ≤ 0.10%.

RESULTS

5. RESULTS

5.1. FEASIBILITY OF ASD PRODUCTION USING FLUID BED AS AN ALTERNATIVE TO SPRAY DRYER

The objective of this study was to assess the viability of producing a homogeneous and stable ASD of LM2 and HPMCAS-MG in a weight ratio of 1:5 via fluid bed top-spray granulation, as an alternative to spray drying. Glatt GPCG-2 LabSystem fluid bed granulator with top-spray configuration was used for this investigation, aiming to simulate the spray drying system and to promote the agglomeration of particles easier to form into tablets. For the production of spray dried product, Büchi Mini spray dryer equipped with Inert Loop B-295 was used.

5.1.1. Formulation

The formulation initially designed for spray drying with LM2 and HPMCAS-MG in a 1:5 ratio was modified to be compatible with fluid bed technology. In the production of ASD using conventional fluid bed top-spray technology, it is essential to incorporate an inert excipient into the container, known as the substrate. This substrate serves as the base onto which the solution containing the drug substance and polymer is sprayed. In this study, MCC was selected as the substrate, which was the filler used in preformulation work for further processing the SDD into tablet form. Given the substantial quantity of solids to be sprayed over the substrate, constituting 73.85% of the total tablet weight, the entire amount of MCC in the formulation was used as the substrate of the ASD. Formulations are described in Table 20 and Table 21.

Acetone was the solvent selected to dissolve the drug substance and HPMCAS-MG. The solvent selection was based on the following criteria:

- The high solubility of both LM2 and HPMCAS-MG in this solvent.
- Its classification as a solvent with low toxic potential (Class 3) according to the ICH Q3C classification. In contrast, both DCM and MeOH are categorized as solvents to be limited in pharmaceutical products (Class 2) due to their inherent toxicity.
- The reported low viscosity (< 200 mPa·s) of HPMCAS solutions in acetone, even when concentrated up to 15% w/w (84).
- It is the solvent used by the RLD.

In general, fluid bed technology offers operating temperatures that are relatively lower than those used in spray drying. The maximum inlet temperature can vary depending on the equipment model and design. For this work, Büchi Mini Spray Dryer B-290 and Glatt GPCG-2 LabSystem fluid bed were used, which maximum inlet temperature are 220ºC and 120ºC, respectively. Considering that acetone has a boiling point of approximately 56ºC, this solvent was deemed suitable for fluid bed granulation.

Table 20. Qualitative and quantitative composition of tablets manufactured via spray drying.

Ingredients	Function	%	mg/ tablet
SOLID DISPERSION			
LM2	Drug substance	12.308	80.000
Hypromellose acetate succinate	Carrier	61.538	400.000
Acetone [1]	Solvent	q.s.	3520.000
INTRAGRANULAR PHASE			
Microcrystalline cellulose	Filler	8.327	54.125
Croscarmellose sodium	Disintegrant	4.000	26.000
Anhydrous colloidal silica	Glidant	0.250	1.625
Magnesium stearate	Lubricant	0.500	3.250
EXTRAGRANULAR PHASE			
Microcrystalline cellulose	Filler	8.327	54.125
Croscarmellose sodium	Disintegrant	4.000	26.000
Anhydrous colloidal silica	Glidant	0.250	1.625
Magnesium stearate	Lubricant	0.500	3.250
UNCOATED TABLET WEIGHT		100.000	650.000

[1] Acetone is evaporated during the manufacturing process.

Table 21. Qualitative and quantitative composition of tablets manufactured via fluid bed top-spray granulation.

Ingredients	Grade	%	mg/ tablet
INTRAGRANULAR PHASE/ SOLID DISPERSION			
LM2	Drug substance	12.308	80.000
Hypromellose acetate succinate	Carrier	61.538	400.000
Microcrystalline cellulose	Filler/ substrate	16.654	108.250
Acetone[1]	Solvent	q.s.	2720.000
EXTRAGRANULAR PHASE			
Croscarmellose sodium	Disintegrant	8.000	52.000
Anhydrous colloidal silica	Glidant	0.500	3.250
Magnesium stearate	Lubricant	1.000	6.500
UNCOATED TABLET WEIGHT		100.000	650.000

[1] Acetone is evaporated during the manufacturing process.

5.1.2. Manufacturing process

The preparation of ASD by either spray drying or fluid bed top-spray granulation involves three main steps: feed solution preparation, granulation/spray drying, and secondary drying. The critical factors of each process step were evaluated from an industrial perspective, aiming to address the advantages and limitations of fluid bed top-spray technology for the production of ASD, as an alternative to spray drying.

5.1.2.1. Solution preparation step

In this process step, LM2 drug substance and HPMCAS-MG are dissolved in an appropriate amount of acetone at room temperature, yielding a turbid yellowish solution without undissolved particles.

The amount of solvent required for processing the ASD is a key factor from industrial perspective, as it directly affects the spraying time. Additionally, it is also relevant in terms of costs and environmental impact.

According to solubility tests, the solubility of LM2 and HPMCAS-MG in acetone solution are around 0.50 g/mL and 0.14 g/mL, respectively, at room temperature. This equals to a maximum concentration in solution of LM2 and HPMCAS-MG of 39% w/w and 15%w/w, respectively. Therefore, the maximum solids concentration in solution was limited by the HPMCAS-MG. To prevent the precipitation of components during the spraying step, the solids concentration in acetone was reduced to a 2.5% w/w and 12.5% w/w for LM2 and HPMCAS-MG, respectively, resulting in a total concentration of solids of 15.0% w/w.

This solution concentration was suitable for processing with GPCG-2 fluid bed, but it was required to reduce the total concentration to 12.0% w/w when using Mini spray dryer B-290 due to observed nozzle clogging. This may be attributed to the smaller nozzle size and/or the slower feed rate required for spray drying with this equipment (refer to Table 22).

Based on these observations, the amount of solvent required for fluid bed granulation could be the same or lower than the one required for spray drying.

5.1.2.2. Granulation/spray drying and secondary drying steps

The process parameters applied for granulation/ spray drying and secondary drying are summarized in Table 22, together with the response factors considered critical from process feasibility perspective.

Table 22. Process parameters GPCG-2 fluid bed granulator and Mini spray dryer B-290.

	Fluid bed top-spray granulation	**Spray drying**
Spraying process parameters		
Equipment	Glatt GPCG-2 LabSystem fluid bed	Büchi Mini spray Dryer B-290

	Fluid bed top-spray granulation	**Spray drying**
Spraying process parameters		
Solids batch size (g)	543	591
Container size (L)	3	~ 10
Initial container load (%)	11%	*Not applicable*
Nozzle type	Tow-fluid nozzle	Two-fluid nozzle
Nozzle hole size (mm)	1.0	0.7
Feed rate (g/mL)	Average: 21	8.6
Atomization pressure (bar)	2.0 – 2.2	1.7 [1]
Drying gas	Air	Nitrogen
Inlet air/ Drying gas flow rate (m^3/h)	25 – 60	35
Inlet air/gas temperature (ºC)	55 – 75	66
Product/ Outlet temperature (ºC)	43 ± 3ºC	48 ± 3ºC
Drying process parameters		
Equipment	Glatt GPCG-2 LabSystem fluid bed	Memmert Ule 4000 vacuum drying oven
Inlet air flow rate (m^3/h)	60	*Not applicable*
Inlet air temperature (ºC)	62	50
Product temperature (ºC)	50	*Not applicable*
Drying time	30 min	30 min
Response factors		
Final container load (%)	72%	*Not applicable*
Spraying process time (min)	140	575
Yield (%)	86%	65%
Residual acetone content (ppm)	1583	2049

[1] Spray gas flow in L/h is given by the equipment. The equivalent atomization pressure was calculated using Fliegner formula, which relates the mass flow through an orifice in a pipe with the pressure, temperature, orifice section, shape factor and Fliegner's constant.

Based on the process parameters and response factors evaluated (refer to Table 22), fluid bed granulator with top-spray configuration was deemed feasible for the production of an ASD of LM2 and HPMCAS-MG in 1:5 ratio. The following observations were made:

- A slightly higher product temperature than the typically used for wet granulation in fluid bed was targeted, aiming to promote a fast evaporation of the solvent and reduce the risk of drug substance crystallization. With this objective, the inlet air temperature fell within the typical range for wet granulation in fluid bed, remaining well below the equipment's maximum threshold of 120ºC, thereby demonstrating the feasibility of the process.

- In fluid bed process, a significant increase in the container load occurs throughout the spraying step, being approximately 62%. This contrasts with spray drying, which is a continuous process and product is gathered in a separate collector from the drying chamber.
- Fluid bed proved to be successful in reducing the acetone content well below the ICH Q3C limit of 5000 ppm within a reasonable timeframe in this laboratory scale evaluation, demonstrating an evaporation capacity of acetone of at least 1.26 kg/h.
- Fluid bed top-spray granulation and drying resulted in a reasonable process time and yield considering the type of process and scale, being faster and yielding in greater output compared to spray drying process. This difference is mainly attributed to the feasibility of setting a faster feed rate and higher concentration of solids in solution in the fluid bed granulation process. However, it should be considered that the process time and yield of both technologies are significantly influenced by the equipment size and process parameters. Therefore, it is important to acknowledge the limitations when attempting to directly compare the process time and yield of both technologies.

Therefore, the main challenge in the production of the presented ASD formulation via fluid bed top-spray granulation was the high percentage of solids to be sprayed onto the substrate (MCC), as LM2 and HPMCAS-MG in a weight ratio of 1:5 constitutes the 73.85% w/w of the total tablet weight. This results in an increase of the container load throughout the spraying process due to the spraying of a high percentage of solids. Nevertheless, the initial container load should be enough to spray the feed solution over it. Therefore, the batch size should be carefully defined.

The maximum batch size ($\mathrm{Batch}_{\mathrm{max}}$) can be calculated as per the following equation:

$$\mathbf{Batch_{max}} = [\mathrm{V} \times 0.8 \times \mathrm{BD_{SGD}}] = [3000 \times 0.8 \times 0.25] = 600\ \mathrm{g}$$

Where:

- V is the container working volume in mL,
- 0.8 is the 80% of the container working volume, which is the maximum container load recommended for granulation in GPCG-2 fluid bed,
- $\mathrm{BD}_{\mathrm{SGD}}$ is the bulk density of the SGD product in g/mL. This value can be taken from experimental data, if available. Otherwise, a worst-case value of around 0.2 g/mL could be taken for SGD-MCC-based products and recalculated once experimental data are available.

After determining the maximum batch size (600 g in this case), the initial container load should be calculated as per the following equation:

$$\mathbf{Load_{initial}} = [(\mathrm{Q_{substrate}} \times 100)/(\mathrm{BD_{substrate}} \times \mathrm{V})] = [(110 \times 100)/(0.30 \times 3000] = 12\%$$

Where:

- $Q_{substrate}$ is the amount of substrate (MCC) in g,
- $BD_{substrate}$ is the substrate bulk density in g/mL,
- V is the container working volume in mL.

These calculations highlight the high increase of container load throughout spraying step and emphasizes the significance of obtained SGD density. Formulation and process parameters should be carefully defined to avoid an excessively high final container load, while having enough substrate at the beginning of the process to spray the feed solution over it.

Considering these calculations and steering clear of reaching the maximum occupancy recommended, a smaller SGD batch size of 543 g was defined for this experiment, equivalent to a final blend batch size of 600 g. Consequently, this resulted in a lower initial container load. The initial and final container load were calculated as per the following equations:

$$\mathbf{Load_{initial}} = [(100 \times 100)/(0.30 \times 3000] = 11\%$$

$$\mathbf{Load_{final}} = [(\mathrm{Q_{SGD}} \times 100)/(\mathrm{BD_{SGD}} \times \mathrm{V})] = [(543 \times 100)/(0.25 \times 3000] = 72\%$$

Where:

- Q_{SGD} is the amount of SGD in g,
- BD_{SGD} is the SGD bulk density in g/mL,
- V is the container working volume in mL.

While the final load is within the recommended working range, the initial container load is nearly three times below the minimum recommended load of 30%. Nevertheless, this experiment proved the feasibility of the process, resulting in a higher yield than the one obtained in spray dryer under the evaluated process conditions at the laboratory scale.

The change of the container load throughout spraying process made necessary to adjust some process parameters such as inlet air flow, feed rate, and atomization air pressure. Initially, lower feed rate, atomization pressure, and air flow were established, gradually increasing in tandem with the rising quantity of substrate. The inlet air temperature was adjusted accordingly to maintain the desired product temperature. Even with the initially reduced feed rate, the process time was shorter than that of spray drying under the evaluated conditions at the laboratory scale.

5.1.3. ASDs physical characterization

The obtained SGD and SDD were subjected to XRPD and MDSC analysis to confirm the formation of a homogeneous ASD. Additionally, a comparison of the physical properties of both products was carried out in terms of water content (by means of LOD), density, flow properties, and particles morphology and size (by means of SEM).

Figure 20 displays the XRPD diffractograms confirming the feasibility of producing an ASD of LM2 and HPMCAS-MG in a weight ratio of 1:5 via either fluid bed top-spray granulation or spray drying. The absence of distinct peaks corresponding to crystalline forms of the drug substance in the XRPD patterns indicates the amorphous solid state for the material. The diffraction peak observed at a 22-23º in the SGD sample corresponds to the MCC (see Figure 69 in annex), while the peak at 2θ angle around 21.5º in the SDD sample belongs to the cling foil used during the measurement (see Figure 75 in annex).

Figure 21 presents the MDSC reversing heat flow curve of the SGD powder, revealing a single T_g at around 108ºC, indicative of the formation of a homogeneous ASD of LM2 and HPMCAS-MG. A similar T_g was obtained for SDD powder, suggesting no influence of the technology used on the T_g of this ASD.

As expected and shown in Table 23, fluid bed top-spray granulation resulted in larger particles compared to spray drying due to the agglomeration of ASD and substrate (MCC) particles. Furthermore, fluid bed yielded denser powder with improved flow properties compared to spray dryer, eliminating the necessity of introducing a dry granulation step prior to tableting.

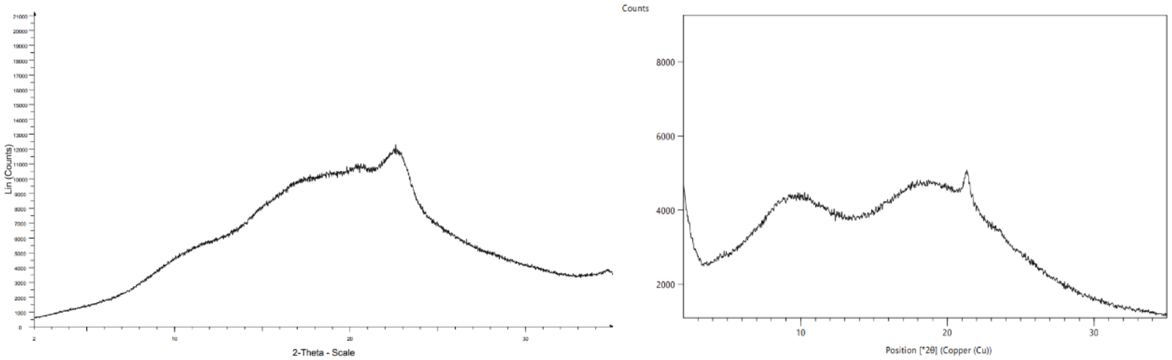


Figure 20. XRPD results of SGD obtained in GPCG-2 fluid bed (left) and SDD obtained in Mini spray dryer B-290 (right).

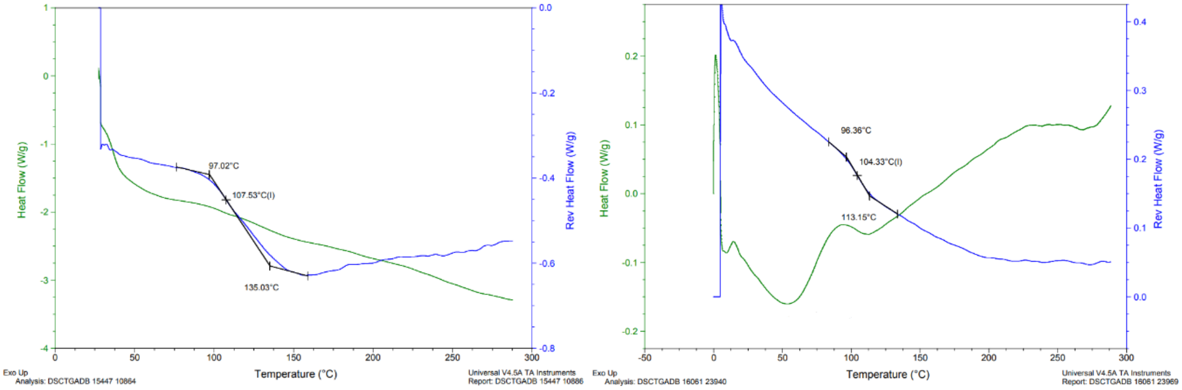
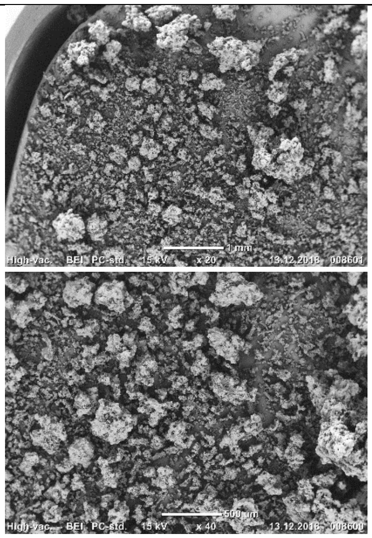
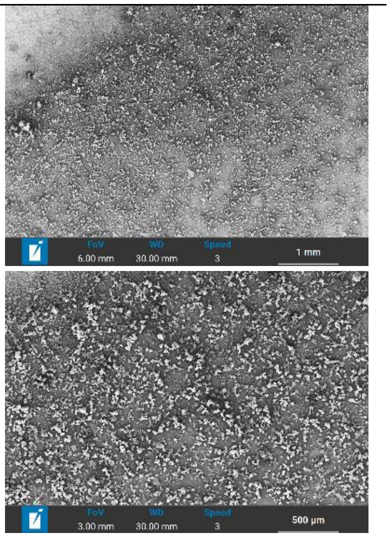
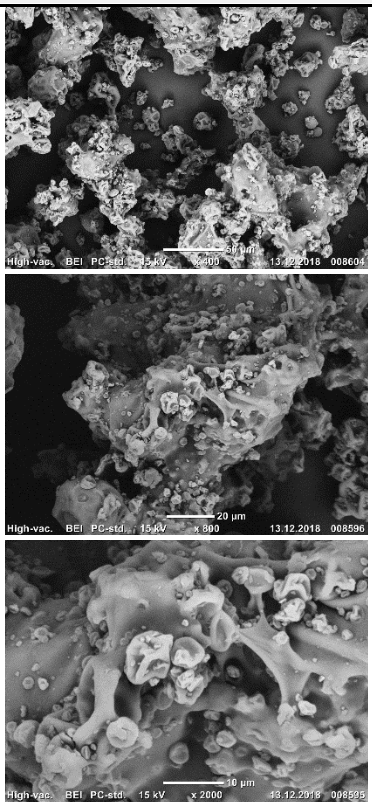
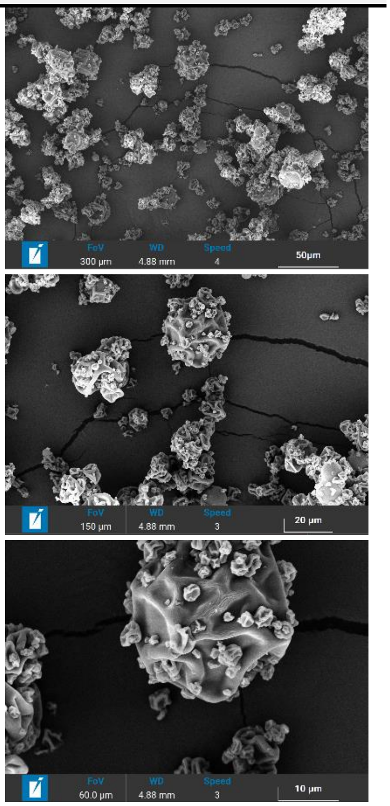


Figure 21. MDSC results of SGD obtained in GPCG-2 fluid bed (left) and SDD obtained in Mini spray dryer B-290 (right).

Table 23. Physical properties of ASDs obtained via granulation in GPCG-2 fluid bed and spray drying in Mini spray dryer B-290.

Manufacturing process	Fluid bed top-spray granulation	Spray drying
Appearance	White to off-white powder	White to off-white powder
Loss on drying (%)	0.9	1.2
Bulk density (g/mL)	0.25	0.19
Tapped density (g/mL)	0.33	0.33
Hausner ratio	1.32	1.74
Carr Index (%)	24	42
Flow by Hausner and Carr Index	Passable	Very, very poor
SEM		

Manufacturing process	Fluid bed top-spray granulation	Spray drying
		

5.1.4. ASDs hygroscopicity

Hygroscopicity plays a crucial role in assessing storage conditions and overall stability of the ASDs. The absorption of water may lead to a reduction in the T_g and trigger crystallization of the amorphous drug substance, thereby affecting the long-term stability of the product. In the case of ASDs produced via fluid bed top-spray granulation, the addition of MCC as a substrate introduces an additional consideration regarding hygroscopicity. MCC, being inherently hygroscopic, has the propensity to absorb moisture from the environment. As a result, the ASD produced in fluid bed (SGD), which incorporates MCC as a substrate, may exhibit higher hygroscopicity compared to ASDs produced via spray drying (SDD). Therefore, understanding the hygroscopic behaviour of the ASD produced via fluid bed becomes essential for ensuring its long-term stability and effectiveness as a pharmaceutical product.

Water uptake of the SDD and SGD material obtained was measured using DVS technique. Figure 22 and Figure 23 show the DVS sorption and desorption kinetic data (the change in mass (dm) and humidity (RH) as a function of time) and isotherm plot at 25ºC and 40ºC.

Examining the DVS change in mass plots (kinetic data), both materials exhibited similar water uptake behaviour and the process is perfectly reversible, as the initial dry mass is recovered after the first cycle. Both material absorbed approximately 6.0% of water at 25ºC and 5.0% at 40ºC, placing them within the Ph. Eur. classification of moderately hygroscopic materials.

The isotherm plot reveals a gap of hysteresis between absorption and desorption isotherms. This indicates that these materials have a bulk absorption, meaning that the water molecules not only pile up on the surface but also go through the bulk of the material. This gap of hysteresis diminishes at higher temperature due to the increased energy input, thereby reducing the energy required for desorption.

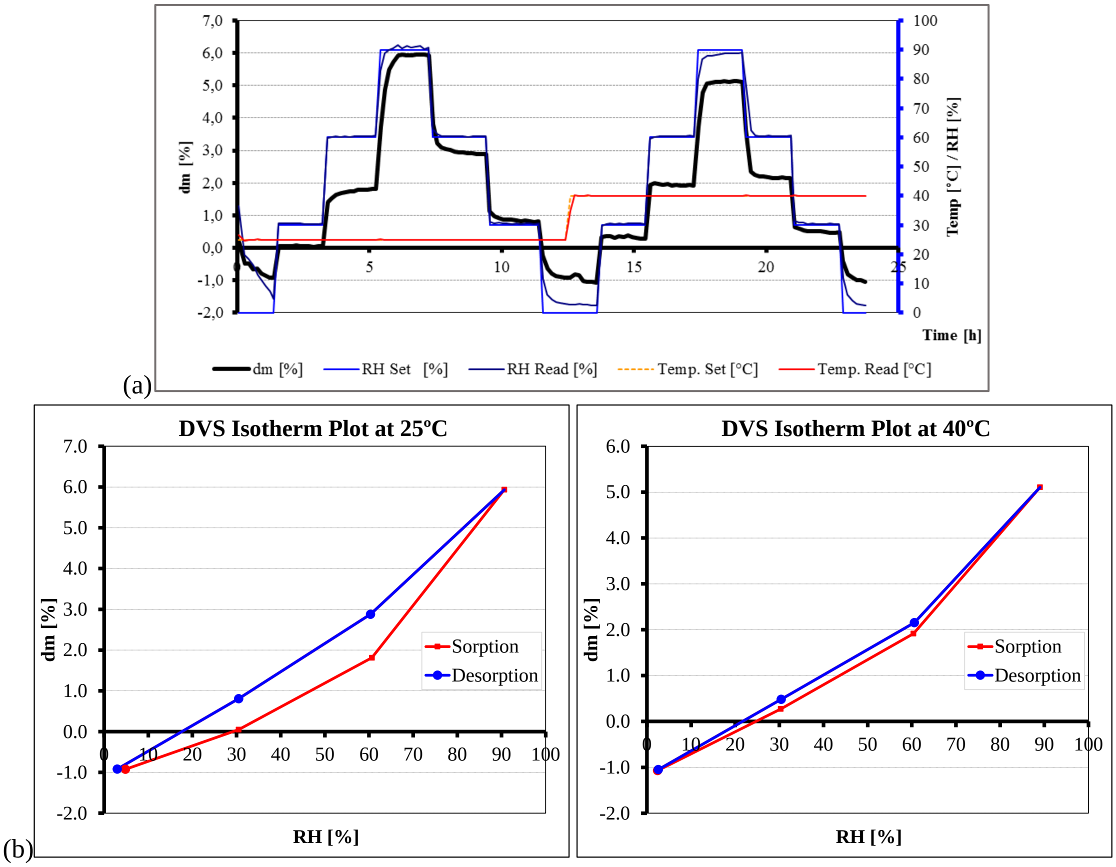


Figure 22. DVS measurements of amorphous SDD of LM2 and HPMCAS-MG in ratio 1:5: (a) change in mass plot and (b) isotherm plot at 25ºC and 40ºC.

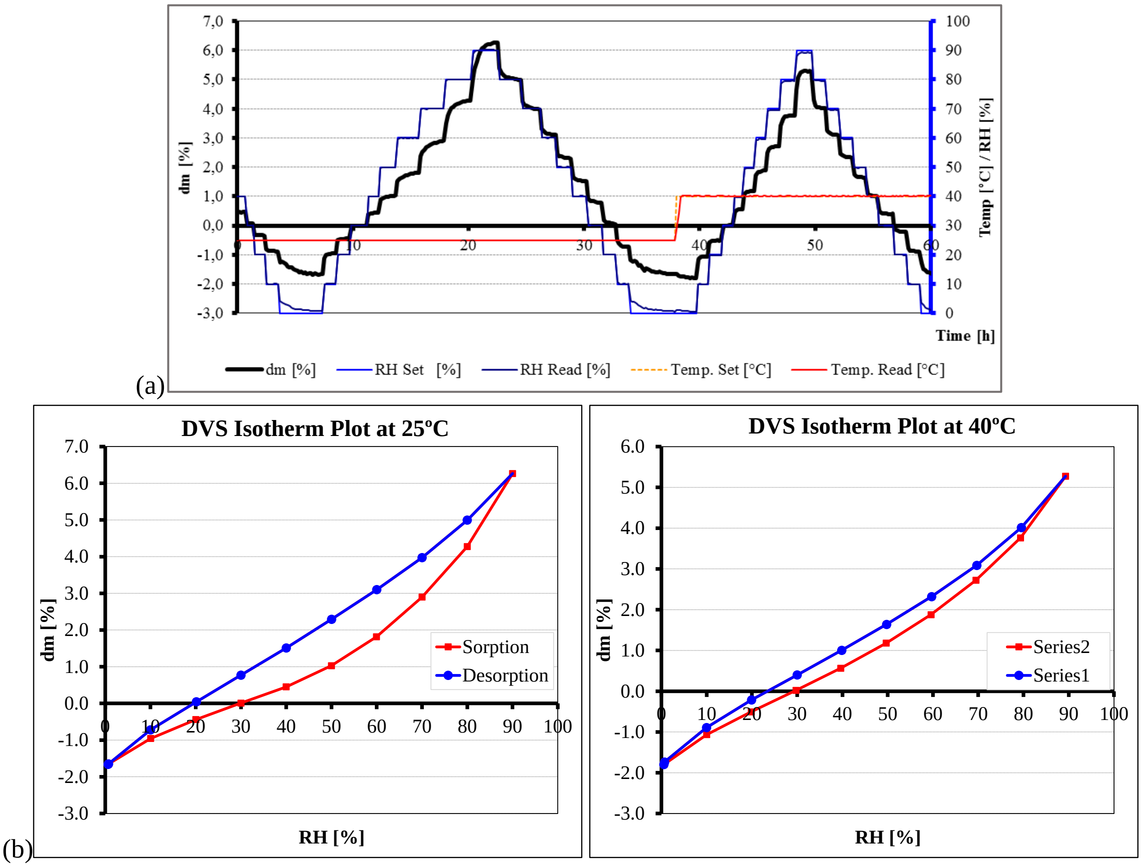


Figure 23. DVS measurements of amorphous SGD of LM2 and HPMCAS-MG in ratio 1:5 and MCC as substrate: (a) change in mass plot and (b) isotherm plots at 25ºC and 40ºC.

5.1.5. Granules characterization

As highlighted in section 5.1.5, a dry granulation step prior to tableting was not required for SGD obtained via fluid bed top-spray granulation, given the good power flow properties for tableting process. In contrast, SDD obtained via spray drying exhibited very poor flow properties. Consequently, a dry granulation step was required to enhance its flow characteristics prior to tableting.

Table 24 provides an overview of the physical properties of the milled granules obtained after dry granulation of SDD material with intragranular excipients. Additionally, Figure 24 compares the PSD of the milled granules with that of the SGD obtained with fluid bed and de-agglomerated through a 0.8 mm mesh. As expected, the milled granules resulting from the dry granulation exhibited improved flow properties in comparison to the original SDD (refer to Table 23). Furthermore, the PSD analysis (see Figure 24) showed a wider range and coarser particles compared to the SGD produced via fluid bed top-spray granulation.

Table 24. Physical properties of milled granules obtained by dry granulation of SDD material with intragranular excipients.

Attributes	**Results**
Appearance	White to off-white granulate powder
Bulk density (g/mL)	0.52
Tapped density (g/mL)	0.64
Hausner ratio	1.23
Carr Index (%)	18
Flow by Hausner and Carr Index	Fair

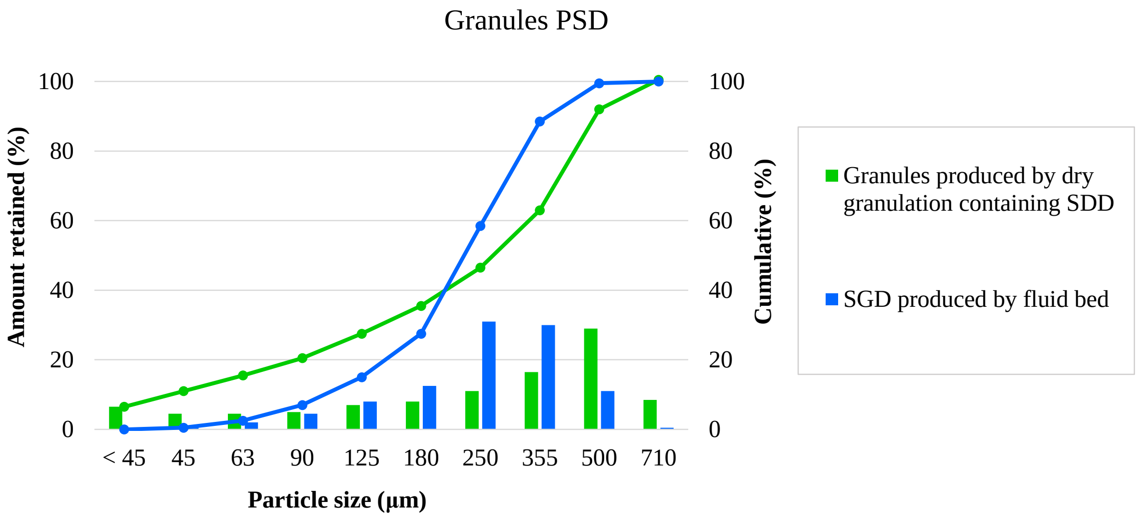


Figure 24. PSD comparison between the granules obtained by dry granulation containing SDD and SGD produced by fluid bed.

5.1.6. Final blend characterization

Table 25 presents a comparison of the characterization results of the final blend formulated with either SGD or SDD materials. The final blend formulated with SGD exhibited a lower density compared to the blend containing SDD material. This difference arose because the latter underwent a dry granulation prior blending with the extragranular excipients, aimed to improve its flow properties.

Table 25. Characterization of final blend containing either SGD or SDD materials.

ASD process	**Fluid bed top-spray granulation**	**Spray drying**
Appearance	White to off-white powder	White to off-white powder
LOD (%)	1.1	1.6
Bulk density (g/mL)	0.28	0.53
Tapped density (g/mL)	0.36	0.67
Hausner ratio	1.28	1.28
Carr Index (%)	22	22
Flow by Hausner and Carr Index	Passable	Passable

5.1.7. Tablets physical characterization and dissolution profile

Table 26 presents a comparison of the characterization results of the uncoated tablets containing either SGD or SDD materials. Similar tablets characteristics were obtained in both cases. These results demonstrate the feasibility of producing tablets formulated with SGD, exhibiting a good tensile strength (1.7 MPa), low variation in tablet weight, and fast disintegration time.

Table 26. Characterization of uncoated tablets formulated with either SGD or SDD materials.

ASD process	**Fluid bed top-spray granulation**	**Spray drying**
Average weight (mg)	652.7 (RSD 0.9%)	652.3 (RSD 0.5%)
Tensile strength (MPa)	1.7	1.8
Friability (%)	0.1	0.0
Disintegration time (min)	< 2	< 5

Further evaluation was conducted on the compression properties of the final blend formulated with SGD material, applying different compression forces and plotting them against the resulting tensile strength. As shown in Figure 25, the final blend showed excellent compression properties, producing tablets with high tensile strength at relatively low compression forces, considering the large dimensions of the tablets (18 x 10 mm).

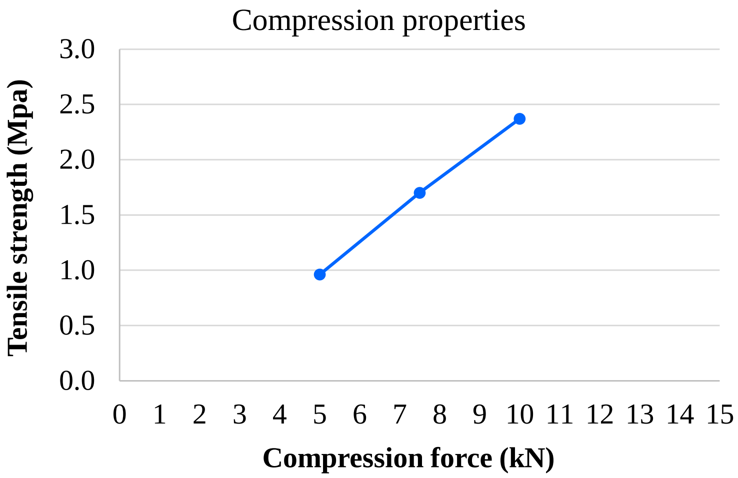


Figure 25. Tensile strength as a function of compression force of SGD final blend.

The dissolution profiles of uncoated tablets of both formulations were assessed and the comparison of the obtained profiles is illustrated in Figure 26. It was observed that tablets formulated with SGD exhibited a significantly slower dissolution profile in comparison to tablets containing SDD material (α<0.05 in all amounts released between formulations from the start to 150 minutes).

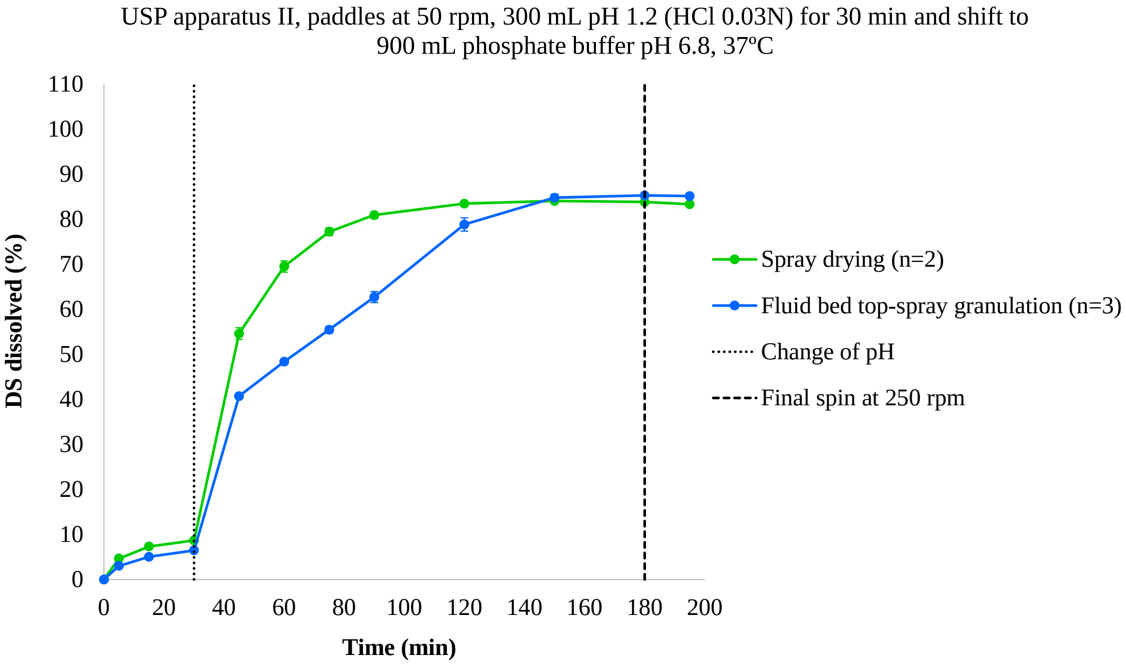


Figure 26. Dissolution profile of uncoated tablets with ASD of LM2 and HPMCAS-MG produced via either spray drying or fluid bed top-spray granulation.

5.1.8. Stability comparison

The choice between fluid bed top-spray granulation and spray drying processes for the production of ASD can significantly influence the stability of the final product. Thus, studies were conducted to evaluate the chemical and physical stability of film-coated tablets formulated with either SGD or SDD materials.

Tablets were film-coated, following the procedure described in section 4.1.6, and stored under elevated temperature and humidity conditions (40ºC and 75%RH) to accelerate potential degradation processes. Additionally, the tablets were packaged in two types of blister packaging materials offering different levels of protection: Al/Al (providing higher protection) and Triplex 180 (offering higher permeability to oxygen and humidity). Stability study design is summarized in Table 27. The following aspects of the film-coated tablets were considered for this assessment:

1. Amorphous solid state
2. Dissolution profile
3. Chemical properties: assay and impurities growth

Table 27. Stability study design.

ASD manufacturing process	Spray drying	Fluid bed top-spray granulation
Downstream processing	Dry granulation, final blending, tableting, and film-coating	Final blending, tableting, and film-coating
DS supplier	Aurisco	Aurisco
Packaging configurations	Al/Al blister Triplex 180 blister	Al/Al blister Triplex 180 blister
Storage conditions	40ºC / 75%RH	40ºC / 75%RH
Last sampling point	6 months	6 months

5.1.8.1. Amorphous solid state stability

The physical stability of the ASD in the final drug product was assessed using XRPD and MDSC. XRPD results (Figure 27 and Figure 28) confirmed the absence of LM2 drug substance crystalline forms, as evidenced by the lack of distinct peaks corresponding to LM2 crystalline forms. The peaks observed aligned with the characteristic patterns of Opadry® yellow 03F32518 and magnesium stearate (see Figure 74 and Figure 72 in annex). Furthermore, MDSC reversing heat flow curves (Figure 29 and Figure 30) revealed a single T_g at around 102 – 104ºC in all samples, indicating no reduction of the T_g and the absence of amorphous-amorphous phase separation or crystallization throughout storage.

These results supported the feasibility of fluid bed for the production of a stable ASD of LM2 and HPMCAS-MG, presenting it as an alternative to spray drying.

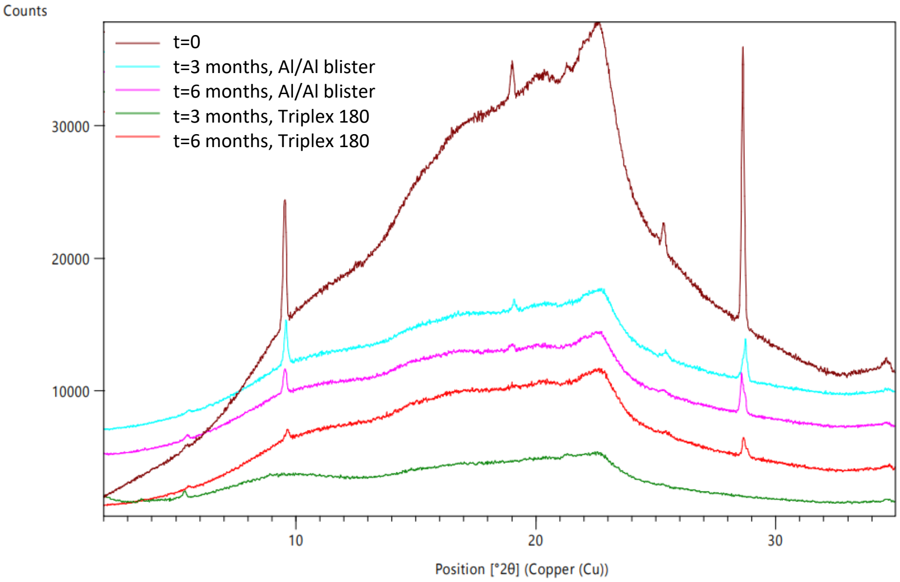


Figure 27. XRPD diffractogram of SDD-based film-coated tablets at initial time point (t=0) and after storage at 40ºC/75%RH in different packaging materials.

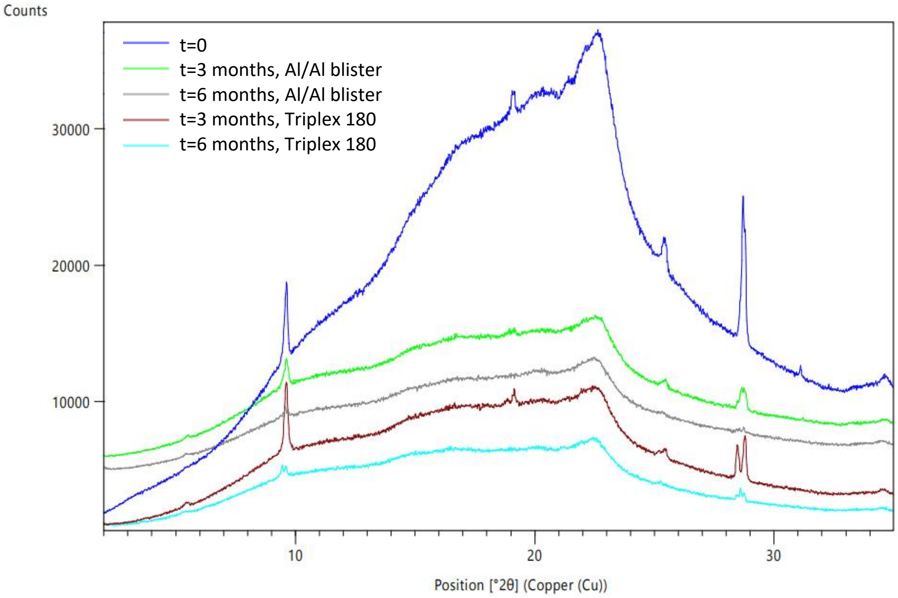


Figure 28. XRPD diffractogram of SGD-based film-coated tablets at initial time point (t=0) and after storage at 40ºC/75%RH in different packaging materials.

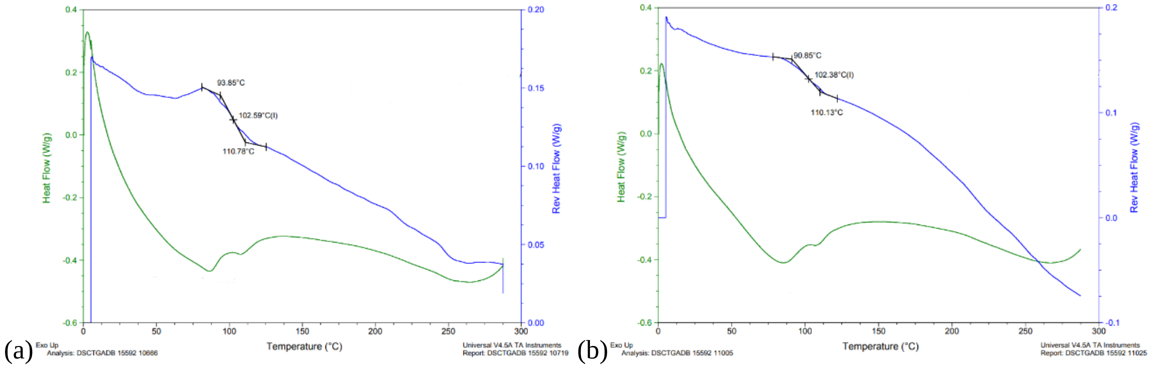


Figure 29. MDSC curves of film-coated tablets containing SDD material after 6 months of storage at 40ºC/75%RH in (a) Al/Al blister and (b) Triplex 180 blister.

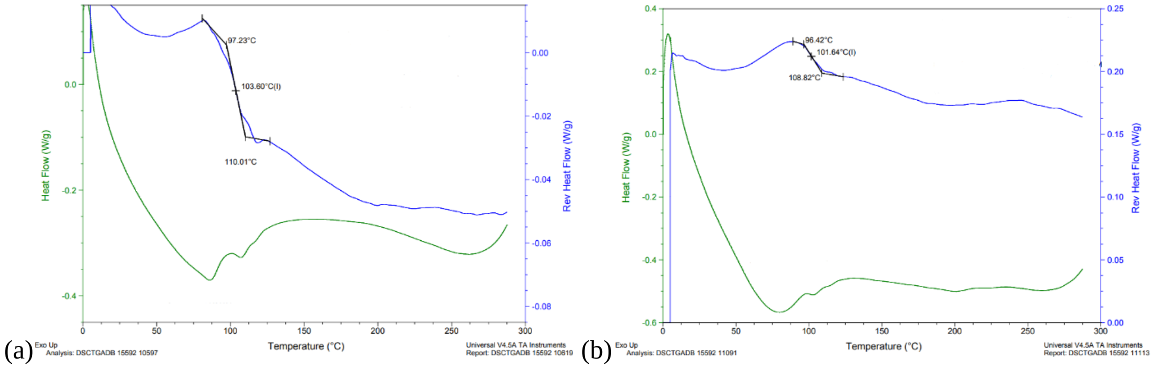


Figure 30. MDSC curves of film-coated tablets containing SGD material after 6 months of storage at 40ºC/75%RH in (a) Al/Al blister and (b) Triplex 180 blister.

5.1.8.2. Dissolution profile

The stability of the drug products dissolution profiles was assessed using a QC dissolution method capable of dissolving the total amount of drug substance. A pH 6.8 medium was chosen due to the higher solubility of the drug substance at this pH, although the addition of a surfactant (SLS) was required. The dissolution method procedure is detailed in section 4.4.7.3. The results obtained, presented in Figure 31 and Figure 32, demonstrate that the dissolution profile of both film-coated tablet formulations remained stable throughout storage as no significant differences were observed along the period and conditions studied (α n.s.).

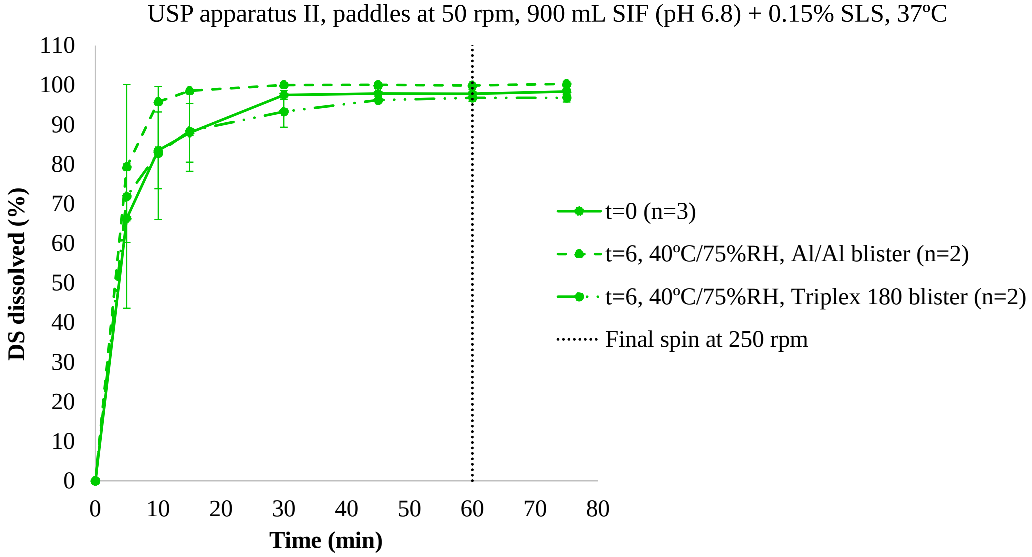


Figure 31. Dissolution profile stability of SDD-based film-coated tablets packaged in either Triplex 180 or Al/Al blisters at 40ºC/75%RH.

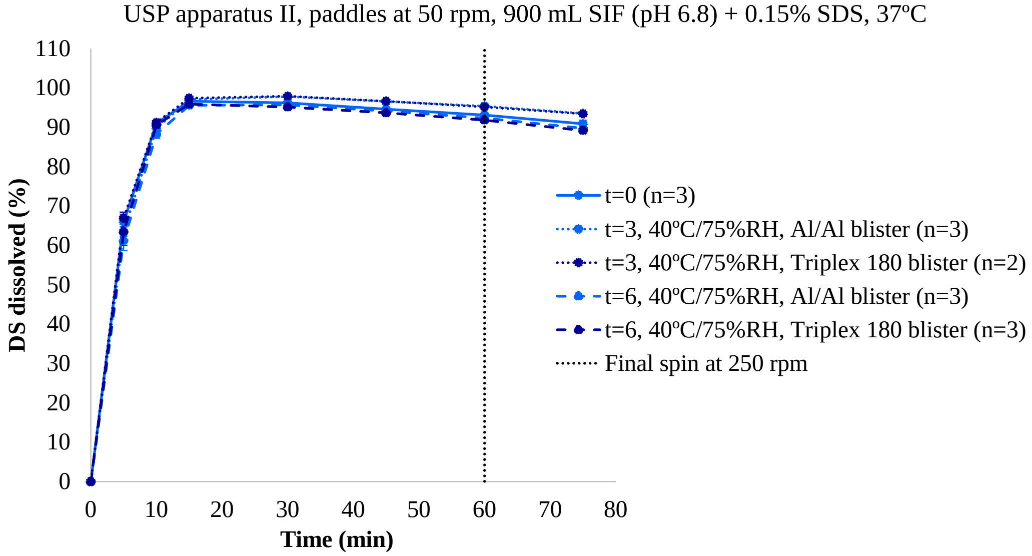


Figure 32. Dissolution profile stability of SGD-based film-coated tablets packaged in either Triplex 180 or Al/Al blisters at 40ºC/75%RH.

5.1.8.3. Assay and impurities

The stability of the drug products assay and impurities growth are summarized in Table 28 and Table 29. These results demonstrated that the assay of both formulations remained stable throughout storage. However, a slightly higher degradation is noted in tablets produced by fluid granulation compared to the ones produced by spray drying, as evidenced by an increase in one impurity, which is an oxo-analog of LM2 formed by oxidation.

Nevertheless, even after 6 months of storage at accelerated conditions, the level of this impurity remains very low and is deemed acceptable from a safety standpoint.

Table 28. Assay and impurities growth throughout stability of SDD-based film-coated tablets packaged in either Triplex 180 or Al/Al blisters at 40ºC/75%RH.

Description		**Film-coated tablets formulated with SDD material**				
Storage conditions		40ºC/75%RH				
Packaging material		NA	Al/Al blister		Triplex 180 blister	
Storage time (months)		0	3	6	3	6
Assay		97.8%	97.6%	99.3%	97.1%	97.9%
Impurities	**Impurity 1**	< 0.10%	< 0.10%	< 0.10%	< 0.10%	< 0.10%
	Largest unspecified	< 0.10%	< 0.10%	< 0.10%	< 0.10%	< 0.10%
	Total unspecified	< 0.10%	< 0.10%	< 0.10%	< 0.10%	< 0.10%
	Total	< 0.10%	< 0.10%	< 0.10%	< 0.10%	< 0.10%

Table 29. Impurities growth throughout stability of SGD-based film-coated tablets packaged in either Triplex 180 or Al/Al blisters at 40ºC/75%RH.

Description		**Film-coated tablets formulated with SGD material**				
Storage conditions		40ºC/75%RH				
Packaging material		NA	Al/Al blister		Triplex 180 blister	
Storage time (months)		0	3	6	3	6
Assay		100.1%	100.2%	101.3%	99.6%	100.1%
Impurities	**Impurity 1**	< 0.10%	< 0.10%	0.11%	< 0.10%	0.11%
	Largest unspecified	< 0.10%	< 0.10%	< 0.10%	< 0.10%	< 0.10%
	Total unspecified	< 0.10%	< 0.10%	< 0.10%	< 0.10%	< 0.10%
	Total	< 0.10%	< 0.10%	0.11%	< 0.10%	0.11%

5.2. DEVELOPMENT OF ASD PROTOTYPES USING FLUID BED TECHNOLOGY

5.2.1. QTPP

Taking into consideration the drug substance properties, the characteristics of the RLD, and the RLD label and target patient population, a QTPP was defined for the development of an immediate release film-coated tablet with an ASD of LM2 produced by fluid bed top-spray granulation.

Table 30. QTPP of generic LM2 film-coated tablets.

QTPP elements		**Target**	**Justification**
Pharmaceutical dosage form		Immediate release film-coated tablets	Pharmaceutical equivalence requirement: same as RLD
Strength		40 and 80 mg. Proportional.	Pharmaceutical equivalence requirement: same as RLD
Administration route		Oral	Pharmaceutical equivalence requirement: same as RLD
Pharmacokinetics		Bioequivalent to RLD	Bioequivalent to RLD: needed to ensure safety and efficacy
Drug product quality attributes	Identification	Positive for LM2	Needed for labeled claim, safety, and efficacy
	Appearance	Lower strength: 10 mm, round, yellow film-coated tablet with inscription Higher strength 17 x 9 mm, oval, yellow film-coated tablet with inscription	Marketing requirement, patient acceptability, and compliance with FDA guideline "Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules"
	Solid state form	Amorphous	The same as the RLD. It may be needed for therapeutic efficacy
	Assay	100% of label claim (95.0-105.0%)	Needed for therapeutic safety and efficacy
	UDU	Complies with Ph. Eur. 2.9.40 or USP <905>	Needed for therapeutic safety and efficacy
	Friability (uncoated tablets)	NMT 1.0% Complies with Ph. Eur. 2.9.7 or USP <1216>	Compendia requirement for tablets. Resistant enough for handling/coating
	Hardness	To be set during development	Needed to ensure integrity of dosage forms throughout manufacturing, handling, storage and transport
	Disintegration time	To be set during development Complies with Ph.Eur. 2.9.1 or USP <701>	Needed to ensure safety and efficacy.
	Dissolution profile	Comparable to RLD and meets relevant pharmacopeia requirement Complies USP monograph (if applicable, when posted)	Needed to ensure safety and efficacy. Regulatory requirement: discriminatory and meet biowaiver requirements.
	Impurities	Specified and unspecified impurities meet ICH Q3B and ICH M7 if applicable	Need to therapeutic safety and efficacy
	Residual solvents	Complies with Ph. Eur 5.4 or USP <467> and ICH Q3C	Needed to ensure safety
	Water content	To be set during development	Pharmaceutical development purposes

QTPP elements		Target	Justification
	Microbial limits	Complies with Ph. Eur. 2.6.12 and 2.6.13 or USP <61> and <62>	Needed to ensure safety
Packaging		Packaging qualified as suitable for this drug product	Needed to achieve the target shelf life and to ensure tablet integrity during shipping
Shelf life		At least 3 years	Same shelf life as RLD: needed for commercialization

Table 31 summarizes the quality attributes of LM2 film-coated tablets and indicates which were classified as drug product CQAs. The identified CQAs are discussed in detailed in subsequent drug substance and formulation risk assessments.

Table 31. Drug product CQAs.

QTPP element	Target	CQA?	Justification of the CQAs
Identification	Positive for LM2	Yes*	Although identification is critical for safety and efficacy, this CQA can be effectively controlled by the quality management system and will be monitored at drug product release. Formulation and process variables do not affect identity. Therefore, this CQA will not be discussed during formulation and process development.
Appearance	Lower strength: 10 mm, round, yellow film-coated tablet with inscription Higher strength 17 x 9 mm, oval, yellow film-coated tablet with inscription	Yes	Appearance is a routine test for compendia requirements for tablets. To get tablets with a correct visual inspection has a low affect on safety and efficacy but is needed for patient acceptability. The target for tablet shape is set based on the RLD to ensure similar ease of swallowing and patient acceptability as described in FDA "Size, shape, and other physical attributes of generic tablets and capsules" guidance. Both formulation and process steps can influence this CQA.
Solid state form	Amorphous as RLD	Yes	LM2 is a BCS class II (low solubility, high permeability) substance with low aqueous solubility across the physiological pH range. An amorphous solid dispersion is used by the RLD to enhance the solubility of the DS and ensure rapid and complete dissolution. The use of a crystalline form is expected to provide slower drug dissolution than RLD and affect efficacy. For that reason, the solid state form is considered as a CQA. Formulation and process variables can affect the solid state form.

QTPP element	Target	CQA?	Justification of the CQAs
Assay	100% of label claim (95.0-105.0%)	Yes	Assay variability will affect safety and efficacy. Formulation and process variables may affect this CQA.
UDU	Complies with Ph. Eur. 2.9.40 or USP <905>	Yes	Variability in UDU will affect safety and efficacy. Both formulation and process variables affect this CQA.
Friability (uncoated tablets)	NMT 1.0% Complies with Ph. Eur. 2.9.7 or USP <1216>	No	A target of NMT 1.0% mean weight loss is set according to the compendia requirement and to minimize post-marketing complaints regarding tablet appearance. This target friability assures a low affect on safety and efficacy and minimize customers complaints.
Hardness	To be set during development	Yes	Failure to meet the hardness specification could affect the integrity of the dosage forms throughout the manufacturing process and shelf-life. It will affect patients acceptability. Both formulation and process variables can affect this CQA.
Disintegration time	To be set during development Complies with Ph. Eur. 2.9.1 or USP <701>	Yes	Failure to meet the disintegration time specification could affect bioavailability, therefore efficacy and safety. Both formulation and process variables can affect this CQA.
Dissolution profile	Comparable to RLD and meets relevant pharmacopeia requirement Complies USP monograph (if applicable, when posted)	Yes	Failure to meet the dissolution specification could affect bioavailability, therefore efficacy and safety. Both formulation and process variables can affect this CQA.
Impurities	Specified and unspecified impurities meet ICH Q3B and ICH M7 if applicable	Yes	Impurities can affect safety and should be controlled based on ICH requirements or RLD characterization to limit patient exposure. Formulation and process variables can affect this CQA. In case any unspecified impurity will be above the specification limit, it has to comply with ICH Q3B and ICH M7.
Residual solvents	Complies with Ph. Eur. 5.4 or USP <467> and ICH Q3C	Yes	Residual solvents can affect safety. This CQA will be discussed during formulation and process development.
Water content	To be set during development based on the final selected formulation	Yes	Water content may affect degradation and microbial growth of the product affecting safety. This CQA will be discussed during formulation and process development.

QTPP element	Target	CQA?	Justification of the CQAs
Microbial limits	Complies with Ph. Eur. 2.6.12 & 2.6.13 or USP <61> and <62>	Yes*	Non-compliance with microbial limits will affect patient safety. Water activity (a_w) of the formulation will be measured. If a_w is below 0.6 the risk of microbial growth is considered very low.

*Formulation and process variables are unlikely to affect the CQA. Therefore, the CQA will not be investigated and discussed in detail in subsequent risk assessment and pharmaceutical development. However, the CQA remains a target element of the product profile and should be addressed accordingly.

5.2.2. Drug substance initial risk assessment

A risk assessment of the DS attributes was performed to evaluate the influence that each attribute could have on the DP CQAs. The outcome of the assessment and the accompanying justification is provided below. The relative risk ranking system was used throughout pharmaceutical development and is summarized in Table 32.

Table 32. Overview of relative risk ranking system.

High	Risk is unacceptable. Further investigation is needed to reduce the risk.
Medium	Risk is acceptable. Further investigation may be needed in order to reduce the risk.
Low	Broadly acceptable risk. No further investigation is needed.

Based upon physicochemical and biological properties of the DS, the initial RA of DS attributes on DP CQAs is presented in Table 33, and the justification for the risk assignment is given in Table 34. According to the risk assessment provided, the DS solid state form and chemical stability are identified as the primary attributes posing risks to affect the quality of the DP. Consequently, formulation studies were carried out to assess and mitigate these risks.

Table 33. Initial RA for DS attributes.

DP CQA	Critical parameters of LM2 DS									
	Appearance	Solid state form	PSD	Hygroscopicity	Solubility	Moisture content	Residual solvents	Process impurities	Chemical stability	Flow properties
Appearance	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Solid state form	Low	Medium	Low	Low	Low	Low	Low	Low	Low	Low
Assay	Low	Low	Low	Low	Low	Low	Low	Low	Medium	Low
UDU	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Hardness	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Disintegration time	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low

DP CQA	Critical parameters of LM2 DS									
	Appearance	Solid state form	PSD	Hygroscopicity	Solubility	Moisture content	Residual solvents	Process impurities	Chemical stability	Flow properties
Dissolution profile	Low	High	Low	Low	Low	Low	Low	Low	Low	Low
Residual solvents	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Stability (Impurities & WC)*	Low	Medium	Low	Low	Low	Low	Low	Low	Medium	Low

*General impurities are considered in this DP CQA. In case of some impurity needs to be identified a full RA will be initiated.

Table 34. Justification for the initial RA of the DS attributes.

DS attributes	DP CQAs	Justification
Appearance	Appearance	The risk that the appearance of the DS will affect the DP CQAs is considered low. This is primarily due to the dissolution of the DS during the manufacturing process of the DP and the production of a homogeneous ASD. Additionally, the subsequent film-coating of the tablet further mitigates the risk by providing uniform external layer.
	Solid state form	
	Assay	
	UDU	
	Hardness	
	Disintegration time	
	Dissolution profile	
	Residual solvents	
	Stability (Impurities & WC)	
Solid state form (DS raw material present in crystalline Form A, but amorphous DS produced in final DP)	Appearance	The risk is low considering that the DS is dissolved to form an ASD and that tablets are film-coated.
	Solid state form	DS solid state form will have a direct influence on this DP CQA. The DS is initially in the crystalline form A but is intended to be dissolved and transformed into an amorphous solid state during the manufacturing process of the final DP. While the risk of the solid state form of the DS raw material is considered low given the described process, amorphous material tends to exhibit higher reactivity compared to their crystalline counterparts due to their disordered molecular structure and higher free energy. This may lead to recrystallization during storage. To address this risk, the amorphous DS is stabilized in an ASD with a polymeric carrier. Stability studies conducted during feasibility phase (see section 5.1.8) demonstrated that the amorphous DS is stable in an ASD with HPMCAS-MG. Nevertheless, the risk is considered medium until additional stability data of proposed prototypes are generated.
	Assay	Low influence of the DS solid state form is expected on these DP CQAs considering that the DS crystalline form A will be dissolved
	UDU	
	Hardness	

DS attributes	DP CQAs	Justification
	Disintegration time	during the DP manufacturing process and dispersed into a polymeric carrier. The risk is low.
	Dissolution profile	Apparent solubility can differ from different solid state forms affecting DP dissolution profile. As previously mentioned, DS crystalline form A is going to be processed into a stabilized ASD during the manufacturing process of the DP. DS in amorphous state exhibits a higher free energy which results in enhanced dissolution profile. Therefore, the risk is considered high.
	Residual solvents	DS form A supplied meets the requirements of residual for pharmaceutical articles in the current USP/NF General Chapter <467>, Ph. Eur. General Chapter 5.4, and ICH Q3C. Therefore, the contribution of residual solvents from the DS is limited. The risk is considered low.
	Stability (Impurities & WC)	DS with different solid state forms may have different chemical stability affecting DP stability. During the manufacturing process of the DP, the amorphous DS is intended to be obtained. As previously mentioned, amorphous material tends to exhibit higher reactivity and free energy compared to their crystalline counterparts. This can result in higher chemical degradation and water uptake. Considering the stability studies carried out during feasibility studies on formulation containing LM2 ASD (see section 5.1.8), low growth of impurities were observed after 6 months of storage at 40ºC/75%RH in both Al/Al and Triplex 180 blisters. Nevertheless, the risk is considered medium until additional stability data on proposed prototypes are generated.
PSD	Appearance Solid state form Assay UDU Hardness Disintegration time Dissolution profile Residual solvents Stability (Impurities & WC)	No influence of the DS PSD on these CQAs is expected considering that the DS is going to be dissolved and processed into an ASD. The risk is low.
Hygroscopicity	Appearance	It is not expected that the hygroscopicity of the DS will effect the DP appearance. The risk is considered low.
	Solid state form	LM2 crystalline form A is non-hygroscopic. However, DS will be present in its amorphous form in the final DP, which tend to be more hygroscopic compared to their crystalline counterparts. Higher absorption of moisture from the surrounding environment can lead to recrystallization, assay reduction due to DS degradation, impurities growth, and changes in dissolution rate. Considering the stability studies carried out during feasibility studies on formulation containing an LM2 ASD (see section
	Assay	

DS attributes	DP CQAs	Justification
		5.1.8), DS amorphous state, assay, and dissolution profile showed to be stable after 6 months of storage at 40ºC/75%RH in both Al/Al and Triplex 180 blisters. Therefore, the risk is considered low and is mainly associated to the rest of formulation components.
	UDU	No influence of DS hygroscopicity on this DP CQA is expected. The risk is low.
	Hardness	Hygroscopic drug substances can absorb moisture from the air, leading to an increase in the overall moisture content of the tablet. Excessive moisture can cause the tablet to swell or disintegrate, affecting its integrity and dissolution characteristics. However, the risk is considered low as, during feasibility studies (see section 5.1.8), the dissolution profile showed to be stable after 6 months of storage at 40ºC/75%RH in both Al/Al and Triplex 180 blisters. Therefore, the risk is mainly associated to the rest of formulation components.
	Disintegration time	
	Dissolution profile	The risk is considered low. Refer to the rational provided for the solid state form and assay CQAs.
	Residual solvents	No influence of DS hygroscopicity on this DP CQA is expected. The risk is low.
	Stability (Impurities & WC)	The risk is considered low. Refer to the rational provided for the solid state form and assay CQAs.
Solubility	Appearance	Solubility does not affect these CQAs. The risk is low.
	Solid state form	
	Assay	
	UDU	
	Hardness	
	Disintegration time	
	Dissolution profile	LM2 is practically insoluble in water between pH 1 and 11, and it is classified as a BCS class II compound. While equilibrium solubility is intrinsic to the DS, apparent solubility can differ from different solid state forms affecting DP dissolution profile and bioavailability. During the manufacturing process of the DP, LM2 crystalline material is dissolved and processed into a stabilized ASD. Considering that the same strategy is followed by the RLD, the risk is considered low, as it is mainly associated to the DS solid state form.
	Residual solvents	Solubility does not affect these CQAs. The risk is low.
	Stability (Impurities & WC)	
Moisture content	Appearance	Moisture content does not affect this CQA. The risk is low.
	Solid state form	The water content in the LM2 crystalline form A is very low, not exceeding 0.5%. Consequently, the risk of affecting these DP CQAs is deemed low.
	Assay	
	UDU	

DS attributes	DP CQAs	Justification
	Hardness	
	Disintegration time	
	Dissolution profile	
	Residual solvents	Moisture content does not affect this CQA. The risk is low.
	Stability (Impurities & WC)	The water content in the LM2 crystalline form A is very low, not exceeding 0.5%. Consequently, the risk of affecting DP stability is considered low.
Residual solvents	Appearance	Residual solvents are controlled in the DS specification and comply with ICH Q3C. Within this range, residual solvents are unlikely to influence these DP CQAs. The risk is low.
	Solid state form	
	Assay	
	UDU	
	Hardness	
	Disintegration time	
	Dissolution profile	
	Residual solvents	
	Stability (Impurities & WC)	
Process impurities	Appearance	Total impurities are controlled in the DS specification (NMT 1.0%). Impurity limits comply with ICH Q3A recommendations. Within this range, process impurities are unlikely to influence these CQAs. The risk is low.
	Solid state form	
	Assay	
	UDU	
	Hardness	
	Disintegration time	
	Dissolution profile	
	Residual solvents	
	Stability (Impurities & WC)	
Chemical stability	Appearance	DS chemical stability is unlikely to influence these DP CQAs. The risk is considered low.
	Solid state form	
	Assay	LM2 DS chemical stability may affect DP purity profile and consequently assay. The crystalline DS is transformed into amorphous during the DP manufacturing process. Amorphous forms generally exhibit lower chemical stability. Nevertheless, stability studies carried out during feasibility studies on formulation containing an LM2 ASD (see section 5.1.8), demonstrated that DP assay was stable after 6 months of storage at 40ºC/75%RH in both Al/Al and Triplex 180 blisters. The risk is considered medium until additional stability data on proposed prototypes are generated.
	UDU	These CQAs are unrelated to DS chemical stability. The risk is low.
	Hardness	
	Disintegration time	
	Dissolution profile	
	Residual solvents	

DS attributes	DP CQAs	Justification
	Stability (Impurities & WC)	The risk is high. Refer to the justification provided for assay.
Flow properties	Appearance	During the manufacturing process of the DP, DS is dissolved in an appropriate solvent and molecularly dispersed into a polymeric carrier matrix. Thus, the DS flow properties will not affect these DP CQAs. The risk is low.
	Solid state form	
	Assay	
	UDU	
	Hardness	Flow properties of the DS do not affect these CQAs. The risk is low.
	Disintegration time	
	Dissolution profile	
	Residual solvents	
	Stability (Impurities & WC)	

5.2.3. Formulation initial risk assessment

One of the aims of this work was to develop different formulation prototypes of immediate-release film-coated tablets comprising an ASD of LM2 with a polymeric carrier prepared by fluid bed top-spray granulation. This work was done taking as a reference the higher strength of the drug product, which was subsequently used to conduct an *in vivo* pilot BA study.

Considering that LM2 drug substance is a BCS class II compound, the formulation components, and the manufacturing process (fluid bed granulation, tableting, and film-coating), a risk assessment was carried out to identify the critical formulation variables and their influence on DP CQAs prior to initiating formulation studies.

The outcome of the initial RA of the formulation variables is presented in Table 35 and the justification of the risk assignment is given in Table 36. The DS attributes ranked as high/medium risk in the initial RA of the DS (see Table 33) were included as part of the initial RA of the formulation.

Table 35. Initial RA of the formulation variables.

Drug product CQAs	Critical parameters of formulation components									
	DS		Carrier	Solvent	Filler	Glidant	Disintegrant	Surfactant	Lubricant	Coating agent
	Solid state form	Chemical stability	Type, grade, and %	Type	Type, grade and %	%	Type and %	Type and %	Type and %	Type and weight gain
Appearance	Low	Low	High	Medium	Medium	Low	Low	Low	Medium	Low
Solid state form	Medium	Low	High	High	High	Low	Medium	High	Low	Low
Assay	Low	Medium	High	High	Medium	Medium	Low	Low	Low	Low
UDU	Low	Low	Low	High	Medium	Medium	Low	Low	Low	Low
Hardness	Low	Low	High	Medium	High	Low	Low	Low	Medium	Low
Disintegration time	Low	Low	Medium	Medium	High	Low	High	High	Medium	Low
Dissolution profile	High	Low	High	Medium	High	Low	High	High	Medium	Low
Residual solvents	Low	Low	High	High	Low	Low	Low	Low	Low	Low
Stability (Impurities & WC)*	Medium	Medium	High	High	High	Low	Low	High	Low	Low

*General impurities are considered in this DP CQA. In case of some impurity needs to be identified a full RA will be initiated.

Table 36. Justification for the initial RA of the formulation variables.

Formulation variable	**DP CQAs**	**Justification**
Solid state form (DS raw material present in crystalline Form A, but amorphous DS produced in final DP)	Appearance	The risk is low considering that the DS is dissolved to form an ASD and that tablets are film-coated.
	Solid state form	DS solid state form will have a direct influence on this DP CQA. The DS is initially in the crystalline form A but is intended to be dissolved and transformed into an amorphous solid state during the manufacturing process of the final DP. While the risk of the solid state form of the DS raw material is considered low given the described process, amorphous material tends to exhibit higher reactivity compared to their crystalline counterparts due to their disordered molecular structure and higher free energy. This may lead to recrystallization during storage. To address this risk, the amorphous DS is stabilized in an ASD with a polymeric carrier. Stability studies conducted during feasibility phase (see section 5.1.8) demonstrated that the amorphous DS is stable in an ASD with HPMCAS-MG. Nevertheless, the risk is

Formulation variable	DP CQAs	Justification
		considered medium until additional stability data of proposed prototypes are generated.
	Assay UDU Hardness Disintegration time	Low influence of the DS solid state form is expected on these DP CQAs considering that the DS crystalline form A will be dissolved during the DP manufacturing process and dispersed into a polymeric carrier. The risk is low.
	Dissolution profile	Apparent solubility can differ from different solid state forms affecting DP dissolution profile. As previously mentioned, DS crystalline form A is going to be processed into a stabilized ASD during the manufacturing process of the DP. DS in amorphous state exhibits a higher free energy which results in enhanced dissolution profile. Therefore, the risk is considered high.
	Residual solvents	DS form A supplied meets the requirements of residual for pharmaceutical articles in the current USP/NF General Chapter <467>, Ph. Eur. General Chapter 5.4, and ICH Q3C. Therefore, the contribution of residual solvents from the DS is limited. The risk is considered low.
	Stability (Impurities & WC)	DS with different solid state forms may have different chemical stability affecting DP stability. During the manufacturing process of the DP, the amorphous DS is intended to be obtained. As previously mentioned, amorphous material tends to exhibit higher reactivity and free energy compared to their crystalline counterparts. This can result in higher chemical degradation and water uptake. Considering the stability studies carried out during feasibility studies on formulation containing LM2 ASD (see section 5.1.8), low growth of impurities were observed after 6 months of storage at 40ºC/75%RH in both Al/Al and Triplex 180 blisters. Nevertheless, the risk is considered medium until additional stability data on proposed prototypes are generated.
Chemical stability	Appearance Solid state form	DS chemical stability is unlikely to influence these DP CQAs. The risk is considered low.
	Assay	LM2 DS chemical stability may affect DP purity profile and consequently assay. The crystalline DS is transformed into amorphous during the DP manufacturing process. Amorphous forms generally exhibit lower chemical stability. Nevertheless, stability studies carried out during feasibility studies on formulation containing an LM2 ASD (see section 5.1.8), demonstrated that DP assay was stable after 6 months of storage at 40ºC/75%RH in both Al/Al and Triplex 180 blisters. The risk is considered medium until additional stability data on proposed prototypes are generated.
	UDU Hardness Disintegration time	These CQAs are unrelated to DS chemical stability. The risk is low.

Formulation variable	DP CQAs	Justification
	Dissolution profile	
	Residual solvents	
	Stability (Impurities & WC)	The risk is high. Refer to the justification provided for assay.
Carrier – type, grade and %	Appearance	The carrier is dissolved during the manufacturing process. The carrier type, grade and percentage might affect the solution viscosity, potentially affecting the SGD properties such as density and PSD. These properties, in turn can affect powder compression characteristics and, ultimately, tablet appearance. In feasibility studies with HPMCAS-MG, tablets without defects and low friability were obtained. Given that HPMCP HP-55 will also be evaluated as a polymeric carrier, and that it constitutes a significant percentage of the total tablet weight, the associated risk is considered high.
	Solid state form	Carrier type, grade, and ratio to DS are critical for stabilizing the DS in amorphous state. HPMCAS-MG demonstrated to be effective during feasibility studies. Nevertheless, HPMCP HP-55 will be evaluated as alternative polymeric carrier. Consequently, the risk of affecting this CQA is assessed as high.
	Assay	DS is intended to be molecularly dispersed within the polymeric carrier matrix, so both components will be in close contact. Carrier type, grade and percentage can affect the chemical stability of the DS and consequently it can directly influence the DP assay and impurities growth. In feasibility studies (refer to section 5.1.8), DP formulated with HPMCAS-MG as carrier showed stable assay values after 6 months of storage at 40ºC/75%RH in both Al/Al and Triplex 180 blisters. Nevertheless, the risk is considered high as HPMCP HP-55 will be evaluated.
	UDU	Given that the DS is intended to be dispersed at a molecular level within the polymeric carrier matrix, and that the resulting ASD will constitute a high proportion of the total tablet weight, the risk is considered low.
	Hardness	The compression properties of the carrier might affect tablet binding and, consequently, tablet hardness. Given its significant percentage in the formulation, the risk is initially considered high.
	Disintegration time	Polymers such as HPMCAS and HPMCP, among others, are used as carriers for ASDs. However, these polymers also exhibit enteric properties. Thus, the choice of carrier type, grade, and percentage could affect the wettability of the tablet, subsequently affecting its disintegration time. Considering that a fast tablet disintegration time (< 2 min) was obtained during feasibility studies with HPMCAS-MG, the risk is initially considered medium.

Formulation variable	**DP CQAs**	**Justification**
	Dissolution profile	Polymeric carriers can play a role on DS solubility enhancement and consequently on dissolution profile. Thus, the carrier type, grade, and percentage can have an effect on this DP CQA. The risk is considered high.
	Residual solvents	Carrier should meet the requirements of residual solvents for pharmaceutical articles in the current USP/NF General Chapter <467>, Ph. Eur. General Chapter 5.4 and ICH Q3C. Hence, the contribution of residual solvents from the carrier should be limited. Nevertheless, since the carrier is intended to be dissolved in an organic solvent, it could play a role in the solvent removal due to carrier – solvent interaction. In feasibility trials with HPMCAS-MG and acetone, no issues to reduce acetone content below the limit of 5000 ppm were observed (Table 22). Nevertheless, considering that HPMCP HP-55 will be evaluated as alternative polymer, the risk is initially considered high.
	Stability (Impurities & WC)	Since an ASD with a polymeric carrier is intended to be developed, both DS and carrier will be in close contact. Carrier type, grade, and percentage could promote the degradation of the DS and could directly influence DP stability. Considering that HPMCP HP-55 will be evaluated as alternative polymers to HPMCAS-MG, the risk is considered high until further assessment is conducted.
Solvent – type	Appearance	The solvent type might affect the solution viscosity, potentially affecting the SGD properties such as density and PSD. These factors, in turn, may affect powder compression characteristics and, consequently, the appearance of the tablet. In feasibility studies, acetone was selected as a solvent for the dissolution of the DS and HPMCAS-MG, leading to tablets without defects and low friability. A proper solvent type should be selected for dissolution of HPMCP HP-55. The risk is considered medium until further evaluation is carried out.
	Solid state form	Complete dissolution of both the DS and carrier in the solvent is essential to achieve a homogeneous ASD after spraying and throughout storage. Acetone was selected as the solvent to dissolve the DS and HPMCAS-MG, given their sufficiently high solubility to prevent any precipitation or phase separation during the spraying process, which could lead to DS crystallization. HPMCP HP-55, which will be evaluated as alternative polymeric carrier, also demonstrates sufficiently high solubility in several organic solvents. Nevertheless, the risk is regarded as high until studies with this polymer are conducted.
	Assay	DS is dissolved in the solvent, so these components are in close contact. Solvent can affect the chemical stability of the DS and consequently can directly influence DP assay, UDU, and

Formulation variable	DP CQAs	Justification
	UDU	impurities. In feasibility studies (refer to section 5.1.8), DP formulated with acetone and HPMCAS-MG showed stable assay values after 6 months of storage at 40ºC/75%RH in both Al/Al and Triplex 180 blisters. Nevertheless, the risk is considered high until studies with the solvent selected for HPMCP HP-55 polymer are carried out.
	Hardness	Solvent type could have an influence on SGD properties such as PSD and density. This could have an influence on powder compression properties and, consequently, on tablet hardness, disintegration time, and dissolution profile. Nevertheless, these SGD properties can also be controlled by fluid bed process parameters. Thus, the risk is considered medium.
	Disintegration time	
	Dissolution profile	
	Residual solvents	Considering that the DS is practically insoluble in water, organic solvents need to be used. The volatility of the solvent, its solubility in the matrix, and the efficiency of the manufacturing process in removing residual solvents are key factors on the residual solvents level. In feasibility trials acetone was selected as the solvent to dissolve the DS and HPMCA-MG. No issues to reduce acetone content below the limit of 5000 ppm were observed (Table 22). Nevertheless, the risk is considered high until studies with the solvent selected for HPMCP HP-55 polymer are carried out.
	Stability (Impurities & WC)	The risk is high. See justification given for assay and UDU.
Filler – type, grade and %	Appearance	The filler will be used as a substrate for the ASD. The type, grade, and percentage of filler can have an influence on powder density and compression properties, which in turn can influence DP appearance. Considering that a filler with good density and compression properties will be selected and that tablets with good appearance were obtained in feasibility studies, the risk is initially considered medium.
	Solid state form	The stability of the amorphous DS in the final DP will be mainly affected and controlled by the carrier, the solubility of the DS on the selected solvent, and manufacturing process parameters. However, considering the close contact of the filler with the ASD, it could play a role on the recrystallization of the DS. During feasibility studies, MCC was used a substrate and amorphous solid state should to be stable after 6 months of storage at 40ºC/75%RH in both Al/Al and Triplex 180 blisters. Nevertheless, different filler type and percentage will be evaluated. Therefore, the risk is considered high until further evaluation is carried out.
	Assay	The filler type and grade can show different densities and flow properties which can have an influence on blending and tableting

Formulation variable	**DP CQAs**	**Justification**
	UDU	(die filling) steps. Thus, DP assay and UDU could be affected by the filler type, grade, and percentage. Considering that fillers with good flow and compression properties will be selected, the risk is considered medium.
	Hardness	Different type, grade, and percentage of filler could exhibit different solubility and compression properties which can have an influence on the tablet hardness, disintegration time and, ultimately, the dissolution profile. Different filler type and percentage will be evaluated. The risk is initially considered high.
	Disintegration time	
	Dissolution profile	
	Residual solvents	Residual solvents content in the DP is mainly related to the solvent used to dissolve the DS and the carrier, and also to the manufacturing process parameters. Additionally, filler should meet the requirements of residual solvents for pharmaceutical articles in the current USP/NF General Chapter <467>, Ph. Eur. General Chapter 5.4 and ICH Q3C. Thus, the contribution of residual solvents from the filler should be limited. The risk is considered low.
	Stability (Impurities & WC)	In feasibility studies, stability of a formulation with MCC as substrate of the ASD showed a low level of impurities growth, indicating no incompatibility between DS and MCC. Considering that alternative filler types will be evaluated, the risk is considered high until further evaluation is conducted.
Glidant – %	Appearance	Glidant usually represents a low percentage on the total formulation. Thus, the risk to influence the DP appearance is considered low.
	Solid state form	The stability of the amorphous DS in the final DP will be mainly affected and controlled by the carrier, the solubility of the DS on the selected solvent, and manufacturing process parameters. No influence of the glidant on this CQA is expected. The risk is considered low.
	Assay	In general, glidant is used to improve flow properties of blends. Therefore, a blend with poor flowability properties may influence assay and UDU. Considering the high percentage of ASD in the formulation, the risk is considered medium.
	UDU	
	Hardness	It is not expected that the glidant affect these CQAs due to its low amount in the formulation. The risk is considered low.
	Disintegration time	
	Dissolution profile	
	Residual solvents	Anhydrous colloidal silica is intended to be used as glidant. This excipient does not contain any solvent listed in class 1, class 2 or class 3, nor any other specified or unspecified solvent. Thus, the risk is considered low.
	Stability (Impurities & WC)	During feasibility studies, stability studies were carried out on a formulation containing anhydrous colloidal silica as glidant. Low

Formulation variable	DP CQAs	Justification
		level of impurities growth was observed, indicating no incompatibility between DS and this excipient. The risk is considered low.
Disintegrant – type and %	Appearance	The disintegrant usually represents a low percentage on the total tablet formulation. Thus, the risk to influence the DP appearance is considered low.
	Solid state form	Croscarmellose sodium will be used as disintegrant. The addition of this excipient in the intragranular phase (as a substrate) will be evaluated. Considering the close contact of the disintegrant with the ASD and that croscarmellose sodium is hygroscopic, it could play a role on the recrystallization of the DS. During feasibility studies, this disintegrant was added extragranularly and amorphous DS should to be stable after 6 months of storage at 40ºC/75%RH in both Al/Al and Triplex 180 blisters. Therefore, the risk is considered medium until further evaluation is carried out.
	Assay	No influence on flow and compression properties is expected considering its low proportion in the formulation. Therefore, it is unlikely to affect any of these DP CQAs. The risk is considered low.
	UDU	
	Hardness	
	Disintegration time	Disintegrant agent has a direct influence on DP disintegration time and, consequently, it may influence DP dissolution. The risk is high.
	Dissolution profile	
	Residual solvents	Croscarmellose sodium will be used as disintegrant. Ethanol, a class 3 solvent, is used as a process aid in the manufacture of croscarmellose sodium. However, level of ethanol in this excipient is controlled below 100 ppm, well below the ICH Q3D acceptance limit. Therefore, the risk is considered low.
	Stability (Impurities & WC)	During feasibility studies, stability studies were carried out on a formulation containing an ASD produced by fluid bed top-spray granulation and croscarmellose sodium as disintegrant. Low level of impurities growth was observed, indicating no incompatibility between DS and this excipient. The risk is considered low.
Surfactant – type and %	Appearance	The addition of a surfactant may be required to enhance drug product dissolution profile. If the surfactant is added in the formulation, it will constitute a small percentage of the overall tablet weight. Thus, the risk of affecting the drug product's appearance is deemed to be low.
	Solid state form	Research studies reveal that incorporating a surfactant within an ASD can enhance the stability of the amorphous state. Nevertheless, contradictory results have been presented in other studies. As a result, the risk is initially considered high.
	Assay	

Formulation variable	**DP CQAs**	**Justification**
	UDU	DS is intended to be molecularly dispersed in the polymer and, if present, the surfactant. Therefore, no influence of the surfactant on these CQAs is expected. The risk is low.
	Hardness	Since the surfactant would represent a low percentage on the total formulation, its influence on DP hardness is expected to be low.
	Disintegration time	Surfactant type, grade, and percentage could have an influence on DP disintegration time and dissolution rate by improving the wettability and solubility of the DS. The risk is considered high.
	Dissolution profile	
	Residual solvents	The surfactant should meet the requirements of residual solvents for pharmaceutical articles in the current USP/NF General Chapter <467>, Ph. Eur. General Chapter 5.4 and ICH-Q3C. Thus, the contribution of residual solvents from the surfactant should be limited. The risk is considered low.
	Stability (Impurities & WC)	The surfactant will be in close contact with the drug substance and could promote degradation reactions. The risk is considered high until further evaluation is carried out.
Lubricant – type and %	Appearance	The primary function of a lubricant is to minimize die wall friction and prevent punch adhesion. Consequently, the type, grade, and percentage of lubricant can influence the drug product appearance. Magnesium stearate is chosen as the lubricant, and a standard percentage (0.5% w/w/) will be used. Thus, the initial risk is deemed to be medium.
	Solid state form	The stability of the amorphous DS in the final DP will be mainly affected and controlled by the carrier, the solubility of the DS on the selected solvent, and manufacturing process parameters. No influence of the lubricant on this CQA is expected. The risk is considered low.
	Assay	Since the amount of lubricant used is low and its influence on flow is minimal, it is unlikely to influence none of these DP CQAs. The risk is considered low.
	UDU	
	Hardness	Most of the lubricants exhibit a hydrophobic nature and they are usually used in smaller amount than any other ingredient in the formulation. When lubrication of the blend is performed, lubricant particles may adhere to the surface of the other particles. An over-lubrication due to excessive lubricant can form a coherent film on the surface of the filler/binder, thus negatively affecting tablet binding and leading to a drop in hardness of the resulting tablets. Besides, it may delay both disintegration time and dissolution profile. Magnesium stearate will be used as lubricant. Considering that lubricant percentage will be low in the formulation, the risk is initially considered medium.
	Disintegration time	
	Dissolution profile	
	Residual solvents	Magnesium stearate will be used as lubricant. This excipient does not contain any solvent listed in class 1, class 2 or class 3, nor any other specified or unspecified solvent. The risk is considered low.

Formulation variable	DP CQAs	Justification
	Stability (Impurities & WC)	During feasibility studies, stability studies were carried out on a formulation containing an ASD produced by fluid bed top-spray granulation and magnesium stearate as lubricant. Low level of impurities growth was observed, indicating no incompatibility between DS and this excipient. The risk is considered low.
Coating agent - type and weight gain (%)	Appearance	Coating agent type and weight gain have a direct influence on DP appearance. Considering that a ready to use film-coating system (Opadry® 03F220119 yellow) will be used and that tablets with good appearance were obtained in feasibility studies, the risk is deemed to be low.
	Solid state form	According to previous experience, the macrogol content in the coating agent might influence the stability of the amorphous DS in the final DP. The risk is mitigated considering the feasibility studies stability studies, where tablets coated with the selected film-coating agent (Opadry® 03F220119 yellow) showed to be stable after 6 months of storage at 40ºC/75%RH in both Al/Al and Triplex 180 blisters. The risk is considered low.
	Assay	No influence on this CQA is expected. The risk is low.
	UDU	
	Hardness	The film-coating can slightly modify the tablet hardness. The risk is medium. However, no influence on disintegration time and dissolution profile is expected. Therefore, the risk is considered low.
	Disintegration time	
	Dissolution profile	
	Residual solvents	According to the information provided by the coating agent supplier, this excipient meets the requirements of residual solvents for pharmaceutical articles in the current USP/NF General Chapter <467> and ICH-Q3C. Only Class 2 and Class 3 solvents are likely to be present but below the Option 1 limit and residual Class 3 solvents are below 0.5%. Therefore, the risk is considered low.
	Stability (Impurities & WC)	During feasibility studies, stability studies were carried out on a formulation containing an ASD produced by fluid bed top-spray granulation and Opadry® 03F220119 yellow as film-coating agent. Low level of impurities growth was observed, indicating no incompatibility between DS and this excipient. The risk is considered low.

5.2.4. Formulation studies to enhance dissolution profile

As discussed in section 5.1.7 on page 97, although it was feasible to produce an ASD of LM2 and HPMCAS-MG in a 1:5 weight ratio via fluid bed top-spray granulation as an alternative to spray drying, it resulted in a slower dissolution profile. Consequently, studies were conducted with the aim of enhancing the dissolution profile of the drug product.

Based on the initial formulation risk assessment presented in Table 35, the following formulation variables might affect the drug product dissolution profile:

1. Disintegrant percentage
2. Filler/ substrate amount and SGD particle size
3. Filler/ substrate type
4. Surfactant addition

The influence of these variables was not only evaluated on drug product dissolution profile but also on the high/medium risked CQAs.

Throughout the preformulation studies, it was found that increasing the proportion of the carrier (HPMCAS-MG) had a positive effect on the drug product dissolution profile. Nevertheless, a lower ratio of LM2 to HPMCAS-MG (e.g., ratio 1:6) was deemed suboptimal for fluid granulation. This was due to the high percentage of solids in the feed solution, comprising 86.15% w/w of the total tablet weight, leaving insufficient quantity for substrate and extragranular excipients. While increasing the tablet size could be a possibility, the goal remained to develop a tablet with a weight and size comparable to that of the RLD. Therefore, this formulation variable was not further evaluated using fluid bed technology.

5.2.4.1. Disintegrant percentage

In feasibility studies, the total amount of disintegrant (8.0% w/w of croscarmellose sodium) was incorporated in the extragranular phase. However, incorporating a portion of the disintegrant into the intragranular phase may enhance the dissolution profile of the drug product. Croscarmellose sodium, known for its rapid water absorption and swelling properties in aqueous environments, could accelerate the disintegration of granules formed during fluid bed granulation into smaller particles. This would increase the surface area available for dissolution, thereby facilitating drug release.

The influence of incorporating croscarmellose sodium into the intragranular phase at concentrations of either 4.0% or 8.0% w/w of the total tablet weight was assess on drug product disintegration time, dissolution profile, and solid state form, i.e. CQAs with a medium/high risk of being affected by the disintegrant (refer to Table 35).

Formulations evaluated in this study are presented in Table 37. Batches of 600 g of final blend were produced following the procedure described in sections 4.1.2 and 4.1.5.

Table 37. Qualitative and quantitative composition of tablets with different intragranular and extragranular disintegrant percentages.

Amount of intragranular/ extragranular disintegrant (%)		**0% / 8%**		**4% / 4%**		**8% / 0%**	
Ingredients	**Function**	**%**	**mg/ tablet**	**%**	**mg/ tablet**	**%**	**mg/ tablet**
INTRAGRANULAR PHASE							
LM2	Drug substance	12.308	80.000	12.308	80.000	12.308	80.000
Hypromellose acetate succinate	Carrier	61.538	400.000	61.538	400.000	61.538	400.000
Microcrystalline cellulose	Filler/substrate	16.654	108.250	16.654	108.250	16.654	108.250
Croscarmellose sodium	Disintegrant	-	-	4.000	26.000	8.000	52.000
Acetone [1]	Solvent	q.s.	2720.000	q.s.	2720.000	q.s.	2720.000
EXTRAGRANULAR PHASE							
Croscarmellose sodium	Disintegrant	8.000	52.000	4.000	26.000	-	-
Anhydrous colloidal silica	Glidant	0.500	3.250	0.500	3.250	0.500	3.250
Magnesium stearate	Lubricant	1.000	6.500	1.000	6.500	1.000	6.500
UNCOATED TABLET WEIGHT		100.000	650.000	100.000	650.000	100.000	650.000

[1] Evaporated during the manufacturing process.

5.2.4.1.1. SGDs characterization results

The solid state form of the obtained SGDs was determined by XRPD. Diffractograms depicted in Figure 33 confirmed the amorphous state of all SGDs obtained, as no distinct peaks corresponding to crystalline forms of LM2 drug substance were detected. The peaks observed correspond to the MCC and the cling foil used during the measurements (see Figure 69 and Figure 75, respectively, in annex).

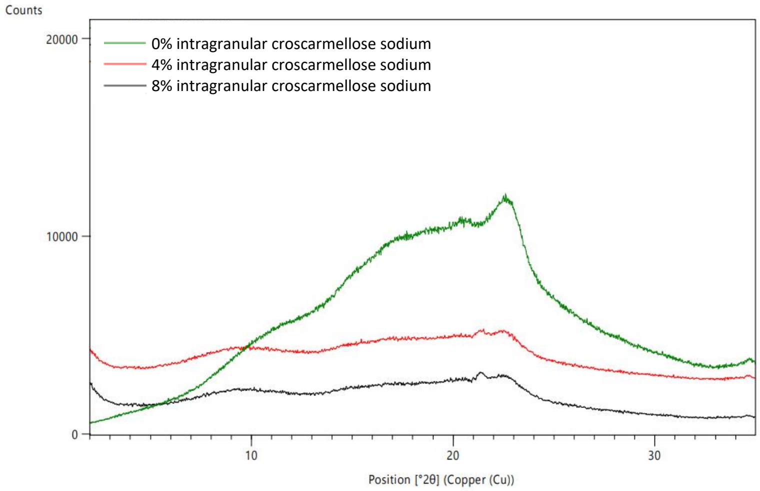


Figure 33. XRPD diffractograms of SGDs containing different percentage of intragranular croscarmellose sodium (disintegrant).

5.2.4.1.2. Tablets characterization results

Table 38 presents a summary of the physical characterization results for uncoated tablets containing different percentages of intragranular and extragranular croscarmellose sodium. Additionally, Figure 34 compares the dissolution profiles of these tablets with those of uncoated tablets formulated with the SDD obtained via spray drying, serving as reference.

The addition of intragranular croscarmellose sodium, coupled with a subsequent reduction of its extragranular amount, was found to have no effect on tablets disintegration time. However, this formulation variable exhibited a significant influence on the dissolution profile of the drug product. As shown in Figure 34, the addition of intragranular disintegrant resulted in a faster dissolution profile ($\alpha<0.05$), with comparable outcomes noted for both evaluated intragranular percentages (4% and 8% w/w) (α n.s.). In light of these findings, intragranular disintegrant was incorporated in subsequent studies. Nonetheless, increasing the percentage beyond the assessed level was deemed undesirable, given that a higher percentage of croscarmellose sodium than commonly used in tablet formulations (up to 5% w/w) was already employed.

Table 38. Physical properties of uncoated tablets obtained.

Intragranular/ extragranular disintegrant (%)	**0% / 8%**	**4% / 4%**	**8% / 0%**
Average weight (mg)	652.7 (RSD 0.9%)	654.5 (RSD 0.6%)	656.6 (RSD 0.3%)
Tensile strength (MPa)	1.7	1.5	1.5
Friability (%)	0.1	Negligible	Negligible
Disintegration time (min)	< 2	< 1	< 1

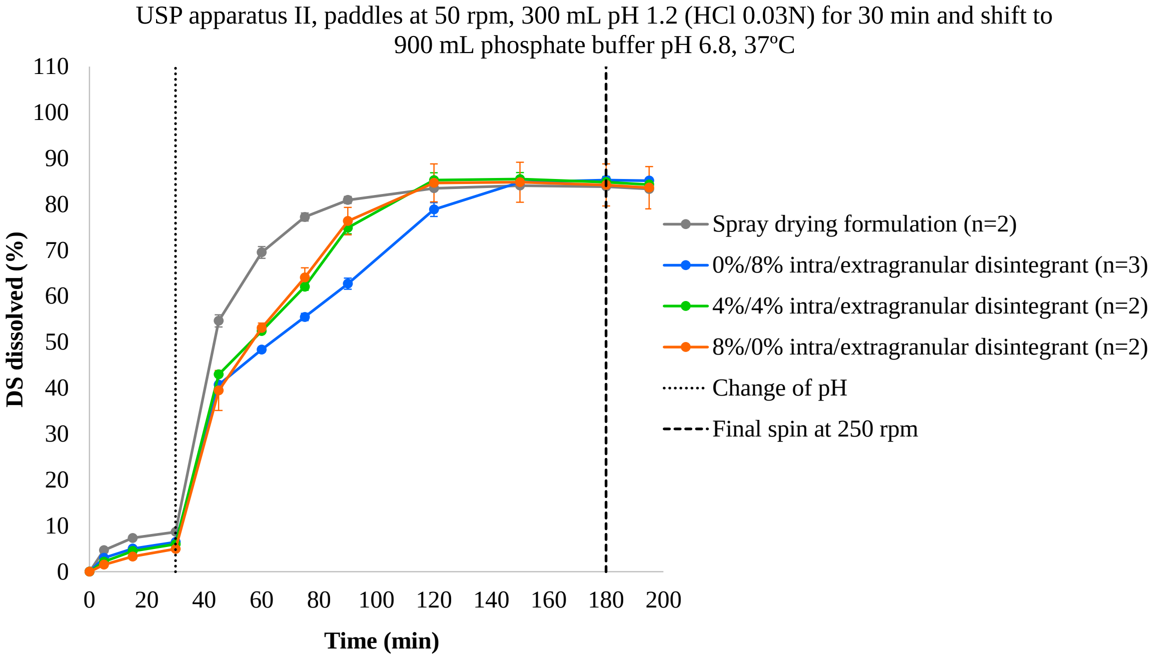


Figure 34. Dissolution profile of tablets with different intra/extragranular disintegrant distribution.

5.2.4.2. Filler/ substrate amount and SGD particle size

Considering that during the fluid bed top-spray granulation the agglomeration of particles occur, whereas spray drying yields small and individual ASD particles, the slower dissolution profile observed in tablets containing SGD might be related to the lower surface area of the SGD particles compared to the SDD. With this rational in mind, two approaches were investigated with the objective of enhancing the dissolution profile of the drug product:

1. Increasing the amount of substrate (MCC from 16.7% to 34.0% w/w) where the feed solution is sprayed over to increase the number of particles and thereby increase the surface area. In order to increase the substrate amount, the final tablet weight had to be increased from 650 mg to 850 mg, while keeping the percentage of the rest of components constant.
2. Reducing the particle size of the SGD by means of a more vigorous milling process. The obtained SGDs were milled through a smaller mesh size (0.5 mm instead of 0.8 mm) using a more vigorous milling conditions (hammer mill instead of manual sieve).

On the contrary, one could think that the release of the drug substance might be delayed because of interactions between the ASD and the substrate. To explore this hypothesis, it was investigated the reduction of the amount of substrate (MCC from 16.7% to 8.7% w/w) combined with a vigorous milling process.

The influence of these variables were evaluated on drug product solid state form, hardness, disintegration time, and dissolution profile, i.e. CQAs with a high risk of being affected by the filler/substrate (refer to Table 35). Furthermore, the SGD powder density and PSD were determined.

Formulations evaluated in this study are presented in Table 39. Batches of 600 - 1000 g of final blend were produced following the procedures described in sections 4.1.2 and 4.1.5, applying a vigorous milling through a hammer mill equipped with a 0.5 mm mesh size.

The results of these studies were compared to those of the SGD-based tablets reported in previous section 5.2.4.1, manufactured with 16.7% w/w of MCC as a substrate, 8.0% w/w of intragranular croscarmellose sodium, and subjected to manual de-agglomerated through a 0.8 mm mesh size.

Table 39. Qualitative and quantitative composition of tablets with different substrate (intragranular MCC) amount.

Amount of intragranular MCC amount (%)		**8.7%**		**16.7%**		**34.0%**	
Ingredients	**Function**	**%**	**mg/ tablet**	**%**	**mg/ tablet**	**%**	**mg/ tablet**
INTRAGRANULAR PHASE							
LM2	Drug substance	12.308	80.000	12.308	80.000	9.412	80.000
Hypromellose acetate succinate	Carrier	61.538	400.000	61.538	400.000	47.059	400.000
Microcrystalline cellulose	Filler/ substrate	8.654	56.250	16.654	108.250	34.029	289.250
Croscarmellose sodium	Disintegrant	8.000	52.000	8.000	52.000	8.000	68.000
Acetone [1]	Solvent	q.s.	2720.000	q.s.	2720.000	q.s.	2720.000
EXTRAGRANULAR PHASE							
Microcrystalline cellulose	Filler	8.000	52.000	-	-	-	-
Anhydrous colloidal silica	Glidant	0.500	3.250	0.500	3.250	0.500	4.250
Magnesium stearate	Lubricant	1.000	6.500	1.000	6.500	1.000	8.500
UNCOATED TABLET WEIGHT		650.000	100.000	100.000	650.000	100.000	850.000

[1] Acetone is evaporated during the manufacturing process.

5.2.4.2.1. SGDs characterization results

The solid state form of the obtained SGDs was determined by XRPD. Diffractograms depicted in Figure 35 confirmed the amorphous state of all SGDs obtained, as no distinct peaks corresponding to crystalline forms of LM2 drug substance were detected. The peaks observed correspond to the MCC and the cling foil used during the measurements (see Figure 69 and Figure 75, respectively, in annex).

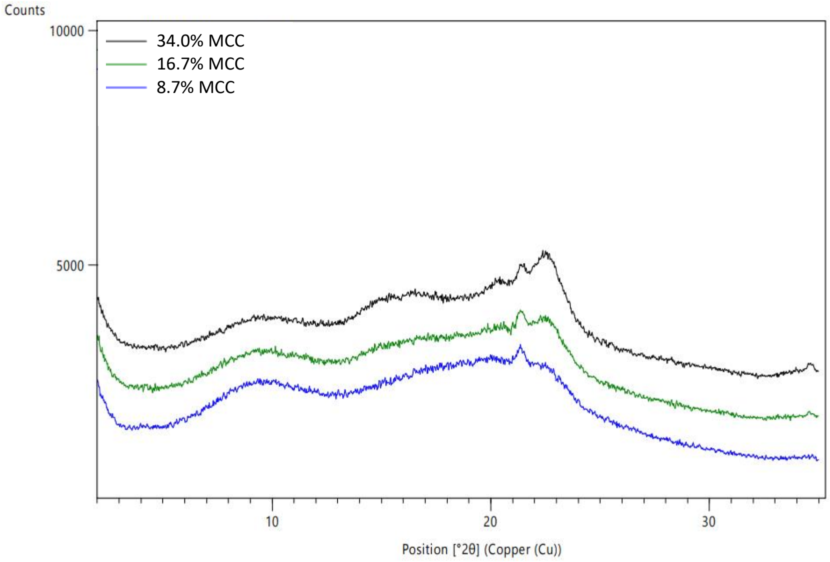


Figure 35. XRPD diffractograms of SGD with different percentage of MCC (substrate) based on the total tablet weight.

SEM microphotographs of the obtained SGDs prior to milling step are depicted in Figure 36 for the formulation containing 8.7% w/w of MCC substrate, in Figure 37 for the formulation containing 16.7% w/w of MCC substrate, and in Figure 38 for the formulation containing 34.0% w/w of MCC substrate. In all cases, substantial particle agglomeration is evident, with no significant differences between the three formulations.

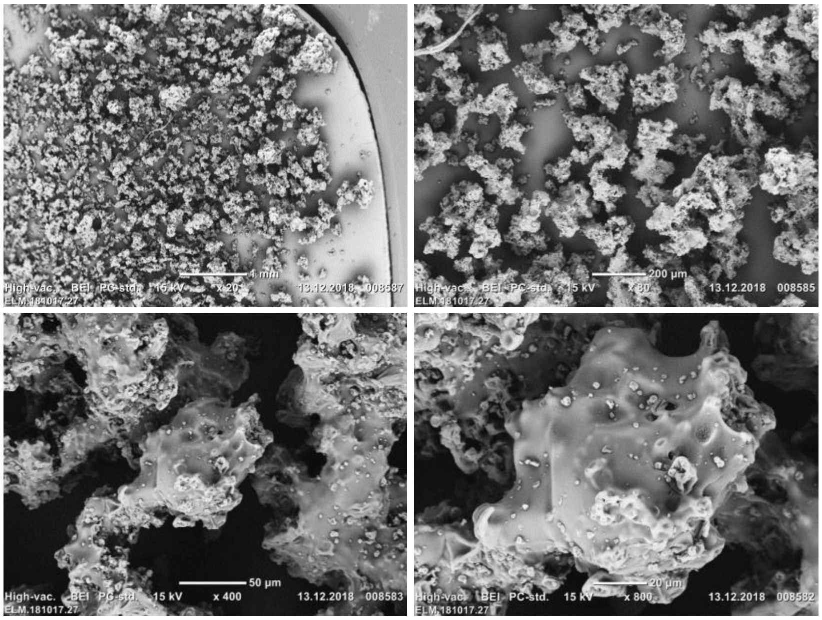


Figure 36. SEM pictures of SGD with 8.7% w/w of substrate (MCC) based on the total tablet weight.

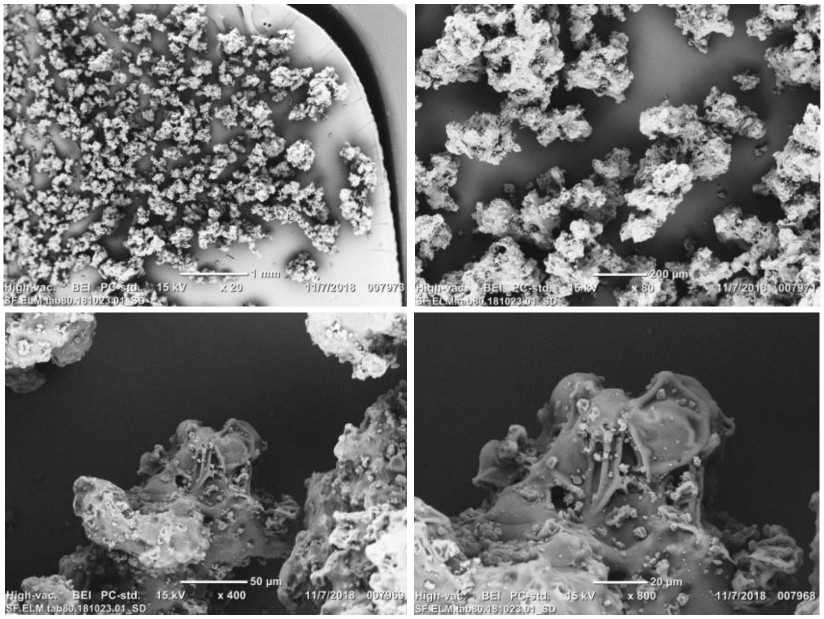


Figure 37. SEM pictures of SGD with 16.7% w/w of substrate (MCC) based on the total tablet weight.

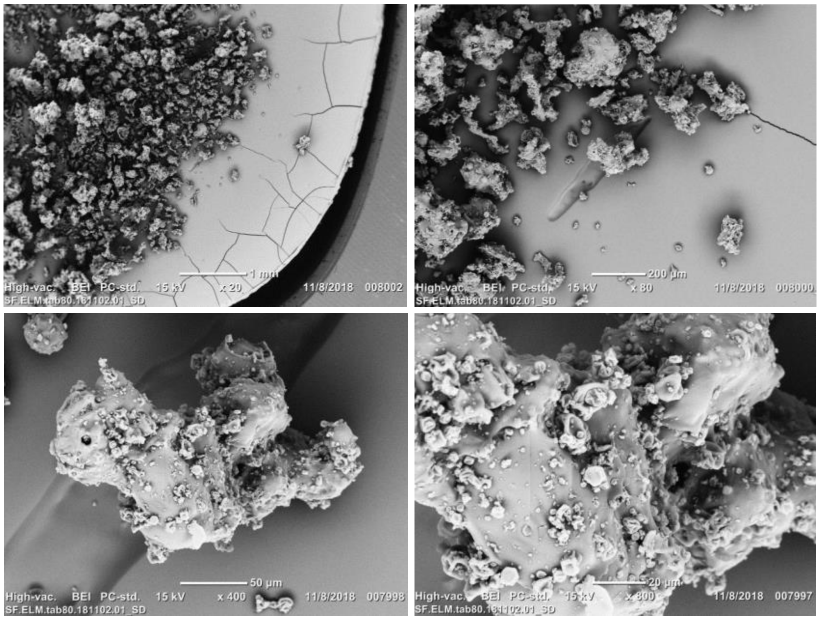


Figure 38. SEM pictures of SGD with 34.0% w/w of substrate (MCC) based on the total tablet weight.

The results of density, flow characteristics, and PSD of the SGDs obtained after milling are presented in Table 40 and Figure 39. An influence of the milling process on SGD density was observed, being higher when a more vigorous milling was applied (hammer mill with 0.5 mm mesh size). This is attributed to the reduction of the particle size shown in Figure 39. On the other hand, no influence of the percentage of substrate on these SGD physical characteristics was observed.

Table 40. Density and flow characteristics of SGDs with different amount of MCC (substrate) and milling process.

Milling process	**Manual sieve with 0.8 mm mesh size**	**Hammer mill with 0.5 mm mesh size**		
Amount of intragranular MCC amount (% w/w)	**16.7%**	**8.7%**	**16.7%**	**34.0%**
Bulk density (g/mL)	0.22	0.28	0.29	0.27
Tapped density (g/mL)	0.27	0.35	0.36	0.35
Hausner ratio	1.22	1.28	1.25	1.29
Carr Index (%)	18	22	20	22
Flow by Hausner and Carr Index	Fair	Passable	Fair	Passable

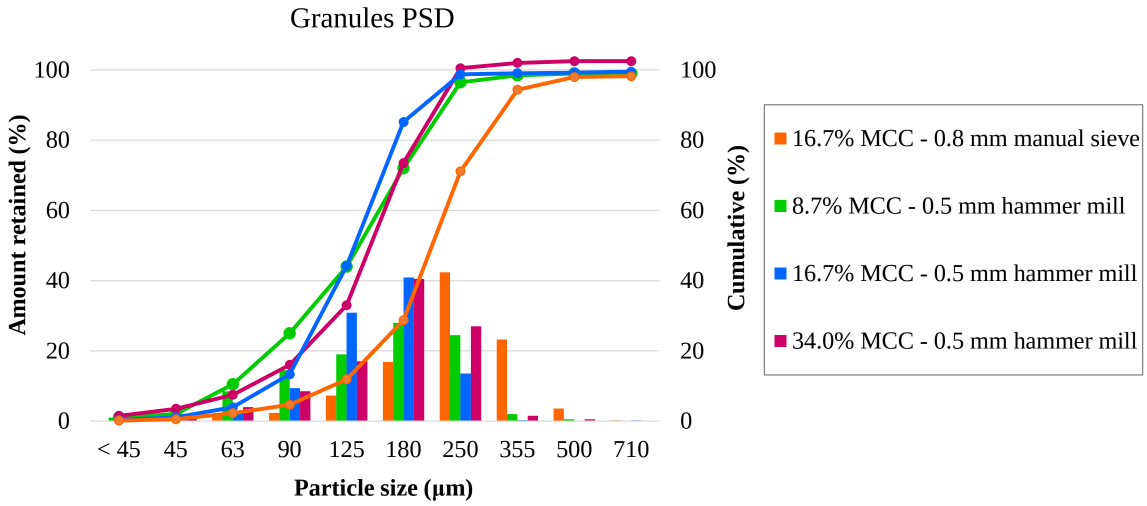


Figure 39. PSD of SGDs with different percentages of MCC (substrate) and milling process.

5.2.4.2.2. Tablets characterization results

XRPD analysis were conducted on uncoated tablets to verify that a more vigorous milling process did not induced recrystallization of the amorphous drug substance, as mechanical stress such as milling or compressing can promote molecular mobility in ASDs (1). Results shown in Figure 40 confirm that LM2 drug substance was present in an amorphous solid state in the uncoated tablets, as no distinct peaks corresponding to crystalline forms of LM2 were detected. The peaks observed correspond to MCC, magnesium stearate, and the cling foil used during the measurements (see Figure 69, Figure 72, and Figure 75, respectively, in annex).

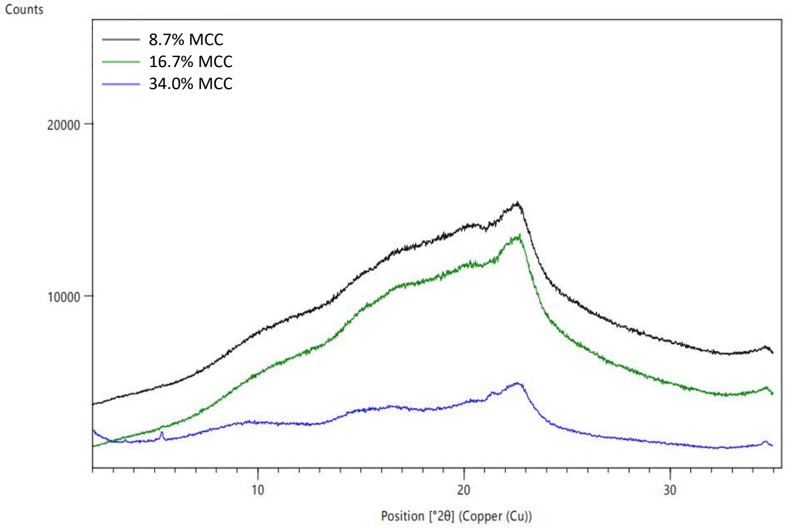


Figure 40. XRPD results of uncoated tablets different percentages of MCC (substrate).

Table 41 presents a summary of the physical characterization results of uncoated tablets containing different percentage of MCC substrate and milling process. Additionally, Figure 41 compares the dissolution profile obtained from these tablets with those of uncoated tablets formulated with SDD obtained via spray drying, serving as reference.

Despite the different tablet weight among formulations, tablets exhibiting low friability and rapid disintegration times were produced in all cases. With regard to dissolution profile, no significant influence of the increase of the amount of substrate (intragranular MCC) and reduction of SGD particle size by means of a more vigorous milling was found. Therefore, the initial hypotheses were not confirmed. Differences were only observed between the sample prepared by spray drying and the rest of the tablets, between 40 and 100 minutes of testing ($\alpha<0.05$). Considering the marketing preference for a tablet size similar to that of the RLD, alongside the preference for a larger amount of substrate from a manufacturing perspective, 16.7% w/w of substrate was chosen for subsequent studies.

From an industrial standpoint, a gentle milling procedure and a larger mesh size are favoured. Nonetheless, a higher powder density was necessary to overcome the challenges in achieving the target tablet weight with the final punches design (17 x 9 mm). Given the desire for tablets of comparable dimensions to the RLD and the fact that a more vigorous milling process enhances powder density, this milling approach was selected for subsequent studies.

Table 41. Physical properties of uncoated tablets obtained.

Amount of intragranular MCC amount (%)	**16.7%**	**8.7%**	**16.7%**	**34.0%**
Milling	**Manual sieve with 0.8 mm mesh size**	**Hammer mill with 0.5 mm mesh size**		
Average weight (mg)	656.6 (RSD 0.3%)	650.5 (RSD 0.7%)	657.2 (RSD 0.4%)	852.9 (RSD 0.2%)
Tensile strength (MPa)	1.5	1.7	1.7	1.4
Friability (%)	Negligible	0.12	Negligible	Negligible
Disintegration time (min)	< 1	< 1	< 2	< 2

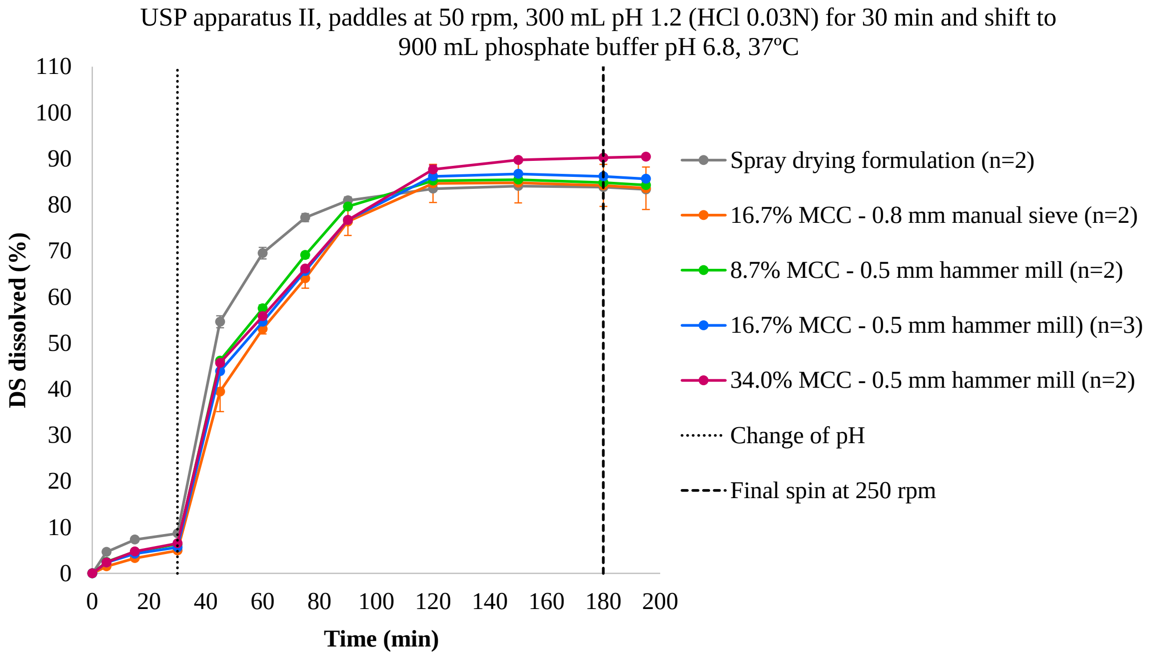


Figure 41. Dissolution profile of tablets with different percentages of MCC (substrate) and milling process.

5.2.4.3. Filler/ substrate type

The filler/substrate type can play a role on the drug substance release due to several aspects such as wettability and chemical interactions. Considering that the ASD produced is in close contact with the substrate, an alternative substrate type, substituting the MCC (water-insoluble filler but swells upon contact with aqueous solutions) for mannitol (water-soluble filler).

The influence of this formulation variable was evaluated on drug product solid state form, hardness, disintegration time, and dissolution profile, i.e. CQAs with high risk of being affected by the substrate type (see Table 35). Furthermore, the SGDs powder density and PSD were determined and assessed.

Formulations evaluated in this study are presented in Table 42. In this study and subsequent ones, a concentration of 4% w/w of croscarmellose sodium was included in both intragranular and extragranular phase. Although comparable dissolution profiles were obtained with either 4/4% or 8/0% of intra/extragranular croscarmellose sodium (refer to section 5.2.4.1), the addition of disintegrant in both phases was preferred to avoid potential tablet disintegration issues throughout storage. Final blend batch sizes of 600 g (with MCC) and 650 g (with mannitol) were produced following the procedure described in sections 4.1.2 and 4.1.5, applying a vigorous milling through a hammer mill equipped with a 0.5 mm mesh size.

Table 42. Qualitative and quantitative composition of tablets with different substrate type.

Substrate type		Microcrystalline cellulose		Mannitol	
Ingredients	**Function**	**%**	**mg/tablet**	**%**	**mg/tablet**
INTRAGRANULAR PHASE					
LM2	Drug substance	12.308	80.000	12.308	80.000
Hypromellose acetate succinate	Carrier	61.538	400.000	61.538	400.000
Microcrystalline cellulose	Filler/ substrate	16.654	108.250	-	-
Mannitol	Filler/ substrate	-	-	16.654	108.250
Croscarmellose sodium	Disintegrant	4.000	26.000	4.000	26.000
Acetone [1]	Solvent	q.s.	2720.000	q.s.	2720.000
EXTRAGRANULAR PHASE					
Croscarmellose sodium	Disintegrant	4.000	26.000	4.000	26.000
Anhydrous colloidal silica	Glidant	0.500	3.250	0.500	3.250
Magnesium stearate	Lubricant	1.000	6.500	1.000	6.500
UNCOATED TABLET WEIGHT		100.000	650.000	100.000	650.000
Opadry® 03F220119 yellow	Coating agent	-	-	3.000	19.500
Purified water [1]	Suspension liquid	-	-	q.s.	q.s.
FILM-COATED TABLET WEIGHT		-	-	103.000	669.500

[1] Evaporated during the manufacturing process.

5.2.4.3.1. SGDs characterization results

The results of density, flow character, and PSD of the obtained SGDs after milling through a hammer mill equipped with 0.5 mm mesh size are summarized in Table 43 and Figure 42. These results indicate no significant influence of the filler type, MCC or mannitol, on these SGD characteristics.

Table 43. Density and flow character of SGDs with different either MCC or mannitol as substrate.

Substrate type	MCC	Mannitol
Bulk density (g/mL)	0.29	0.28
Tapped density (g/mL)	0.35	0.36
Hausner ratio	1.23	1.23
Carr Index (%)	18	18
Flow by Hausner and Carr Index	Fair	Fair

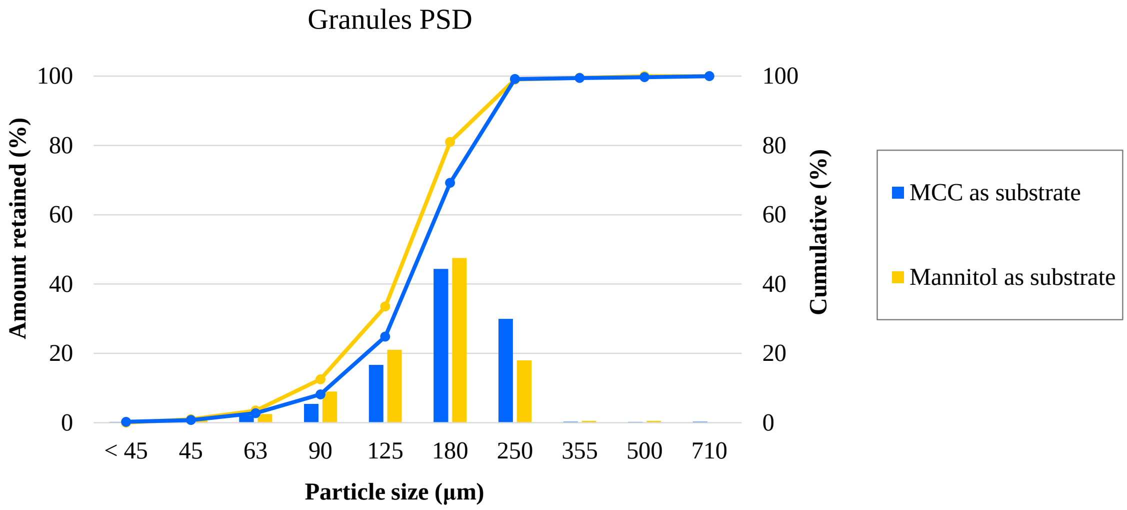


Figure 42. Particle size distribution of SGDs with either MCC or mannitol as substrate.

5.2.4.3.2. Tablets characterization results

The results of the physical characterization of uncoated tablets containing different substrate types are summarized in Table 44. Additionally, Figure 43 compares the dissolution profile obtained from these tablets with those of uncoated tablets formulated with SDD obtained via spray drying, serving as reference.

Tablets with similar tensile strength, low friability, and fast disintegration time were produced in both cases. The substrate type, either MCC or mannitol, was found to have no significant influence on tablets dissolution profile ($\alpha<0.05$). Both samples showed slower drug release than spray drying samples at pH 1.2 and pH 6.8 until the 75 minutes ($\alpha<0.05$).

Table 44. Physical properties of uncoated tablets obtained.

Substrate type	**MCC**	**Mannitol**
Tensile strength (MPa)	1.7	1.8
Friability (%)	Negligible	0.01
Disintegration time (min)	< 2	< 3

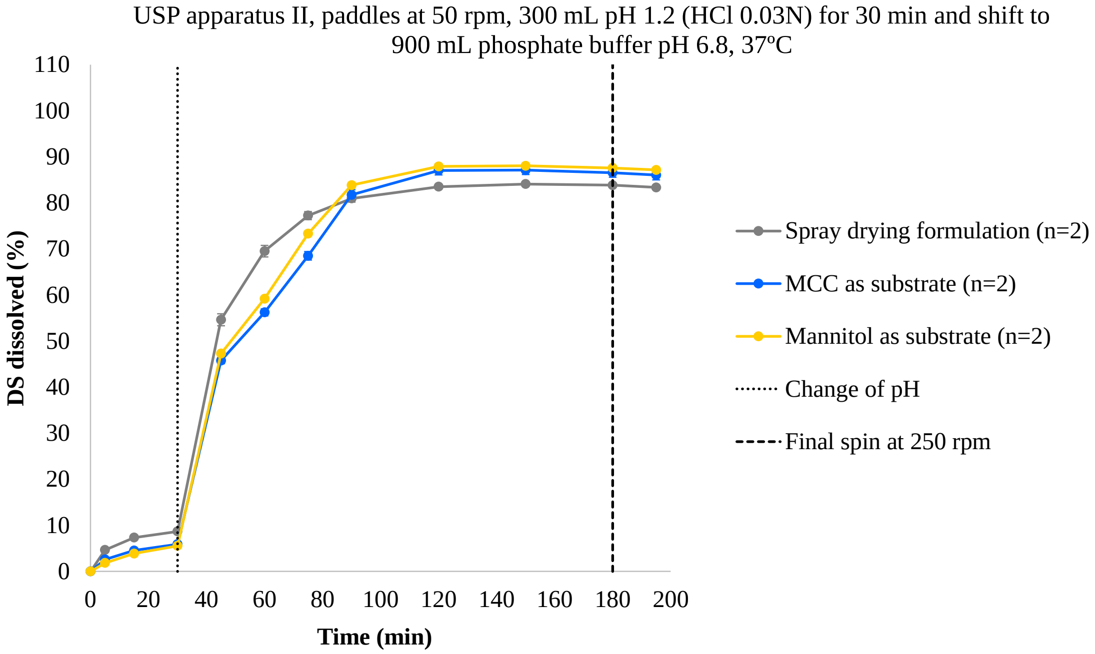


Figure 43. Dissolution profile of tablets containing SGD with either MCC or mannitol as substrate.

5.2.4.3.3. *Stability*

With the objective to evaluate the influence of the substrate type on the stability of the amorphous solid state, assay, impurities growth, and water content, tablets formulated with mannitol were film-coated following the procedure outlined in section 4.1.6, packaged in Al/Al blisters, and stored under accelerated conditions (40ºC/75%RH).

XRPD and MDSC analysis were conducted at the initial time point (t=0) and throughout the storage period. XPRD diffractograms shown in Figure 44 confirm that drug substance was present in amorphous solid state without any evidence of recrystallization during storage, as no distinct peaks of crystalline forms of LM2 drug substance were detected. The peaks observed correspond to Opadry® yellow 03F32518, magnesium stearate, and mannitol (see Figure 74, Figure 72, and Figure 73 in annex). Furthermore, MDSC reversing heat flow curve, in Figure 45, revealed a single T_g at approximately 103ºC, indicating the formation of a homogeneous ASD without phase separation. Both heat flow and reversing heat flow curves revealed a melting temperature around 168ºC corresponding to the melting temperature of mannitol.

The stability of the film-coated tablets' water content, assay, and impurities growth are summarized in Table 45. These results demonstrated no significant changes in water content and assay, and no growth of impurities.

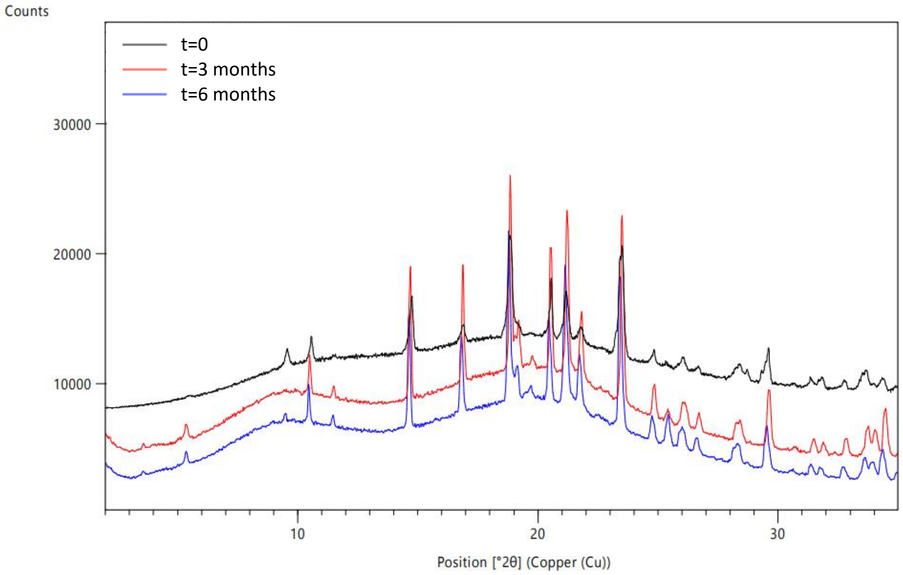


Figure 44. XRPD diffractogram of film-coated tablets containing with mannitol as substrate at initial time point (t=0) and after either 3 or 6 months of storage at 40ºC/75%RH in Al/Al blisters.

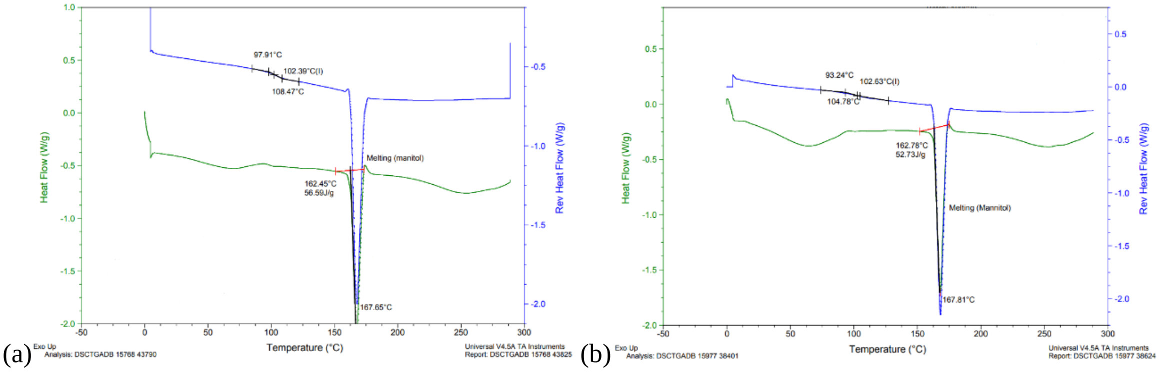


Figure 45. MDSC curves of film-coated tablets containing with mannitol as substrate at (a) initial time point (t=0) and (b) after 6 months of storage at 40ºC/75%RH in Al/Al blisters.

Table 45. Assay and impurities growth throughout stability in Al/Al blisters at 40ºC/75%RH of film-coated tablets containing mannitol as substrate.

	Storage conditions	NA	40ºC/75%RH	
	Storage time (months)	0	3	6
	Water content	1.8%	*Not tested*	1.6%
	Assay	99.9%	100.1%	100.8%
Impurities	**Impurity 1**	< 0.10%	< 0.10%	< 0.10%
	Largest unspecified	< 0.10%	< 0.10%	< 0.10%
	Total unspecified	< 0.10%	< 0.10%	< 0.10%
	Total	< 0.10%	< 0.10%	< 0.10%

Given that the substrate type (either MCC or Mannitol) exhibited no significant influence on drug product dissolution profile and other drug product CQAs ranked with high risk to be effected (i.e., solid state form, hardness, disintegration time, and stability), either of these substrates could be used. Nevertheless, MCC was selected for subsequent studies to minimize differences in formulation and process compared to the RLD.

5.2.4.4. Surfactant addition

Several research articles highlight that incorporating a surfactant, such as poloxamer 188, as part of the ASD of DS and polymeric carrier, can enhance the dissolution profile (2,11,12,21,40,85). These ASD are referred to as ternary solid dispersions.

The effect of incorporating poloxamer 188 as part of the ASD was evaluated on DP solid state form, disintegration time, dissolution profile, and stability, i.e. CQAs with high risk of being influenced by the addition of a surfactant (see Table 35). Formulations evaluated in this study are presented in Table 46. A batch of 2.5 kg of final blend was produced with 1.5% of poloxamer 188 as part of the ASD, following the procedure described in sections 4.1.2 and 4.1.5, and applying a vigorous milling through a hammer mill equipped with 0.5 mm mesh size. The results were compared to those of the SGD-based tablets reported in previous section 5.2.4.3, with 16.7% w/w of MCC substrate, and milled through a hammer mill equipped with 0.5 mm mesh size.

Table 46. Qualitative and quantitative composition of tablets with or without poloxamer 188.

Amount of surfactant (%)		**0% surfactant**		**1.5% poloxamer 188**	
Ingredients	**Function**	**%**	**mg/tablet**	**%**	**mg/tablet**
INTRAGRANULAR PHASE					
LM2	Drug substance	12.308	80.000	12.308	80.000
Hypromellose acetate succinate	Carrier	61.538	400.000	61.538	400.000
Poloxamer 188	Surfactant	-	-	1.500	9.750
Microcrystalline cellulose	Filler/ substrate	16.654	108.250	15.154	98.500
Croscarmellose sodium	Disintegrant	4.000	26.000	4.000	26.000
Acetone [1]	Solvent	q.s.	2720.000	q.s.	2720.000
Purified water [1]	Solvent	-	-	q.s.	87.750
EXTRAGRANULAR PHASE					
Croscarmellose sodium	Disintegrant	4.000	26.000	4.000	26.000
Anhydrous colloidal silica	Glidant	0.500	3.250	0.500	3.250
Magnesium stearate	Lubricant	1.000	6.500	1.000	6.500
UNCOATED TABLET WEIGHT		100.000	650.000	100.000	650.000
Opadry 03F220119 yellow	Coating agent	3.000	19.500	3.000	19.500
Purified water [1]	Suspension liquid	q.s.	q.s.	q.s.	q.s.
FILM-COATED TABLET WEIGHT		103.000	669.500	103.000	669.500

[1] Evaporated during the manufacturing process.

5.2.4.4.1. Tablets characterization results

The results of the physical characterization of uncoated tablets with and without poloxamer 188 are summarized in Table 47. Additionally, Figure 46 compares the dissolution profile obtained from these tablets with those of uncoated tablets formulated with SDD obtained via spray drying, serving as reference.

As shown in Table 47, tablets with fast disintegration times were obtained in both cases. On the contrary, as observed in Figure 46, the addition of 1.5% of poloxamer 188 as part of the ASD was found to have a positive effect on tablets dissolution profile ($\alpha<0.05$). This behaviour is attributed to the wettability and solubility enhancement properties of poloxamer 188.

Table 47. Physical properties of uncoated tablets obtained.

Amount of surfactant	**0% surfactant**	**1.5% Poloxamer 188**
Tensile strength (MPa)	1.7	1.9
Friability (%)	Negligible	Negligible
Disintegration time (min)	< 2	< 2

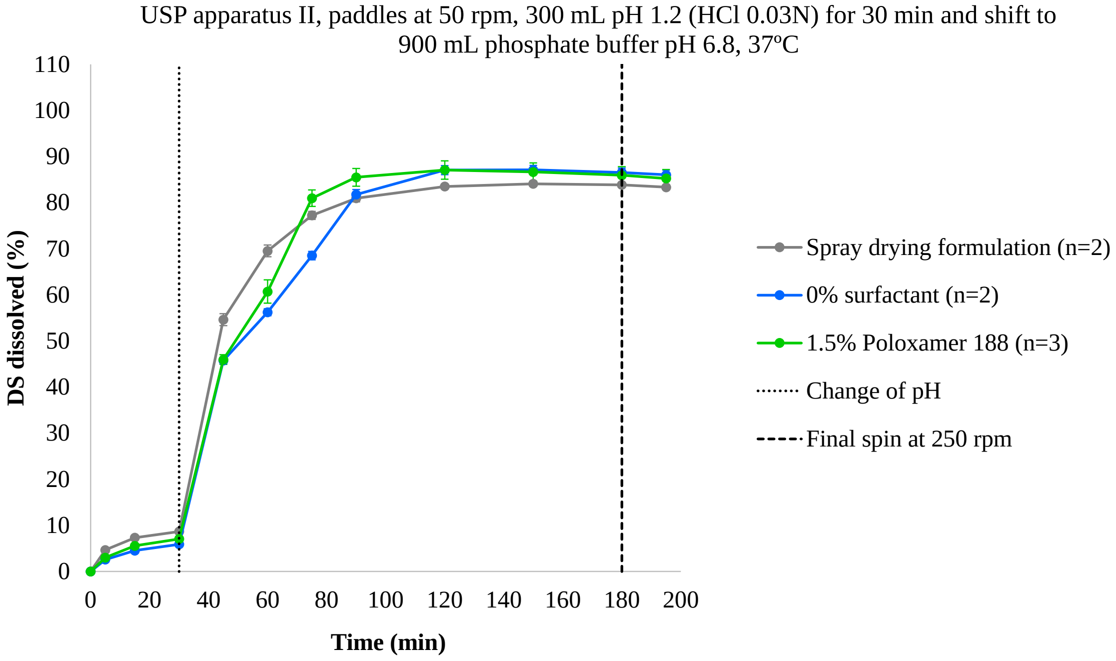


Figure 46. Dissolution profile of tablets formulated with SGD with and without Poloxamer 188.

Tablets were film-coated following the procedure outlined in 4.1.6, and XRPD and MDSC analysis were conducted to assess the solid state form and uniformity of the ASD. Results shown in Figure 47 confirmed that the addition of poloxamer 188 did not promote the recrystallization of the amorphous drug substance, as evidenced by the absence of distinct peaks corresponding to crystalline forms of LM2. The peaks observed correspond to Opadry® yellow 03F32518 and magnesium stearate (see Figure 74 and Figure 72 in annex). Furthermore, MDSC reversing heat flow curve revealed a single T_g at around 100ºC, indicating the formation of a homogeneous ASD without phase separation.

In prior feasibility studies, the T_g of LM2 and HPMCAS-MG in ratio 1:5 and without surfactant was approximately 108ºC. These results suggest that the incorporation of poloxamer 188 leads to nearly no reduction of the ASD T_g, even though its plasticizing properties.

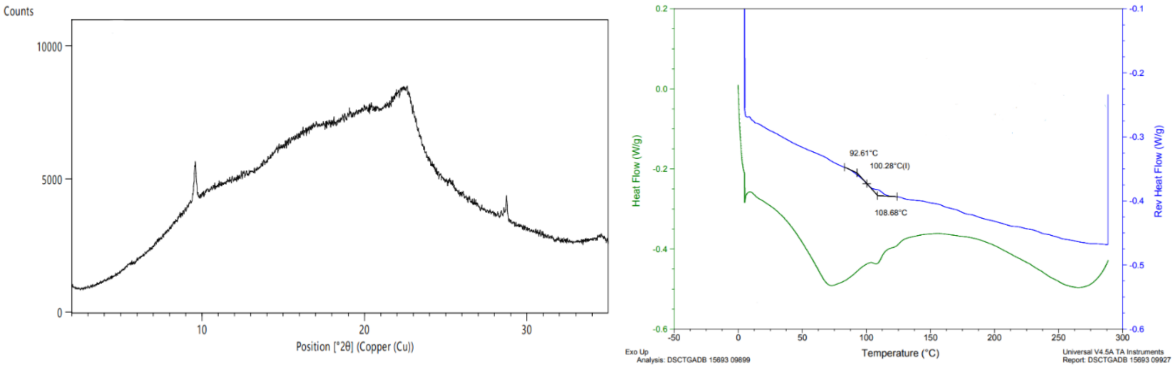


Figure 47. XRPD and MDSC results of film-coated tablets containing SGD of LM2, HPMCAS-MG, and poloxamer 188.

5.2.4.4.2. Stability

With the objective to evaluate the influence of the poloxamer 188 addition on the stability of the amorphous solid state, water content, assay, impurities growth, and dissolution, film-coated tablets were packaged in Al/Al blisters and stored under accelerated (40ºC/75%RH) and long-term (25ºC/60%RH) conditions. The stability results are presented in section 5.2.8 (prototype A). XRPD and MDSC analysis shown in Figure 58 and Figure 59 confirmed the stability of the amorphous drug substance in the final drug product after 6 months of storage at 40ºC/75%RH in Al/Al blisters. Dissolution profile with QC dissolution method (Figure 64), and water content, assay, and impurities (Table 57) also showed to remain stable along the aforementioned conditions.

Given the enhanced dissolution profile achieved with the addition of poloxamer 188 within the ASD, along with the favourable stability of the product, this formulation was deemed a promising candidate for evaluation in an *in vivo* pilot BA study.

5.2.5. Formulation studies with an alternative polymeric carrier to HPMCAS

The selection of an appropriate polymer is crucial in modifying the physicochemical attributes of drugs. The polymer not only stabilize the drug in amorphous solid state during manufacturing and storage, but also facilitates the maintenance of a supersaturated solution which is essential for drug absorption, thereby enhancing bioavailability (2).

HPMCP HP-55 was investigated as an alternative polymer to HPMCAS-MG for the formulation containing an ASD of LM2 produced by fluid bed top-spray granulation. The presence of a phthalic acid group in the HPMCP polymer confers its enteric properties. This group is expected to play a key role in bonding with drugs and has been used as the matrix for forming ASDs in various studies (40).

HPMCP HP-55 showed greater solubility in a mixture of acetone and water (95:5 w/w) than in pure acetone (Table 48). Consequently, this solvent mixture was selected for this investigation with a 13.0% w/w of HPMCP HP-55 concentration in solution.

Table 48. Solubility of HPMCP HP-55 in acetone and mixture of acetone:water.

Solvent	g of HPMCP HP55/ mL of solvent	Maximum solids concentration in solution (%)
Acetone	0.157	16.7
Acetone:water 95:5 (w/w)	0.198	20.0

The effect of the polymer type (HPMCP HP-55 instead of HPMCAS-MG) and percentage (weight ratios of 1:5 and 1:4 of LM2 to HPMCP HP-55) was first evaluated on the viability of achieving an ASD of LM2. Then, the influence of the polymer type was further evaluated on drug product residual solvents, appearance, assay, hardness, disintegration time, dissolution profile, and stability (impurities and WC), i.e. CQAs at high/medium risk of being influenced by the carrier type (as outlined in Table 35). Furthermore, SGD powder density and PSD were determined and assessed.

Formulations evaluated in this study are presented in Table 49. Batches of 2.0 kg were produced following the procedure described in sections 4.1.2 and 4.1.5. The results were compared to those of the SGD of LM2 and HPMCAS-MG in ratio 1:5 and MCC as substrate, reported in sections 5.2.4.3 and 5.2.4.4.

Table 49. Qualitative and quantitative composition.

Weight ratio of LM2 to HPMCP HP-55		**Ratio 1:5**		**Ratio 1:4**	
Ingredients	**Function**	**%**	**mg/ tablet**	**%**	**mg/ tablet**
INTRAGRANULAR PHASE					
LM2	Drug substance	12.308	80.000	12.308	80.000
Hypromellose phthalate	Carrier	61.538	400.000	49.231	320.000
Microcrystalline cellulose	Filler/ substrate	16.654	108.250	28.962	188.250
Croscarmellose sodium	Disintegrant	4.000	26.000	4.000	26.000
Acetone [1]	Solvent	q.s.	2467.077	q.s.	1958.460
Purified water [1]	Solvent	q.s.	129.846	q.s.	103.077
EXTRAGRANULAR PHASE					
Croscarmellose sodium	Disintegrant	4.000	26.000	4.000	26.000
Anhydrous colloidal silica	Glidant	0.500	3.250	0.500	3.2500
Magnesium stearate	Lubricant	1.000	6.500	1.000	6.500
UNCOATED TABLET WEIGHT		100.000	650.000	100.000	650.000
Opadry® 03F220119 yellow	Coating agent	3.000	19.500	3.000	19.500
Purified water [1]	Not applicable	q.s.	q.s.	q.s.	q.s.
FILM-COATED TABLET WEIGHT		103.000	669.500	103.000	669.500

[1] Evaporated during the manufacturing process.

5.2.5.1.1. SGDs solid state form

The solid state form of the obtained SGDs was determined by XRPD. Results in Figure 48 confirmed that LM2 in amorphous solid state was obtained in all cases, as no distinct peaks corresponding to crystalline forms of LM2 were observed. The peaks observed correspond to the MCC and Vaseline used during the measurement (see Figure 69 and Figure 76 in annex).

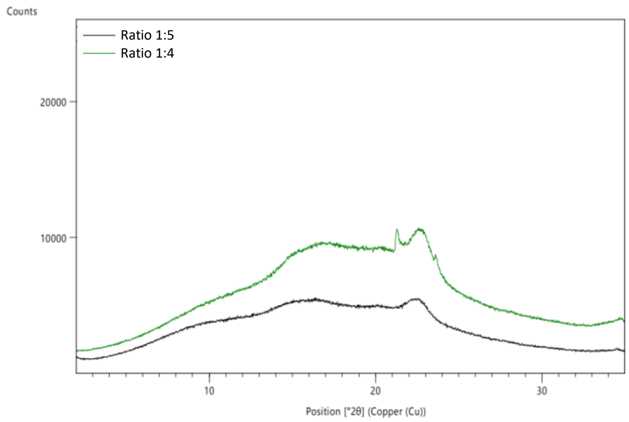


Figure 48. XRPD diffractograms of SGDs with different weight ratios of LM2 to HPMCP HP-55.

5.2.5.1.2. Influence of polymer type on residual solvents in SGD

The influence of the polymer type (HPMCAS-MG or HPMCP HP-55) and the weight ratio of LM2 to HPMCP HP-55 (ratios 1:4 or 1:5) was assessed regarding residuals acetone content in SGD. Two batches of 2.0 kg formulations based on HPMCP HP-55 (refer to Table 49) were compared to one batch of 2.5 kg formulation based on HPMCAS-MG and containing poloxamer 188 (refer to Table 46). Acetone content measurements were conducted right after fluid bed granulation and after various drying times (15, 30, 45, and 60 min).

From results illustrated in Figure 49, it is evident that acetone removal is more challenging with HPMCP HP-55 compared to HPMCAS-MG, suggesting a stronger interaction between acetone and HPMCP HP-55 polymer. No significant influence was observed within the proportions of HPMCP HP-55 evaluated.

The objective was to achieve an acetone level below 5000 ppm, in accordance with the limit stated in the ICH Q3C for Class 3 solvents under option 1. Hence, a drying time of ≥ 15 minutes was defined for formulations based on HPMCAS-MG, whereas a drying time of ≥ 45 minutes was defined for those based on HPMCP HP-55 polymer.

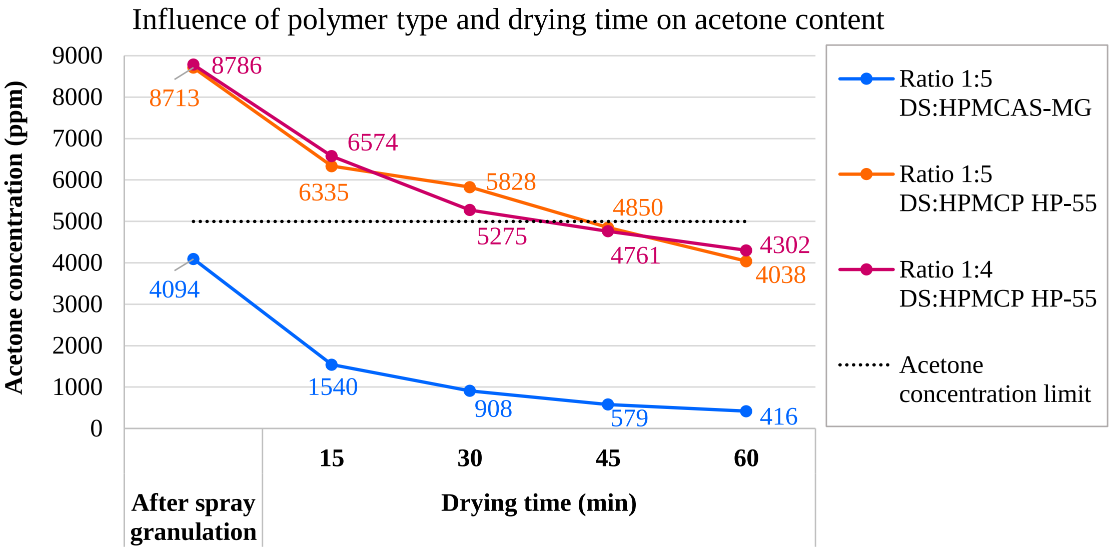


Figure 49. Influence of polymer type and percentage on residual acetone content in SGD.

5.2.5.1.3. SGD characterization results

The results of density, flow characteristics, and PSD of the obtained SGDs after milling through a hammer mill and equipped with 1.0 mm mesh size are summarized in Table 50 and Figure 41. These results are compared to those obtained for SGD of LM2 and HPMCAS-MG in ratio 1:5, after milling through a hammer mill and equipped with 0.5 mm mesh size. For formulations based on HPMCP HP-55, a 1.0 mm mesh size was used, as no significant difference in ASD density was observed among mesh sizes ranging from 0.5 mm to 1.0 mm. This study, which is beyond the scope of this thesis, is not included as it does not align with the primary focus of this research. Considering the industrial preference for larger mesh sizes to achieve higher output, the 1.0 mm mesh size was selected for formulations based on HPMCP HP-55.

SGDs with similar PSD but slightly lower density were obtained when using HPMCP HP-55 polymer instead of HPMCAS-MG, regardless of the amount of HPMCP HP-55 studied. However, powder with good enough flow properties were obtained for tableting.

Table 50. Density and flow character of SGDs of LM2 and HPMCP HP-55 in ratios 1:4 and 1:5, and compared to a SGD of LM2 and HPMCAS-MG in ratio 1:5.

Polymer type	**HPMCAS-MG**	**HPMCP HP-55**	
Ratio LM2:Polymer	**Ratio 1:5**	**Ratio 1:5**	**Ratio 1:4**
Bulk density (g/mL)	0.29	0.25	0.25
Tapped density (g/mL)	0.35	0.32	0.31
Hausner ratio	1.23	1.29	1.28
Carr Index (%)	18	23	22
Flow by Hausner and Carr Index	Fair	Passable	Passable

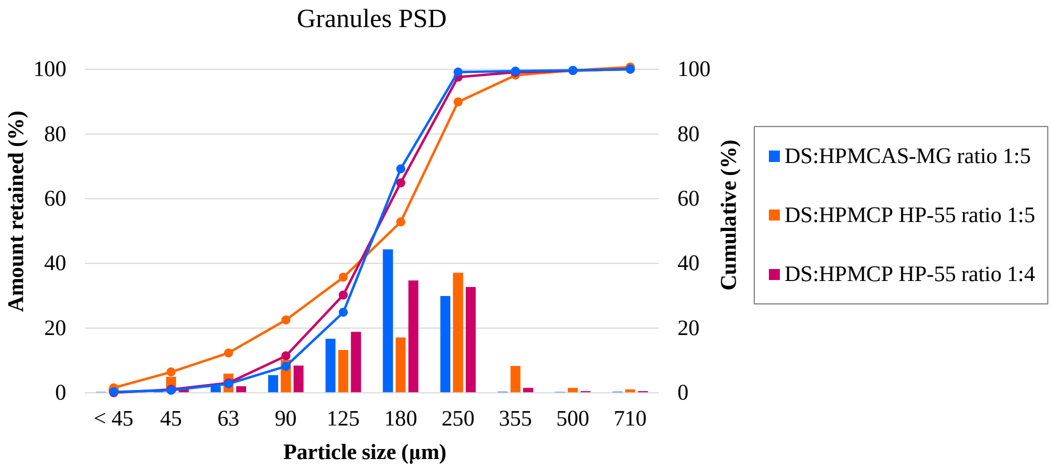


Figure 50. PSD of SGDs of LM2 and HPMCP HP-55 in ratios 1:4 and 1:5, and compared to a SGD of LM2 and HPMCAS-MG in ratio 1:5.

5.2.5.1.4. Tablets characterization results

The results of the physical characterization of uncoated tablets are summarized in Table 51. The dissolution profiles obtained are compared in Figure 51 together with the one of uncoated tablets formulated with SDD obtained via spray drying (considered as reference).

Although tablets with no defects and similar disintegration times were obtained in all cases, a much faster dissolution profile was obtained for tablets containing HPMCP HP-55 than those containing HPMCAS-MG. As shown in Figure 51, LM2 SGD formulated with either HPMCP HP-55 or HPMCAS-MG achieved a similar level of supersaturation, with both polymers effectively maintaining this supersaturation for 3 hours. Nevertheless, SGD of LM2 and HPMCP HP-55 in both ratios 1:5 and 1:4 exhibited a faster release, surpassing even the release profile obtained for tablets containing LM2 SDD material. Significant differences in drug release at pH 1.2 and 6.8 until 120 min was observed ($\alpha<0.05$).

Table 51. Physical properties of uncoated tablets obtained.

Polymer type	**HPMCAS-MG**	**HPMCP HP-55**	
Ratio LM2:Polymer	**Ratio 1:5**	**Ratio 1:5**	**Ratio 1:4**
Appearance	No defects	No defects	No defects
Tensile strength (MPa)	1.7	2.0	2.0
Friability (%)	Negligible	Negligible	Negligible
Disintegration time (min)	< 2	< 3	< 3

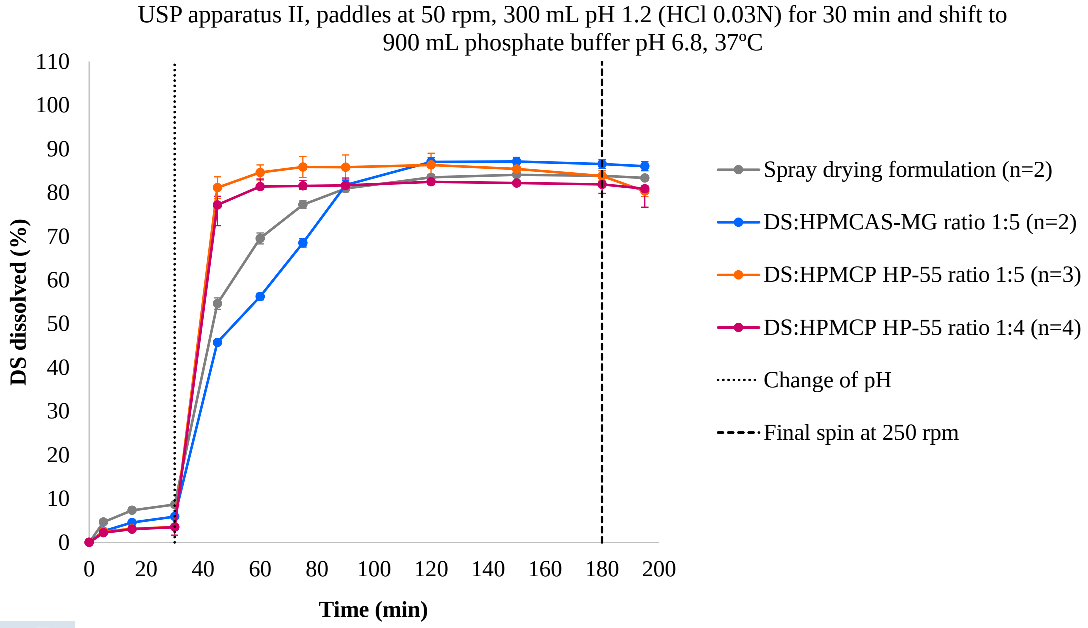


Figure 51. Dissolution profile of tablets containing SGDs of LM2 and HPMCP HP-55 in ratios 1:4 and 1:5.

Tablets were film-coated, following the procedure described in section 4.1.6, and subjected to XRPD and MDSC analysis. Results shown in Figure 47 confirm that drug substance was present in amorphous solid state in all cases, as no distinct peaks corresponding to crystalline forms of LM2 were observed. The peaks observed correspond to Opadry® yellow 03F32518, magnesium stearate, and cling foil used during the measurement (see Figure 74, Figure 72, and Figure 75 in annex). Additionally, MDSC reversing heat flow curve revealed a single T_g at around 124ºC (for ratio 1:5) and 111ºC (for ratio 1:4), indicating the formation of a homogeneous ASD without phase separation.

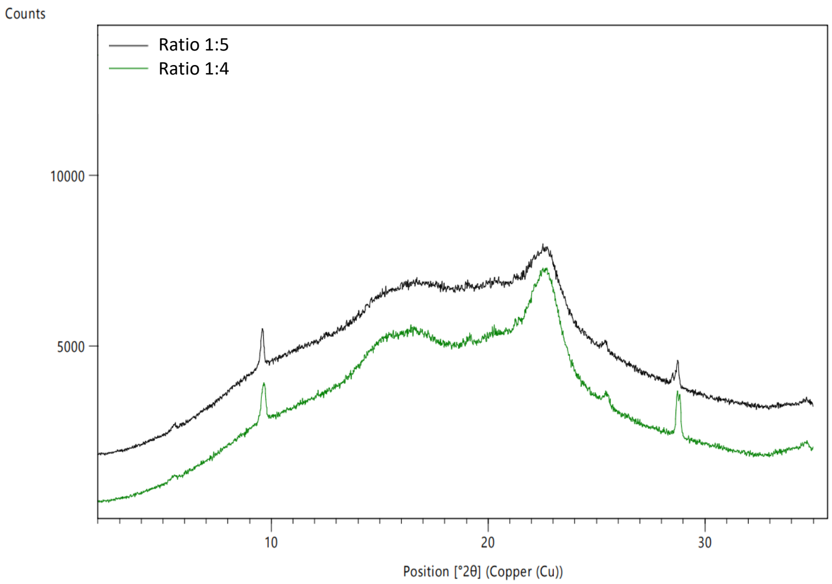


Figure 52. XRPD diffractograms of film-coated tablets containing SGD of LM2 and HPMCP HP-55 in different ratios.

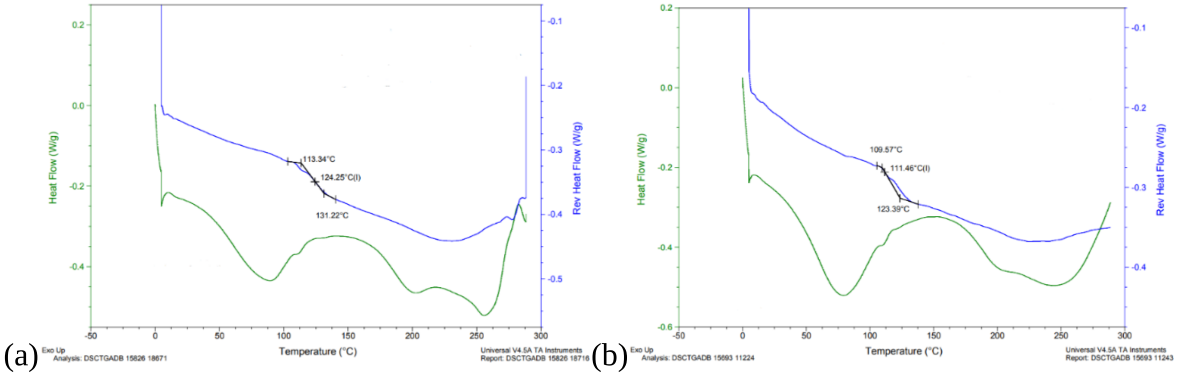


Figure 53. MDSC of film-coated tablets containing SGD of LM2 in different ratios (a) ratio 1:5 and (b) ratio 1:4.

5.2.5.1.5. Stability

The stability of the amorphous solid state, the dissolution profile, water content, assay, and impurities is presented in section 5.2.8 (prototypes B and C). XRPD and MDSC results shown from Figure 60 to Figure 63 confirmed the stability of the amorphous DS in the final drug product after 6 months of storage at 40ºC/75%RH in Al/Al blisters. Dissolution profile with QC dissolution method (Figure 65 and Figure 66), and water content, assay, and impurities (Table 58 and Table 59) also showed to remain stable at the aforementioned conditions.

Given the enhanced dissolution profile achieved with HPMCP HP-55 polymer, along with the favourable stability of the product, these two formulations were deemed a promising candidate for evaluation in an *in vivo* pilot BA study.

5.2.6. Prototypes selected for *in vivo* pilot bioavailability clinical study

Considering the formulation studies presented, three different LM2 film-coated tablets prototypes of the higher strength were tested in an *in vivo* pilot BA study against two RLD film-coated tablets of the lower strength:

- **Prototype A**: SGD of LM2:HPMCAS-MG in ratio 1:5 + 1.5% of poloxamer 188, with MCC as substrate
- **Prototype B**: SGD of LM2:HPMCP HP-55 in ratio 1:5, with MCC as substrate
- **Prototype C**: SGD of LM2:HPMCP HP-55 in ratio 1:4, with MCC as substrate

Formulations are detailed in Table 52.

Table 52. Qualitative and quantitative composition of LM2 film-coated tablets prototypes of the higher strength tested in an *in vivo* pilot BA clinical study.

Polymer type		**HPMCAS-MG**		**HPMCP HP-55**			
Ratio LM2:Polymer		**1:5**		**1:5**		**1:4**	
Substrate		**MCC**		**MCC**		**MCC**	
Surfactant		**1.5% Poloxamer 188**		**0%**		**0%**	
Prototype		**Prototype A**		**Prototype B**		**Prototype C**	
Ingredients	**Grade**	**%**	**mg/tab**	**%**	**mg/tab**	**%**	**mg/tab**
INTRAGRANULAR PHASE							
LM2	Not applicable	12.308	80.000	12.308	80.000	12.308	80.000
Hypromellose acetate succinate	AQOAT AS-MG	61.538	400.000	-	-	-	-
Hypromellose phthalate	HPMCP HP-55	-	-	61.538	400.000	49.231	320.000
Poloxamer 188	Kolliphor P188	1.500	9.750	-	-	-	-
Microcrystalline cellulose	Vivapur 102	15.154	98.500	16.654	108.250	28.962	188.250
Croscarmellose sodium	Ac-Di-Sol	4.000	26.000	4.000	26.000	4.000	26.000
Acetone [1]	Emprove	q.s.	2720.000	q.s.	2467.077	q.s.	1958.460
Purified water [1]	Not applicable	q.s.	87.750	q.s.	129.846	q.s.	103.077
EXTRAGRANULAR PHASE							
Croscarmellose sodium	Ac-Di-Sol	4.000	26.000	4.000	26.000	4.000	26.000
Anhydrous colloidal silica	Aerosil 200VV Pharma	0.500	3.250	0.500	3.250	0.500	3.2500
Magnesium stearate	Ligamed MF-2-V-MB	1.000	6.500	1.000	6.500	1.000	6.500
UNCOATED TABLET WEIGHT		100.000	650.000	100.000	650.000	100.000	650.000
Opadry 03F	Opadry® 03F220119 yellow	3.000	19.500	3.000	19.500	3.000	19.500
Purified water [1]	Not applicable	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
FILM-COATED TABLET WEIGHT		103.000	669.500	103.000	669.500	103.000	669.500

[1] Evaporated during the manufacturing process.

5.2.7. Manufacturing process for *in vivo* pilot BA study

Figure 54 illustrates the manufacturing process flow chart followed for the production of batches of the three selected prototypes (refer to Table 52) intended to be tested in the *in vivo* pilot BA study. Being for human use, all three batches were manufactured in accordance with GMP standards.

Additionally, process flow diagram is depicted in Figure 55, where each manufacturing step is listed in the sequence of occurrence. It also presents the critical material attributes (CMAs) and process parameters (CPPs) that can potentially affect intermediate and finished product quality attributes. The material attributes of the input materials and the process parameters used at the very first process step determine the quality attributes of the output material (intermediate) produced at this step. These quality attributes become material attributes for the next step. Together with process parameters of each step, it determines quality attributes of that step. This cycle repeats itself until the final process step in which final drug product is manufactured and the product quality attributes are evaluated. This flow diagram was used to guide the risk assessments and control strategy performed during process development.

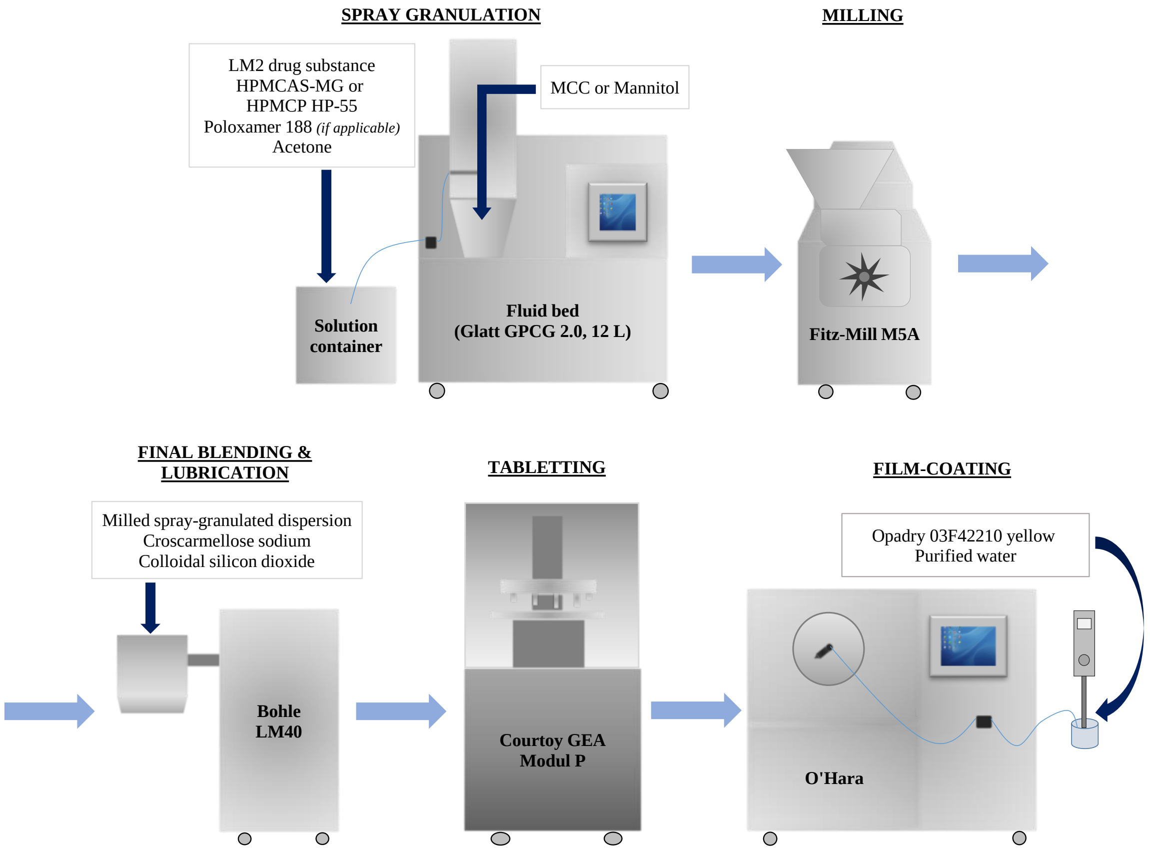
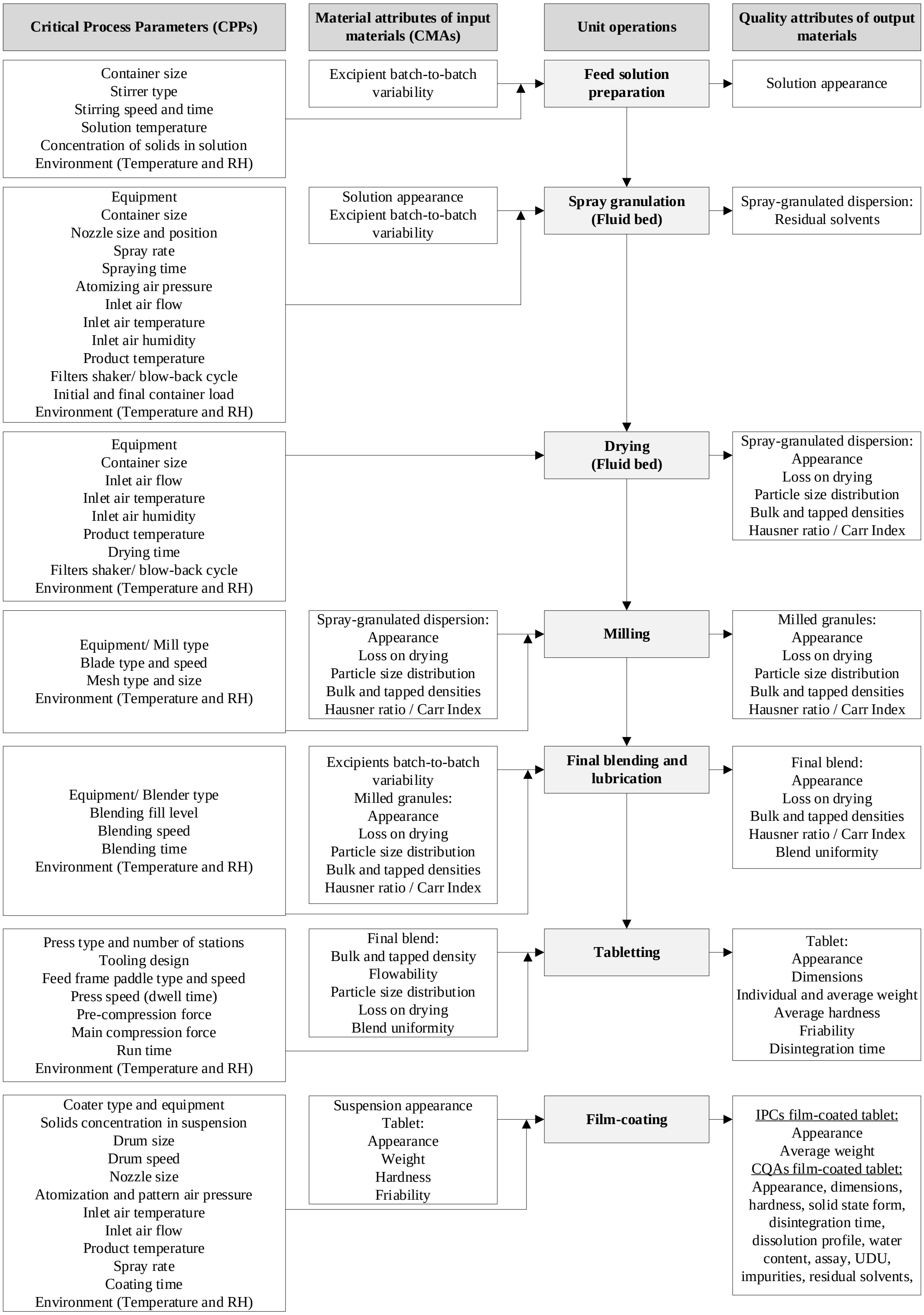


Figure 54. Manufacturing process flow chart.



Critical Process Parameters (CPPs)	Material attributes of input materials (CMAs)	Unit operations	Quality attributes of output materials
Container size Stirrer type Stirring speed and time Solution temperature Concentration of solids in solution Environment (Temperature and RH)	Excipient batch-to-batch variability	**Feed solution preparation**	Solution appearance
Equipment Container size Nozzle size and position Spray rate Spraying time Atomizing air pressure Inlet air flow Inlet air temperature Inlet air humidity Product temperature Filters shaker/ blow-back cycle Initial and final container load Environment (Temperature and RH)	Solution appearance Excipient batch-to-batch variability	**Spray granulation (Fluid bed)**	Spray-granulated dispersion: Residual solvents
Equipment Container size Inlet air flow Inlet air temperature Inlet air humidity Product temperature Drying time Filters shaker/ blow-back cycle Environment (Temperature and RH)		**Drying (Fluid bed)**	Spray-granulated dispersion: Appearance Loss on drying Particle size distribution Bulk and tapped densities Hausner ratio / Carr Index
Equipment/ Mill type Blade type and speed Mesh type and size Environment (Temperature and RH)	Spray-granulated dispersion: Appearance Loss on drying Particle size distribution Bulk and tapped densities Hausner ratio / Carr Index	**Milling**	Milled granules: Appearance Loss on drying Particle size distribution Bulk and tapped densities Hausner ratio / Carr Index
Equipment/ Blender type Blending fill level Blending speed Blending time Environment (Temperature and RH)	Excipients batch-to-batch variability Milled granules: Appearance Loss on drying Particle size distribution Bulk and tapped densities Hausner ratio / Carr Index	**Final blending and lubrication**	Final blend: Appearance Loss on drying Bulk and tapped densities Hausner ratio / Carr Index Blend uniformity
Press type and number of stations Tooling design Feed frame paddle type and speed Press speed (dwell time) Pre-compression force Main compression force Run time Environment (Temperature and RH)	Final blend: Bulk and tapped density Flowability Particle size distribution Loss on drying Blend uniformity	**Tabletting**	Tablet: Appearance Dimensions Individual and average weight Average hardness Friability Disintegration time
Coater type and equipment Solids concentration in suspension Drum size Drum speed Nozzle size Atomization and pattern air pressure Inlet air temperature Inlet air flow Product temperature Spray rate Coating time Environment (Temperature and RH)	Suspension appearance Tablet: Appearance Weight Hardness Friability	**Film-coating**	IPCs film-coated tablet: Appearance Average weight CQAs film-coated tablet: Appearance, dimensions, hardness, solid state form, disintegration time, dissolution profile, water content, assay, UDU, impurities, residual solvents,

Figure 55. Process flow diagram.

5.2.7.1. Control strategy

Table 53 presents the control strategy prepared for the production of GMP batches of the three prototypes selected. The control strategy is a planned set of controls, derived from current process understanding, to ensure consistent performance and product quality. The control strategy includes excipient material attributes to be controlled, equipment operating conditions, and IPCs. The ultimate objective is to demonstrate that the manufacturing process for these three batches under GMP conditions was thoroughly regulated and monitored.

This control strategy should be updated after the outcome of *in vivo* pilot BA study, once more extensive studies on process parameters with high risk to the CQAs of the drug product are conducted.

Table 53. Control strategy for laboratory-scale production of generic LM2 film-coated tablets prototypes of the higher strength.

Factor	Attributes or parameters	Range studied at laboratory-scale			Purpose of control
		Prototype A 2.5 kg final blend	**Prototype B 2.0 kg final blend**	**Prototype C 2.0 kg final blend**	
Raw material attributes					
Hypromellose acetate succinate	Viscosity[1]	2.4 – 3.6 mPa·s	Not applicable	Not applicable	To ensure the production and stabilization of amorphous drug substance, dissolution, and batch-to-batch consistency
	Acetyl content	7.0 – 11.0%			
	Succinoyl content	10.0 – 14.0%			
	Methoxy content	21.0 – 25.0%			
	Hydroxypropoxy content	5.0 – 9.0%			
Hypromellose phthalate	Viscosity[2]	*Not applicable*	32 – 48 mPa·s	32 – 48 mPa·s	
	Phthalyl content		27.0 – 35.0%	27.0 – 35.0%	
	Methoxy content		18.0 – 22.0%	18.0 – 22.0%	
	Hydroxypropoxy content		5.0 – 9.0%	5.0 – 9.0%	
Poloxamer 188	Average molecular mass	7680 – 9510	*Not applicable*	*Not applicable*	
Microcrystalline cellulose	Particle size distribution	d_{10}: 20 – 50 µm d_{50}: 90 – 150 µm d_{90}: 190 – 300 µm	d_{10}: 20 – 50 µm d_{50}: 90 – 150 µm d_{90}: 190 – 300 µm	d_{10}: 20 – 50 µm d_{50}: 90 – 150 µm d_{90}: 190 – 300 µm	To ensure sufficient flowability and batch-to-batch consistency
Croscarmellose sodium	Settling volume	10.0 – 30.0 mL	10.0 – 30.0 mL	10.0 – 30.0 mL	To ensure disintegration of granules and tablets, and batch-to-batch consistency
	Degree of substitution	0.63 – 0.85	0.63 – 0.85	0.63 – 0.85	
	Particle size distribution	$d_{10} \leq 25$ µm d_{50}: 25 – 55 µm $d_{90} \geq 60$ µm	$d_{10} \leq 25$ µm d_{50}: 25 – 55 µm $d_{90} \geq 60$ µm	$d_{10} \leq 25$ µm d_{50}: 25 – 55 µm $d_{90} \geq 60$ µm	

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[1] Viscosity of 2.00 g of HPMCAS, previously dried, in 100.0 g of a sodium hydroxide aqueous solution (4.3 mg/mL of sodium hydroxide in carbon dioxide-free water) at 20 ± 0.1ºC.

[2] Viscosity of 10 g of HPMCP, previously dried at 105ºC for 1 h, in 90 g of a mixture of equal masses of methanol and methylene chloride by mixing and shaking.

Factor	**Attributes or parameters**	**Range studied at laboratory-scale**			**Purpose of control**
		Prototype A 2.5 kg final blend	**Prototype B 2.0 kg final blend**	**Prototype C 2.0 kg final blend**	
Anhydrous colloidal silica	Specific surface area	175 – 225 m^2/g	175 – 225 m^2/g	175 – 225 m^2/g	To ensure sufficient flowability and batch-to-batch consistency
Magnesium stearate	Specific surface area	6 – 10 m^2/g	6 – 10 m^2/g	6 – 10 m^2/g	To ensure sufficient lubrication and reduce the risk of retarded disintegration and dissolution
	Particle size distribution	$d_{10} \leq 10$ µm d_{50}: 7 – 11 µm $d_{90} \leq 35$ µm	$d_{10} \leq 10$ µm d_{50}: 7 – 11 µm $d_{90} \leq 35$ µm	$d_{10} \leq 10$ µm d_{50}: 7 – 11 µm $d_{90} \leq 35$ µm	
Feed solution preparation process parameters					
Feed solution preparation (drug substance and polymer)	Container size	15 – 20 L	15 – 16 L	15 – 16 L	To ensure the complete dissolution of drug substance and polymer, ensure the production of an homogeneous ASD with no phase separation, and enhance drug product dissolution profile
	Stirrer type	IKA R 1300 Dissolver stirrer	IKA R 1300 Dissolver stirrer	IKA R 1300 Dissolver stirrer	
	Stirrer speed	15 L: 750 - 1200 rpm 20 L: 420 – 900 rpm	15 L: 470 - 1200 rpm 16 L: 230 – 430 rpm	15 L: 560 - 860 rpm 16 L: 230 – 360 rpm	
	Stirring time DS	5 – 10 min	5 – 10 min	5 – 10 min	
	Stirring time polymer	15 – 35 min	15 – 35 min	15 – 35 min	
	Solution temperature	Room temperature	Room temperature	Room temperature	
	Concentration of solids in solution	15.0% w/w (12.5% polymer)	15.6% w/w (13.0% polymer)	16.3% w/w (13.0% polymer)	
Poloxamer 188 aqueous solution	Container size	1 L	*Not applicable*	*Not applicable*	
	Stirrer type	IKA R 1345 Propeller stirrer, 4-bladed			
	Stirring speed	440 – 480 rpm			
	Stirring time	15 – 25 min			
	Solution temperature	Room temperature			
	Concentration of solids in solution	10.0% w/w			

Factor	Attributes or parameters	Range studied at laboratory-scale			Purpose of control
		Prototype A 2.5 kg final blend	Prototype B 2.0 kg final blend	Prototype C 2.0 kg final blend	
Feed solution preparation IPCs					
Solution appearance		Yellowish turbid solution without undissolved particles	Yellowish solution without undissolved particles	Yellowish solution without undissolved particles	To ensure the dissolution of drug substance and polymer
Granulation and drying process parameters					
Granulation[3]	Equipment	Glatt GPCG-2 top-spray configuration	Glatt GPCG-2 top-spray configuration	Glatt GPCG-2 top-spray configuration	Fixed due to equipment availability and batch size
	Container size	12 L	12 L	12 L	
	Nozzle size and position	1.2 mm Upper position	1.2 mm Upper position	1.2 mm Upper position	To ensure fast evaporation of solvent to yield an stable ASD
	Warm-up time	10 – 15 min	10 – 15 min	10 – 15 min	
	Spray rate	18 – 33 g/min Avg.: 30 - 33 g/min	21 – 36 g/min Avg.: 34 g/min	27 – 46 g/min Avg.: 34 - 42 g/min	
	Spraying time	390 – 420 min	262 – 278 min	180 – 223 min	
	Atomizing air pressure	2.2 – 2.8	2.0 – 2.8 [1]	2.0 – 2.5 [1]	
	Inlet air flow	45 – 95 m^3/h	50 – 100 m^3/h	50 – 85 m^3/h	
	Inlet air temperature	59 – 72ºC	67 – 79ºC	71 – 75ºC	
	Inlet air humidity	4.1 – 11.5 g/kg	4.0 – 10.0 g/kg	3.5 – 6.1 g/kg	
	Product temperature	43 ± 3ºC	43 ± 3ºC	43 ± 3ºC	
	Initial and final container load	~ 13%/ 82%	~ 12%/ 75%	~ 18%/ 79%	

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[3] At the beginning of the process, a lower feed rate, atomization pressure, and air flow were set due to the lower amount of substrate in the fluid bed chamber. It was steadily increased in correlation with the increasing amount of substrate. Inlet air temperature was adjusted accordingly to maintain the desired product temperature.

Factor	**Attributes or parameters**	**Range studied at laboratory-scale**			**Purpose of control**
		Prototype A 2.5 kg final blend	**Prototype B 2.0 kg final blend**	**Prototype C 2.0 kg final blend**	
	Filters shaker/ blow-back cycle	Synchronous 5 sec. shaking every 80 – 200 sec.	Synchronous 5 sec. shaking every 80 – 200 sec.	Synchronous 5 sec. shaking every 80 – 200 sec.	To avoid built up of particles on the surface of the fabric filter bags
Drying	Equipment	Glatt GPCG-2	Glatt GPCG-2	Glatt GPCG-2	Fixed due to equipment availability and batch size
	Container size	12 L	12 L	12 L	
	Inlet air flow	70 – 90 m^3/h	80 m^3/h	70 – 90 m^3/h	To ensure the reduction of residual acetone content
	Inlet air temperature	60 – 70ºC	67 – 79ºC	64 – 70ºC	
	Inlet air humidity	4.8 – 7.1 g/kg	3.8 – 7.3 g/kg	3.5 – 6.6 g/kg	
	Product temperature	45 – 50ºC	45 – 50ºC	45 – 50ºC	
	Drying time	15 – 60 min	45 – 60 min	45 – 60 min	
	Filters shaker/ blow-back cycle	Synchronous 5 sec. shaking every 60 – 80 sec.	Synchronous 5 sec. shaking every 60 – 80 sec.	Synchronous 5 sec. shaking every 60 – 80 sec.	To avoid built up of particles on the surface of the fabric filter bags
Drying IPCs					
Process yield		90 – 97%	93 – 97%	93 – 97%	To control process performance
Granules appearance		White to off white granulated powder			For information only
Granules loss on drying		1.1 – 1.3%	0.8 – 1.0%	1.1 – 1.3%	
Granules particles size distribution		> 355 µm: 45-51% 180-355 µm: 31-40% 125-180µm: 7% < 125 µm: 8-13%	> 355 µm: 45% 180-355 µm: 31% 125-180µm: 10% < 125 µm: 15%	> 355 µm: 28% 180-355 µm: 58% 125-180µm: 9% < 125 µm: 6%	
Granules bulk density		0.21 – 0.24 g/mL	0.21 g/mL	0.19 g/mL	
Granules tapped density		0.27 – 0.31 g/mL	0.27 g/mL	0.25 g/mL	
Hausner ratio		1.30 – 1.32	1.32	1.30	
Carr Index		23 – 24%	24%	23%	

Factor	Attributes or parameters	Range studied at laboratory-scale			Purpose of control
		Prototype A 2.5 kg final blend	**Prototype B 2.0 kg final blend**	**Prototype C 2.0 kg final blend**	
Flow character		Passable	Passable	Passable	
Milling process parameters					
Milling	Mill type/ Equipment	Impact mill/ Fitz-Mill	Impact mill/ Fitz-Mill	Impact mill/ Fitz-Mill	To increase granules bulk density
	Blade type	Hammer	Hammer	Hammer	
	Blade speed	4000 rpm	4000 rpm	4000 rpm	
	Mesh type	Round	Round	Round	
	Mesh size	0.5 mm	1.0 mm	1.0 mm	
Milling IPCs					
Granules appearance		White to off-white granulated powder without agglomerates			For information only
Granules loss on drying		1.7%	1.4%	1.5%	
Granules particles size distribution		> 355 µm: 3-4% 180-355 µm: 57-80% 125-180µm: 9-10% < 125 µm: 6-30%	> 355 µm: 5-11% 180-355 µm: 54-62% 125-180µm: 13-14% < 125 µm: 18-23%	> 355 µm: 3% 180-355 µm: 67-69% 125-180µm: 16-19% < 125 µm: 11-12%	
Granules bulk density		0.31 – 0.32 g/mL	0.25 – 0.26 g/mL	0.25 – 0.26 g/mL	
Granules tapped density		0.39 – 0.41 g/mL	0.32 – 0.35 g/mL	0.31 – 0.32 g/mL	
Hausner ratio		1.19 – 1.33	1.29 – 1.32	1.25 – 1.28	
Carr Index		16 – 25	23 – 24	20 – 22	
Flow character		Passable – Fair	Passable	Passable – Fair	
Final blending and lubrication process parameters					
Final blending and lubrication	Blender type/ Equipment	Bohle LM40 – 10 L/ Diffusion mixer	Bohle LM40 – 10 L/ Diffusion mixer	Bohle LM40 – 10 L/ Diffusion mixer	To ensure consistent blending of granules and extragranular excipients, while
	Blender fill level	~ 70%	~ 70%	~ 70%	
	Blending speed	20 rpm	20 rpm	20 rpm	

Factor	Attributes or parameters	Range studied at laboratory-scale			Purpose of control
		Prototype A 2.5 kg final blend	Prototype B 2.0 kg final blend	Prototype C 2.0 kg final blend	
	Blending time	10 min (without magnesium stearate) 3 min (with magnesium stearate)	10 min (without magnesium stearate) 3 min (with magnesium stearate)	10 min (without magnesium stearate) 3 min (with magnesium stearate)	avoiding over-lubrication
Final blending and lubrication IPCs					
Final blend appearance		White to off-white powder without agglomerates			For information only
Final blend loss on drying		1.3 – 2.0%	1.5 – 1.9%	2.0 – 2.2%	
Final blend bulk density		0.31 – 0.35 g/mL	0.28 – 0.29 g/mL	0.27 – 0.28 g/mL	
Final blend tapped density		0.40 – 0.44 g/mL	0.35 – 0.36 g/mL	0.34 g/mL	
Hausner ratio		1.19 – 1.28	1.23 – 1.24	1.22 – 1.25	
Carr Index		21 – 22	18 – 19	18 – 20	
Flow character		Passable	Fair	Fair	
Blend uniformity and assay		RSD 0.3% 98.8% w/w	RSD 0.2% 97.8% w/w	RSD 0.8% 99.0% w/w	To ensure well distribution of the drug substance
Tableting process parameters					
Tableting	Press type/ Equipment	Rotary tablet press/ GEA Courtoy Modul P	Rotary tablet press/ GEA Courtoy Modul P	Rotary tablet press/ GEA Courtoy Modul P	To ensure all tablet CQAs (assay, UDU, dissolution) are met consistently
	Number of stations	5	5	5	
	Tooling design	17 x 9 mm, oval, biconcave, embossed on both sides	17 x 9 mm, oval, biconcave, embossed on both sides	17 x 9 mm, oval, biconcave, embossed on both sides	
	Feed frame paddle type	Flat	Flat	Flat	
	Feed frame paddle speed	1st: 10 rpm 2nd: 12 rpm	1st: 10-12 rpm 2nd: 12-14 rpm	1st: 10 rpm 2nd: 12 rpm	
	Press speed (dwell time)	20	20	20	

Factor	Attributes or parameters	Range studied at laboratory-scale			Purpose of control
		Prototype A 2.5 kg final blend	**Prototype B 2.0 kg final blend**	**Prototype C 2.0 kg final blend**	
	Pre-compression force	1.5 kN	1.5 kN	1.5 kN	
	Main compression force	5 – 20 kN Target: 12 - 14 kN	6 – 12 kN Target: 9 – 11 kN	6 – 12 kN Target: 9 – 11 kN	
	Run time	30 min	30 min	30 min	
Tableting IPCs					
Tablet appearance		White to off white, oval tablet debossed on both sides			To ensure all tablet CQAs are met consistently
Individual weight		650.0 mg ± 5%			
Average weight		650.0 mg ± 2%			
Average hardness		Target: 180 N Studied: 57 – 335 N	Target: 230 N Studied: 141 – 290 N	Target: 230 N Studied: 140 – 298 N	
Length		17.0 ± 0.1 mm	17.0 ± 0.1 mm	17.0 ± 0.1 mm	
Thickness		Target: 6.0 ± 0.1 mm Studied: 5.6 - 7.4 mm	Target: 6.5 ± 0.1 mm Studied: 6.5 - 6.8 mm	Target: 6.4 ± 0.1 mm Studied: 6.3 - 6.7 mm	
Friability		< 0.1%	< 0.1%	< 0.1%	
Disintegration time		< 4 min	< 2 min	< 3 min	
Film-coating process parameters					
Film-coating	Coater type/ Equipment	Perforated pan coating system/ O'Hara Labcoat M	Perforated pan coating system/ O'Hara Labcoat M	Perforated pan coating system/ O'Hara Labcoat M	To ensure that all tablet CQAs and release tests are met consistently
	Solids concentration in solution	15.0% w/w	15.0% w/w	15.0% w/w	
	Drum size	7.2 L	7.2 L	7.2 L	
	Drum speed	12 rpm	12 – 15 rpm	12 – 15 rpm	
	Nozzle size	0.8 mm	0.8 mm	0.8 mm	
	Atomization pressure	1.2 bar	1.2 bar	1.2 bar	
	Pattern pressure	1.2 bar	1.2 bar	1.2 bar	

Factor	Attributes or parameters	Range studied at laboratory-scale			Purpose of control
		Prototype A 2.5 kg final blend	Prototype B 2.0 kg final blend	Prototype C 2.0 kg final blend	
	Inlet air temperature	60 – 70ºC	60 – 70ºC	60 – 70ºC	
	Inlet air flow	150 m^3/h	150 m^3/h	150 m^3/h	
	Product temperature	42 – 44ºC	42 – 44ºC	42 – 44ºC	
	Spray rate	14 rpm	14 rpm	14 rpm	
	Coating time	58 min	40 min	55 min	
Film-coating IPCs					
Coated tablets appearance		Oval, yellow film-coated tablet debossed on both sides, and without defects			To ensure that all tablet CQAs and release tests are met consistently
Average weight		Average uncoated tablet weight + 3.0% weight increase			

5.2.7.2. Release tests

The release results for the three batches produced under GMP conditions and for the RLD are provided in Table 54 and Table 55, respectively. These batches were subsequently used to conduct the *in vivo* pilot BA study. All results were within the stablished specifications, showing a fast disintegration time and dissolution profile (> 85% dissolved in 15 minutes).

Table 54. Release tests and results of generic LM2 film-coated tablets of the higher strength.

Product	Specifications	Prototype A	Prototype B	Prototype C
Appearance	Oval, yellow film-coated tablet debossed on both sides	Complies	Complies	Complies
Dimensions (mm) • Length • Width • Thickness	 17.1 ± 0.2 9.1 ± 0.2	 17.2 9.1 6.0	 17.2 9.2 6.6	 17.3 9.2 6.4
Average hardness (N)	≥ 200	238	272	277
Solid state form (XRPD and MDSC)	Amorphous	Amorphous See t=0 in Figure 58 and Figure 59	Amorphous See t=0 in Figure 60 and Figure 61	Amorphous See t=0 in Figure 62 and Figure 63
Disintegration time (min)	≤ 15	< 4	< 2	< 2
Dissolution profile (QC method)	≥ 85% dissolved in 15 minutes	See Figure 56	See Figure 56	See Figure 56
Water content (%)	For information only	1.9	2.5	2.7
Assay (%)	95.0 – 105.0% of label claim	100.8	98.7	99.3
UDU • Mean (%) • Max. (%) • Min. (%) • RSD (%) • AV	Complies with Ph.Eur.2.9.40 and USP <905>	 101.1 101.9 100.2 0.6 1.4	 98.9 100.1 97.9 0.6 1.4	 99.8 102.1 97.9 1.2 2.9
Impurities (%) • Impurity 1 • Largest unspecified • Total unspecified • Total	 ≤ 0.2 ≤ 0.2 ≤ 1.0 ≤ 1.0	 ≤ 0.1 ≤ 0.1 ≤ 0.1 ≤ 0.1	 ≤ 0.1 ≤ 0.1 ≤ 0.1 ≤ 0.1	 ≤ 0.1 ≤ 0.1 ≤ 0.1 ≤ 0.1
Residual acetone content (ppm)	≤ 5000	< 500	2338	2312

Table 55. Release tests and results of RLD of the lower strength.

Product	Results
Assay (%)	99.2
Solid state form (XRPD)	Amorphous (see Figure 77 in annex)
Disintegration time (min)	< 2

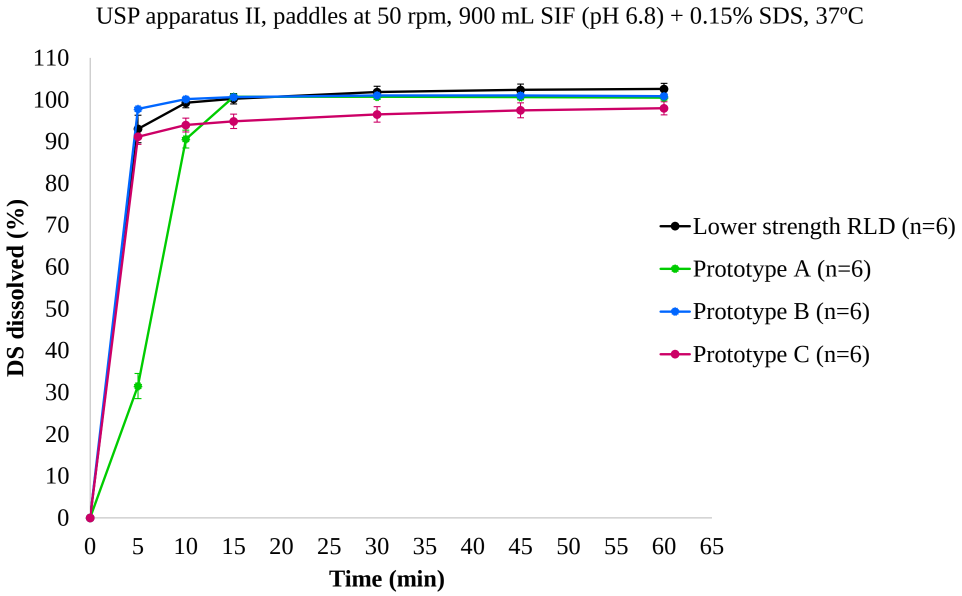

Figure 56. Dissolution profile of generic prototypes A, B, and C of LM2 film-coated tablets using QC dissolution method.

5.2.7.3. Dissolution profile using two-step method

In addition to the release tests, dissolution profiles of all three batches were measured using the two-step dissolution method used throughout development. Results are depicted in Figure 57 and compared with those of two RLD tablets of the lower strength.

In line with previous results, formulations with HPMCP HP-55 showed a faster release profile at pH 6.8 than the formulation with HPMCAS-MG + poloxamer 188 and the RLD, showing higher level of supersaturation at the initial time points (at 45 and 60 min). Nevertheless, formulations with HPMCP HP-55 showed some precipitation after the rapid release, which could suggest a lower precipitation inhibition potential than HPMCAS-MG.

On the other hand, formulation with HPMCAS-MG + poloxamer 188 showed a slightly slower release at pH 6.8 than the RLD at the initial time points (at 45 and 60 min). However, a higher level of supersaturation was achieved from 75 to 150 minutes.

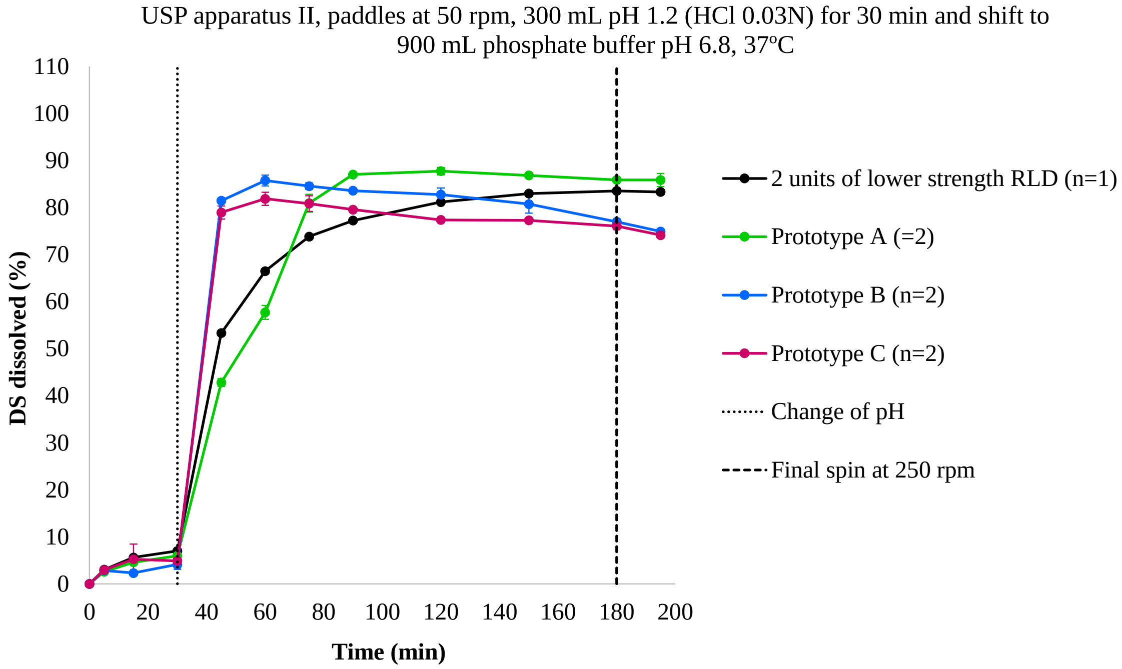

Figure 57. Dissolution profile of generic prototypes A, B, and C of LM2 higher strength film-coated tablets using two-step dissolution method and compared to two RLD tablets of the lower strength.

5.2.8. Stability studies

Stability studies of the three prototypes selected (refer to Table 52) were carried out with the aim to study the influence of the excipients and the manufacturing process on drug product stability, and verify the suitability of the prototypes to be tested in a *in vivo* pilot BA study. Stability studies were conducted under ICH accelerated (40ºC/75%RH) and long-term (25ºC/60%RH) conditions in Al/Al blisters. The stability study design is summarized in Table 56. The CQAs considered for drug product stability assessment were the following:

1. Amorphous solid state
2. Dissolution profile
3. Water content
4. Assay and impurities growth

Table 56. Stability study design.

Prototype	A	B	C
DS supplier	Synthon s.r.o		
Packaging configuration	Al/Al blister		
Storage conditions	40ºC / 75%RH and 25ºC/60%RH		
Last sampling point	6 months		

5.2.8.1. Amorphous solid state

The stability of the amorphous drug substance in the final drug product was assessed using both XRPD and MDSC techniques. Samples stored at 40ºC/75%RH were analysed as a worst case scenario.

XRPD diffractograms and MDSC reversing heat flow curves obtained at the different stability time points are presented in Figure 58 and Figure 59 for prototype A; in Figure 60 and Figure 61 for prototype B; and in Figure 62 and Figure 63 for prototype C. The results revealed that drug substance remained in amorphous solid state in all three prototypes throughout storage, without evidence of phase separation or crystallization.

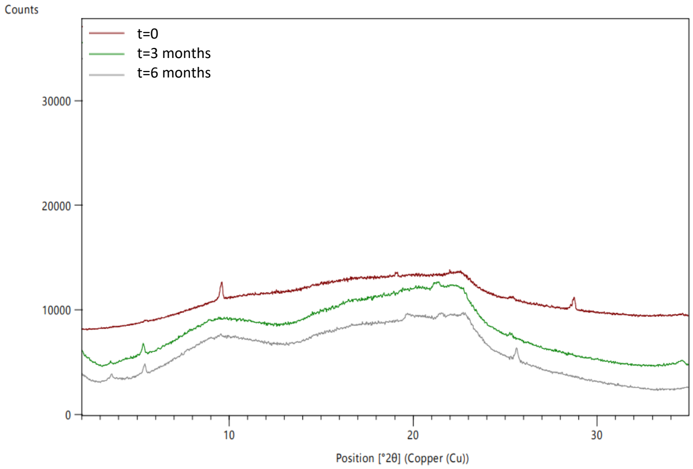

Figure 58. XRPD diffractogram of prototype A film-coated tablets at initial time point (t=0) and after either 3 or 6 months of storage at 40ºC/75%RH in Al/Al blisters. The peaks observed correspond to Opadry® yellow 03F32518 and magnesium stearate (see Figure 74 and Figure 72 in annex).

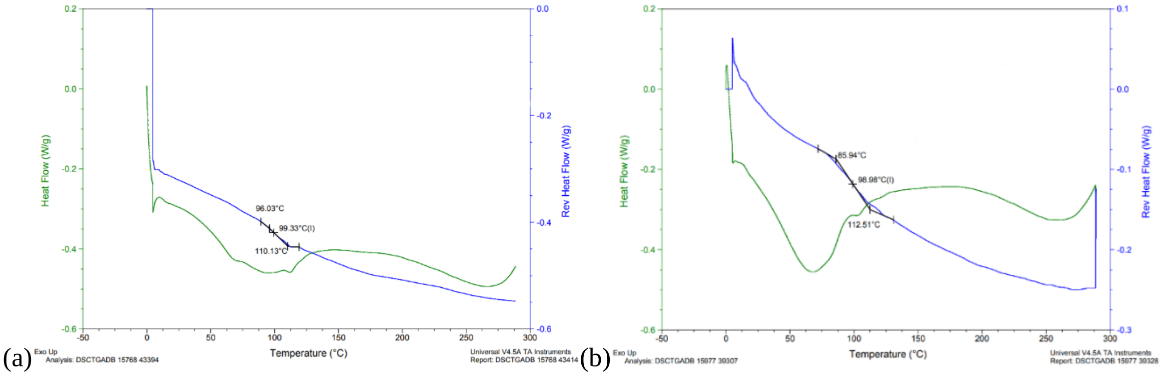

Figure 59. MDSC curves of prototype A film-coated tablets (a) at t=0 and (b) after 6 months of storage at 40ºC/75%RH in Al/Al blisters.

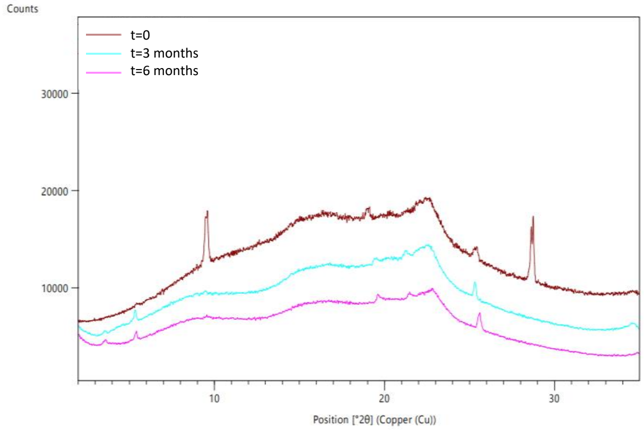

Figure 60. XRPD diffractogram of prototype B film-coated tablets at initial time point (t=0) and after either 3 or 6 months of storage at 40ºC/75%RH in Al/Al blisters. The peaks observed correspond to Opadry® yellow 03F32518 and magnesium stearate (see Figure 74 and Figure 72 in annex).

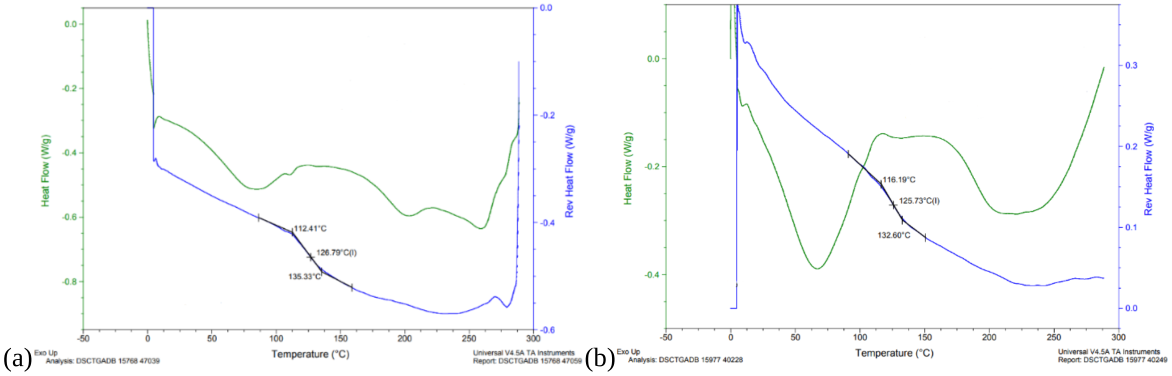

Figure 61. MDSC curves of prototype B film-coated tablets (a) at =0 and (b) after 6 months of storage at 40ºC/75%RH in Al/Al blisters.

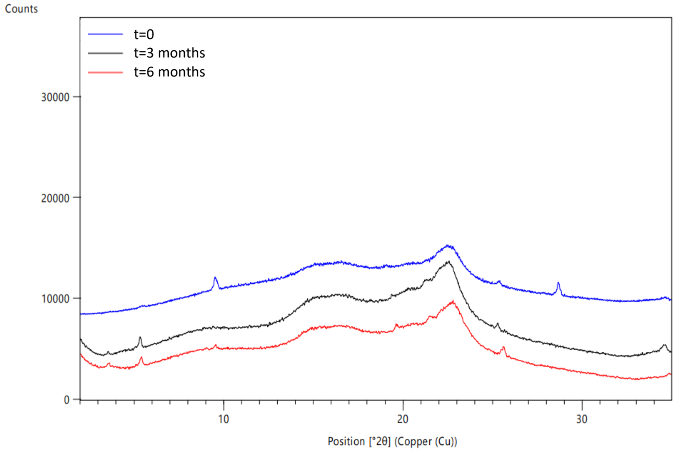

Figure 62. XRPD diffractogram of prototype C film-coated tablets at initial time point (t=0) and after either 3 or 6 months of storage at 40ºC/75%RH in Al/Al blisters. The peaks observed correspond to Opadry® yellow 03F32518 and magnesium stearate (see Figure 74 and Figure 72 in annex).

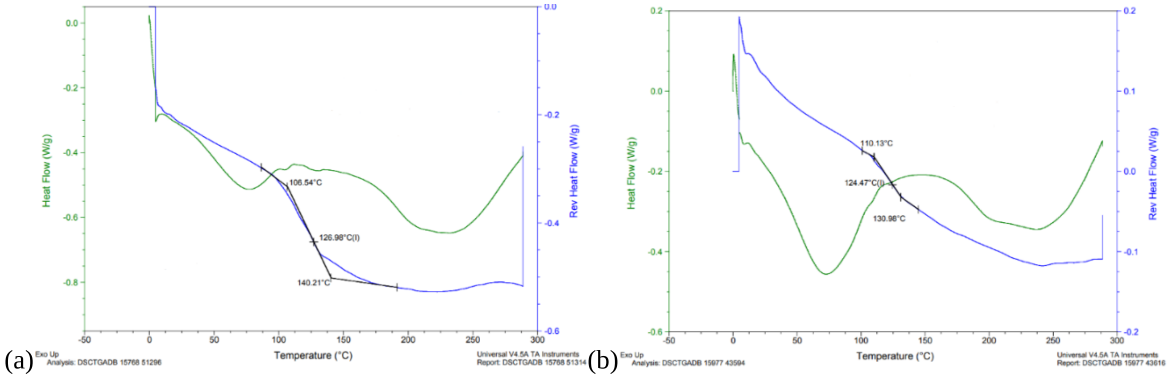

Figure 63. MDSC curves of prototype C film-coated tablets (a) at t=0 and (b) after 6 months of storage at 40ºC/75%RH in Al/Al blisters.

5.2.8.2. Dissolution profile

Similarly to feasibility studies (refer to section 5.1.8.2), the stability of the dissolution profile of all three prototypes was assessed using a QC dissolution method capable of dissolving the total amount of drug substance (pH 6.8 + 0.15% SDS). The results obtained, depicted in Figure 64, Figure 65, and Figure 66, revealed that the dissolution profiles of all drug product prototypes remained stable throughout storage, showing no significant differences along the studied periods and conditions.

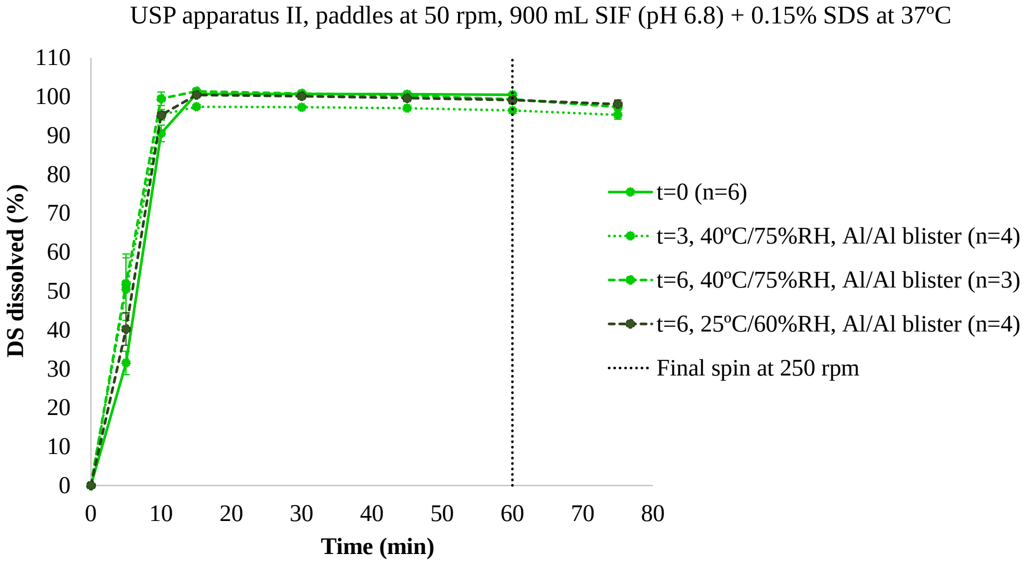

Figure 64. Dissolution profile stability of prototype A film-coated tablets in Al/Al blisters at 40ºC/75%RH.

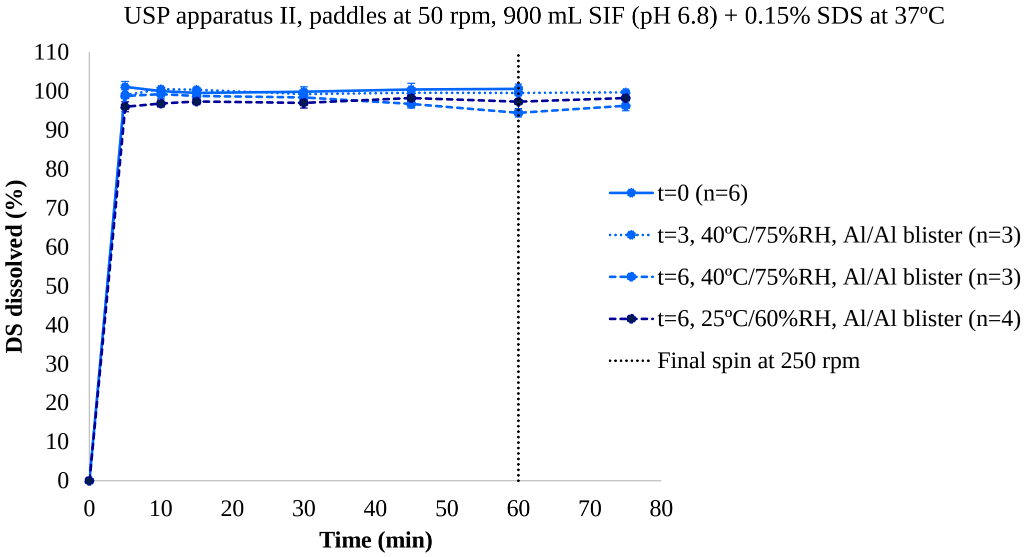

Figure 65. Dissolution profile of prototype B film-coated tablets in Al/Al blisters at 40ºC/75%RH.

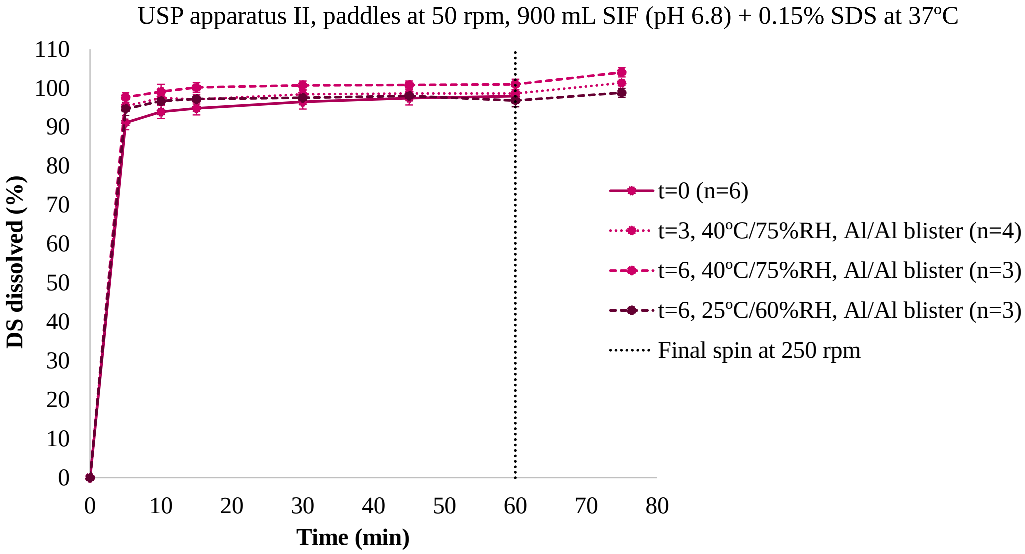

Figure 66. Dissolution profile stability of prototype C film-coated tablets in Al/Al blisters at 40ºC/75%RH.

5.2.8.3. Water content, assay, and impurities

The stability of the water content, assay, and impurities growth of all three prototypes are summarized in Table 57, Table 58, and Table 59. In line with the findings from feasibility studies (5.1.8.3), no significant changes on assay were observed throughout storage and slight increase of one impurity (Impurity 1) was observed, but well below the limit.

Table 57. Assay and impurities growth throughout stability of prototype A film-coated tablets in Al/Al blisters at 40ºC/75%RH.

Description		Prototype A			
Packaging material		Al/Al blister			
Storage conditions		NA	40ºC/75%RH		25ºC/60%RH
Storage time (months)		0	3	6	6
Water content		1.9%	*Not tested*	2.0%	2.0%
Assay		100.8%	101.2%	101.3%	101.3%
Impurities	Impurity 1	< 0.10%	< 0.10%	0.10%	< 0.10%
	Largest unspecified	< 0.10%	< 0.10%	< 0.10%	< 0.10%
	Total unspecified	< 0.10%	< 0.10%	< 0.10%	< 0.10%
	Total	< 0.10%	< 0.10%	0.10%	< 0.10%

NA = not applicable

Table 58. Assay and impurities growth throughout stability of prototype B film-coated tablets in Al/Al blisters at 40ºC/75%RH.

Description		Prototype B			
Packaging material		Al/Al blister			
Storage conditions		NA	40ºC/75%RH		25ºC/60%RH
Storage time (months)		0	3	6	6
Water content		2.5%	*Not tested*	2.7%	2.6%
Assay		98.7%	98.8%	98.8%	99.2%
Impurities	Impurity 1	< 0.10%	< 0.10%	0.12	< 0.10%
	Largest unspecified	< 0.10%	< 0.10%	< 0.10%	< 0.10%
	Total unspecified	< 0.10%	< 0.10%	< 0.10%	< 0.10%
	Total	< 0.10%	< 0.10%	0.12%	< 0.10%

NA = not applicable

Table 59. Assay and impurities growth throughout stability of prototype C film-coated tablets in Al/Al blisters at 40ºC/75%RH.

Description		Prototype C			
Packaging material		Al/Al blister			
Storage conditions		NA	40ºC/75%RH		25ºC/60%RH
Storage time (months)		0	3	6	6
Water content		2.7%	*Not tested*	2.7%	2.8%
Assay		99.3%	99.4%	98.3%	98.6%
Impurities	Impurity 1	< 0.10%	< 0.10%	0.10	< 0.10%
	Largest unspecified	< 0.10%	< 0.10%	< 0.10%	< 0.10%
	Total unspecified	< 0.10%	< 0.10%	< 0.10%	< 0.10%
	Total	< 0.10%	< 0.10%	0.10%	< 0.10%

NA = not applicable

5.2.9. Updated risk assessment of drug product formulation

Based on the outcome of formulation investigations, the risk assessments were revised prior conducting the *in vivo* pilot BA study to determine the actual risk status. The updated risk assessment is detailed in Table 60 and the rationale for reducing the risks is provided in Table 60.

Table 60. Updated RA of the formulation variables.

Drug product CQAs	Critical parameters of formulation components									
	DS		Carrier	Solvent	Filler	Glidant	Disintegrant	Surfactant	Lubricant	Coating agent
	Solid state form	Chemical stability	Type, grade, and %	Type	Type, grade and %	%	Type and %	Type and %	Type and %	Type and weight gain %
Appearance	Low*	Low*	Low	Low	Low	Low*	Low*	Low*	Low	Low*
Solid state form	Low	Low*	Low	Low	Low	Low*	Low	Low	Low*	Low*
Assay	Low*	Low	Low	Low	Low	Low	Low*	Low*	Low*	Low*
UDU	Low*	Low*	Low*	Low	Low	Low	Low*	Low*	Low*	Low*
Hardness	Low*	Low*	Low	Low	Low	Low*	Low*	Low*	Low	Low*
Disintegration time	Low*	Low*	Low	Low	Low	Low*	Low	Low	Low	Low*
Dissolution profile	Low	Low*	High*	Low	Low	Low*	Medium	High*	Low	Low*
Residual solvents	Low*	Low*	Low	Low	Low*	Low*	Low*	Low*	Low*	Low*
Stability (Impurities & WC)	Low	Low	Low	Low	Low	Low*	Low*	Low	Low*	Low*

*The risk level remained unchanged from the initial risk assessment, and the same justification prevails.

Table 61. Rationale for reducing the risks of the formulation variables.

Formulation variable	DP CQAs	Justification
Solid state form (DS raw material present in crystalline Form A, but amorphous DS produced in final DP)	Appearance	Initial justification prevails.
	Solid state form	Amorphous DS showed to be stable in all three DP prototypes selected after 6 months of storage at 40ºC/75%RH and packaged in Al/Al blisters (refer to section 5.2.8.1). The risk is reduced from medium to low.
	Assay	Initial justification prevails.
	UDU	
	Hardness	

Formulation variable	DP CQAs	Justification
	Disintegration time	
	Dissolution profile	Dissolution profile showed to be stable in all three DP prototypes selected after 6 months of storage at 40ºC/75%RH and packaged in Al/Al blisters (refer to section 5.2.8.2). The risk is reduced from high to low.
	Residual solvents	Initial justification prevails.
	Stability (Impurities & WC)	No increase of water content and low growth of impurities were observed in all three DP prototypes after 6 months of storage at 40ºC/75%RH and 25ºC/60%RH in Al/Al blisters (refer to section 5.2.8.3). The risk is reduced from medium to low.
Chemical stability	Appearance	Initial justification prevails.
	Solid state form	
	Assay	Assay values close to 100% were obtained in all three DP prototypes. Furthermore, assay showed to be stable after 6 months of storage at 40ºC/75%RH and 25ºC/60%RH in Al/Al blisters (refer to section 5.2.8.3). The risk is reduced from medium to low.
	UDU	Initial justification prevails.
	Hardness	
	Disintegration time	
	Dissolution profile	
	Residual solvents	
	Stability (Impurities & WC)	No increase of water content and low growth of impurities were observed in all three DP prototypes after 6 months of storage at 40ºC/75%RH and 25ºC/60%RH in Al/Al blisters (refer to section 5.2.8.3). The risk is reduced from medium to low.
Carrier – type, grade and %	Appearance	The carrier type showed a slight influence on the density of the milled SGD, being higher when HPMCAS-MG polymer was used compared to HPMCP HP-55. Consequently, this led to the production of thicker tablets (refer to control strategy in Table 53). Nevertheless, despite these variations, tablets without defects and low friability were obtained in all prototypes. Therefore, the risk is reduced from high to low.
	Solid state form	Amorphous DS was produced and stabilized into ASDs with either HPMCAS-MG in ratio 1:5, or HPMCP HP-55 in ratios 1:5 and 1:4. Amorphous DS showed to be stable in all three DP prototypes selected after 6 months of storage at 40ºC/75%RH and packaged in Al/Al blisters (refer to section 5.2.8.1). Hence, the risk is reduced from high to low.
	Assay	DP assay showed to be stable in all three DP prototypes after 6 months of storage at 40ºC/75%RH and 25ºC/60%RH in Al/Al blisters (refer to section 5.2.8.3). The risk is reduced from high to low.
	UDU	Initial justification prevails.

Formulation variable	DP CQAs	Justification
	Hardness	Final blend with good compression properties were obtained for all prototypes within a wide range of compression forces, reaching high tablet hardness (refer to control strategy in Table 53) and without affecting the drug product dissolution profile. Hence, the risk is reduced from high to low.
	Disintegration time	The polymer type, grade and percentage could affect wettability of the tablet and consequently disintegration time. Although enteric polymers, HPMCAS-MG and HPMCP HP-55, in a high percentage were selected, tablets with fast disintegration time (< 4 min) were obtained in all cases. Thus, the risk is reduced from medium to low.
	Dissolution profile	Formulations with DS:HPMCAS-MG in ratio 1:5, and DS:HPMCP HP-55 in ratios 1:5 and 1:4 were selected. Comparable levels of supersaturation were achieved with both polymers and percentages when using the two-step dissolution method. However, tablets formulated with HPMCP HP-55 exhibited a significantly faster dissolution rates compared to those with HPMCAS-MG and the RLD (see Figure 57). On the other hand, similar release profiles were obtained for all three formulations when using QC dissolution method (see Figure 56). Since the biorelevance of the dissolution method is uncertain, the risk remains high and this variable will be evaluated in a pilot BA *in vivo* study.
	Residual solvents	The polymer is dissolved in the organic solvent (acetone or acetone:water 95:5 mixture), thus it could play a role in the removal of the solvent due to their interaction. An influence of the polymer type on residual acetone content was observed, being more challenging with HPMCP HP-55 compared to HPMCAS-MG (refer to Figure 49). Thus, a longer drying time of the SGD is required for formulations with HPMCP HP-55. Nevertheless, in both cases it was feasible to reduce the residual acetone content below 5000 ppm (limit stated in the ICH Q3C guidelines for Class 3 solvents under option 1). Hence, the risk is reduced from high to low.
	Stability (Impurities & WC)	No increase of water content and low growth of impurities were observed in all three DP prototypes after 6 months of storage at 40ºC/75%RH and 25ºC/60%RH in Al/Al blisters (refer to section 5.2.8.3). This suggests that there is no incompatibility between the selected polymeric carriers and the DS. Consequently, the risk is reduced from high to low.
Solvent – type	Appearance	With the selected solvents (acetone/water mixtures), tablets without defects and low friability were obtained for all three DP prototypes. Therefore, the risk is reduced from medium to low.

Formulation variable	DP CQAs	Justification
	Solid state form	To achieve the DS in its amorphous form after spraying and throughout storage, complete dissolution of the DS, polymer, and surfactant (if included) in the solvent is essential. Pure acetone or a mixture of acetone:water at a ratio of 95:5, both at room temperature, were elected as solvents to dissolve both DS and polymers. For the surfactant, it is first dissolved in water and then mixed with the DS and HPMCAS-MG acetone solution. According to solubility tests conducted, the maximum concentration of DS and HPMCAS-MG in acetone solution at room temperature are 39% w/w and 15% w/w, respectively. The maximum concentration of DS and HPMCP HP-55 in a mixture of acetone:water at a ratio of 95:5 at room temperature is 31% w/w and 20% w/w, respectively. Finally, the maximum concentration of poloxamer 188 in aqueous solution at room temperature is approximately 14.9% w/w. To prevent precipitation of components during the spraying step, which could result in DS crystallization, the concentration of solids in the final solutions was reduced. The final concentration of each component in the solution are as follows: • Prototype A: 2.5% w/w of DS and 12.5% w/w of HPMCAS-MG in pure acetone at room temperature. This solution is subsequently mixed with an aqueous solution of 10.0% w/w of poloxamer 188. • Protoype B: 2.6% w/w of DS and 13.0% w/w of HPMCP HP-55 in a mixture of acetone:water 95:5 solution at room temperature. • Protoype C: 3.3% w/w of DS and 13.0% w/w of HPMCP HP-55 in a mixture of acetone:water 95:5 solution at room temperature. The solubility of DS, polymers, and surfactant in the selected solvents is deemed sufficiently high. Moreover, homogenous and stable ASDs were obtained in all cases. Consequently, the risk is reduced from high to low.
	Assay	With the selected solvents, good assay, UDU, and purity profile are obtained for all three prototypes (refer to Table 54). Thus, the risk is reduced from high to low.
	UDU	
	Hardness	Final blend with good compression properties were obtained for all prototypes within a wide range of compression forces, reaching high tablet hardness (refer to control strategy in Table 53) and without affecting the drug product disintegration time and dissolution profile. Hence, the risk is reduced from medium to low.
	Disintegration time	
	Dissolution profile	
	Residual solvents	As detailed in the carrier's section, despite the necessity of applying different drying times between prototypes, it was feasible to reduce the residual acetone content below 5000 ppm for all three

Formulation variable	**DP CQAs**	**Justification**
		prototypes (the limit specified in the ICH Q3C guidelines for Class 3 solvents under option 1). Hence, the risk is reduced from high to low.
	Stability (Impurities & WC)	The risk is reduced form high to low. Refer to the justification provided for assay and UDU.
Filler – type, grade and %	Appearance	The total amount of filler is added in the intragranular phase to serve as a substrate of the ASD. Different filler types (MCC and mannitol) along with different percentages of MCC (ranging from 8.7 to 34.0% w/w) were evaluated. Tablets without defects and with low friability were obtained in all cases. This was confirmed with all three DP prototypes selected (containing 15.2 – 29.0% w/w of MCC) for the pilot BA *in vivo* study. Therefore, the risk is reduced from medium to low.
	Solid state form	Different filler types (MCC and mannitol) along with different percentages of MCC (ranging from 8.7 to 34.0% w/w) were evaluated. In all cases, an amorphous SGD was obtained (refer to sections 5.2.4.2 and 5.2.4.3). Furthermore, stability tests conducted over 6 months of storage at 40ºC/75%RH in Al/Al blisters demonstrated the stability of the amorphous form when either MCC or mannitol were used as substrate. The stability was confirmed with all three DP prototypes selected, which contain 15.2 – 29.0% w/w of MCC. Therefore, the risk is reduced from high to low.
	Assay	MCC type 102, ranging from 15.2 – 29.0% w/w, was selected. Flowability properties of the final blend of all three prototypes were good enough, resulting in tablets with low weight variation, and assay and UDU values around 100%. Therefore, the risk is reduced from medium to low.
	UDU	
	Hardness	Different filler types (MCC and mannitol) along with different percentages of MCC (ranging from 8.7 to 34.0% w/w) were evaluated. In all cases, final blend with good compression properties were obtained for all prototypes within a wide range of compression forces, reaching high tablet hardness (refer to control strategy in Table 53) and without affecting the drug product disintegration time and dissolution profile. Hence, the risk is reduced from medium to low.
	Disintegration time	
	Dissolution profile	
	Residual solvents	Initial justification prevails.
	Stability (Impurities & WC)	No increase of water content and low growth of impurities were observed in all three DP prototypes after 6 months of storage at 40ºC/75%RH and 25ºC/60%RH in Al/Al blisters (refer to section 5.2.8.3). This suggests that there is no incompatibility between the selected filler/substrate (MCC) and the DS. Consequently, the risk is reduced from high to low.
Glidant – %	Appearance	Initial justification prevails.

Formulation variable	DP CQAs	Justification
	Solid state form	Initial justification prevails.
	Assay	Colloidal silicon dioxide was selected as a glidant in a common percentage for a tablet formulation (i.e., 0.50% w/w). Final blends with good flow characteristics were obtained for all three prototypes, resulting in tablets with low weight variation, and assay and UDU values around 100%. Therefore, the risk is reduced from medium to low.
	UDU	
	Hardness	Initial justification prevails.
	Disintegration time	
	Dissolution profile	
	Residual solvents	Initial justification prevails.
	Stability (Impurities & WC)	Initial justification prevails.
Disintegrant – type and %	Appearance	Initial justification prevails.
	Solid state form	8.0% w/w of croscarmellose sodium, 4.0% intragranular and 4.0% extragranular, was selected for all three prototypes. The intragranular and extragranular distribution of the croscarmellose sodium did not show an influence on the DS amorphous stability. Stability tests conducted over 6 months of storage at 40ºC/75%RH in Al/Al blisters demonstrated that amorphous DS remained stable in formulations with and without croscarmellose sodium in the intragranular phase. The stability of the amorphous DS was confirmed with all three DP prototypes selected for the pilot BA *in vivo* study. Therefore, the risk is reduced from high to low.
	Assay	Initial justification prevails.
	UDU	
	Hardness	
	Disintegration time	The influence of distributing 8.0% w/w of croscarmellose sodium between intragranular and extragranular phases on the DP disintegration time and dissolution profile was examined (refer to section 5.2.4.1). While no effect on tablets disintegration time was observed, a significant influence of incorporating intragranular disintegrant was noted on DP dissolution profile. Interestingly, comparable dissolution profile results were obtained for both intragranular percentages evaluated (4% and 8% w/w), resulting in faster dissolution profiles compared to tablets without intragranular disintegrant. For all three prototypes, a total concentration of 8.0% w/w of croscarmellose sodium, divided equally between intragranular and extragranular phases (4.0% each), was selected in order to enhance DP dissolution profile. With the selected type and percentage of disintegrant, prototypes with slower or faster dissolution profile than the RLD are obtained when tested in two-step dissolution method (see Figure 57). The
	Dissolution profile	

Formulation variable	**DP CQAs**	**Justification**
	🟨	risk of the disintegrant percentage of affecting the DP disintegration time is reduced from high to low. However, the risk concerning the DP dissolution profile is only reduced to medium until *in vivo* data becomes available.
	Residual solvents	Initial justification prevails.
	Stability (Impurities & WC)	Initial justification prevails.
Surfactant – type and %	Appearance	Initial justification prevails.
	Solid state form	1.5% w/w of poloxamer 188 is added in solution as part of the ASD of DS and HPMCAS-MG in ratio 1:5 with the aim to enhance drug dissolution. XRPD and MDSC analysis confirmed the production of a homogeneous ASD, without phase separation. Moreover, the amorphous DS showed to be stable after 6 months of storage at 40ºC/75%RH and packaged in Al/Al blisters (refer to section 5.2.8.1). Hence, the risk is reduced from high to low.
	Assay	Initial justification prevails.
	UDU	
	Hardness	Initial justification prevails.
	Disintegration time	The addition of 1.5% of poloxamer 188 showed no influence on DP disintegration time. Therefore, the risk is reduced from high to low.
	Dissolution profile	The addition of 1.5% of poloxamer 188 as part of the ASD was found to have a positive effect on DP dissolution profile when using two-step dissolution method. However, no influence was observed when using QC dissolution method. Since the biorelevance of the dissolution method is uncertain, the risk remains high and will be reassessed after the outcome of the pilot BA *in vivo* study.
	Residual solvents	Initial justification prevails.
	Stability (Impurities & WC)	No increase of water content and low growth of impurities were observed in prototype A, containing 1.5% of poloxamer 188, after 6 months of storage at 40ºC/75%RH and 25ºC/60%RH in Al/Al blisters (refer to section 5.2.8.3). This suggests that there is no incompatibility between poloxamer 188 and the DS. Consequently, the risk is reduced from high to low.
Lubricant – type and %	Appearance	Magnesium stearate was selected as the lubricant, at a standard percentage of 0.5% w/w. Tablets without defects were consistently obtained for all three prototypes and throughout this work. Consequently, the risk is reduced form medium to low.
	Solid state form	Initial justification prevails.
	Assay	Initial justification prevails.
	UDU	

Formulation variable	**DP CQAs**	**Justification**
	Hardness	With the selected lubricant type and percentage, final blend with good compression properties were obtained for all three prototypes within a wide range of compression forces, reaching high tablet hardness (refer to control strategy in Table 53) and without affecting the drug product disintegration time and dissolution profile. Hence, the risk is reduced from medium to low.
	Disintegration time	
	Dissolution profile	
	Residual solvents	Initial justification prevails.
	Stability (Impurities & WC)	Initial justification prevails.
Coating agent - type and weight gain (%)	Appearance	Initial justification prevails.
	Solid state form	Initial justification prevails.
	Assay	Initial justification prevails.
	UDU	
	Hardness	Initial justification prevails.
	Disintegration time	
	Dissolution profile	
	Residual solvents	Initial justification prevails.
	Stability (Impurities & WC)	Initial justification prevails.

DISCUSSION


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6. DISCUSSION

The formulation of ASDs stands out as a highly effective strategy for enhancing the dissolution and/or apparent solubility of poorly soluble drugs. However, commonly used technologies for ASD preparation, such as spray drying and hot melt extrusion, pose challenges for the pharmaceutical industry limiting the commercial applications, especially in the generic industry, since they often involve high investments. Hence, a comprehensive assessment of conventional pharmaceutical technologies like fluid bed for the industrial production of ASDs holds significant value for the pharmaceutical industry.

Although fluid bed technology is recognized for the production of ASDs, the number of marketed ASD-products produced with this technology is notably lower compared to spray drying and hot melt extrusion. Nevertheless, fluid bed is a well-known conventional technology available in the majority of pharmaceutical companies specialized in solid dosage forms. Therefore, it was deemed valuable to assess the feasibility, advantages, and limitations of fluid bed technology for ASDs production in comparison to spray drying. Some authors have performed comparative studies between fluid bed bead coating system and spray drying (59,86,87). Nevertheless, few studies have been reported with fluid bed top-spray system (53–56), which typically results in highly porous particles with enhanced flowability and compressibility, ideal for tableting (50).

Another challenge faced in the development of generic ASD products is avoiding patent infringement. Typically, the innovator secures patents for critical elements of the formulation, like the specific polymer type and amount, thereby forcing the reformulation of generic products. HPMCAS stands out as one of the most frequently used polymers in marketed ASD-based products. Therefore, the investigation of alternative polymers in terms of ASD stability, dissolution, and *in vivo* bioavailability holds significant value.

In this work, we explored the potential of fluid bed top-spray granulation as an alternative to spray drying for the production of ASDs intended for immediate release film-coated tablets. We conducted a comparative analysis of the physical properties, stability, and dissolution profiles of ASDs obtained through both techniques in laboratory scale. Additionally, we developed three different prototypes using fluid bed technology and different polymeric carriers (HPMCAS-MG and HPMCP HP-55), with the aim of achieving dissolution profiles and levels of supersaturation comparable to those of the spray dried formulation. To culminate our investigation, an *in vivo* pilot BA study was conducted to compare the pharmacokinetic behaviour of the three prototypes developed via fluid bed granulation with that of the marketed formulation produced by spray drying.

For this investigation, we took as a reference a marketed ASD-based film-coated tablet formulated with a BCS class 2 drug substance (referred to as LM2) and HPMCAS, which is produced by spray drying.

Preformulation studies in spray dryer, aimed to comprehend the formulation of the RLD, demonstrated that the amount of HPMCAS-MG play a crucial role in enhancing the solubility and dissolution profile of LM2, with increased drug supersaturation level with increasing HPMCAS-MG weight percentage in the ASD. These results confirmed the importance of selecting appropriate ratios of drug to polymeric carrier in the development of ASDs. This behaviour was also observed by other authors like Curatolo et al. (88). This is attributed to the properties of HPMCAS-MG as, when partially ionized at pH 6.0, the charge on the polymer can minimize the formation of large polymer aggregates, thereby maintaining stability of drug-polymer colloids in aqueous solution. Furthermore, due to the amphiphilic nature of HPMCAS, LM2 can interact with the hydrophobic regions of the polymer and remain as stable colloids in aqueous solution (89). Based on preformulation studies, the RLD seems to have an ASD of LM2 and HPMCAS-MG in a weight ratio of 1:5. Consequently, this ratio and grade of polymer were adopted as a reference for further investigation into the feasibility of producing an ASD by fluid bed top-spray granulation.

Feasibility studies with fluid bed top-spray configuration validated that, although the ASD of LM2 and HPMCAS-MG in 1:5 ratio represented a high percentage of the total tablet weight (i.e., 73.9% w/w), this technology is viable to produce a homogeneous and stable ASD. This was confirmed by XRPD and MDSC analysis (Figure 20, Figure 21, Figure 28, and Figure 30). Both spray drying and fluid bed top-spray granulation yielded an ASD with a high T_g ranging from 105 to 108ºC. Given that the T_g exceeds the storage temperatures by 50ºC (as per ICH storage conditions of 25ºC and 40ºC), significant mobility of the amorphous drug within the dispersion, which could lead to crystallization, was not anticipated. Moreover, the resulting amorphous SGD obtained using fluid bed exhibited comparable water uptake levels to the amorphous SDD obtained by spray drying, measuring approximately 6.0% at 25ºC and 5.0% at 40ºC (Figure 22 and Figure 23), categorizing them as moderately hygroscopic materials according to Ph. Eur. standards. Hence, water uptake appears to be primarily dictated by the ASD components (LM2 and HPMCAS-MG), with negligible contribution of the MCC used as substrate.

Considering that a comparable T_g and water uptake were obtained for both SDD and SGD materials, a similar level of protection during storage was expected. This was confirmed through stability studies conducted in blisters with different levels of protection (Al/Al and Triplex 180). Drug products formulated with either SDD or SGD material showed to be stable in terms of amorphous solid state, dissolution profile, assay, and impurities for at least 6 months at 40ºC/75%RH (see section 5.1.8).

Fluid bed top-spray granulation technique was able to produced amorphous SGD with enhanced flow characteristics compared to the amorphous SDD powder (Table 23), attributed to the agglomeration of ASD and substrate (MCC) particles. This avoided the necessity of a dry granulation prior to tableting step and resulted in a final blend with favourable compression properties (Figure 25). However, tablets formulated with SGD powder exhibited a statistically significant slower dissolution profile than those formulated with SDD material (Figure 26). This difference is attributed to the smaller particle size of the amorphous SDD obtained by spray drying, contrasting with the agglomerates or granules formed during fluid bed top-spray granulation. In the latter process, the solution sprayed, containing LM2 and HPMCAS-MG dissolved, induces the aggregation of substrate particles leading to the formation of agglomerates or granules. In contrast, spray drying yields small and individual ASD particles. This is apparent from the SEM pictures presented in Table 23. Despite the SDD material is later dry granulated, the absence of a liquid binder can result in less cohesive and softer granules. Furthermore, intragranular components functioning as disintegrant (i.e., croscarmellose sodium and microcrystalline cellulose) are part of the granules, which promote the fast release of small ASD particles.

From manufacturing process standpoint, fluid bed top-spray technology was deemed feasible for the production of ASD of LM2 and HPMCAS-MG in 1:5 ratio, offering an alternative to spray drying. Below, we discuss the favourable points and limitations of using this technology for this purpose.

Favourable points:

1. **Enough evaporation capacity.**
   The evaporation in spray dryer occurs within milliseconds due to the high gas temperature. In fluid bed a similar inlet air temperature and a faster feed rate were applied. Even with these worse conditions, a homogeneous ASD was obtained in fluid bed in shorter times than in the spray dryer for a similar batch size, suggesting enough evaporation capacity of fluid bed technology under the evaluated process conditions in laboratory scale. This capacity is primarily attributed to the higher concentration of solids in solution and the extended exposure of the product to temperature throughout the entire process duration, including spraying and drying. The obtained SGD exhibited acetone content below the ICH Q3C limit of 5000 ppm. The extended exposure of the product to temperature when using fluid bed did not have a significant negative effect to the obtained ASD in terms of homogeneity (single T_g was obtained), assay, and impurities.

2. **Secondary drying in the same equipment.**

   The high evaporation capacity of the fluid bed for the formation of ASD was also demonstrated during the drying process, proving to be successful in reducing the acetone content well below the ICH Q3C limit of 5000 ppm within a reasonable timeframe in laboratory scale. In the spray dryer the acetone content cannot usually be reduced below 5000 ppm, making necessary another equipment for the secondary drying (36). In our case the equipment used for secondary drying was a vacuum drying oven (refer to Table 22 in section 5.1.2.2).

   It was confirmed that the ability to evaporate the solvent is also influenced by the polymer type used. Acetone content results depicted in Figure 49 suggest that, when using HPMCAS-MG as polymer, the secondary drying could even be avoided under the applied laboratory-scale process conditions (12 L container and 2.36 kg SGD batch size). However, when using HPMCP HP-55 as polymer, a longer secondary drying period was required.

   The ability to conduct the secondary drying in the same equipment, despite polymers exhibiting different levels of resistance to solvent removal, indicates that fluid bed technology is a cost-effective method for manufacturing ASD.

3. **Reasonable process time and fast feed rate.**

   Fluid bed process resulted in a reasonable process time considering the nature of the process and the scale of operation. It was feasible to set a fast feed rate, averaging 1.3 kg/h when fluid bed was equipped with 3 L container and 2.0 kg/h when equipped with 12 L container. A faster feed rate could be set in the 12 L scale, however it was limited by the pump and spraying tube available.

   Moreover, a reasonable process time would be required in an industrial fluid bed (e.g., Glatt WS Combo 250). For the production of a 100,000 tablets of the higher strength, which is the batch size usually required for the validation of the drug product manufacturing process, 61.4 kg of SGD would be required. Due to equipment working volume, the production of two SGD sub-batches of 30.7 kg would be necessary. Considering a standard feed rate of 300 g/min (equivalent to 18 kg/h), spraying process of each sub-batch would be around 9.2 h resulting in a total of 18.4 h for the production of both. On the other hand, in an industrial spray dryer (e.g., GEA PSD-2), and considering a standard feed rate of 30 kg/h for an acetone solution, spraying process of the same feed solution would take around 11 h. Nevertheless, a secondary drying in a separate equipment would be required, which usually takes longer in larger scales.

4. **High process yield.**

   Fluid bed process exhibited high process yields, being around 86% in smaller batch produced of 0.57 kg (refer to Table 22) and even up to 97% in batches of 1.89 – 2.36 kg (refer to Table 53). This demonstrates the process efficiency and productivity.

Limitations:

1. **Increase of container load during spraying**.

   When the amount of solids to be sprayed is much higher than the amount of substrate, controlling the initial and final container load becomes a critical factor for determining the batch size. This was our case, as the amount of solids (LM2 and HPMCAS-MG/HPMCP HP-55) was three times the amount of substrate, with an increase of container load from 10 – 15% to 75 – 80%. This made necessary to adjust some process parameters throughout spraying process, i.e. inlet air flow, feed rate, and atomization air pressure. These adjustments were successfully implemented showing the adaptation capacity of the process in fluid bed.

   The differences in initial and final container load may make challenging the scale-up as the batch size is limited by the container occupancy. This emphasizes the significance of product density. Nonetheless, this may not be presented as a limitation if the difference between the amount of solids and substrate is lower.

2. **High solvent amount.**

   In formulations comprising a high percentage of ASD, such as the one used in this investigation, a considerable quantity of solvent is required for dissolving both the drug substance and polymer. Consequently, for the manufacture of commercial batches, a substantial amount of solvent must be stored in the warehouse. This requirement can pose a challenge for pharmaceutical companies specialized in solid dosage forms due to the need for specialized safety measures in storing organic solvents. On the contrary, companies focused on drug substance or spray dried products production are typically better equipped to handle this demand.

Based on this evaluation, although fluid bed top-spray granulation presents some challenges, it was deemed viable for the production of homogeneous and stable LM2 ASD with HPMCAS-MG in ratio 1:5. Nevertheless, before proceeding with an *in vivo* pilot BA study, efforts were made to enhance the dissolution profile.

Various formulation variables based on HPMCAS-MG were evaluated with this objective, guided by a formulation risk assessment (Table 35) following the QbD approach. The identified high-risk variables affecting the dissolution profile of the drug product were the disintegrant percentage, the substrate amount and type, and the addition of a surfactant as part of the ASD. Furthermore, the influence of the SGD particle size on dissolution was also deemed relevant for evaluation. A significant enhancement of the dissolution profile was found with the addition of disintegrant in the intragranular phase (4 – 8% w/w of croscarmellose sodium as substrate) and the addition of a surfactant as part of the ASD (1.5% w/w of poloxamer 188), as evidenced in Figure 34 and Figure 46, respectively. Conversely, varying the substrate amount (ranging from 8.7 to 34.0% w/w of MCC) or the type of substrate (MCC or mannitol) did not significantly affect the dissolution profile, as demonstrated in Figure 41 and Figure 43, respectively.

Based on the findings from these *in vitro* studies, a fluid bed formulation comprising an ASD of LM2 and HPMCAS-MG in a weight ratio of 1:5 and 1.5% w/w of poloxamer 188, along with 4% w/w of intragranular disintegrant, emerged as a promising candidate for further assessment in an *in vivo* pilot BA study against the RLD. XRPD and MDSC analysis confirmed that the addition of poloxamer 188 as part of the ASD did not induce the crystallization of the amorphous LM2 and revealed a single T_g throughout storage in Al/Al blisters (refer to Figure 58 and Figure 59), indicating the formation of a homogeneous and stable ASD without phase separation. Furthermore, stability studies conducted at 40ºC/75%RH and 25ºC/60%RH demonstrated that the drug product remained stable in terms of dissolution profile, assay, impurities, and water content for at least 6 months in Al/Al blisters (Figure 64 and Table 57), suggesting a shelf-life of at least 12 months according to ICH Q1E guidelines (90).

As part of this work, HPMCP HP-55 was assessed as a potential alternative polymer to HPMCAS-MG, being both cellulose derivatives with enteric properties but differing in substituent groups, which can influence solubility and pH sensitivity. Notably, HPMCP HP-55 and HPMCAS-MG start to dissolve at pH 5.5 and pH 6.0, respectively. These differences can influence aspects such as the formation, stability, and dissolution of ASDs. Experiments conducted using fluid bed top-spray technology and HPMCP HP-55 as polymeric carrier, at LM2:HPMCP HP-55 weight ratios of 1:4 and 1:5, demonstrated the viability of producing homogeneous and stable ASDs (refer to Figure 60 - Figure 63). These ASDs exhibited a comparable level of supersaturation to those formulated with an ASD of LM2:HPMCAS-MG in a 1:5 ratio, yet they showcased a faster dissolution profile followed by slight precipitation tendency. Furthermore, drug products formulated with amorphous SGDs of LM2:HPMCP HP-55 in 1:4 and 1:5 ratios showed to be stable in terms of dissolution profile, assay, impurities, and water content for at least 6 months at both 40ºC/75%RH and 25ºC/60%RH in Al/Al blisters (Figure 65, Figure 66, Table 58 and Table 59). This suggested a shelf-life of at least 12 months according to ICH Q1E guidelines (90).

Overall, these findings suggest that HPMCP HP-55 could serve as a promising alternative to HPMCAS-MG in enhancing LM2 solubility and dissolution profile.

CONCLUSION

7. CONCLUSION

This study confirms the feasibility of fluid bed top-spray technology as an alternative to spray drying for the production of stable ASDs intended for immediate release tablets, while the marketed ASD-based products manufactured using fluid bed technology are primarily pellets into capsule dosage form.

- Formulation of ASD using fluid bed technology offers clear advantages from manufacturing process perspective. Firstly, both spraying and secondary drying can be carried out in a single equipment setup. Secondly, the fluid bed produces ASD granules with improved physical properties, avoiding the need for an additional granulation step prior tableting. These benefits render this technology more cost-effective than spray dryer, as it eliminates the necessity for additional equipment such as vacuum drying oven and roller compactor, which are typically required for spray dried products to obtain granules with good quality.
- On the contrary, the main constrain in using fluid bed for the production of ASDs within conventional facilities for manufacturing solid oral dosage form arises from the necessity of using large quantities of organic solvents. These solvents could generate explosive atmosphere due to their low boiling point, which can lead to the formation of easily ignitable atmospheres when exposed to oxygen. Consequently, adherence to ATEX (explosive atmospheres) regulations (Real Decreto 681/20039) becomes essential for the used equipment, the manufacturing facilities, and the storage procedures.
  Secondly, another consideration concerns to the batch size dependency on the ratio of substrate to drug substance+polymer, which is presented as a potential constrain.
- The comprehensive assessment of fluid bed technology for the production of ASD, particularly with low soluble drug substance and HPMCAS or HPMCP as polymers, offers valuable insights into formulation optimization and potential commercial applications. The *in vitro* dissolution findings indicated the necessity of incorporating a surfactant into the ASD based on HPMCAS when using fluid bed technology instead of spray dryer.
- Moreover, ASD-based tablets produced via fluid bed top-spray granulation and formulated with both evaluated polymers exhibited good stability profiles, being comparable to that of ASD-based tablets produced via spray drying with HPMCAS.

Overall, this work contributes to advancing pharmaceutical development and emphasizes the significance of exploring manufacturing technologies and polymers for ASD production.


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ANNEX

9. ANNEX

9.1. SOLUBILITY TESTS OF LM2 IN VARIOUS ORGANIC SOLVENTS

Table 62. Solubility of LM2 in acetone as function of temperature.

T (°C)	(g/ml)
23	0.45
26	0.5
26.5	0.55
28	0.61
32.5	0.67
46	0.8

Table 63. Solubility of LM2 in dichloromethane as function of temperature.

T (°C)	(g/ml)
20.5	0.45
21.8	0.5
25	0.55
31	0.61

Table 64. Solubility of LM2 in ethyl acetate as function of temperature.

T (°C)	(g/ml)
22	0.098
23.6	0.125
49.5	0.184
57.2	0.216
62	0.25
66.7	0.286

Table 65. Solubility of LM2 in methanol as function of temperature.

T (°C)	(g/ml)
22.3	0.047
33.9	0.071
41.2	0.098
50.9	0.125
58.8	0.184
60	0.216

Table 66. Solubility of LM2 in ethanol as function of temperature.

T (°C)	(g/ml)
24	<0.014
57	0.05

Table 67. Solubility of LM2 in isopropanol as function of temperature.

T (°C)	(g/ml)
24	<0.010
76	<0.060

9.2. XRPD DIFFRACTOGRAMS

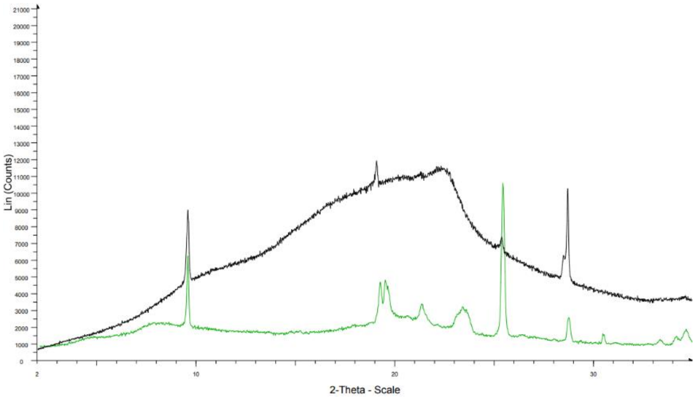


Figure 67. XRPD diffractogram of the higher strength of the RLD in black and Opadry 03F220119 yellow in green.

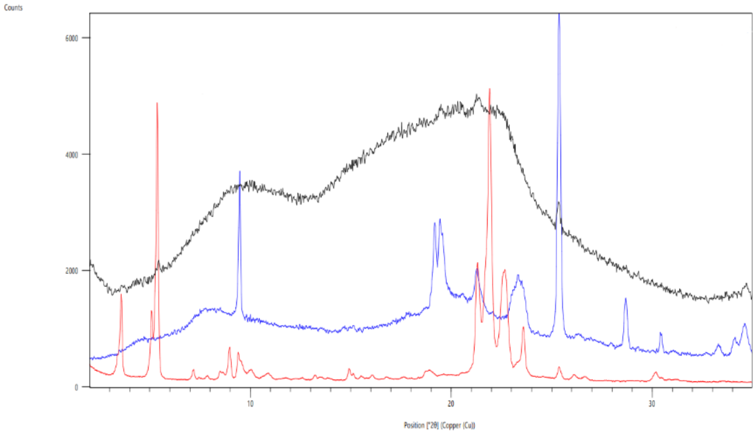


Figure 68. XRPD diffractogram of the lower strength of the RLD in black, Opadry 03F220119 yellow in blue, and magnesium stearate in red.

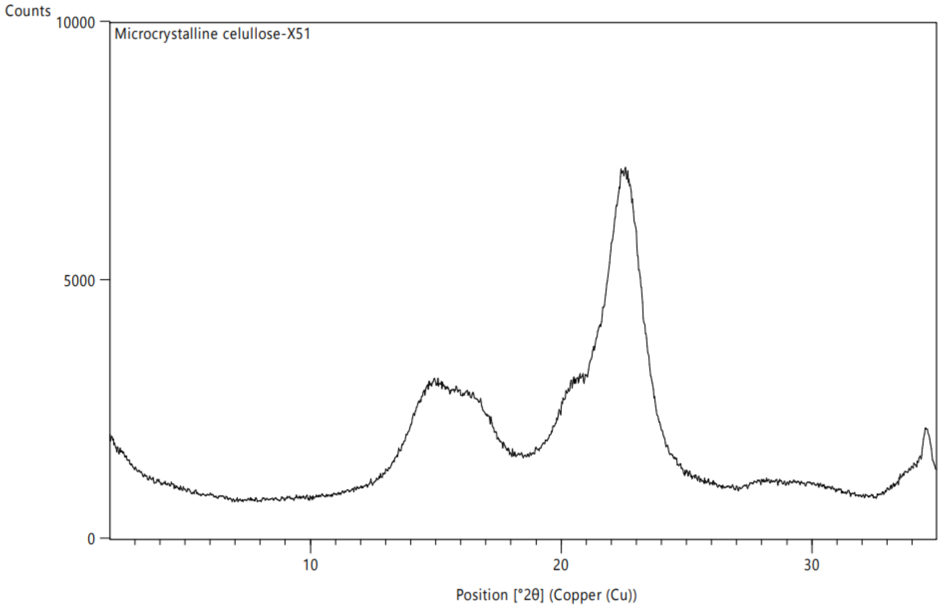


Figure 69. XRPD diffractogram of microcrystalline cellulose.

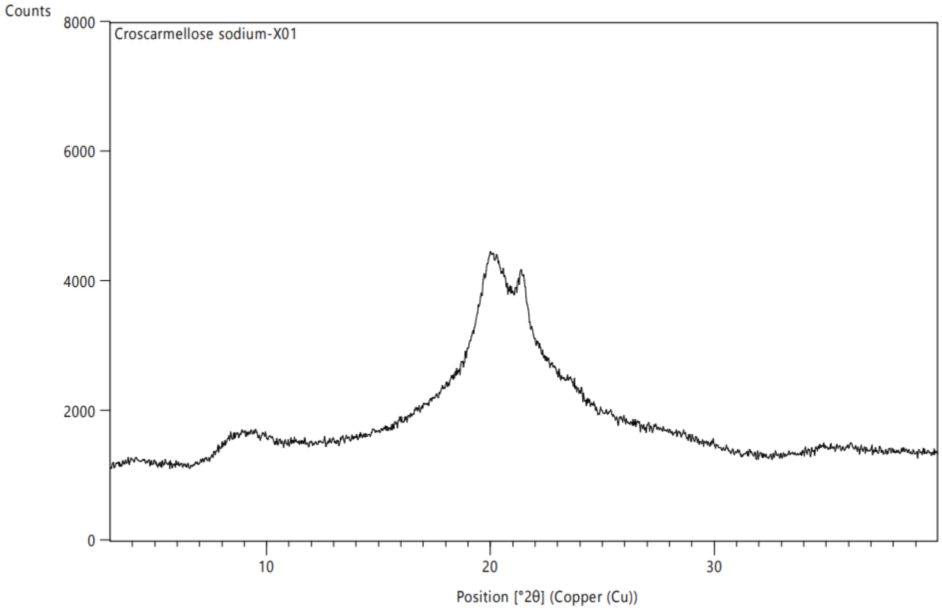


Figure 70. XRPD diffractogram of croscarmellose sodium.

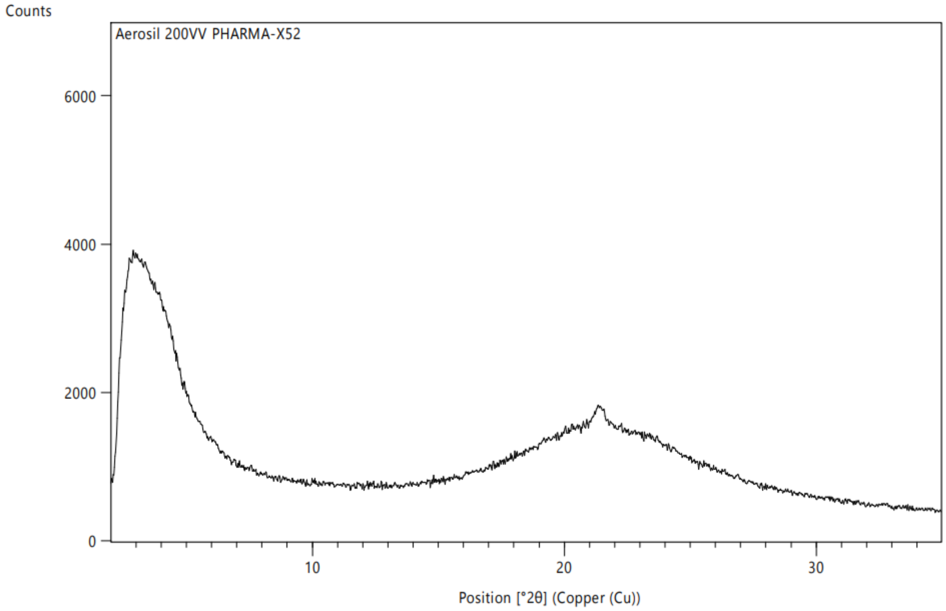


Figure 71. XRPD diffractogram of anhydrous colloidal silica.

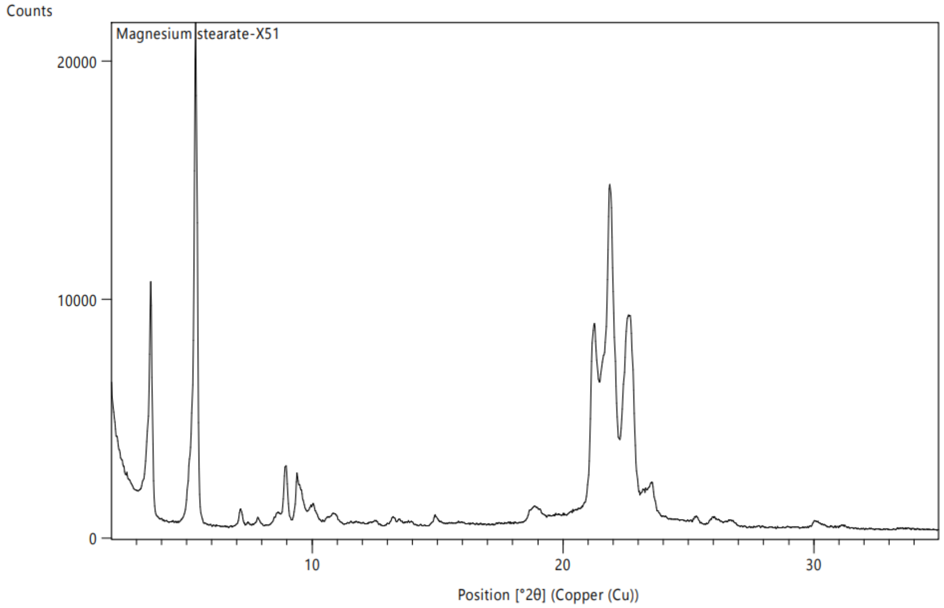


Figure 72. XRPD diffractogram magnesium stearate.

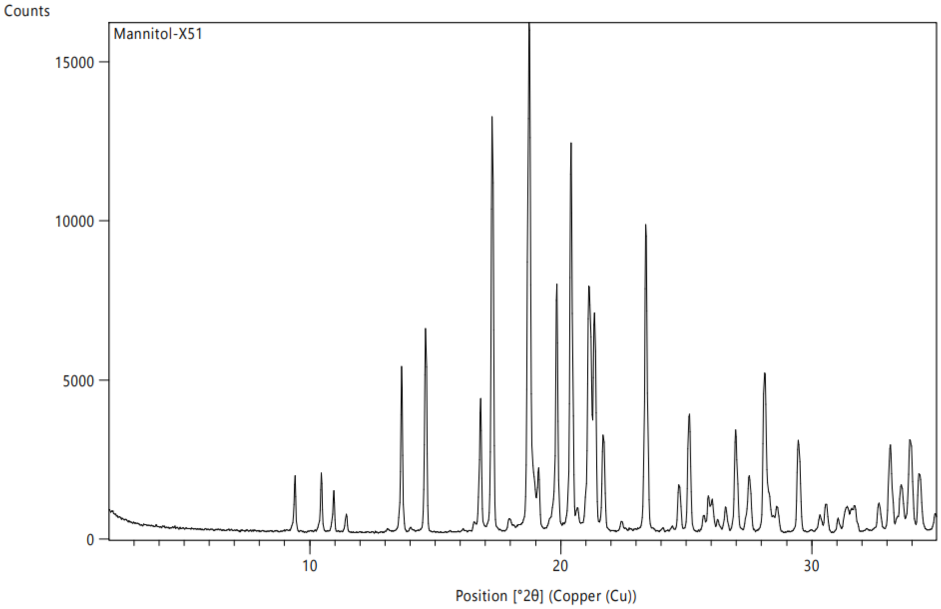


Figure 73. XRPD diffractogram of mannitol.

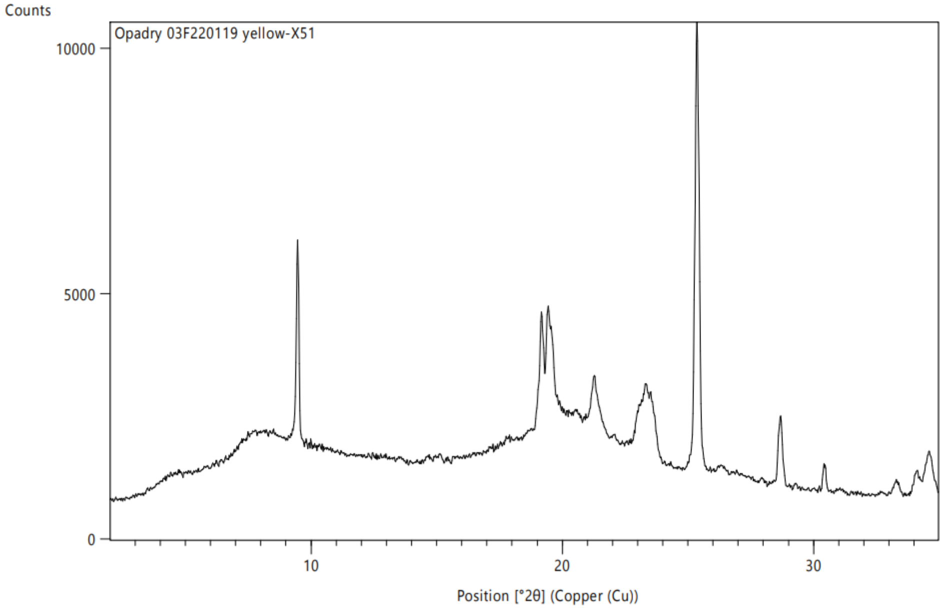


Figure 74. XRPD diffractogram of Opadry® 03F220119 yellow.

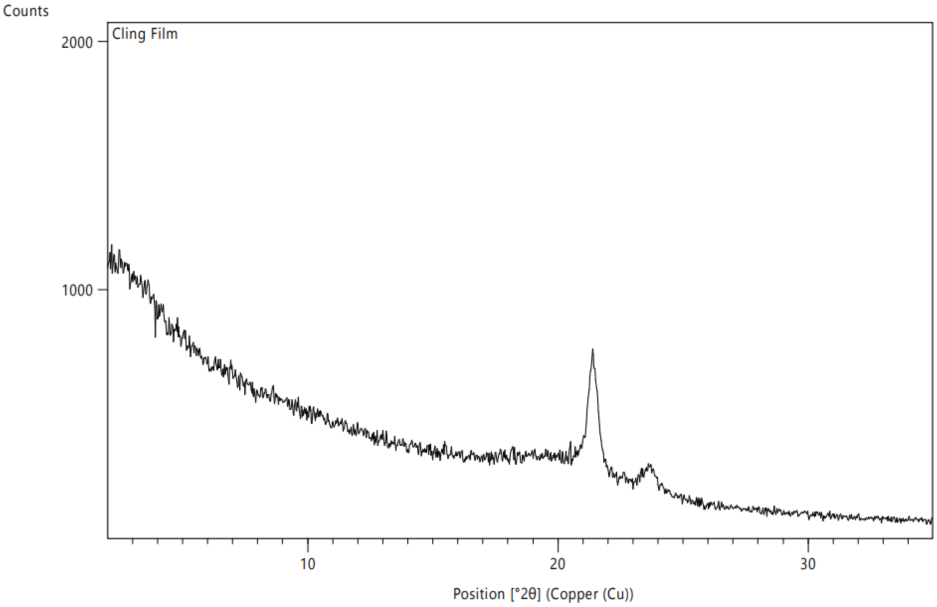


Figure 75. XRPD diffractogram of cling foil.

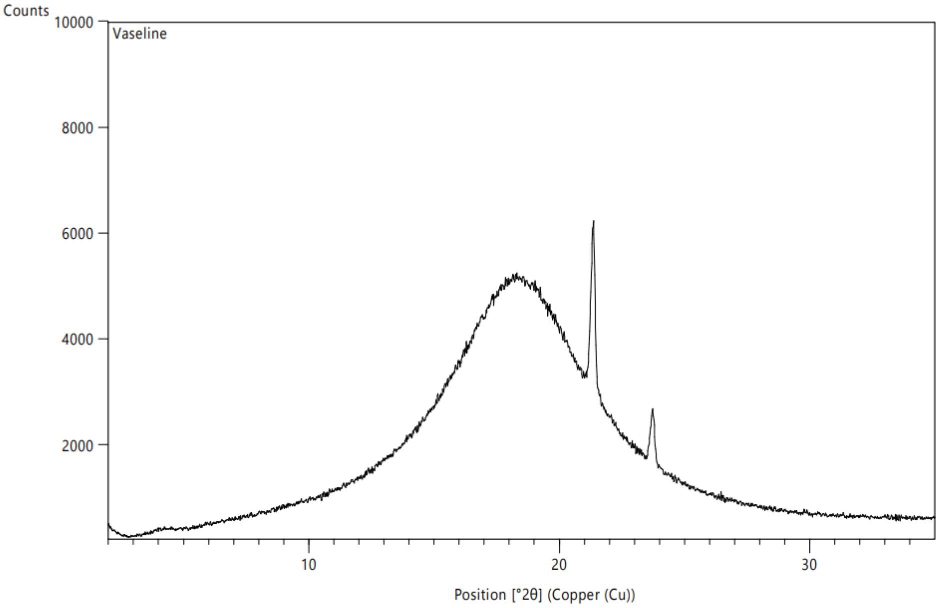


Figure 76. XRPD diffractogram Vaseline.

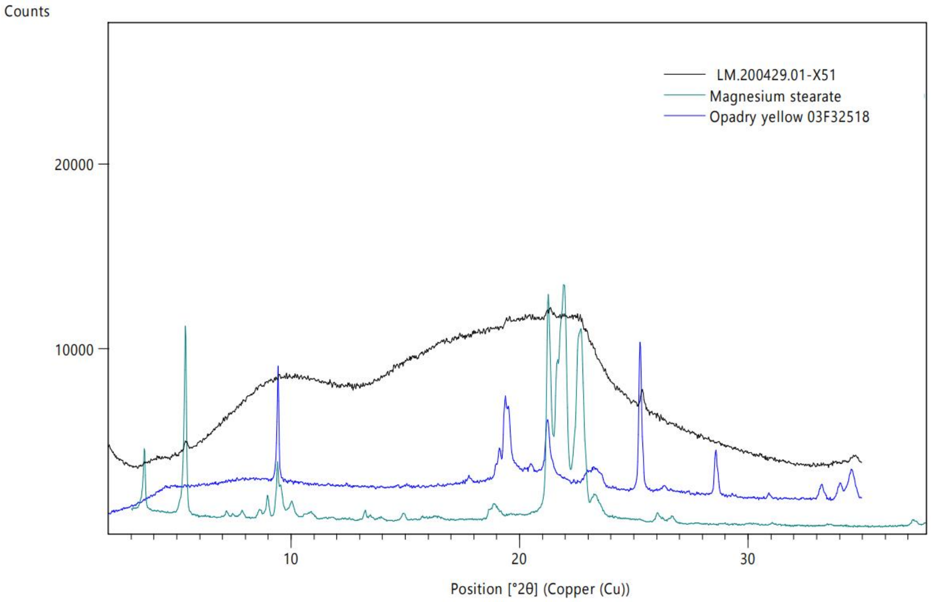


Figure 77. XRPD diffractogram of the lower strength of the RLD in black, Opadry 03F220119 yellow in blue, and magnesium stearate in light green.

APPENDIX

10. APPENDIX

10.1. CONFLICT OF INTEREST

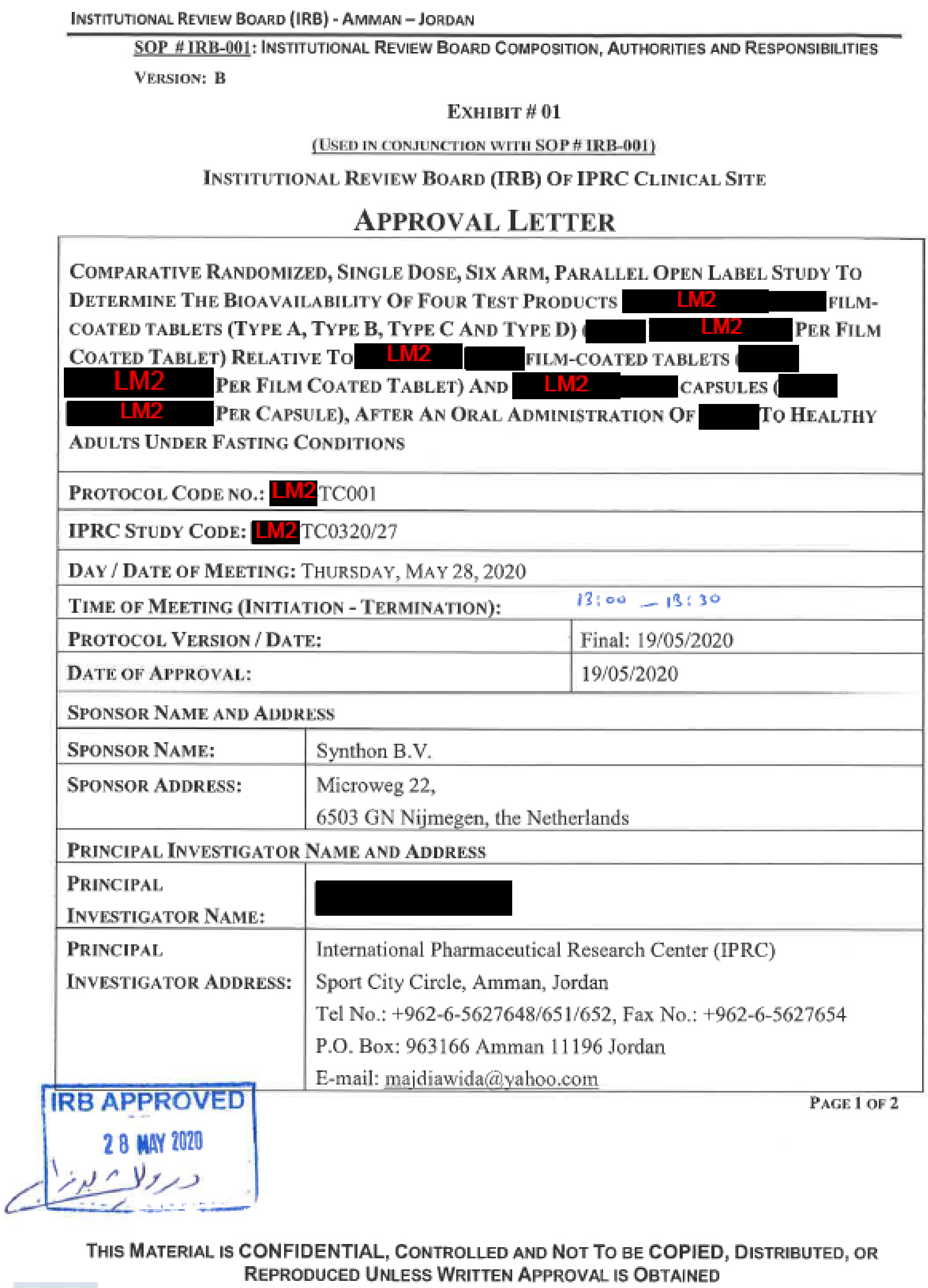
The doctoral student declares that there is no conflict of interest regarding the doctoral thesis.

10.2. FIGURES AUTHORSHIP

The author declares that all unreferenced figures of this thesis are of her authorship.

10.3. CLINICAL STUDY

In the present thesis, the *in vivo* pilot BA study was performed in healthy male volunteers with 60 subjects, i.e. n=15 per treatment. The study was conducted in Amman (Jordan) by a Contract Research Organization (CRO), known as the International Pharmaceutical Research Center (IPRC). Approval for the study was granted by the Institutional Review Board (IRB)/ Ethics Committee. IPRC IRB is Compliant with Good Clinical Practice guidelines.



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(USED IN CONJUNCTION WITH SOP # IRB-001)

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APPROVAL LETTER

COMPARATIVE RANDOMIZED, SINGLE DOSE, SIX ARM, PARALLEL OPEN LABEL STUDY TO DETERMINE THE BIOAVAILABILITY OF FOUR TEST PRODUCTS [redacted] FILM-COATED TABLETS (TYPE A, TYPE B, TYPE C AND TYPE D) ([redacted] [redacted] PER FILM COATED TABLET) RELATIVE TO [redacted] [redacted] FILM-COATED TABLETS ([redacted] [redacted] PER FILM COATED TABLET) AND [redacted] CAPSULES ([redacted] [redacted] PER CAPSULE), AFTER AN ORAL ADMINISTRATION OF [redacted] TO HEALTHY ADULTS UNDER FASTING CONDITIONS

PROTOCOL CODE NO.: [redacted]TC001	
IPRC STUDY CODE: [redacted]TC0320/27	
DAY / DATE OF MEETING: THURSDAY, MAY 28, 2020	
TIME OF MEETING (INITIATION - TERMINATION): 13:00 – 13:30	
PROTOCOL VERSION / DATE:	Final: 19/05/2020
DATE OF APPROVAL:	19/05/2020
SPONSOR NAME AND ADDRESS	
SPONSOR NAME:	Synthon B.V.
SPONSOR ADDRESS:	Microweg 22, 6503 GN Nijmegen, the Netherlands
PRINCIPAL INVESTIGATOR NAME AND ADDRESS	
PRINCIPAL INVESTIGATOR NAME:	[redacted]
PRINCIPAL INVESTIGATOR ADDRESS:	International Pharmaceutical Research Center (IPRC) Sport City Circle, Amman, Jordan Tel No.: +962-6-5627648/651/652, Fax No.: +962-6-5627654 P.O. Box: 963166 Amman 11196 Jordan E-mail: majdiawida@yahoo.com

IRB APPROVED
28 MAY 2020

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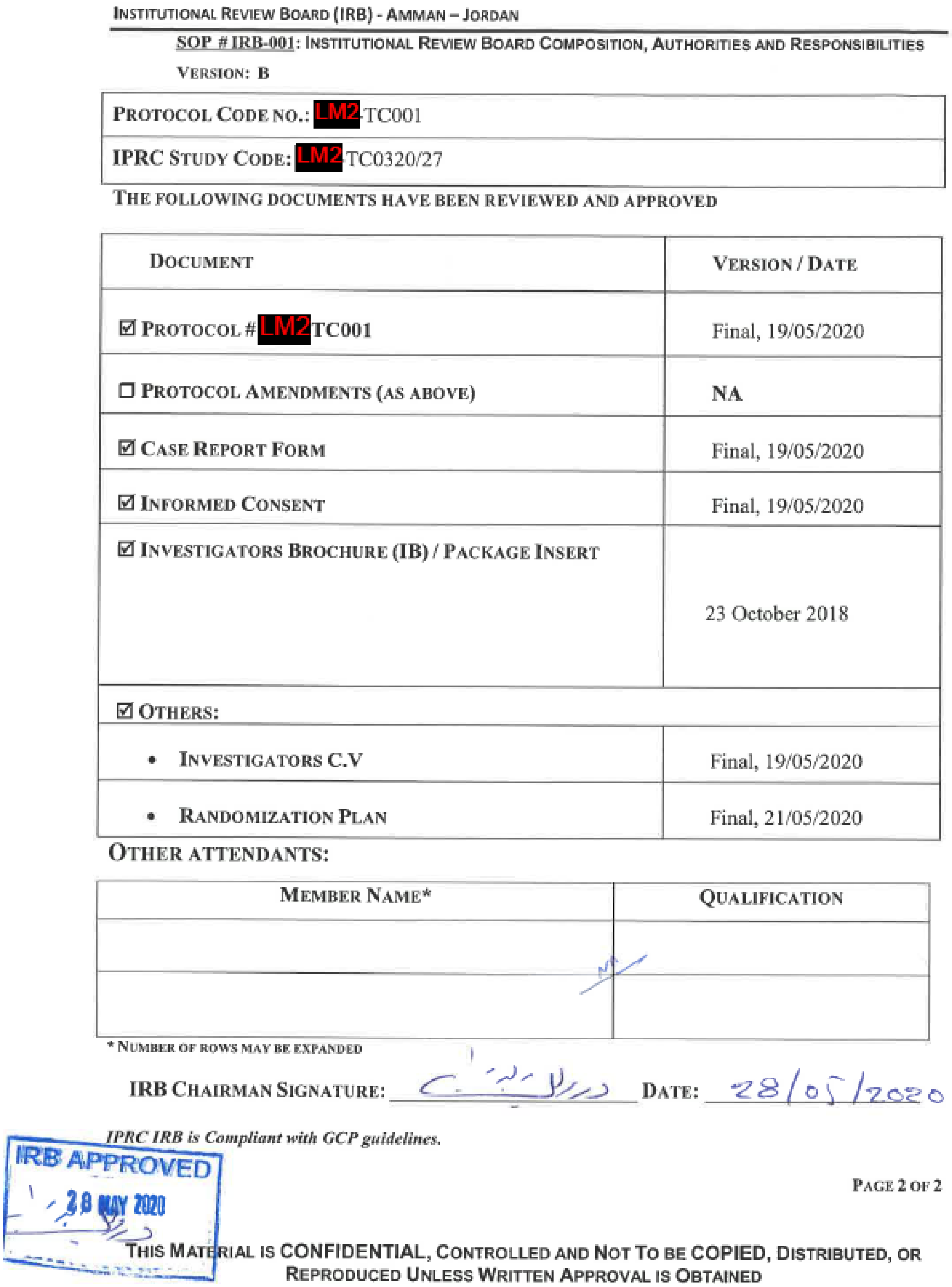

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THE FOLLOWING DOCUMENTS HAVE BEEN REVIEWED AND APPROVED

DOCUMENT	VERSION / DATE
☑ PROTOCOL #[redacted]TC001	Final, 19/05/2020
☐ PROTOCOL AMENDMENTS (AS ABOVE)	NA
☑ CASE REPORT FORM	Final, 19/05/2020
☑ INFORMED CONSENT	Final, 19/05/2020
☑ INVESTIGATORS BROCHURE (IB) / PACKAGE INSERT	23 October 2018
☑ OTHERS:	
• INVESTIGATORS C.V	Final, 19/05/2020
• RANDOMIZATION PLAN	Final, 21/05/2020

OTHER ATTENDANTS:

MEMBER NAME*	QUALIFICATION

* NUMBER OF ROWS MAY BE EXPANDED

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In the present thesis, it is demonstrated the potential of fluid bed top-spray technology as an alternative to spray drying for the production of amorphous solid dispersions (ASDs) intended for immediate drug release systems, i.e. tablets.
Comparative analysis of ASDs physical properties, stability, and dissolution profiles obtained via both technologies were conducted. The effect of formulation variables, using fluid bed, was evaluated guided by a Quality by Design (QbD) approach. Finally, three ASD-based prototypes produced using fluid bed top-spray and different polymeric carriers (HPMCAS-MG and HPMCP HP-55) were developed followed by an in vivo pilot bioavailability study comparing their pharmacokinetic behaviour with a marketed spray dried formulation.