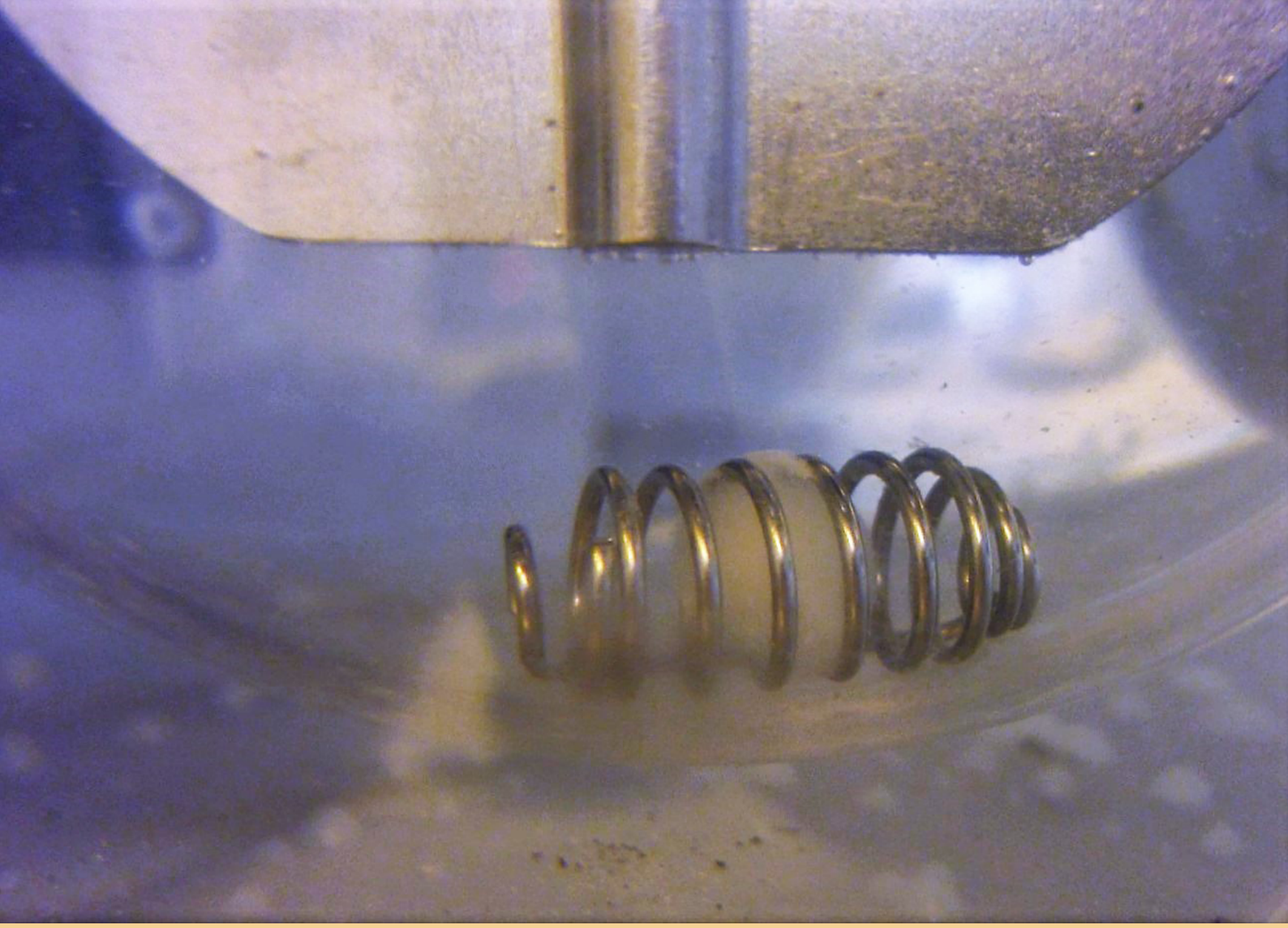

Sara Sofia Dias Cardoso

GENERIC DRUG PRODUCT DEVELOPMENT OF A MODIFIED-RELEASE ORAL DOSAGE FORM

Dissertation to obtain the Master degree in Medicine Tecnologies, performed under the scientific supervision of Professor Carla Sofia Pinheiro Vitorino and of Doctor Alberto Gabriel Leitão da Silva (Bluepharma, Indústria Farmacêutica S.A.) and presented to the Faculty of Pharmacy of the University of Coimbra

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ABSTRACT

The present project aims at developing a generic extended-release drug product for oral administration in the pharmaceutical form of uncoated tablets. The project was developed at Bluepharma Indústria Farmacêutica, S.A. and is referred to as Blue055, in accordance with the company's confidentiality policy.

The main objectives of the project are to develop a formulation and a manufacturing process and to produce prototypes capable of mimicking the *in vitro* behaviour of the reference product. Specifically, the release profile of the drug substance should be similar to that of the reference product. The influence of the drug substance and excipient variables in the modelling of the release of the drug substance was evaluated, as well as the influence of the parameters of the process. In addition, the parameters tested to obtain the pharmaceutical form, either formulation or process, were adequately analysed and evaluated following a Quality by Design approach for further implementation at pilot and industrial scale.

During the pharmaceutical development, all the ICH Guidelines Q8 (R2), Q6A, Q2 (R), Q3B, Q3C and Guideline for bioequivalence, United States Pharmacopoeia and cGMPs requirements were taken into account in order to produce a high-quality final product, and to guarantee its performance in terms of safety and efficacy.

The parameters of the formulation studied were drug substance particle size, diluent grade and amount of, hydroxypropylmethylcellulose (HPMC) grade, amount, viscosity, particle size and hydroxypropyl content, and disintegrant amount. All the above variables influenced dissolution behaviour.

The process parameters considered for analysis included dry granulation process, blending and lubrication times. It was observed that roller gap has an impact on drug product assay, blend uniformity and dissolution profile.

The application of the Quality by design (QbD) concept has clearly enabled a systematic approach to designing and developing pharmaceutical formulations and manufacturing processes to ensure product quality.

Keywords: generic drug, extended-release, pharmaceutical development, formulation, manufacturing process, functional excipient.

RESUMO

O presente projeto visa o desenvolvimento de um medicamento genérico de libertação prolongada para administração oral, sob a forma farmacêutica de comprimidos não revestidos. O projeto foi desenvolvido na Bluepharma Indústria Farmacêutica, S.A. e foi referido como Blue055, de acordo com a política de confidencialidade da empresa.

Os principais objetivos do projeto foram desenvolver uma formulação, um processo de fabrico e produzir protótipos capazes de mimetizar o comportamento *in vitro* do produto de referência. Especificamente, o perfil de libertação da substância ativa deverá ser semelhante ao do produto de referência. Para tal, foi avaliada a influência de diferentes variáveis quer da substância ativa quer dos excipientes na modelação da libertação da substância ativa, bem como dos parâmetros do processo. Adicionalmente, os parâmetros testados para obtenção da forma farmacêutica, quer de formulação quer de processo, foram adequadamente analisados e avaliados com base numa abordagem *Quality by Design* para uma posterior implementação à escala piloto e industrial.

Durante o desenvolvimento farmacêutico foram considerados todos os requisitos das *Guidelines* ICH Q8 (R2), Q6A, Q2(R), Q3B, Q3C e da *Guideline* de Bioequivalência, requisitos da Farmacopeia dos Estados Unidos e cumprimento das cGMPs, com o objetivo de produzir um produto final com elevada qualidade, de forma a garantir o seu desempenho a nível da segurança e eficácia terapêutica.

Os parâmetros da formulação estudados foram: o tamanho de partícula da substância ativa, o grau e a quantidade de diluente, o grau, quantidade, viscosidade, tamanho de partícula e teor de hidroxipropilo de hidroxipropilmetilcelulose (HPMC), quantidade de desagregante e quantidade de surfactante. Observou-se que o perfil de dissolução é afetado por estes parâmetros.

Os parâmetros de processo estudados foram: granulação seca, tempo de mistura e tempo de lubrificação. Observou-se que o processo de granulação tem impacto no doseamento, na uniformidade da mistura e no perfil de dissolução do produto acabado.

A implementação do conceito *Quality by Design* (QbD) permitiu claramente uma abordagem sistemática para projetar e desenvolver formulações farmacêuticas e processos de fabrico, de forma a garantir a qualidade do produto.

Palavras-chave: medicamento genérico, libertação prolongada, desenvolvimento farmacêutico, parâmetros de formulação, parâmetros de processo, excipientes.

CONTENTS

ABBREVIATIONS and ACRONYMS

BU – Blend uniformity

C – Complies

CMA's – Critical Material Attributes

CPP's – Critical Process Parameters

CQA – Critical Quality Attributes

CR – controlled release

DoE – Design of Experiments

DP – Drug Product

DS – Drug Substance

e.g. – for example

EMA – European Medicines Agency

ER – Extended Release

Eur. Ph. – European Pharmacopeia

FDA – Food and Drug Administration

GI – Gastrointestinal

cGMP – Current Good Manufacturing Practices

GRAS – Generally Recognized as Safe

HPMC – Hydroxypropyl methylcellulose

ICH – International Conference on Harmonization

JP – Japanese Pharmacopeia

LH – low hydroxypropyl content

LV – low viscosity

MR – Modified Release

NC – not comply

ND – not detected

NP – not performed

OGD – Office of Generic Drugs

PAT – Process Analytical Technology

pH – potential of hydrogen

PSD – Particle Size Distribution

QbD – Quality by Design

QbT – Quality by Testing

QTPP – Quality Target Product Profile

RLD – Reference Listed Drug

RSD – Relative Standard Deviation

SDC – Self diffusion coefficient

SLS – sodium lauryl sulphate

SPEC – Specification

USP – United States Pharmacopoeia

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CHAPTER I

INTRODUCTION

1. Introduction

Immediate-release (IR) oral drug products, such as tablets and capsules, are the most conventional dosage forms. The formulation in this dosage forms is directed with the purpose of releasing the drug substance immediately after oral administration, no deliberate effort is made to modify the drug release rate. Generally, result in relatively fast drug absorption and onset of associated pharmacodynamics effects (Qiu *et al.,* 2016).

Many of the currently prescribed drug substances have a short therapeutic action, which often involves repeated dosing by the patient over shorter time intervals. This fact causes large variations in the plasma concentration of the drug, which can lead to periods in which a subtherapeutic plasma concentration occurs and others where the drug toxicity thresholds may be exceeded. In view of these facts, it can be stated that only for a short period of time the desired concentration of drug is obtained.

To overcome this situation, the formulator may choose to modulate the release of the drug from the pharmaceutical system and even its uptake into the body, so that the plasma concentrations remain within the therapeutic limits for the intended period of time.

1.1 Modified-release oral dosage forms

A formulation is the composition of a drug product (DP) that contains the drug substance (DS) and other inactive ingredients. Each inactive ingredient in the formulation is used to serve specific purposes, so as to ensure the product performance and compliance. For example, common inactive ingredients in a tablet formulation include diluents, binders, disintegrates, lubricants, glidants, colorants, and other special ingredients that may facilitate absorption or modify drug release.

The pattern of drug release from MR dosage forms is deliberately changed from that of a conventional (IR) dosage formulation to achieve a desired therapeutic objective or better patient compliance.

Thus, MR dosage form is a formulation in which the drug release characteristics of time course or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms. (Qiu *et al.,* 2016).

The use of technology in the development of modified-release (MR) pharmaceutical products has sparked interest not only in the formulation of products involving new drugs, but also in the development of products already marketed, wherein the composition of molecules appears to continue exerting a relevant role in therapy.

1.1.1 Definition

In order to obtain the effect described above, various strategies can be used by the formulator, with formulation modulation being one of the main ones. These pharmaceutical systems are generally referred to as MR dosage forms which, depending on the characteristics of the release of the drug from the pharmaceutical system, may be classified as: extended release and delayed release dosage forms (Figure 1).

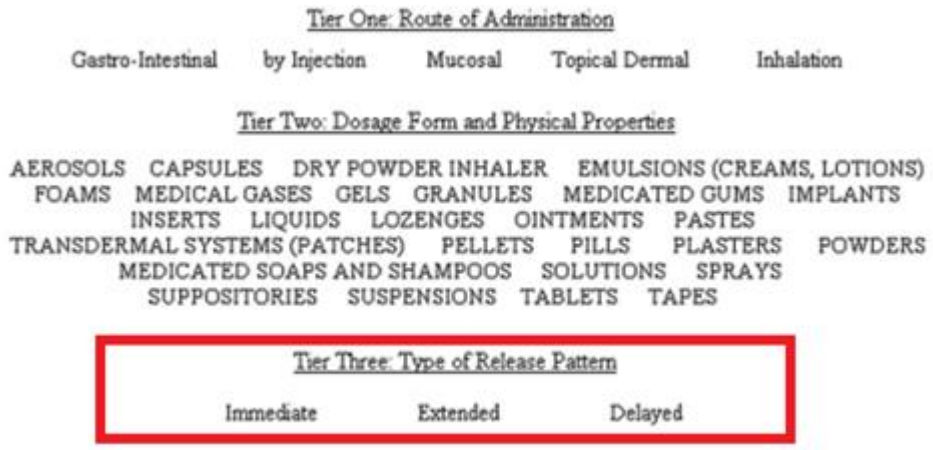

Figure 1 Compendial taxonomy for pharmaceutical dosage forms. (USP, 2009).

According to the USP, extended-release (ER) is a descriptive term for a dosage form that is deliberately modified to protract the release rate of the DS, compared to that observed from an IR dosage form. The term is synonymous to prolonged or sustained-release. Many ER dosage forms have a pattern of release that begins with a "burst effect" that mimics an IR followed by a slower release of the remaining DS in the dosage form (USP, 2009). Extended release results from a specific formulation process and/or a special manufacturing method.

The other term focuses on delayed-release forms. According to this type, a dosage form is deliberately modified to delay release of the DS for some period of time after initial

administration. The release of the DS is prevented in the gastric environment, but promoted in the intestinal fluid; this term is synonymous to Enteric-Coated or Gastro-Resistant (USP, 2009).

Other authors still refer another type of MR pharmaceutical forms, which are the sequential release forms. Sequential release forms are a type of MR pharmaceutical form, which is characterized by a sequential release of the active substance(s). Sequential release can also be obtained from a specific formulation process and/or a special manufacturing method (Prista *et al.,* 2003; Vila Jato, 2000).

Figure 2 represents the typical plasma concentration profiles of the drug as a function of time, including both immediate and modified release oral dosage forms.

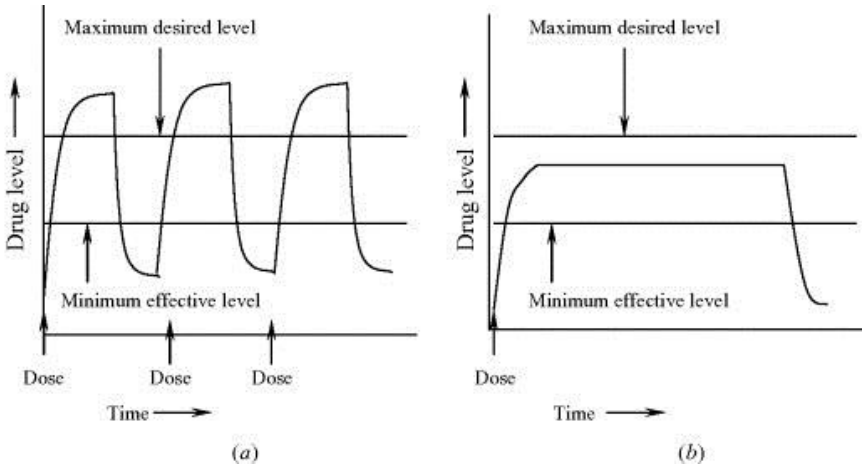

Figure 2 Profile of drug level in blood: (a) immediate release; (b) modified release (Anal, 2007).

More specifically, a modified drug release system can be a device or pharmaceutical form that controls the release of the drug substance in the place of absorption throughout the gastrointestinal tract and the drug absorption time to reach the desirable plasma profiles (Berner and Dinh, 1992; Qui and Zhang, 2000).

Nowadays, there are numerous pharmaceutical forms of modified release. The terminology used to define the oral pharmaceutical forms of modified release is very broad. Nevertheless, several other classification proposals have been suggested (ICH, 1991; Moller and Siewert, 1996; Eur. Ph., 2017).

1.1.2 Advantages and disadvantages

The modification of the availability pattern of the DS can be justified by the advantages, when compared with conventional forms, in compliance with one or more

objectives, namely (Veiga, 1989; Longer and Robinson, 1990; Salsa *et al.*, 1997; Prista *et al.*, 2002; Vila Jato, 2000):

- reduction of local and systemic side effects;
- possibility of using a smaller amount of drug, situation that allows to reduce the side effects by avoiding overtaking the drug toxicity threshold that sometimes occur with repeated administration of conventional forms, and also by reducing drug accumulation during treatment;
- greater selectivity of pharmacological activity;
- minimization of "peaks and valleys" in the bloodstream, thus resulting in a more constant or prolonged therapeutic effect; for drugs with relatively short half-lives, MR forms may be of interest for maintenance of blood levels for a longer period of time;
- reduction of GI tract irritation and side effects, maintaining drug levels within a desired range and optimization of the application of the pharmaceutical form in question.

Additionally, for the pharmaceutical industry and the patient, there are economic advantages in the use of these pharmaceutical forms. Although the initial unit cost of these systems is higher than conventional forms, the average cost of treatment is usually inferior when using conventional-release pharmaceutical forms.

However, it should be noted that the use of modified-release pharmaceutical forms is not at all excluded from inconvenience, of which it is referred:

- risk of drug accumulation, due to the slow elimination rate in the case of prolonged treatments; and in case of manifestation of symptoms of intolerance or intoxication, the difficulty of a rapid elimination of the organism from these forms;

- difficulty in adapting the dosage to different inter-individual pharmacokinetics;

- weak or null efficacy of the medication, in the case of DS being of low absorption by the intestinal mucosa, or due to an excessive swelling of the formulation, which can lead to a delay in the initial action (Welling, 2002).

Most of the modified oral pharmaceutical forms currently available on the market are based on: I) osmotic systems; II) membrane-controlled systems; III) pH-independent

formulations; and, IV), monolithic or matrix systems, among others. These latter are the ones used in this work.

Particularly interesting, it results in the use of matrix systems consisting of one or more polymers, due to the advantages inherent to these types of systems, including low cost, effectiveness, versatility, easy preparation, among others (Ebube and Jones, 2004).

The classification of matrix tablets, in which the DS is uniformly distributed in a matrix, is based on several criteria: i) matrix structure; ii) kinetics of release, tending to zero order; iii) properties related to DS release mechanisms, such as diffusion, degradation/erosion and release by an activation process (Vila Jato, 2000); iv) chemical nature and properties of the materials used.

1.1.3 Modified Release Systems

The mechanism of drug release always depends on the properties of the polymer (s) employed in the formulation. Taking into account the aforementioned aspects, matrix systems can be classified in detail according to what is shown in Table I (Buri, 1987).

Table I Classification of matrix systems. (Buri, 1987)

Mineral Matrices	**Hydrophilic Matrices***	**Inert Matrices**	**Lipid Matrices**	**Biodegradable Matrices**
Active substance retained on carrier	Unlimited swelling, diffusion release	Controlled release by diffusion	Diffusion release	Non lipid
Active substance adsorbed onto carrier	Limited swelling, controlled release by swelling		Release by erosion of the surface	

*Matrices used in the present work.

1.1.4 Hydrophilic Matrices

Hydrophilic matrices are the most popular systems for modulating drug release. They may be divided into systems, which maintain their constant shape and in systems which vary in shape and volume, increasing in volume at an initial stage as soon as they are brought into contact with the dissolution medium, then degrading and decreasing in volume. The process of releasing a drug from such a pharmaceutical system is briefly described below.

In general, the swellable matrices are activated by water, and the release of drugs from such pharmaceutical systems is controlled by interactions between water, polymers and the active substance.

The penetration of water into the matrix system is the first step in the process of polymer swelling, followed by the process of dissolution of the active substance (Harland *et al.,* 1988). The presence of water decreases the glass transition temperature of the polymer (e.g. for hydroxypropylmethylcellulose such temperature drops from 184 to 37°C (Bettini *et al.,* 2001), which causes a state transition from the glassy material to the malleable state, forming a gelled layer.

This process has the effect of increasing the mobility of the polymer chains, which helps the transport of the already dissolved active substance.

The relaxation phenomenon of the polymer determines the increase in matrix volume, which may affect the mechanism of release of the DS from the matrix system.

Depending on the characteristics of the macromolecule, the amount of polymer in the malleable state at the surface of the matrix varies, which implies the variation in thickness of the gelled layer. Among the characteristics of the polymer also depends the mechanism of disappearance of the matrix, which can be either by dissolution or by erosion. The thickness of the gelled layer depends on the extent of water penetration into the system, the disintegration of the polymer chains and the transfer of polymer and DS into the dissolution medium (Bruschi, 2015).

At an early stage, the rate of water penetration in the system is higher than the rate of disintegration of the polymer chains, with a thick gelled layer forming rapidly. However, due to the increased diffusion distance, the water penetration rate decreases to a level similar to that of the disintegration of the polymer chains, there being almost no changes in the thickness of the gelled layer, since the two processes of destruction and formation of the gelled layer are equivalent (Bruschi, 2015).

The release kinetics of drugs from matrix systems of this type is directly related to the thickness variation of the gelled layer (Bettini *et al.,* 1994).

Thus, it varies from an initial Fickian process to an anomalous (non-Fickian) process, ending with the characteristics of a first-order process, which is explained further below.

However, these three phases are not always observed during the drug release period from the matrix system, in particular due to the low disintegration rates of some polymers, such as hydroxypropylmethylcellulose (Colombo *et al.,* 1995). Briefly, gelled layer formation can be said to be a prime factor in such drug delivery control mechanisms.

The phenomena that govern the formation of the gelled layer comprise water penetration, swelling of the polymer, dissolution and diffusion of the active substance, and erosion of the polymer matrix. Since control of the release of the drug substance is achieved by controlling the diffusion of the molecules through the gelled layer, and that layer is susceptible to dissolution or erosion, such processes must be controlled in order to be able to control the release of the drug substance.

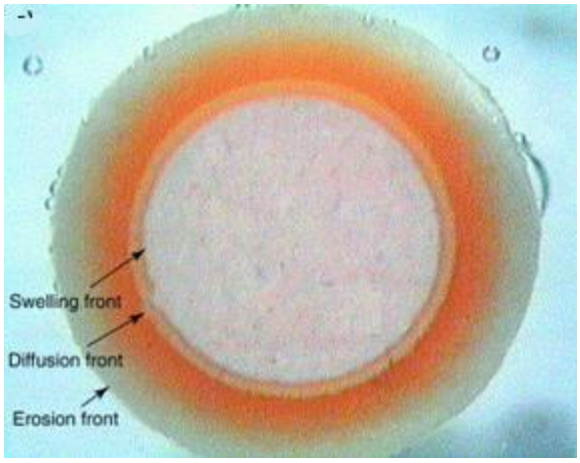

Figure 3 Fronts during the swelling–dissolution process (Colombo *et al.*, 2000)

Since the gelled layer plays such an important role in this type of release control mechanism, it is desirable to delimit its borders. These borders correspond to the fronts that separate the different phases of the matrix. The movement of these fronts is responsible for the formation dynamics of the gelled layer. The thickness of the gelled layer is then defined by the front separating the matrix from the dissolution medium, or erosion front, and the front separating the malleable polymer layer from the glassy or swelling polymer (Colombo *et al.,* 2000). Consequently, erosion and swelling can be considered as the factors responsible for controlling the thickness of the gelled layer. A third front (Bettini *et al.,* 1994; 2002), or dissolution front, has also been described in matrices containing poorly soluble drugs, such as diclofenac. This third front results from the precipitation, already in the gelled layer, of the poorly soluble drug that was dispersed in the glass matrix in the vitreous state. This front then corresponds to the boundary between dissolved drug and undissolved drug.

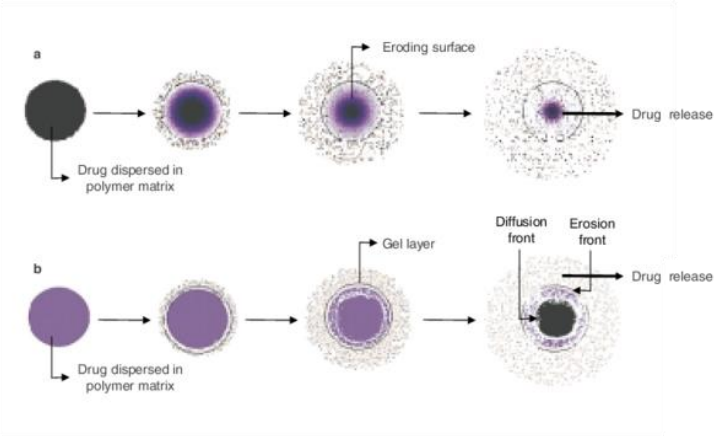

Figure 4 Schematic representation of drug release from matrix diffusion controlled-release drug delivery systems with the drug homogenously dispersed in: (a) an erodible polymer matrix; and (b) a hydrophilic, swellable polymer matrix. (Varma et al., 2004)

The displacement of the swelling front is associated with the water penetration rate in the matrix system, the dissolution front at the dissolution rate of the drug and the erosion front at the erosion rate of the matrix.

The velocity and release kinetics of a drug are controlled by the variation of thickness of the gelled layer, which is determined by the movements of the different fronts.

Using sufficiently soluble polymers, it is possible to keep the thickness of the gelled layer constant, since the matrix fronts move in a synchronized manner, which allows a zero-order release kinetics to be achieved (Bettini *et al.*, 2014)

Briefly, the mechanisms of release of a drug from an intumescent matrix are the diffusion of the drug through the gelled layer and the transport of drug, due to relaxation of the polymer. The rate of diffusion of the active substance depends on the dissolution of the active substance and the matrix erosion, since these two processes directly affect the concentration gradient of the drug in the gelled layer.

This release process, which as has been seen does not follow the diffusion mechanism described by Fick, can nevertheless be described by a simple semi-empirical equation (Peppas, 1986; Colombo *et al.*, 1987).

$$Q = kt^n$$

Equation 1 Semi-empirical equation of diffusion mechanism

In this equation, Q represents the drug fraction released in a given time period t, k is the specific rate of the process, which incorporates the characteristics of the polymer and the drug, while n is the diffusional exponent. Several studies (Baneja, 1986) have shown that the value of n is indicative of the type of release mechanism that occurs in the system. For n=0.5, the drug follows a Fickian diffusion mechanism, which is known to be driven by chemical gradient differences. At n=1, the drug is released according to a relaxation transport, which is associated with stresses and with phase transitions in the hydrated polymers. For n values between 0.5 and 1, non-Fickian diffusion is often observed as a result of the combined contribution of drug diffusion and polymer erosion.

Nicholas Peppas, (Peppas *et al.*, 1989), in an attempt to describe this type of transport, introduced a second term in the previous equation:

$$Q = k_1 t^n + k_2 t^{2n}$$

Equation 2 Semi-empirical equation of diffusion mechanism proposed by Peppas *et al.*, 1989.

Where $\mathbf{k_1}$ and $\mathbf{k_2}$ are constants that reflect the relative contributions of the Fickian and relaxation mechanisms. This equation has been applied quite successfully in describing the release of drugs from hydrophilic polymer matrices. In such modified delivery systems, various mechanisms may be modulated so as to obtain the desired release profile. The suitable choice of the hydrophilic polymers constituting the matrix allows an appropriate association of the swelling, dissolution and erosion mechanisms, in order to modulate the release kinetics to the desired therapeutic effect.

1.1.5.1 Hydrophilic Matrices with Unlimited Swelling

Unlimited swelling matrices are pharmaceutical forms consisting of drug substance incorporated in hydrophilic polymers. When in contact with the dissolution medium or with biological fluids throughout the dissolution process, they may maintain their structure more or less constant and/or undergo gelation of the macromolecules throughout the surface. This gelled layer establishes a diffusion barrier of DS molecules to the outside (Siepmann and Peppas, 2001). As the polymeric excipient hydrates, the gelation proceeds at a characteristic rate for the solid core where the polymer is in an anhydrate state. Therefore, the release rate and erosion mechanism of the gelled outer layer are important in the process of drug release (Buri and Doelker, 1980).

In these systems, when the drug is highly water soluble, the amount of DS dissolved is proportional to the square root of time, and there are equations describing release kinetics from this type of matrix (Higuchi, 1961, 1963).

In addition to the advantages of the above mentioned MR dosage forms, the following may be added (Malfroid and Bentejac, 1982; Veiga, 1989):

- simple technology;
- safety of the excipients;
- soft consistency of the hydrated form in the GI tract;
- possibility of incorporating a high amount of DS;
- release of the active substance relatively independent of the physiological variables.

1.1.5.2 Hydrophilic Matrices with limited Swelling

In limited swelling matrices, the rate of solvent penetration into the matrix and the molecular relaxation of the polymer are the factors controlling the release of the active substance upon steady state. This objective is achieved by the use of polymers (with slow hydration), which in the anhydrous state should be vitreous at body temperature and undergo macromolecular relaxation that in contact with the dissolution medium or biological fluids, facilitate a quantitative diffusion of the drug through gelled layer. It should be noted that in these systems a zero order drug release kinetics is often obtained. A number of synthetic polymers are used for the preparation of such matrices, same of these examples are the Poly(hydroxyethyl methacrylate) (PHEMA), Polyvinyl alcohol (PVA) and Ethyl vinyl acetate (PVA) (Bruschi, 2015).

1.1.5.3 The use of polymers in the development of modified release dosage forms

Generally, MR oral systems rely on simple principles, such as diffusion, dissolution and permeability, to achieve objectives as constant drug release rates. Polymers are, due to their characteristics, materials of choice for the construction of systems of this type. In fact, the polymers offer a wide variety of properties, such as diffusibility, permeability and solubility, which can be combined to achieve the desired type of drug release. In addition, polymers can be easily and by various methods processed into membranes or pharmaceutical forms, such as tablets, the active ingredients or other excipients being readily

incorporated by chemical or physical methods. Thus, the drugs can be dispersed or dissolved in the polymers to form matrix pharmaceutical systems.

1.1.5.4 Properties of the polymers which modify the release of the active substances

In order to select suitable materials that control the DS release flow from the pharmaceutical system, it is necessary to be well aware of the characteristics and properties of the polymers, in particular their structural characteristics, diffusion characteristics and their solubility.

1.1.5.5 Diffusibility

The diffusibility is the component of permeability that takes into account the geometric limitations encountered by the diffusing species as they traverse the polymer film. In general, the diffusibility increases when the ratio between the volume of free polymer and the size of the diffusing species increases. The following table (Jacobs *et al.*, 1993) presents a set of factors and how they affect the diffusibility of a molecule in a polymer medium.

Table 2 Factors that affect the diffusibility of a drug in a polymeric medium. (Jacobs *et al.,* 1993)

Increased factor	**Diffusibility effect**
Intermolecular forces	▼
Segmental Mobility	▲
Molecular mass of the permeant molecule	▼
Polymer crystallinity	▼
Plasticity	▲
Copolymerization	▲
Temperature	▲
Glass transition	▼

1.1.5.6 Solubility

The addition of other components, such as the drug or solvents, to the polymers may cause changes in the intermolecular polymeric forces and consequently alter the physical properties of the polymers.

The solubility parameters of the polymers, which also describe intermolecular forces, are widely described in the literature provided by the manufacturers. The choice of an ideal solvent for dissolving a polymer for further processing should be made by comparing the solubility parameters of the polymer and the solvent. In general, polymers and solvents with similar parameters will be compatible with each other.

1.1.5.7 Structural Considerations

The structure of the polymer used in the MR pharmaceutical system is a very important parameter in determining the drug release mechanism. The diffusion of a drug molecule dispersed in a polymer depends on the porous structure of the polymer, as the DS diffuses through the pores filled with solvent. Consequently, as porosity increases, drug release increases (Peppas *et al.*, 2000). Thus, for macroporous polymers it may be necessary to adjust the diffusion coefficient by correcting porosity, tortuosity or partition coefficients. For microporous polymers other factors, such as steric hindrance should be taken into account in addition to the above parameters. Other important structural parameters affecting diffusibility include the degree of crystallinity of the polymer, its degree of swelling, molecular mass and the state of the polymer (vitreous or malleable).

Many MR oral systems (granules or tablets) currently use hydrophilic polymers as release controllers.

The mechanism of drug release is dependent on both swelling and dissolution processes. As an example, one may cite that of tablets in which the drug is dispersed in a matrix of hydroxypropyl- and hydroxymethylcellulose. In this case, the initial part of the release process is marked by swelling, which is due to the state transition of the polymer, from the vitreous to the malleable state, due to the penetration of the water. When the internal concentration of water reaches the critical concentration, the true dissolution process begins. The diffusion through a swollen polymer is much higher than that one which occurs through a non-swollen polymer, the former possibly even approaching the diffusion coefficients occurring in solutions.

From what has been stated in the last paragraphs, it is clear that the **hydration capacity** of a polymer is very important for its performance as a drug release modulator.

The first minutes of the hydration process are the most important and those that most affect the polymeric drug release modulating characteristics (Peppas *et al.*, 1986), which is due to the fact that the first hydration moments correspond to the period in that the gelled layer is formed around the matrix. Several parameters may affect the hydration characteristics of the polymers, being one of the most studied the particle size. In general, it can be stated that larger particles hydrate faster than smaller particles (Reinhart *et al.*, 1981).

On the other hand, the presence of water in a matrix system can have effects, from the point of view of the stability and the rheological behaviour of the system, that must be carefully studied (Colombo *et al.,* 1994).

Another key parameter affecting the release of drugs from matrix systems corresponds to the **viscosity** of the polymer.

The viscosity of the polymer is an indicator of its molecular mass, whereby increasing the mass of polymer in the matrix increases the viscosity thereof. This causes an increase in the viscosity of the gelled layer, making it more resistant to dilution and erosion (Peppas *et al.*, 1995), which hampers and delays the release of the drug from the matrix. It is known that water penetration into the system is the first step in the drug release process; it is also known that the velocity of water penetration in the system depends on the equilibrium between the forces promoting the water intake and the forces opposing that intake - viscosity. Accordingly, viscosity is a drug release modulating factor from polymer matrix systems. Based on this fact, several studies have used the viscosity of the gelling polymer as a drug release modulating factor (Korsmeyer *et al.*, 1983). For example, if it was to facilitate the process of diffusion of the active substance through the gelled layer, it would suffice to reduce the viscosity of the polymer matrix (Peppas, 1985). This is consistent with Stokes law, which regulates the diffusion of a water-soluble drug through a gelled layer, a process that occurs by diffusion. The law states that the diffusion process is slower the more viscous the diffusion medium is (Peppas *et al*., 1989).

Another determining factor for the release characteristics of a drug from a polymer matrix system is the **amount of polymer** used, often represented by the amount of polymer / amount of active ingredient ratio. In fact, the greater the amount of polymer used, the slower the drug release process from the matrix system (Karland *et al.,* 1988). In view of this fact, the proportion of polymer used is a parameter often used to modulate the release of drugs from such systems (Veiga *et al*., 1999).

A parameter that greatly affects the release of drugs from matrix systems and is quite interesting and important, because when not taken into account it may imply inter-batch variability, is the **particle size**.

Several studies (Brannon Peppas *et al.*, 1989) have shown that the mechanism of release of a drug from a matrix system was not always the same by varying the particle size. In addition to ascertaining that as the particle size decreased, drug release also decreased, it was also found that the n-exponent of the Korsmeyer-Peppas equation, which is indicative of the type of preponderant delivery mechanism, increased at as the particle size decreased (Ende *et al.*, 1995).

An explanation was advanced (Caramella *et al.*, 1989) for this fact: when very large particles are used, the swollen polymer particles cannot be conveniently agglutinated. The pressure of these individualized swollen particles causes the system to disintegrate, the polymer acting as a disintegrant. As the particle size lowers, the porosity and tortuosity of the forming structure favours a diffusion release process and the contribution of the erosion of the gelled hydrophilic layer to the drug release process decreases.

The mechanism of release is at this point of the type described by Higuchi (Higuchi, 1961, 1963). By further decreasing the particle size used, there is a significant reduction in system porosity and an increase in tortuosity. The diffusion speed is decreased due to the increase in the average diffusion distance, which is compatible with Fick's law. At this point, the drug delivery mechanism is then dependent on a combination of diffusion and erosion.

In view of the impact of particle size on the drug delivery mechanism, it is easy to see why differences between batches can give rise to different dissolution profiles. However, several authors have established that the effects of particle size used were cushioned when using a polymer concentration greater than 20% (Lee *et al.*, 2000).

For all that has been presented, it may be stated that the type or types of polymers used are a conditioning factor of the release characteristics of a drug from a matrix system, since the type of polymer chosen is a factor of factors such as viscosity, porosity and tortuosity of the gelled layer, parameters which, among others, have a quantitative relationship with the drug release profile from the matrix pharmaceutical system.

1.1.5.8 Polymers Used in Hydrophilic Matrices

The polymers are long chain, high molecular weight compounds, extracted from marine plants, seeds, tree exudates and animal collagen. Some are produced by microbial synthesis and others by the modification of natural polysaccharides. In general, the polymers are characterized by their dissolution or dispersion in the water giving rise to a thickening or increase of viscosity (Singh, 2011). Polymers are also widely used in emulsion stabilization, particle suspension, crystallization control, among other functions. The Food and Drug Administration (FDA) recognizes these compounds as "Generally Recognized As Safe" (GRAS) products.

Hamid Akash *et al*. (2015), proposes the classification of the polymers used to obtain hydrophilic matrices in three main categories according to their origin: i) Natural polymers; ii) Modified or semi-synthetic polymers, based on chemical modifications of natural polymers or polymer-like materials; iii) synthetic polymers prepared by total chemical synthesis (Table 3).

Table 3 Classification of polymers. (Hamid Akash *et al*., 2015)

Natural polymers	**Semi Synthetic polymers**	**Synthetic polymers**
Plant Exudates: Arabic or Acacia Gum Tragacanta Gum Caraia Gum	*Ethercellulose derivatives:* Methylcellulose Ethylcellulose Hydroxyethylcellulose Hydroxypropylcellulose Hydroxypropylmethylcellulose Sodium carboxymethylcellulose	*Vinyl Polymers:* Polyvinylpyrrolidone Polyvinyl Alcohol Polymers of Ethylene Oxide (POLYOX) Olymethacrylates Polymers of acrylic acid (Carbopol)
Extracted from Plants: Pectin	Xanthan gum	
Plant Seeds: Guar Gum	Modified starches	
Algae Extract: Agar-Agar Alginates Carrageenan	Chitosan	

Depending on the aqueous solubility, they may be classified as soluble or insoluble, depending on the electronic charge (cationic, anionic or non-ionic) and according to potential bioadhesive potential (covalent, hydrogen bonds or electrostatic forces) (Salamat-Miller *et al.*, 2005).

Although many of these polymers have been applied in the preparation of MR formulations, cellulose ether derivatives have been the most widely used in recent years (Salsa *et al.*, 1997; Ebube and Jones, 2004, Virtanen *et al.*, 2017; Agarwal *et al.,* 2017). This may be explained in part because other polymers, such as natural gums or even Carbopol®, although having a swelling ability, may undergo pH variations.

Due to the great diversity of existing polymers with consequent differences in properties, some authors designate polymers which have swelling ability and are insoluble in water, whereas water-soluble polymers are termed hydrophilic or hydrodispersible polymers (Peppas *et al.*, 2000).

The most important requirements for the selection of a polymer suitable for the formulation of modified drug delivery systems are: chemical inertia and purity (Tonnesen and Karlsen, 2002); gelling agent concentration (Solomonidou *et al.*, 2001); gelling agent viscosity (Campos-Aldrete and Villafuerte-Robles, 1997); cross-linking degree (Peppas and Ségot-Chicq, 1985; Gander *et al.*, 1986); molecular weight (Tiwari *et al.*, 1999); hydrogen binding capacity (Peppas and Buri, 1985; Park and Robinson, 1987); ionic charge (Park *et al.*, 1989) and hydration capacity (Gu *et al.*, 1998).

1.1.5.8.1 Cellulosic derivatives

Cellulosic derivatives are one of the most widely used polymer groups in the pharmaceutical, food and cosmetic industries. They are available on the market within a wide range of products with an extensive range of physicochemical properties. The applications of the cellulose derivatives are very diversified, existing areas where their wide use is already common and others where research is expanding, such as: i) viscosity regulators in semi-solid preparations and dispersed forms (creams, gels, lotions, suspensions); (ii) taste and aroma correction; (iii) vehicles for cosmetics and topical forms; iv) controlled release dosage forms (Engelhardt, 1995).

Hydroxypropylmethylcellulose

One of the most commonly used cellulose ether derivatives nowadays in the preparation of hydrophilic matrices is hydroxypropylmethylcellulose (HPMC) (Figure 5).

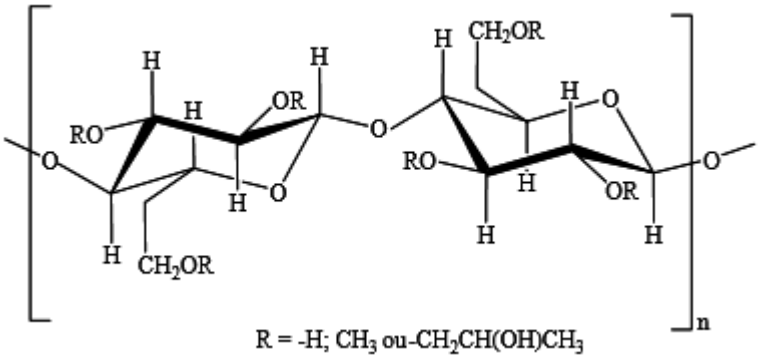

Figure 5 Chemical structure of HPMC

HPMC is currently the most widely used hydrophilic polymer in the development of MR systems (Siepmann and Peppas, 2001). Its main feature is its high intumescence and gelling properties, which are widely used to modulate drug delivery from such systems. Proper understanding of how HPMC allows the modulation of drug release allows it to be used to design the desired release profile. Depending on the solubility of the drug and the desired profile one may play with different types and amounts of HPMC to modulate the release of the drug according to the desired. In view of the foregoing, HPMC has great potential for use in matrix systems, as a model for the release of soluble or insoluble drugs in different concentrations.

As such, HPMC is a polymer whose use in pharmaceutical technology is versatile and well known and described in the three major world pharmacopoeias: United States, European and Japanese. The use of these hydrophilic polymers in controlled release systems has advantages, such as:

- Polymer of a non-ionic nature, characterized by ensuring a suitable release of the active substance from the pharmaceutical form in a high pH range. This is very important in an oral dosage form of controlled release, because of the high range of pH values present at the level of the gastrointestinal tract, thus ensuring adequate release of the active substance to the fullest extent.

- The use of these polymers in the formulation of controlled release systems does not require the use of specific manufacturing processes, and conventional production

processes can be used using conventional direct compression or wet/dry granulation methods without the need to purchase specific equipment.

- Since the effectiveness of these matrix systems is already well known in the "state of the art", and since the processes used are commonly used in the pharmaceutical industry, it allows the time and cost of developing these pharmaceutical forms to be as well as approval procedures by regulatory authorities.

- These polymers are highly compatible with various active substances, in particular as regards their solubility and quantity. Their tolerability is also high in respect of the excipients which may be used.

- The use of cellulose ethers in controlled release systems provides consistent and reproducible release of the active substance, unlike variations in polymers such as guar gum or other vegetal extracts.

It is a polymer whose safety is high and even recognized by the Food and Drug Administration as a raw material for use in the food industry (Dow, 2000). It is described in the literature as being a non-irritating and non-toxic excipient. The World Health Organization (WHO) does not define a maximum daily intake, since levels taken daily do not pose a health risk (FAO/WHO, 1990).

HPMC, also referred to as "Hypromellose" (Ph. Eur., 2005) or methylhydroxypropylcellulose (Feller and Wilt, 1990), is synthesized by the reaction between alkaline cellulose (cellulose previously treated with a sodium hydroxide solution) and a mixture of methylene chloride and propylene oxide (Wallace, 1990; Chan *et al*., 2003).

It appears as a yellow-white powder, practically odourless and tasteless. HPMC is stable (pH between 3.0 and 11.0) and resistant to enzymes but is hygroscopic after drying (Dow Commercial Information, 2002). It dissolves in cold water leading to viscous colloidal solutions and is also soluble in mixtures of methanol and dichloromethane. It is practically insoluble in hot water, chloroform, ethanol (95%) and ether. It has no ionic charges and is non-toxic.

The physicochemical properties of HPMC are strongly affected by:

- content of methoxyl groups;
- content of hydroxypropyl groups;

- molecular weight (Siepmann and Peppas, 2001).

There are various types of HPMCs commercially available which differ in function of the molecular weight (ranging from 10000 to 1500000g/mol), viscosity (ratio between their substituent groups methoxyl ($-OCH_3$) and hydroxypropyl ($-OCH_2-CH(OH)-CH_3$)) and particle size. This allows careful selection of HPMC that best matches the desirable properties of each matrix formulation. Gustafsson *et al.* (1999) found that a high percentage of methoxyl groups can negate the effect of hydroxypropyl groups and lead to a reduction in hydration and swelling of the tablets, resulting in a decreased drug release. USP (USP, 2006) distinguishes four different types of HPMC, classified according to their content in $-OCH_3$ and $-OCH_2CH(CH_3)OH$ radicals: 1828, 2208, 2906 and 2910.

In this nomenclature, the first two numbers indicate the percentage of methoxy groups and the last two numbers indicate the percentage of hydroxypropyl groups, determined after two hours drying at 105°C.

In the nomenclature used by Dow® to classify its HPMC, the letters "E", "F" and "K" identify different types of HPMC with different contents of methoxyl and hydroxypropyl groups, according to USP (USP29 / NF24, 2006; Table 4).

Table 4 Chemical substitution of various types of HPMC. (Dow®, 2000)

Products	**Methoxyl group content (%)**	**Hydroxypropoxyl groups content (%)**	**USP29/NF24**
Methocel® E Premium	28.0 – 30.0	7.0 – 12.0	HPMC 2910
Methocel® F Premium	27.0 – 30.0	4.0 – 7.5	HPMC 2906
Methocel® K Premium	19.0 – 24.0	7.0 – 12.0	HPMC 2208

Types "E" and "K" are most commonly used for modulating drug release. The number following the chemical designation indicates the viscosity of the product in millipascal.second (mPa.s), measured in a 20% aqueous solution at 20°C. Also referred to as viscosity are often the letters "C" and "M" As multiplicative per 100 and per 1000, respectively.

Various suffixes are used to designate special variants of the same product, namely:

- Premium "P" is used to designate products produced according to the Good Manufacturing Practices (GMP) approved by the Food and Drug Administration (FDA), complying with the specifications of the USP and the European Pharmacopoeia (EP).
- Low Viscosity "LV" is used to designate products with low viscosity.
- "CR" of Controlled Release, to designate controlled release products.
- "LH" of Low hydroxypropyl, used in the designation of products with a low content of hydroxypropyl groups.
- European pharmacopeia "EP" indicates that the product meets EP specifications.
- "JP" from Japanese pharmacopeia, states that the product meets the specifications of the Japanese Pharmacopoeia (JP). (Dow, 2000).

The degree of substitution of the polymer influences the release performance of the matrix system, and a possible explanation for this fact is the self-diffusion coefficient (SDC) (Körner *et al.*, 2009).

Differences in the measured SDC between HPMC with the same viscosity but with different degrees of substitution are verified, where the HPMC with the degree of substitution K presents a SDC value for the water in the gelling layer, lower than the polymers with the degree of substitution E and F.

This fact indicates that there is less water mobility in the gelling layer of the polymer with the degree of substitution K, that is, a greater resistance to water diffusion in the matrix system. This will directly imply less diffusion of the drug by the matrix, and indirectly less erosion of the gelling layer. Thus, the release of the drug into a matrix system composed of HPMC with the degree of substitution K will be less than verified in matrix systems composed of polymers with degree of substitution E and F (Rajabi-Siahboomi, 1996).

Due to their relatively hydrophilic nature, hydroxypropyl groups contribute significantly to the rate of hydration of the polymer, unlike the methoxyl groups, which are relatively hydrophobic. That is, HPMC polymers with degree of substitution K will more readily form the release modulating gel layer, inversely to the polymers with the degree of

substitution F, which exhibit the lowest rate of hydration. This is in accordance with the above, in which a matrix composed of HPMC with the degree of substitution K shows a slower release of the active substance (Mitchell, 1990).

The degree of substitution of HPMC has a high impact on the performance of matrix systems, which can be observed through the phenomenon of thermal gelation.

This phenomenon of thermal gelling results in the formation of a reversible gel upon heating of an aqueous solution of HPMC. The temperature of formation of this gel is directly dependent on the degree of substitution of HPMC.

Generally, this phenomenon is directly related to the polymer-polymer interactions, and in an initial state these interactions are minimal since the molecules are hydrated. With the gradual increase in temperature, there is an increasing evaporation of the water of hydration until a dehydration of the polymer occurs. It is at this point that a high increase in the viscosity of the aqueous solution occurs with the formation of a gellant structure with strong polymer-polymer interactions.

It is noted that the gelation temperature of the polymer can be affected by the action of the drugs, some of which can drastically reduce the temperature at which the gel is formed, while others have the reverse action.

The viscosity presented by the different types of HPMC is directly related to the molecular weight of the polymer.

The viscosity value of a polymer is obtained in a 2% (w/w) aqueous solution at 20°C and results from the hydration and extension of the polymer chains, which give greater resistance to the passage of a flow as a consequence of the increased HPMC surface.

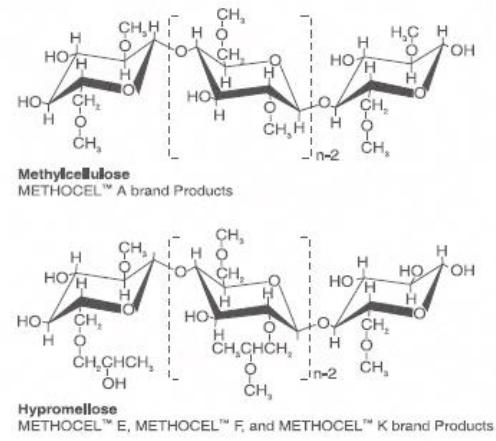

Figure 6 Chemical structure of different types of Methocel®. (Dow, 2000)

The rheology of an aqueous solution of HPMC is affected by several factors such as molecular mass, concentration, temperature and the presence of other solutes in solution.

It is to be noted that HPMC solutions exposed to temperatures below the gelling temperature exhibit a pseudo plastic behaviour, which is augmented by increasing the molecular weight of the polymer and/or the concentration.

Drug release from a HPMC matrix system

Hydrophilic matrix systems containing HPMC are robust, easy-to-produce systems in which the release of the active substance comprises the following steps:

- Initial contact of the polymer with water.
- Hydration of the polymer.
- Dissolution of the polymer.

In a first step, the water comes into contact with the polymer, hydration occurs, with the expansion of the polymer chains and the formation of a gelling layer. This step is crucial for the matrix system, since the occurrence of rapid hydration of the polymer prevents tablet disintegration by forming an outer gelling layer which controls the degree of hydration of the innermost layers of the tablet-pharmaceutical form. This is especially important when matrix systems containing drugs and excipients with high solubility in water are formulated.

As the initially formed gelling layer is fully hydrated, a dissolution of the same in the medium will be observed. This in turn will be replaced by an inner layer that will be successively hydrated giving continuity to the cycle. Thus, it is crucial for the performance of

the modified release pharmaceutical form that this balance is achieved between the hydration of the inner polymer layers and the dissolution of the outer ones. It is this cohesiveness and continuity presented by the cellulose ethers that allows the delay of water inflow and control of drug diffusion.

Initial contact of the polymer with the aqueous medium causes a rapid initial release of the drug in the surface layer, resulting in the so-called burst effect. Subsequently, release of the active substance is slow and gradual as hydration of the innermost layers of the dosage form occurs.

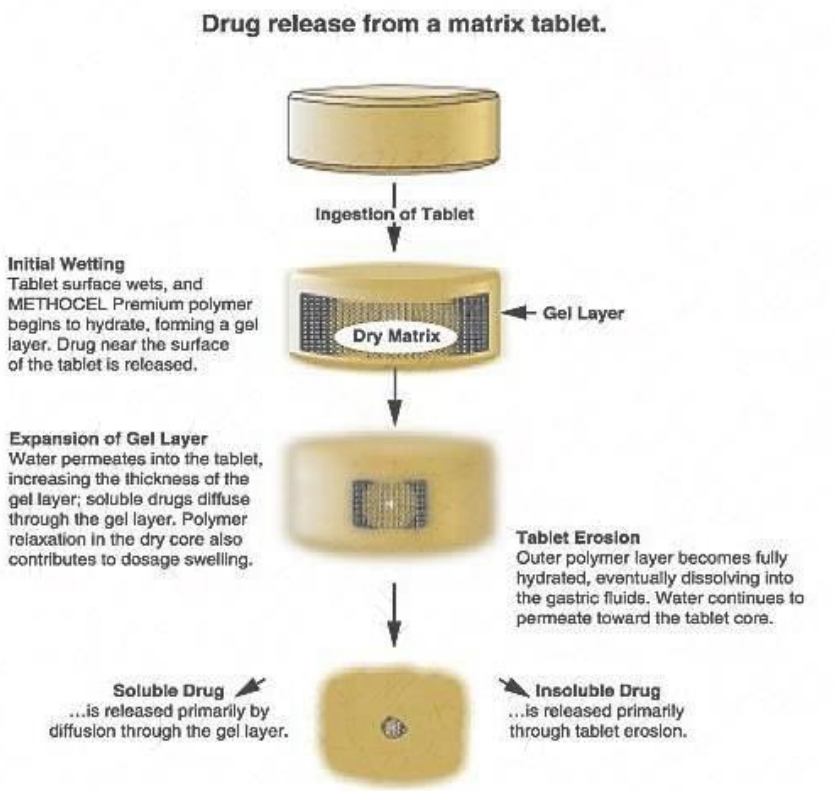

Figure 7 Release of a drug from a matrix system containing HPMC. (Dow®, 2000)

Still to note, in limited swelling matrices, the rate of solvent penetration into the matrix and the molecular relaxation of the polymer are the factors controlling the release of the active substance upon steady state.

In addition to solubility, other factors influence the release of an active substance into a pharmaceutical form, namely:

- HPMC amount;
- HPMC:DS proportion;
- HPMC viscosity;

- DS particle size;
- DS molecular weight;
- Excipients particle size;
- Excipients solubility;
- HPMC replacement grade.

In the case of MR dosage forms, the reference literature recommends, in addition to a basic formulation as simple as possible, the use of 10 to 80% in HPMC in order to delay the release of a drug. However, the amount of HPMC present in a formulation must be sufficient to allow the formation of a uniform gelling layer, which acts as a barrier preventing the immediate release of the drug (Cheong, 1992).

Studies show that an increase in the amount of HPMC in the formulation provides a decrease in the rate of drug release. This is due to the hydration and expansion processes of the polymer chains and their subsequent dissolution, there being a greater resistance to water penetration in the matrix system, the higher the amount of HPMC present in a formulation.

However, increasing the amount of HPMC tends to make the formulation less sensitive to changes in the raw materials and/or manufacturing processes. Further knowledge of the constituents of the formulation and the manufacturing process is therefore necessary in addition to the drug in order to evaluate possible interactions that may affect the drug delivery process in the matrix system.

This knowledge makes it possible to optimize the amounts of excipients to be used, and in particular the amount of HPMC, so that it is not always necessary to increase the amount of the polymer when it is desired to reduce the rate of release. It has been found that matrices that present HPMC in its composition as a modulating agent, both at high and low concentrations, allow the use of insoluble and soluble drugs (Keary, 2001). On the other hand, HPMC presents a considerable swelling facility that allows the rapid formation of a gelled layer that controls the release of drugs (Rodriguez *et al.,* 2000; Li *et al.,* 2005). Wan *et al.* (1993) have shown that the swelling rate of HPMC increases when the concentration and viscosity of the polymer are higher. In turn, studies by Bettini *et al.* (1994) have shown that drug release has been affected by the viscosity of the polymer: an increase in viscosity results in decreased release rate of the drug. This supports the generally accepted hypothesis that

the higher the molecular weight of the polymer, the lower the rate of release of an active substance from the matrix system.

However, there have been reports of some studies in which no differences in the rate of drug release were observed using HPMC with different molecular weights. A study that sought to evaluate the rate of release of salbutamol sulphate tablets from a matrix system tested the following polymers: Methocel® K4M Premium, Methocel® K15M Premium and Methocel® K100M Premium. The results obtained did not show a significantly different release rate of the active substance that supported the generally accepted hypothesis (Bonderoni, 1992).

In another study, this time with promethazine hydrochloride, no differences in drug release rates were observed even using polymers of different molecular weights (Methocel® K4M Premium, Methocel® K15M Premium and Methocel® K100M Premium) (Ford, 1985).

Velasco *et al*. (1999) and Feng *et al*. (2015) investigated the influence of HPMC on the release of diclofenac sodium in matrix tablets. In this study, it was concluded that the factor most affecting the rate of release of the drug from HPMC matrices is the DS/HPMC ratio. An increase in polymer concentration results in an increase in the viscosity of the gel and formation of a gel layer with a broader diffusional pathway. This may result in a decrease in the effective diffusion coefficient of the drug and, consequently, a reduction in its rate of release. According to the same authors, the particle size of the drug and HPMC also influence the drug release parameters.

The particle size of the HPMC is a factor that can affect the performance of a matrix system. The explanation for this fact is based on the larger surface area existing for smaller particles, which allow a better water-polymer interaction and consequently a more effective gelling layer.

Matrix systems composed of a polymer with smaller particles (less than 150μm) allow to form a more effective outer gelling layer, which delays the release of the drug, contrary to what is observed for systems containing larger polymers to 200μm). In this case, the matrix systems are disintegrated without forming an outer gelling layer. Alderman (1984) observed that a matrix system containing riboflavin was unable to form a gelling layer sufficiently effective to avoid premature drug release in the presence of larger particles (200-300μm) in the polymer used. Mitchell *et al.* (1993) have observed that an increase in the

amount of HPMC in the formulation results in a decrease in the importance of the size of the polymer. Mohamed *et al.* (2015), in more recent studies, demonstrated the importance of HPMC particle size in ER matrices, the effects of which are even more obvious for mini-tablets.

Bettini *et al.* (1994) also presented parameters for the release of the drug in three formulations, containing HPMC, to which different values of compression force were applied. In fact, the influence of this technological parameter on release kinetics was insignificant (Veiga, 1989; Chebli and Cartilier, 2000).

The impact of the variable "drug" on a matrix system containing HPMC

The impact on the rate of particle size release of a drug in a matrix system containing HPMC is practically zero except in extreme cases where large active substance particles associated with relatively small amounts of HPMC. These were the conclusions obtained in a study by Ford *et al.* (1985) in which they intended to evaluate the impact of drug particle size variation on the release rate from a matrix system containing HPMC.

An increase in the amount of drug in a formulation normally results in an increase in the rate of release of that drug from a matrix system containing HPMC. However, the opposite can also be seen, with a reduction in the release rate occurring with the increase in the amount of active substance. A possible explanation for this may be related to possible drug-HPMC interactions. Studies developed by Tahara *et al.* (1996) have shown that the solubility of a drug influences the release process from a matrix system. The authors identified three factors responsible for the behaviour of a hydrophilic matrix. Are they:

- Solubility of the active substance.
- Quantity of drug in formulation.
- Porosity of the matrix.

Given these factors, the authors suggest that in drugs with high / medium solubility, the best technique to regulate the rate of release is to control water infiltration in a matrix system. This assertion is supported by the fact that drugs with high solubility had dissolution rates almost identical to the water infiltration rates in the matrix system.

On the other hand, the decrease in the solubility of the drugs leads to the increase of the importance of the erosion phenomenon of HPMC as a crucial factor in the control of the drug release in the matrix system.

In a study developed by Ranga Rao *et al.* (1988) drugs with different solubilities (from 1/0.9 to 1/10000) incorporated into a matrix system containing Methocel® K4M Premium were used. The results obtained show little difference in the rate of release of pindolol (1/10 000 - very sparingly soluble), allopurinol (1/2000 - very sparingly soluble) and salicylic acid (1/460 - sparingly soluble). On the other hand, sodium salicylate (1/0.9 - highly soluble) showed a completely different release profile. Once again, the influence of the solubility of the active substance on the release rate was demonstrated.

Drugs with high solubility and present in high amounts in the formulation are the most complex case of release rate control, since the steps of hydration and gelation of the polymer are crucial to ensure correct release of the drug in the matrix system.

The impact of the excipients on a matrix system containing HPMC

The rate of release of a drug from a matrix system can be affected by the solubility of the diluent. Thus, a soluble diluent such as lactose in contact with a dissolution medium will be solubilized and will increase the porosity of the matrix, resulting in an increase in the rate of erosion thereof and therefore, in a faster dissolution of the drug. This has been studied by several researchers, from which a study carried out by Ford *et al.* (1987) is highlighted. In fact, they attempted to evaluate the effect of different amounts of lactose and calcium phosphate on the release of promethazine hydrochloride from an HPMC-based matrix system. These authors concluded that the solubility of the diluent may be significant in the case of a formulation with a high amount of the active ingredient, as opposed to a low amount of HPMC.

Lubricants may also affect the release of an active substance from a matrix system. This is related to the inherent function of a lubricating agent, in which it is added to a formulation in order to facilitate ejection of the tablet during the compression phase, as well as, to prevent phenomena of sticking of the formulation to the punches.

Magnesium stearate is the benchmark for this class of excipients. It is characterized by an easily deformable structure in mixing and compacting processes, coating the powder/granulate particles as well as the punctures. The phenomenon of excess lubrication

by a hydrophobic substance can affect the release rate of a drug, slowing it down. This fact is evidenced in a study by Sheskey *et al.* (1995) in which different amounts of lubricant (0.2% to 2.0%) were tested with different mixing times (from 2 to 30 minutes) and where a slight impact of the lubricating excipient in the release of the drug.

1.2 Quality by Design

1.2.1 History

Quality by Design (QbD) is increasingly becoming an important and widely used term in the pharmaceutical industry quality system. QbD can be considered to be a holistic, system-based approach to the designing and developing formulation and manufacturing processes which ensures predefined product specifications.

In 2002, in order to establish a more systematic and risk based approach to the development of pharmaceutical products, using the progresses in science and technology, FDA announced the "cGMP for the 21st Century: A Risk based Approach" initiative. (FDA, 2006) This initiative, focused on QbD, and the publication of the Process Analytical Technology (PAT) Guidance in 2004 by the FDA contributed decisively for the modernization of the pharmaceutical industry and challenged them to look beyond the traditional approach of Quality by Testing (QbT). (FDA, 2004) In addition to these new ideas, three important guidance documents were published as part of International Conference on Harmonization (ICH) guidelines: Q8 Pharmaceutical Development and Q9 Quality Risk Management, in 2005, and ICH Q10 Pharmaceutical Quality System, in 2008. These guidance documents implemented together, in a holistic manner, provides an effective system that emphasizes a harmonized science and risk-based approach to product development, assuring an improving in Quality in pharmaceutical industry. (FDA, 2006a), (FDA, 2006b), (FDA, 2008), (FDA, 2009).

In ICH Q8 guidance, the concept of QbD was mentioned, stating that "quality cannot be tested into products, i.e., quality should be built in by design" (FDA, 2006). In 2009, the ICH Q8 guidance was reviewed, clarifying key concepts of the original guidance. Additionally, the principles of QbD were describes and QbD defining as "a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management" (FDA, 2009).

This framework represents a move away from the traditional approach in the industry of QbT and was relatively new to the pharmaceutical industry at the beginning of the twenty-first century. However, it can be found the application of some principles of QbD across the industry long before then, but in an isolated way. Table 7 compares the current state to the desired QbD state.

Table 5 Comparison between the current state and the desired QbD state. (Singh and Sharma, 2014)

Aspect	Current state	Desired QbD state
Pharmaceutical Development	Empirical; typically univariate	Systematic; multivariate experiments
Manufacturing Process	Locked down; validation on three batches; focus on reproducibility	Adjustable within design space; continuous verification within design space; focus on control strategy
Process Control	In-process testing for go/no-go; offline analysis	PAT utilized for feedback and feed forward in real time
Product Specification	Primary means of quality control; based on batch data	Part of overall quality control strategy; based on product performance
Control Strategy	Mainly by intermediate and end product testing	Risk-based; controls shifted upstream; real-time release
Lifecycle Management	Reactive to problems and OoS; post approval changes needed	Continual improvement enabled within design space

In fact, QbD is a comprehensive approach targeting all phases of drug discovery, manufacture, and delivery. The aim is to improve the quality and reduce the costs of medicines for the consumer. This may be an interactive systematic approach and thus the circular design as shown in Figure 9. This circle of QbD can be divided into two general areas, product knowledge and process understanding. These two areas meet in the design space and the interaction of product knowledge and process understanding allows for continuous improvement.

Figure 8 Quality by Design concept. (FDA, 2012)

QbD begins by defining the desired product performance and also by defining a product that meets those performance requirements. The characteristics of the desired product are the basis for designing the manufacturing process, which needs to be monitored in terms of performance. Each of these steps influence each other, continuing the cycle. The inner circle interacts with many other specific measures of pharmaceutical manufacturing, such as specifications, critical process parameters, ensuring the product knowledge and process understanding.

The underlying principles of QbD are explained in the quality guidelines of international conference on harmonization i.e. ICH Q8 Pharmaceutical Development, ICHQ9 Quality Risk Management, and ICH Q10 Pharmaceutical Quality System. Figure 10 presents the guidelines that explain QbD.

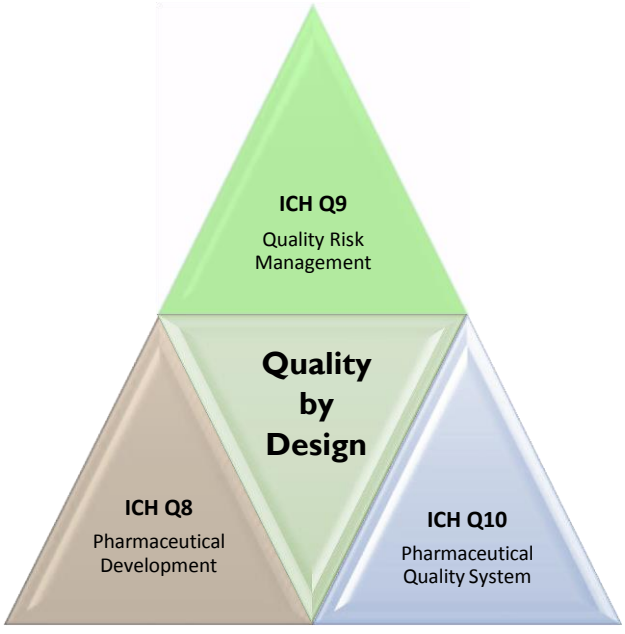

Figure 9 ICH Q8/Q9/Q10 triangle in QbD paradigm.

The application of QbD presents several advantages and can be summarized as (Sangshetti, 2014):

- Patient safety and product efficacy are focused.
- Scientific understanding of pharmaceutical process and methods is done.
- It involves product design and process development.
- Science-based risk assessment is carried.
- Critical quality attributes are identified and their effect on final quality of product is analysed.
- It offers robust method or process.
- Business benefits are also driving force to adopt QbD.

1.2.2 Elements of Quality by Design

ICH guideline Q8 refers all elements of pharmaceutical development included in QbD. In a marketing authorization application, the Pharmaceutical Development section is projected to provide a complete understanding of the product and manufacturing process. The aim of this section is to design a quality product and its manufacturing process to consistently deliver the intended performance of product. The information and knowledge gained from pharmaceutical development studies and manufacturing experience provide scientific understanding to support the establishment of the specifications, and manufacturing controls. During pharmaceutical development, QbD suggests that it should include the following elements:

- Defining the quality target product profile (QTPP).
- Identifying potential critical quality attributes (CQAs).
- Link raw material attributes and process parameters to CQAs and perform risk assessment.
- Developing a design space.
- Designing and implementing control strategy.
- Continuous improvement.

1.2.2.1 Defining Product Design Requirements and Critical Quality Attributes

The product design requirements must be well understood in the early design phase, and they can be found in a Quality Target Product Profile (QTPP). The QTPP is derived from the desired product information and it has been defined as "a prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product" (FDA, 2009). Therefore, pharmaceutical companies construct a target product profile that describes:

- Intended use in clinical setting, route of administration, dosage form, delivery Systems.
- Dosage strength(s), container closure system.
- Therapeutic moiety release or delivery and attributes affecting, Pharmacokinetic characteristics (e.g., dissolution, aerodynamic performance)-
- Drug product quality criteria like sterility, purity, stability and drug release as appropriate for dosage form the intended for marketing.
- The QTPP guides scientists to establish strategies and keep the product developing effort focused and efficient.

In addition to defining the requirements to design the product, the QTPP will help identify critical quality attributes (CQAs). ICH Q8 defines CQA as "a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality" (USP, 2013). CQAs are generally linked with the drug substance, excipients, intermediates (in-process materials) and drug product. Quality risk management tools, found in the ICH Q9 guideline, are often used to identify and prioritize the potential CQAs (FDA, 2006). Relevant CQAs can be identified by a dynamic process quality risk management and experimentation that evaluates the extent to which their variation can have an impact on the ultimate quality product. The accumulated experience, the knowledge obtained from similar products and from literature references are essential to make these risk assessments. Taken together, this data provides a rationale that links the CQA with the safety and efficacy of the product. The outcome of the risk assessment would be a list of CQAs ranked in order of importance. The potential CQAs can be modified when the formulation and manufacturing processes are selected and as product knowledge and process understanding increase.

1.2.2.2 Quality Risk Management in QbD

Risk management has become a priority process in the pharmaceutical industry with the advances in the QbD. As seen before, QbD is based on sound science and quality risk management. It is a systematic approach to development that begins with predefined objectives and an emphasis on product process understanding and process control. In order to achieve this, a risk management process has to be a priority (FDA, 2006).

Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the drug product across the product lifecycle. ICH Q9 discusses the role of risk management in pharmaceutical industry. For pharmaceutical development, ICH Q9 suggests the application of the principles and tools of quality risk management to:

- Select the optimal product design and process design.
- Enhance knowledge of product performance over a wide range of material attributes, processing options, and process parameters.
- Assess the critical attributes of raw materials, solvents, Drug Substance (DS), starting materials, DSs, excipients, or packaging materials.
- To establish appropriate specifications, identify critical process parameters and establish manufacturing controls.
- Decrease variability of quality attributes.
- Assess the need for additional studies relating to scale up and technology transfer.
- Make use of the "design space" concept (see ICH Q8).

Quality risk management supports a scientific and practical approach to decision-making, assessing the probability, severity and sometimes detectability of the risk. In pharmaceutical development, risk assessment is important in identifying which material attributes and process parameters potentially have an effect on product CQAs – Critical Material Attributes (CMAs) and Critical Process Parameters (CPPs). Risk assessment is typically performed early in the pharmaceutical development process and is repeated as more information becomes available and greater knowledge is obtained.

Risks to quality can be assessed in a variety of informal ways (empirical and / or internal procedures) based on, for example, compilation of observations, trends and other information. Such approaches continue to provide useful information that might support topics such as handling of complaints, quality defects, deviations and allocation of

resources (FDA, 2006).

1.2.2.3 Design of Experiments (DoE)

Traditional pharmaceutical development approaches are often limited by experiments that test one-at-a-time variability. Comprehensive Design of Experiments uses multidisciplinary teams to design and execute soundly based statistical designs to gain a full understanding of the product and its manufacturing process. The output of DoE confirms CQAs and CPPs that need to be controlled in the manufacturing process.

In an experiment, one or more factors are deliberately changed in order to observe the effect on one or more response variables. This may lead to an extend number of experiments. In DoE, it is ensured that the selected experiments produce the maximum amount of relevant information, keeping costs low by conducting few experiments (FDA, 2009).

DoE initiates with defining the objectives of an experiment and selecting the process factors for the study. An experimental design is the laying out of a detailed experimental plan in advance of doing the experiment.

The statistical theory underlying DoE generally begins with the concept of process models, and the most common it is the process model of the "black box" type, with several discrete or continuous input factors that can be controlled and one or more measured output responses, as shown in Figure 10. The measured responses describe the properties of the investigated system. By changing the most influential factors (e.g. amount of disintegrant, blending time, compression force) the features of the system might be altered according to a response (e.g. disintegration time, content uniformity, hardness).

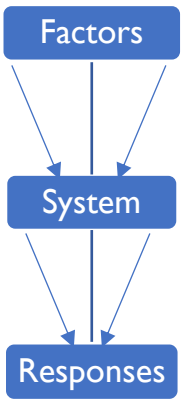

Figure 10 A "Black Box" Process Model Schematic.

Frequently, the experiments are affected by a number of uncontrolled factors that may be discrete, such as different machines or operators, and/or continuous such as ambient temperature or relative humidity.

Once factors have been chosen and responses measured, it is desirable to get an understanding of the relationship between them by linking the factors changes to the responses changes with a mathematical model. In fact, the base for DoE is an approximation of reality with the help of a mathematical model. This model is never a hundred percent right, but simply helps to transport the complexity of the reality into an equation which is easy to handle. The most common empirical mathematical models fit to the experimental data take are polynomial functions, usually in a linear form or quadratic form (Montgomery, 2004).

The choice of an experimental design is an important part of a DoE process, being critical for the success of the study. This choice depends on a number of aspects, including the nature of the problem and study (e.g., a screening, optimization, or robustness study), the factors and interactions to be studied (e.g., four, six, or nine factors, and main effects or two- way interactions), and available resources (e.g., time, labour, cost, and materials) (Montgomery, 2004). Numerous statistical experimental designs are known. The following list gives the commonly used design types:

- Full factorial design.
- Fractional factorial design.
- Central composite design.
- Plackett-Burman design.
- Box-Behnken design.
- Taguchi robust design.

1.2.2.4 Design Space and Control Strategy

A key concept in the QbD paradigm is Design Space – a multidimensional space that encompasses combinations of process inputs (material attributes and process parameters) and the CQAs that provide assurance of suitable product performance. ICH Q8 (R2) guideline introduces the concept of Design Space to the pharmaceutical industry and defines it as "the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide

assurance of quality." (FDA, 2009).

A Design Space is a way to represent the product and process understanding which will be establish (Figure 11). The product and process understanding and Design Space helps to identify and explain the all sources of variability and thus way out from this variability by measuring and controlling the CPPs and CMAs responsible for variability. Finally, this assignment predicts the accurate and reliable product quality attributes within specifications in terms of quality

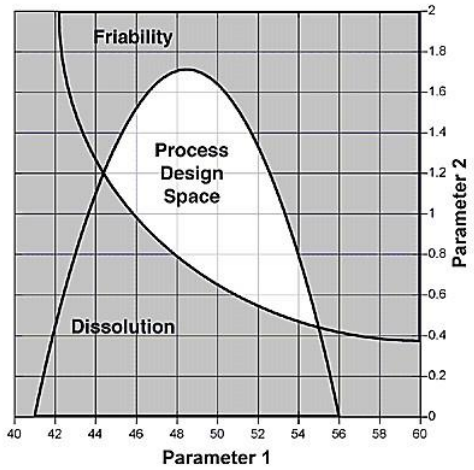

Figure 11 Potential process design space, comprised of the overlap region of design ranges for friability and or dissolution. (ICH Q8(R2), 2009)

Once a sufficient level of product and process understanding is achieved, through Design Space, a Control Strategy should be developed that assures that the process will remain in control within the normal variation in material attributes and process operating ranges. Figure 12 shows how Control Strategy is connected and interacts with Design Space and Knowledge Space.

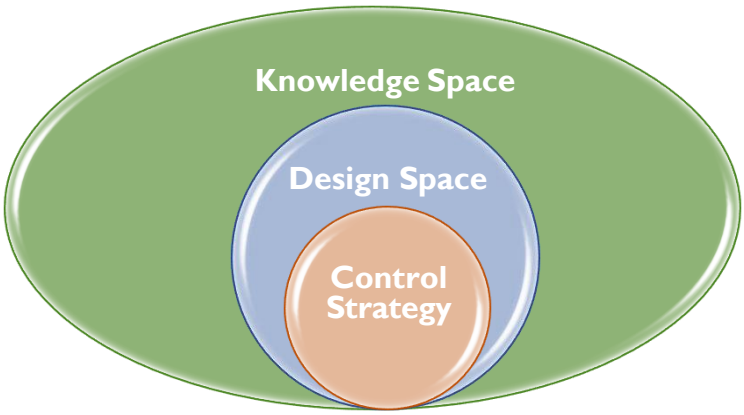

Figure 12 Relationship between Knowledge Space, Design Space, and Control Strategy.

Control Strategy is defined as "a planned set of controls, derived from current product and process understanding that ensures process performance and product quality. Controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control."

A Control Strategy is designed to ensure that a product of required quality will be produced consistently. The elements of the control strategy should describe and justify how in-process controls and the controls of input materials (drug substance and excipients), intermediates (in-process materials), container closure system, and drug products contribute to the final product quality. These controls should be based on product, formulation and process understanding and should include, at a minimum, control of the CPPs and CMAs. In a QbD approach, pharmaceutical development will generate process and product understanding and identify sources of variability. These sources of variability may impact on product quality and therefore should be identified, understood, and subsequently controlled. Product and process understanding, in combination with quality risk management, will support the control of the process such that the variability can be compensated for in an adaptable manner to deliver consistent product quality (FDA, 2009).

Scale-up, technology transfer and manufacturing experience can lead to refinements of the control strategy.

1.2.2.5 Continuous improvement throughout product life cycle

QbD focuses on building quality into the product and manufacturing processes, as well as continuous process improvement. Continuous improvement of a product and process should be employed throughout the lifecycle of a product.

ICH Q10 describes a model for the establishment of an effective Pharmaceutical Quality System (PQS) that can be used by manufacturers implementing QbD systems and can evaluate and improve product quality throughout the product lifecycle (FDA, 2008). In fact, PQS facilitates continuous improvement, helping the identification and implementation of appropriate product and process quality improvements, reducing the variability, and identifying and prioritizing areas for continuous improvement. It is important to share the knowledge gained during development and implementation that is relevant for utilization of

that Design Space on the manufacturing floor and under the PQS. This knowledge can include results of risk assessments, assumptions based on prior knowledge, and statistical design considerations. Relationship among the Design Space, Control Strategy, CQA and QTPP are an important part of this shared knowledge (FDA, 2008).

In the case of changes to an approved design space, appropriate filings should be made to meet regulatory requirements. Movement within the approved design space, as defined in the ICH Q8 (R2) glossary, does not call for a regulatory filing. For movement outside the design space, the use of risk assessment could be helpful in determining the impact of the change on quality, safety and efficacy and the appropriate regulatory filing strategy (FDA, 2009).

1.3 Objectives

The main objective of this work was to develop a generic version of a Drug Product, available on the market, being denominated project Blue055 (strength ≤2.0%) ER tablets, which are therapeutically equivalent to the reference listed drug product (RLD). Additionally, it encompassed the study of the effect of formulation and process variables on formulation performance, taken the QbD concept. QbD comprises all elements of pharmaceutical development mentioned in the ICH guideline Q8 and it will be reflected in this work. Under the concept of QbD, when designing and developing a product, it is needed to define desired product performance and identify CQAs. Taking into consideration this information, the first aim of the project was to define the QTPP and identifying the quality attributes that impact directly the product quality. A key objective of performing a risk assessment in pharmaceutical development is to the identification of formulation and process variables that affect drug product CQAs. Therefore, the second aim was to identify and prioritize formulation and process variables. Under this task, preliminary formulation and manufacturing process studies were carried out in order to understand and mitigate the risk associated to it, especially formulation parameters and process parameters. For that, whenever possible, a DoE was used to understand the interaction between critical formulation and process variables and the quality attributes identified as critical. With particular relevance the study of the impact of HPMC, as controlled release agent on CQAs of an ER tablet.

CHAPTER II

MATERIALS AND METHODS

2. Materials and Methods

2.1 Material

Due to the confidentiality nature of the project, the active substance used in the course of the present work will be designated Blue055 (internal code name at Bluepharma) and it is not possible to provide further details regarding pharmacology, pharmacokinetics and physicochemical characteristics of this drug substance (DS).

The referred DS is a class III molecule, according to the Biopharmaceutics Classification System (BCS) proposed by Amidon *et al.* (1995). Class III consists of water-soluble drugs (i.e., have high C_S - Aqueous Drug Solubility), which do not readily permeate the biomembranes (i.e., have low P_T - Permeability). For these drugs, the rate-limiting factor in drug absorption is their permeability. Including absorption-enhancing excipients (i.e., compounds that decrease the barrier properties of epithelia in the GI tract) in their formulation can enhance their bioavailability (Loftosson, 2015).

In addition to the DS, different excipients were used as components of this formulation. While developing this generic product, preferred choice of excipients was based on the composition given in the RLD prescribing information.

The following table (Table 6) presents the qualitative formulation extracted from the RLD leaflet, and the recommended concentrations of each excipient was extracted from the Handbook of Pharmaceutical Excipients (Rowe *et al.*, 2009).

Table 6 Qualitative composition of the product

Composition	Recommended concentrations for Handbook of Excipients
Drug Substance	≤2.0%
Diluent	NA
Controlled-release agent	15-35%
Disintegrant	5-10%
Surfactant	1.0-2.0%
Glidant	0.1-1.0%
Lubricant	0.25-5.0%

NA: not available.

2.2 Methods

2.2.1 Manufacturing Process

As the product under development is of low dosage (DS≤2.0%), the project presents special challenges to the manufacturing process, which need to be developed in such a way as to meet the quality and safety criteria of the pharmaceutical form. In a first phase, the direct compression technique was tested, but without great success, because the DS was not equally distributed in the mixture. In order to solve this, the slugging technique was used, which led to better results. However, this technique is not feasible on an industrial scale. Dry granulation comes in substitution of the slugging technique, since it is a reproducible technique on an industrial scale with controllable settings.

Note that according to the Guideline on process validation for finished products (EMA, 2014), this process is considered as non-standard process. A non-standard process is determined by a combination of the nature of the active substance, the nature of the finished product, the actual process itself and the production experience of the manufacturer. The manufacture of specialized pharmaceutical dosage forms, e.g. MR preparations or when the unit dose products contain drugs in low content (≤2% of composition) (EMA, 2014), is object of this study. In this case, production scale validation data should be provided in the marketing authorization application dossier unless otherwise justified. Table 7 details the equipment and the associated process used in these studies.

Table 7 Equipment used in formulation development studies.

Process step	**Identification**	**Model**	**Technology**
Blending Lubrication	All-Purpose Motor Drive	Erweka® AR402	Motor drive for mixing, sieving.
	Double Cone Mixer	DKM® < 3L	Mixing powders
Dry Granulation	Roller Compactor	Alexanderwerk® WP120 R&D KIT (25mm)	Roller Compaction
Tabletting	Rotary Tablet Press	Ronchi® FA/8 8 stations	Tablet manufacturing

2.2.2 Analytical Tests

2.2.2.1 Blend Uniformity, Assay and Content Uniformity

The method validation for Blend Uniformity, Assay and Content Uniformity was performed according to ICH Q2 (R1) guidance (Validation of analytical procedures: text and methodology), and carried out according to compendial information, UPS <621>/Ph. Eur. 2.2.29.

2.2.2.2 Dissolution

One of the important steps of the pharmaceutical development was to establish the *in vitro* dissolution method to be used as drug product quality control and performance method to be used throughout the pharmaceutical development work.

As an extended release product, the dissolution medium consists of a biphasic system, wherein the first 2 hours (HCl 0.1N) simulates the gastric fluid and the following 16h (Phosphate buffer pH7.0) mimics the small intestinal tube. The dissolution methods used are as currently recommended by the Division of Bioequivalence of FDA, Office of Generic Drugs (OGD). The method validation was performed according to ICH Q2 (R1) guidance.

2.2.2.3 Hardness

Tablet hardness was determined using the Hardness Tester Dr. Schleuniger® Pharmatron – MultiTest50, for 3 tablets of each test formulation; the average hardness, standard deviation and relative standard variation were determined.

2.2.3 Quality by Design Tools

2.2.3.1 Risk Assessment

Risk assessment was used throughout development to identify potentially high risk formulation and process variables and to determine which studies were necessary to increase our knowledge. Each risk assessment was then updated to capture the reduced level of risk based on our improved product and process understanding. The relative risk of each attribute was ranked as high, medium, or low (Table 10). Those attributes that could have a high impact on the drug product CQAs warranted further investigation, whereas those attributes that had low impact on the drug product CQAs required no further investigation.

Table 8 Overview of relative risk ranking system.

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

This relative risk ranking system was used to assess the risk in the pharmaceutical development of some drug products.

2.2.3.2 Ishikawa Diagram

The Ishikawa diagram is an important scientific tool used to identify and clarify the causes of an effect of interest. When team members construct such a diagram, it allows them to build a visual theory about potential causes and effects that can be used to guide improvement work. Also called fishbone or cause and effect diagram, it can stimulate the formation of hunches worth empirically testing. In addition, the Ishikawa diagram promotes a structured use of major categories of potential causes. As a result, rather than allowing people to focus on a few top-of-the-mind areas, it facilitates deeper thinking about possible causes. Finally, it can help the team answer the question of where to begin the process of improvement. (Pramod *et al.*, 2016)

2.2.3.3 Design of Experiments (DoE)

The design of experiments is an organized and systematic method that allows determining the influence of the factors in the outputs of the process. The use of experimental design is a fundamental tool of QbD (Orlandini, 2012). When doing a DoE, it is necessary to know exactly what the factors are (independent variables), and which parameters are likely to influence the responses (dependent variables). The DoE allows obtaining results in an effective way, since it enables the study of the variation of individual factors and also the interactions among them (Orlandini, 2012). In terms of DoE, two types of design can be chosen: the complete factorial design or the fractional factorial design. A complete factorial design consists of the combination of all factors at all levels, in all possible combinations. This design can be designated by the expression L^K, where k represents the number of factors and L the different levels studied. Experimental planning is usually written in variable coding. So, if the experimental design is composed of two levels, the highest level is coded with (+1) and the lowest with (-1). To perform the experimental designs, the JMP® (SAS® Institute Inc.) software was used.

In this work, the following responses and factors were defined, and are summarized in the Table 9.

Table 9 Factors (independent variables)

Factors	Ranges
Diluent amount	20.0 – 40.0%
Diluent grade	Grade 1 Grade 2 Grade 3 Grade 4
Disintegrant amount	20.0 – 40.0%
HPMC amount	30.0 – 50.0%
HPMC grade	Grade X Grade Y Grade Z
HPMC viscosity	4255 – 130308 mPa.s
HPMC PSD (d_{90})	51.0 – 77.0 µm
HPMC hydroxypropyl content	7.9 – 10.9%
HPMC supplier	Supplier A Supplier B
Surfactant amount	0.0 – 2.0%
Glidant amount	0.0 – 1.0%
Lubricant amount	0.25 – 3.0%
DS PSD (d_{90})	PSD 1 PSD 2 PSD 3 PSD 4 PSD 5
HPMC order of addition	Intragranular Half Intragranular Extragranular
Surfactant order of addition	Intragranular Half Intragranular Extragranular
Glidant order of addition	Intragranular Half Intragranular Extragranular
Roller gap	1.0 – 3.0 mm
Roller pressure	18.0 – 50.0 bar
Final sieve size	0.63 mm 1.00 mm
Final blending time	5 – 20’
Final lubrication time	3 – 10’
Intra-granular phase lubrication time	3 – 10’

Table 10 Responses (dependent variables).

Responses	Goal	Acceptable Ranges
Blend Uniformity	Match target	95 – 105%
Assay	Match target	95 – 105%
Hardness	Match target	20-120N
Dissolution (18 hours)	Match target	NLT 80% (Q)

CHAPTER III

EXPERIMENTAL DESIGN AND RESULTS

3. Formulation and Manufacturing Process Selection

The objective of this project, as already mentioned, was the development of a generic drug product, based on the RLD tablets. For this purpose, the characterization of RLD was firstly performed, aiming at being the subject of comparison for the study that follows (Table 11).

3.1 RLD Characterization

Several batches available on the market were analyzed for characterization of the RLD. The following data refer to the RLD batch chosen to direct the development (Table 11).

Table 11 Blue055 RLD tablets batch characterization.

Strength		≤**2.0%**
Appearance		White, non-scored, standard convex with debossing on one side.
Weight (n=10)	Min	115.4mg
	Max	124.5mg
	Avg	**119.3mg**
Hardness (n=10)	Min	46N
	Max	73N
	Avg	**55N**
Water content (Karl-Fisher)		**4.2%**
Dissolution (release medium)	2h	**32.2%**
	4h	**59.7%**
	8h	**81.8%**
	18h	**95.4%**
Related substances (HPLC)	Single unknown impurity	**0.12%**
	Total impurities	**0.12%**
	Assay (HPLC)	**99.2%**

In Figure 13, it is possible to observe the dissolution profile obtained from the characterized batch.

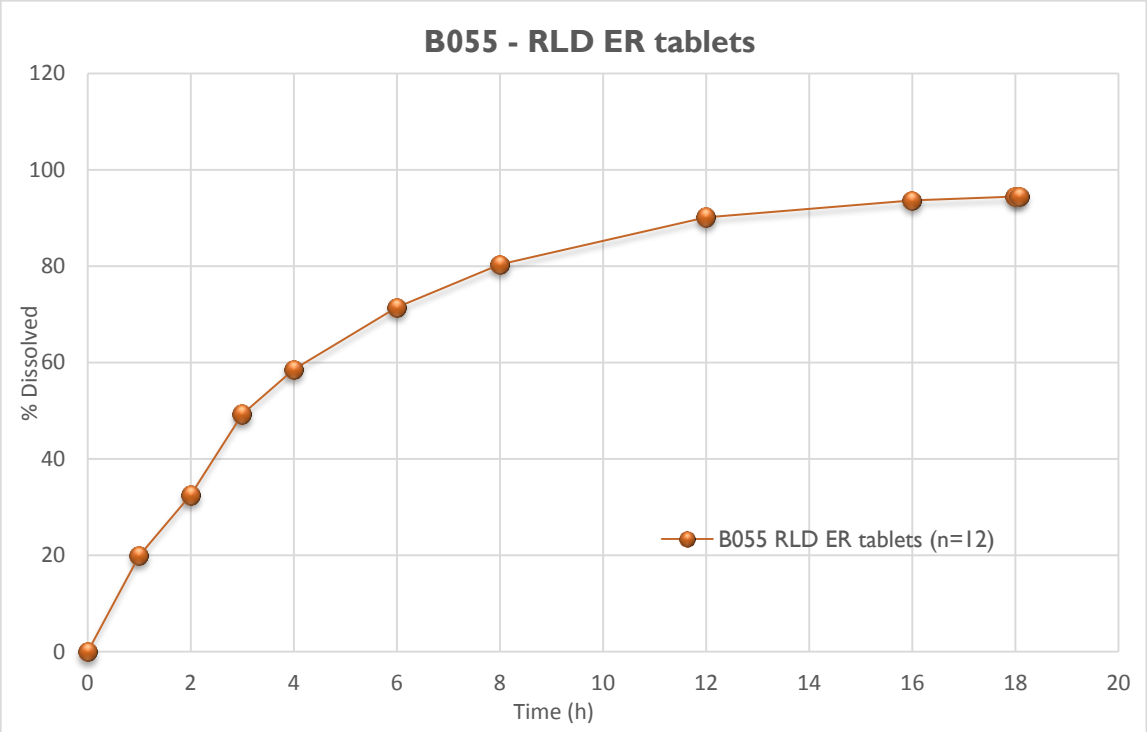

Figure 13 Dissolution profiles of Blue055 – RLD ER tablets, in OGD medium.

3.2 Quality Target Product Profile (QTPP) and Critical Quality Attributes (CQA)

The pharmaceutical development of Blue055 begins with identification of the desired dosage form and performance attributes through the target product profile (Table 12). The pharmaceutical target profile for Blue055 was defined based on the properties of the drug substance and characterization of the RLD product.

Table 12 QTPP for drug product.

QTPP elements	Target
Dosage Form	Tablets
Dosage Design	Extended-release tablets
Dosage Strength	≤2.0%
Route of administration	Oral
Appearance	White, non-scored, bi-convex with debossing on one side
Assay	95-105%
Degradation products	
Any individual unspecified impurity	NMT 0.2%
Total Impurities	NMT 2.0%
Water content	Report value
Content Uniformity	85%-115%
Hardness	20-120N
Friability	NMT 1.0%
Dissolution	2h: 25-45% 4h: 50-70% 8h: 70-90% NLT 80% (Q) at 18 hours
Microbiology	Total yeasts and moulds count: NMT 10^2 CFU/g *E. coli:* Absent/g

As discussed above, the QTPP form the basis for determining the CQAs, critical process parameters (CPPs), and Control Strategy. From the target product profile, the initial CQAs, which were used to define satisfactory quality, were identified. The definition was based on empirical evidence derived from previous experimentation as well as similar experiences with other products. Table 13 indicates which quality attributes were classified as CQAs.

Table 13 Critical Quality Attributes and justification.

CQA	Justification
Assay	Since it is a low dosage pharmaceutical form, this parameter should be monitored to guarantee the respective efficacy and safety.
Blend Uniformity	Since is a low dosage pharmaceutical form, it is critical to evaluate whether DS is evenly distributed.
Dissolution	Since is an extended release dosage pharmaceutical form, it is critical to evaluate the respective *in vitro* performance.
Hardness	This parameter may affect the DS release.
Degradation products	Degradation products may affect the expiry date of the final product.

3.3 Selection of formulation

From the preliminary studies carried out at the laboratory scale formulation, F1 (Table 14) was selected as Leading formulation for the systematic study of the influence of different formulation and process variables, since it provided acceptable performance, and pharmacotechnical properties when compared with RLD. F1 presented a closer similarity with RLD. This was evaluated by calculating the similarity factor, f_2 (see section 3.6), for both dissolution profiles, which was of 85.64 (Figure 14).

Due to the existing confidentiality terms, it is not possible to reveal the qualitative and quantitative composition of the formulation, only the class and the limits used for each excipient and DS (Table 14).

Table 14 Composition of Leading formulation, F1

Ingredient	**%/tablet**
Drug Substance	≤2
Diluent	20-40
HPMC (ER Agent)	30-50
Surfactant	0-2
Disintegrant	20-40
Glidant	0-1
Lubricant	0.25-3
Total	**100.0**

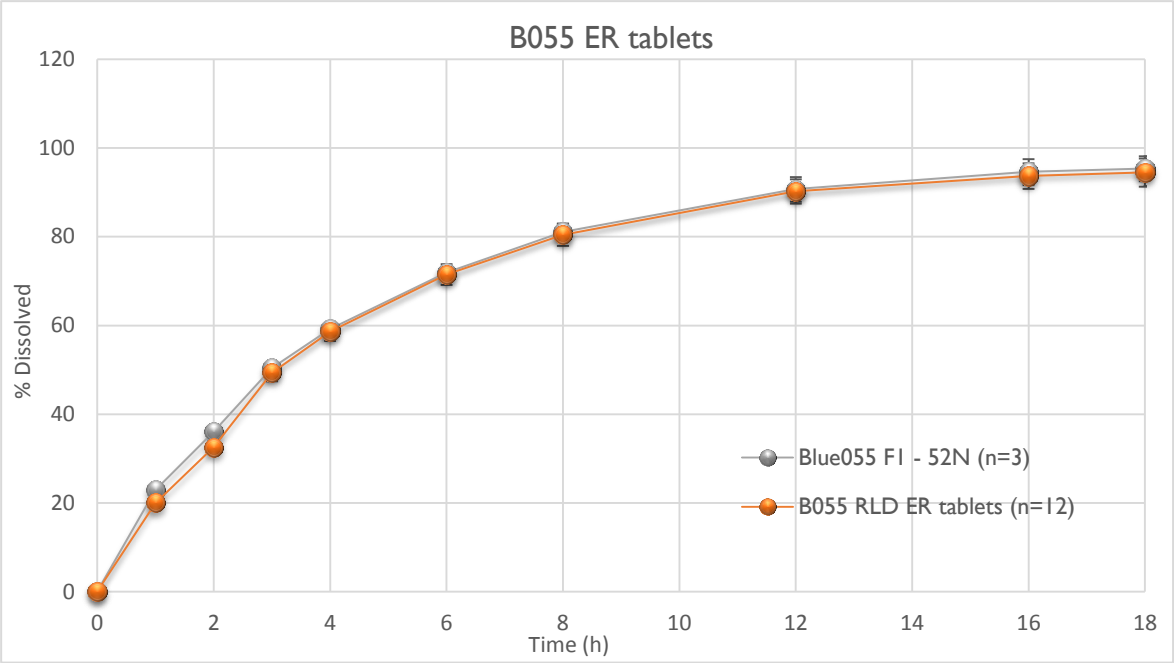

Figure 14 Dissolution profiles of Blue055 RLD ER tablets *versus* Blue055 – F1, in OGD medium.

For all the reasons presented above, the F1 was proposed as **Leading formulation** and was selected as basis for the Design of Experiments.

In order to perform the studies of the formulation variables, intermediate parameters were tested based on the Leading formulation (F1), with the purpose of obtaining an optimized formulation.

3.4 Selection of Manufacturing Process

The manufacturing process selection was based on previous studies performed at laboratorial scale, comprising direct compression and dry granulation, either using roller compaction or slugging.

Dry granulation was selected, because it led to the better results in terms of homogeneity of the drug substance, which is considered a critical attribute, since it is a low dosage pharmaceutical form.

Briefly, the manufacturing process consists of an initial blend, followed by dry granulation to obtain the final granules, which are then lubricated and tabletted. A summary of the manufacturing process is presented in the following flowchart (Figure 15):

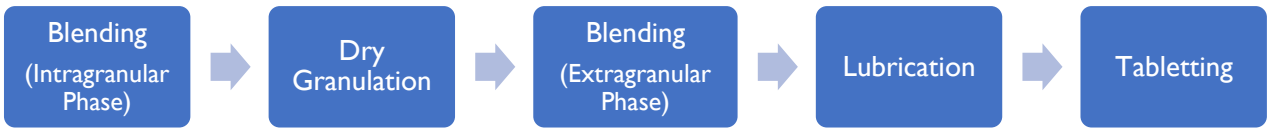

Figure 15 Manufacturing process flowchart.

In order to obtain a better understanding of process variables and find a suitable manufacturing process, intermediate parameters were further tested based on the initial manufacturing process.

3.5 Initial risk assessment

A risk assessment of the overall formulation and process was performed to identify the high risk steps that may affect the CQAs of the final drug product. Using the attributes given above, the team organized a set of CPPs utilizing a risk-based approach to all of the unit operations. This was based on previous experience with this project as well as other similar dosage forms with equivalent or similar manufacturing technology and formulation. The variables were then investigated in order to understand the manufacturing process and formulation variables to develop a control strategy to reduce the risk of out of specification results.

An Ishikawa diagram was used to identify all potential variables on manufacturing process, such as raw materials, blending parameters, dry granulation parameters, compression parameters, and environmental factors, which can have an impact on product quality that can affect the CQAs. Ishikawa diagram helped to assess the risk in the manufacturing process steps (Figure 16).

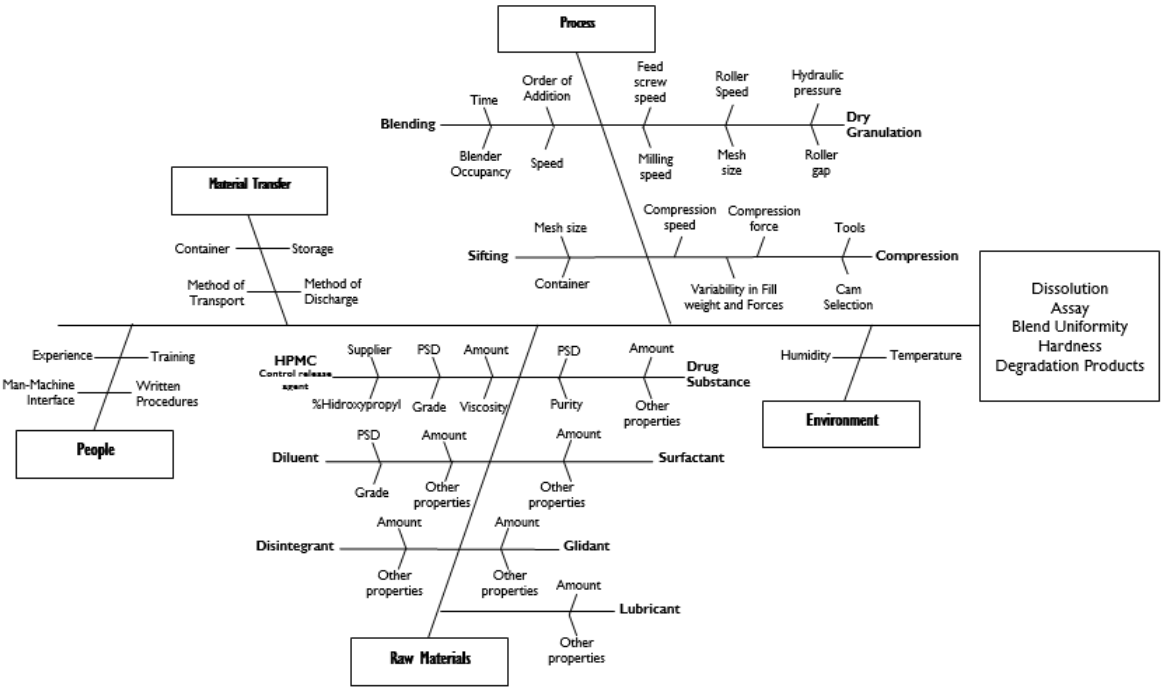

Figure 16 Ishikawa diagram for manufacturing process.

Since handling and production are done under GMP conditions, the environment was not considered critical.

A risk assessment for the variables was performed after defining a Leading formulation composition and process and results are depicted in table 17. This identifies the

formulation and manufacturing process parameters, which require further investigation to determine the appropriate control strategy.

Table 15 Initial risk assessment..

			Drug Product Quality Attributes (CQA)				
		Material Attributes	Assay	BU	Degradation Products	Dissolution	Hardness
Drug Substance		Solid State Form	Low	Low	Low	Low	Low
		Particle Size Distribution	High	High	Low	Medium	Low
		Hygroscopicity	Low	Low	Low	Low	Low
		Solubility	Low	Low	Low	Low	Low
		Moisture Content	Low	Low	Medium	Low	Low
		Residual Solvent	Low	Low	Low	Low	Low
		Process Impurities	Low	Low	Low	Low	Low
		Chemical Stability	Low	Low	Medium	Low	Low
		Flow Properties	Low	Low	Low	Low	Low
Formulation Variables	**Diluent**	Amount	Low	Medium	Low	Medium	Low
		Grade and PSD	Low	High	Low	Medium	Low
	HPMC	Amount	Low	Medium	Low	High	Medium
		Grade	Low	Low	Low	High	Medium
		PSD	Low	Medium	Low	Medium	Low
		% Hydroxypropyl	Low	Low	Low	High	Low
		Supplier	Low	Low	Low	Low	Low
	Disintegrant	Amount	Low	Medium	Low	Medium	Medium
	Surfactant	Amount	Low	Low	Low	High	Low
	Glidant	Amount	Low	Low	Low	Low	Low
	Lubricant	Amount	Low	Low	Low	Medium	Low
Manufacturing Process Variables	**Sifting of Raw Materials**	Mesh Size	Low	Low	Low	Low	Low
	Intragranular Phase Blending	Blender Occupancy	Low	Low	Low	Low	Low
		Blending Time	Medium	Medium	Low	Low	Low
	Intragranular Lubrication	Blending Time	Medium	Medium	Low	Medium	Low
	Dry Granulation	Screw feeder speed	Low	Low	Low	Low	Low
		Roller speed	Low	Low	Low	Medium	Low
		Hydraulic pressure	High	Low	High	High	Low
		Roller gap	High	Low	High	High	Medium
		Mesh size	Low	High	Low	High	Medium
		Milling Speed	Low	Low	Low	Low	Low
	Blending	Blending time	Low	Medium	Low	Low	Low
	Lubrication	Blending time	Low	Medium	Low	Medium	Low
	Compression	Compression speed	Low	Medium	Low	Low	Low
		Compression force	Low	Low	Low	High	Medium

Each formulation component characteristic and manufacturing process parameter that has an identified high risk to impact the drug product CQAs was further evaluated and studied to reduce the risk.

3.6 Considerations for the Interpretation of the Results

For the results obtained in the following sections, and as previously referred (Table 13), the following CQAs were considered:

- Assay
- Dissolution
- Hardness
- Blend uniformity
- Degradation products

All the selected CQAs were checked for compliance according to the established specifications in the QTPP (Table 12).

Assay, dissolution and hardness were taken into account for the statistical evaluation of the tests performed. The statistical evaluation was made using the analysis of differences between the averages with t-Student test, two-tailed, with a significance level of 0.05, in Excel® 2010 software.

Due to the reduced number of samples from assay (n=2), it was not possible to perform the statistical treatment because it influenced the robustness of the statistical method used. As such, assay results were mainly analyzed on the basis meeting the specification (QTPP), with the aim to obtain a 100% target.

The similarity factor (f_2) for the dissolution tests performed was calculated, since the main objective is to have a generic product that matches the RLD behavior.

The similarity factor f_2, was determined according to the Guideline on the Investigation of Bioequivalence (EMA, 2010) following the equation:

$$f_2 = 50 \,.\, log\left[\frac{100}{\sqrt{1 + \frac{\sum_{t=1}^{t=n}[R\,(t) - T\,(t)]^2}{n}}}\right]$$

Note that not all conditions were followed, since only three individual values for every time point for each formulation was performed and more than one mean value of >85% dissolved for each formulations was considered.

According to the guideline, an f_2 value between 50 and 100 suggests that the two dissolution profiles are similar.

Blend uniformity was considered, because when developing a low dosage pharmaceutical form, it is critical to evaluate whether DS is evenly distributed. Since it is not possible to establish this comparison with RLD, the Leading formulation was used as reference.

Degradation products were not taken into account for statistical evaluation; however, they were checked for compliance with the specification, assuring the safety of the product.

Whenever possible, a DoE analysis, comprising full factorial, was performed.

3.7. Drug Product Formulation Development

Taking into account the composition selection mentioned above, it was decided to study different formulation variables to gather a deeper understanding on their impact on the selected CQA.

The formulation variables, termed as critical material attributes (CMA) that were the object of study were: DS particle size, diluent grade, HPMC grade, HPMC Supplier, proportions of the major excipients (diluent, disintegrant and HPMC), proportions of the minor excipients (Surfactant, Glidant and Lubricant).

3.7.1. Drug Substance

Due to the presence of an active substance in a low dosage in the pharmaceutical form, it was important to start investigating the impact of an attribute of the drug substance. For that, it was important to study the impact of particle size distribution (PSD) of DS and analyse the influence at the level of the CQAs.

3.7.1.1 Drug Substance PSD

In order to study the impact of the DS particle size on the drug product performance, four tests were performed using the same formulation and manufacturing process of the previous Leading formulation F1, with the exception of DS particle size (Table 16).

Table 16 Particle size distribution of the DS used for F2-F5.

Test	F2	F3	F4	F5	F1
DS PSD (µm) D_{90}	PSD_2	PSD_3	PSD_4	PSD_5	PSD_1

The test prototypes were compared with the RLD and F1. The summary of the results obtained is presented below (Table 17):

Table 17 Blue055 ER tablets, F2-F5 analytical results with comparison to F1 and RLD.

Test		F2	F3	F4	F5	F1	RLD
Hardness (Mean, N)		55	57	56	59	52	55
Blend Uniformity (Mean±%RSD)		97.6±1.0	98.6±9.9	85.0±3.7	102.6±1.0	93.1±2.0	-
Assay (%)		103.2	107.0	107.0	103.7	101.3	99.2
Degradation products (Total Impurities, %)		ND	ND	ND	ND	ND	0.12
Dissolution (%dissolved)	**2h**	36	31	32	37	36.1	32.2
	4h	57	54	54	59	59.2	59.7
	8h	80	75	79	82	81.0	81.8
	18h	93	90	98	97	95.4	95.4

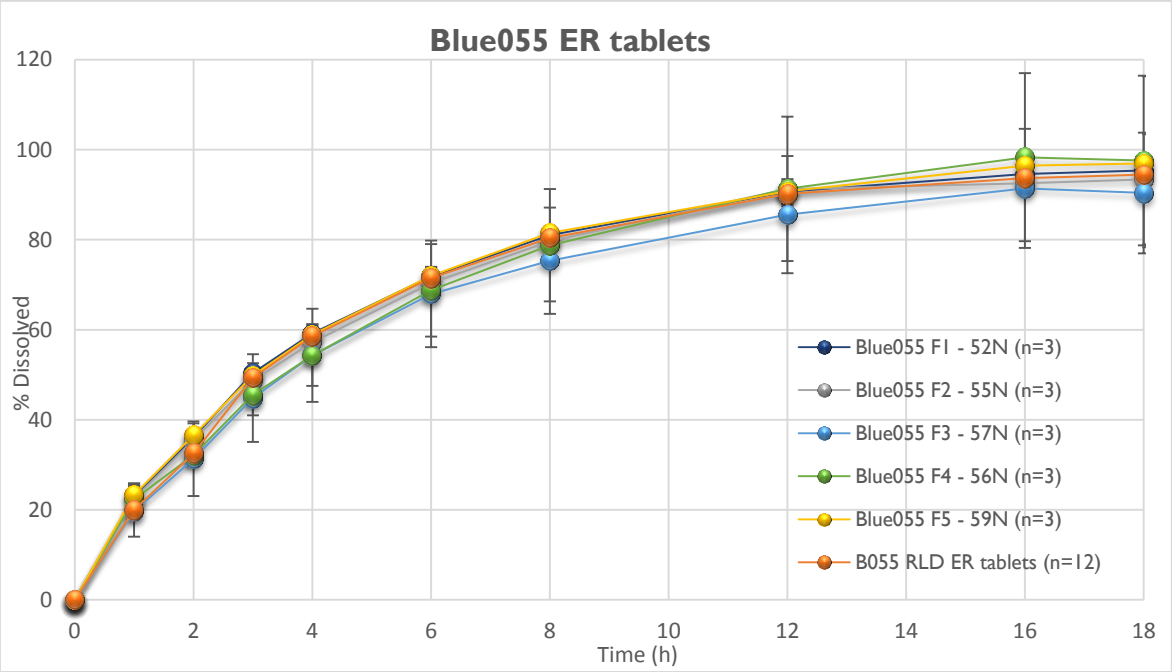

Figure 17 Dissolution profiles of F2 – F5 *versus* F1 *versus* RLD, in OGD medium.

The results for the comparison of the tests with the RLD are presented below (Table 18):

Table 18 Results of the statistical analysis and f2 of the tests compared to RLD.

Test		Assay SPEC 95-105% RSD NMT 5.0%	Dissolution SPEC 18 hours: NLT 80% (Q)	Assay t-test	Hardness t-test	Dissolution f2	
DS PSD	F1	C	C	I	0	0	85.64
	F2	C	C	0	0	0	86.24
	F3	NC	C	0	0	0	71.02
	F4	NC	C	0	0	0	74.99
	F5	C	C	I	0	0	80.72

C – Complies with Specification; NC – Does not Comply with Specification; 0 - not significantly different; I - significantly different.

Although the results have shown a statistically significant difference for the assay, it should be noted that they are compliant with the specification.

Regarding the DS particle size evaluation, it is clear that test F4 led to the poorest blend uniformity (85.0%). Tests F3 and F4 exhibited the worse results, being not compliant with the established specification.

Hardness values obtained are quite similar when compared with the Leading formulation.

In what concerns dissolution results, there is no significant difference between tests F2-F4 and Leading formulation.

Blend uniformity (BU) also reflects the previous observations found for the assay, with DS PSD F3 and F4 leading to heterogeneity in the mixture (Table 19).

Table 19 Results of the statistical analysis of the BU compared to F1.

Test		SPEC Blend Uniformity SPEC 95-105% RSD NMT 5.0%	t-test
DS PSD	F2	C	I
	F3	NC	0
	F4	NC	I
	F5	C	I

C – Complies with Specification; NC – Does not Comply with Specification; 0 – not significantly different; I – significantly different.

In conclusion, DS particle size has a great impact on blend uniformity and assay, but not on the dissolution profile.

3.7.2 Excipients

Most, if not all, drug products could not be made without the use of excipients also called inactive ingredient. An inactive ingredient is any component of a drug product other than the active ingredient. For dissolution studies of a drug, the excipients used in the formulation, despite not exerting a therapeutic effect, may influence the dissolution of the drug in the biological environment and, consequently, its bioavailability. The FDA provides information on inactive ingredients present in FDA-approved drug products, included in the Inactive Ingredient Database, which can be used by industry as an aid in developing drug products.

For the following studies, the excipients which form part of the formulation will be taken into account.

3.7.2.1 Diluent

Diluent is one of the excipients used in the highest amount in the formulation and may have an impact on the pharmacotechnical characteristics of the powder mixture and DS release, as well as on the tablet hardness. For this reason, the impact of Diluent grade was evaluated.

3.7.2.1.1 Impact of Diluent Grade

In order to study the impact of the diluent grade on the DP performance, three tests were performed using the same formulation and manufacturing process of the previous Leading formulation – F1, with the exception of the diluent PSD characteristics (Table 20). These tests are meant to be also compared with the RLD and Leading formulation (Table 21).

Table 20 Grade of the Diluent used for F6-F8.

Test	F6	F7	F8	F1
Diluent grade	Grade 2 *Spray dried with high PSD*	Grade 3 *Spray dried with low PSD*	Grade 4 *Milled with low PSD*	Grade 1 *Milled with high PSD*

The summary of the results obtained is presented below:

Table 21 Blue055 ER tablets, F6-F8 analytical results with comparison to F1 and RLD.

Test		F6	F7	F8	F1	RLD
Hardness (Mean, N)		37	43	41	52	55
Blend Uniformity (%Mean±%RSD)		94.5±1.5	94.6±1.9	90.6±1.9	93.1±2.0	-
Assay (%)		101.7	101.8	98.8	101.3	99.2
Degradation products (Total Impurities, %)		ND	≤0.1	≤0.1	ND	0.12
Dissolution (%dissolved)	**2h**	36.6	36.0	32.8	36.1	32.2
	4h	61.6	60.7	50.8	59.2	59.7
	8h	83.2	82.2	75.0	81.0	81.8
	18h	94.1	94.4	91.3	95.4	95.4

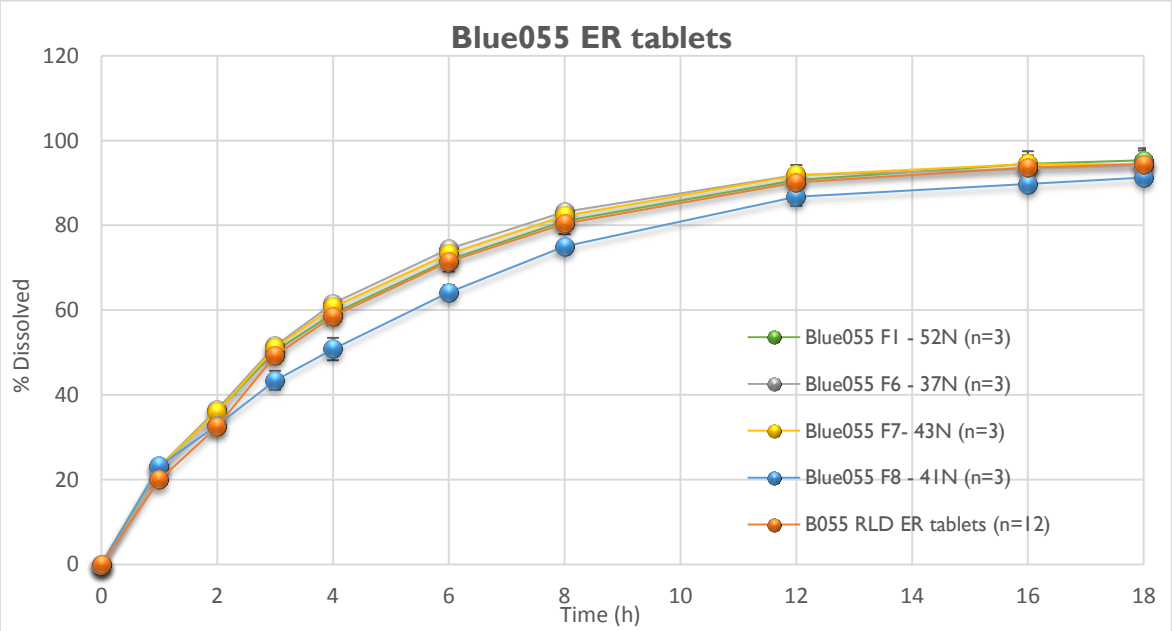

Figure 18 Dissolution profiles of F6-F8 *versus* F1 *versus* RLD, in OGD medium.

The results for the comparison of the tests with the RLD are presented below (Table 22):

Table 22 Results of the statistical analysis and f2 of the tests compared to RLD.

Test		Assay SPEC 95-105% RSD NMT 5.0%	Dissolution SPEC 18 hours: NLT 80% (Q)	Assay t-test	Hardness t-test	Dissolution f2
Diluent grade	F1	C	C	I	0	0	85.64
	F6	C	C	I	I	0	77.78
	F7	C	C	I	I	0	81.63
	F8	C	C	I	I	0	64.67

C – Complies with Specification; NC – Does not Comply with Specification; 0 - not significantly different; I - significantly different.

Regarding the diluent grade, F8 led to lower blend uniformity and tablet assay, which can be explained by the use of a higher particle size leading to lower homogeneity on the distribution of the DS within the final mixture. This way, it is advisable to use lactose with smaller particle size distribution.

The use of diluent with lower PSD seems to lead to higher resistance to crushing of the tablets.

On the other hand, in the case of F6 and F7, blend uniformity and tablets assay were not affected by diluent grade. From the obtained data, the homogeneity of mixture was shown to be affected in the case of using a spray dried or a milled diluent.

Hardness values obtained are statistically lower, when compared to RLD, with exception of the Leading formulation.

Dissolution results were found to be very comparable to RLD and between the different grades, with the exception of trial F18. This fact is explained by the use of diluent having higher PSD, which lead to a slightly slower dissolution and lower assay.

This indicates that, the diluent having low particle size should be used.

3.7.2.2 HPMC

HPMC is a release-modulator agent used. Hence, its amount influences the dissolution rate of the final dosage form and, therefore, optimization of the amount of HPMC in the formulation is crucial.

HPMC is generally available as grades with differences in viscosities. Note that differences in viscosity might influence the dissolution rate of the final dosage form, as mentioned in section 1.1.5.8. Thus, the suitability of the HPMC grade needs to be inspected during the development work.

3.7.2.2.1 Impact of HPMC Grade

To study the impact of the HPMC grade on the DP performance, two tests were performed using the same formulation and manufacturing process of the previous Leading formulation F1, with the exception of the HPMC grade (Table 23). These tests are expected to be also compared with RLD.

Table 23 Grade of the HPMC used for F9-F10.

Test	F9	F10	F1
HPMC grade	Grade Y	Grade Z	Grade X

The summary of the results obtained is presented below (Table 24):

Table 24 Blue055 ER tablets, F9-F10 analytical results with comparison to F1 and RLD.

Test		F9	F10	F1	RLD
Hardness (Mean, N)		64	72	52	55
Blend Uniformity (Mean±%RSD)		97.1±0.6	97.7±3.1	93.1±2.0	-
Assay (%)		103.4	104.7	101.3	99.2
Degradation products (Total Impurities, %)		ND	≤0.1	ND	0.12
Dissolution (%dissolved)	**2h**	37.6	37.9	36.1	32.2
	4h	59.2	62.9	59.2	59.7
	8h	82.8	85.9	81.0	81.8
	18h	95.0	100.0	95.4	95.4

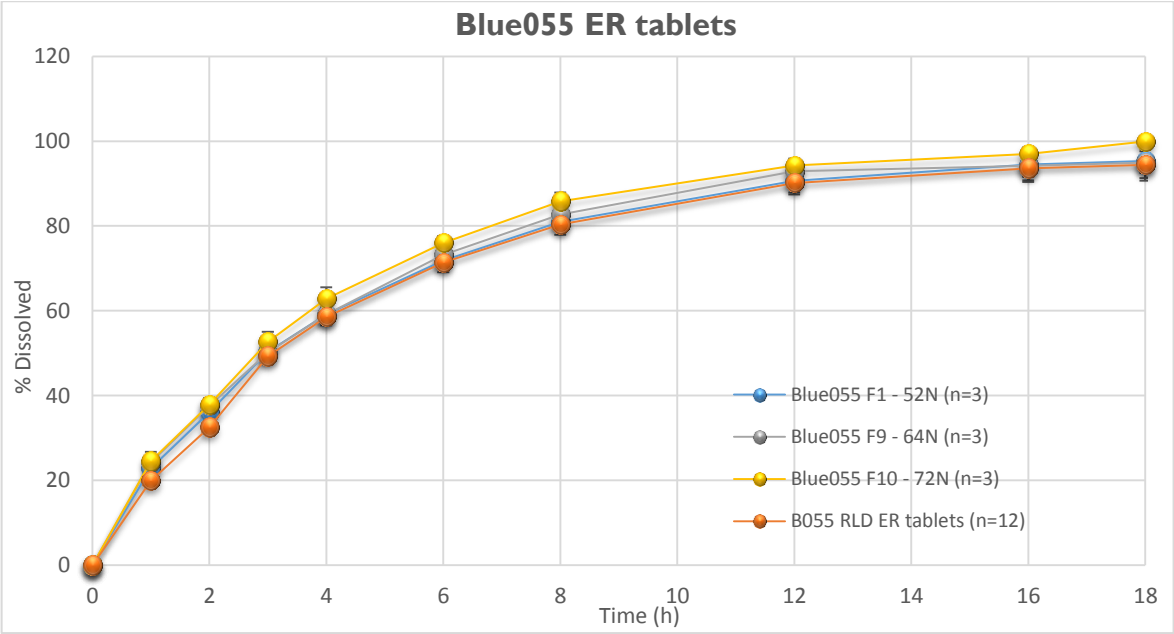

Figure 19 Dissolution profiles of F9-F10 *versus* F1 *versus* RLD, in OGD medium.

The results for the comparison of the tests with the RLD are presented below (Table 25):

Table 25 Results of the statistical analysis and f2 of the tests compared to RLD

Test		Assay SPEC 95-105% RSD NMT 5.0%	Dissolution SPEC 18 hours: NLT 80% (Q)	Assay t-test	Hardness t-test	Dissolution t-test	Dissolution f2
HPMC grade	F1	C	C	I	0	0	85.64
	F9	C	C	I	0	0	77.66
	F10	C	C	I	I	I	66.40

C – Complies with Specification; NC – Does not Comply with Specification; 0 - not significantly different; I - significantly different.

Regarding the HPMC grade, both tests (F9 and F10) led to adequate blend uniformity and tablet assay.

Hardness values tended to be higher for the formulations based on HPMC with Grade Y when compared to RLD.

Dissolution results of test F9 were found to be similar to Leading formulation, while those of test F10 were faster.

HPMC Grade X, led to a dissolution profile closer to RLD, which support the selection of this HPMC Grade on F1.

3.7.2.2.2 Impact of HPMC properties

The impact of different HPMC critical attributes, specifically, viscosity, PSD and hydroxypropyl content, on the DP performance was further inspected in a fine-tuning analysis. Additionally, these variables were tested according to the HPMC provided by two different suppliers.

HPMC - Properties from Supplier A

In order to study the impact of the HPMC critical attributes (viscosity, PSD and hydroxypropyl content) from Supplier A on the DP performance, six tests were performed using the same formulation and manufacturing process of the previous Leading formulation, with the exception of HPMC batch (Table 26). These tests are also meant to be compared with the Leading formulation (F1).

Table 26 Critical parameters of HPMC used in F11-F16.

Test	HPMC Supplier A			
	Viscosity (mPa.s)	**PSD (d_{90})**	**Hydroxypropyl content (%)**	**Attribute**
F11	82841	112	10.5	Low Viscosity
F12	130308	102	10.5	High Viscosity
F13	119270	84	10.2	Low PSD
F14	105705	133	10.6	High PSD
F15	122982	116	9.7	Low Hydroxypropyl
F16	96897	103	10.9	High Hydroxypropyl
F1	121894	109	10.2	Central Point

The summary of the results obtained is presented below:

Table 27 Blue055 ER tablets, F11-F16 analytical results with comparison to F1 and RLD..

Test		F11	F12	F13	F14	F15	F16	F1	RLD
Hardness (Mean, N)		54	56	51	62	62	52	52	55
Blend Uniformity (Mean±%RSD)		84.9±0.7	92.9±0.8	96.2±2.7	97.2±0.9	95.5±0.7	97.0±0.9	93.1±2.0	-
Assay (%)		107.4	100.6	102.3	103.3	102.8	102.1	101.3	99.2%
Degradation products (Total Imp., %)		≤0.1	≤0.1	≤0.1	≤0.1	≤0.1	≤0.1	ND	0.12
Dissolution (%dissolved)	**2h**	32	34	35	37	35	34	36.1	32.2
	4h	52	56	58	61	59	58	59.2	59.7
	8h	71	76	78	82	82	80	81.0	81.8
	18h	83	89	91	95	95	94	95.4	95.4

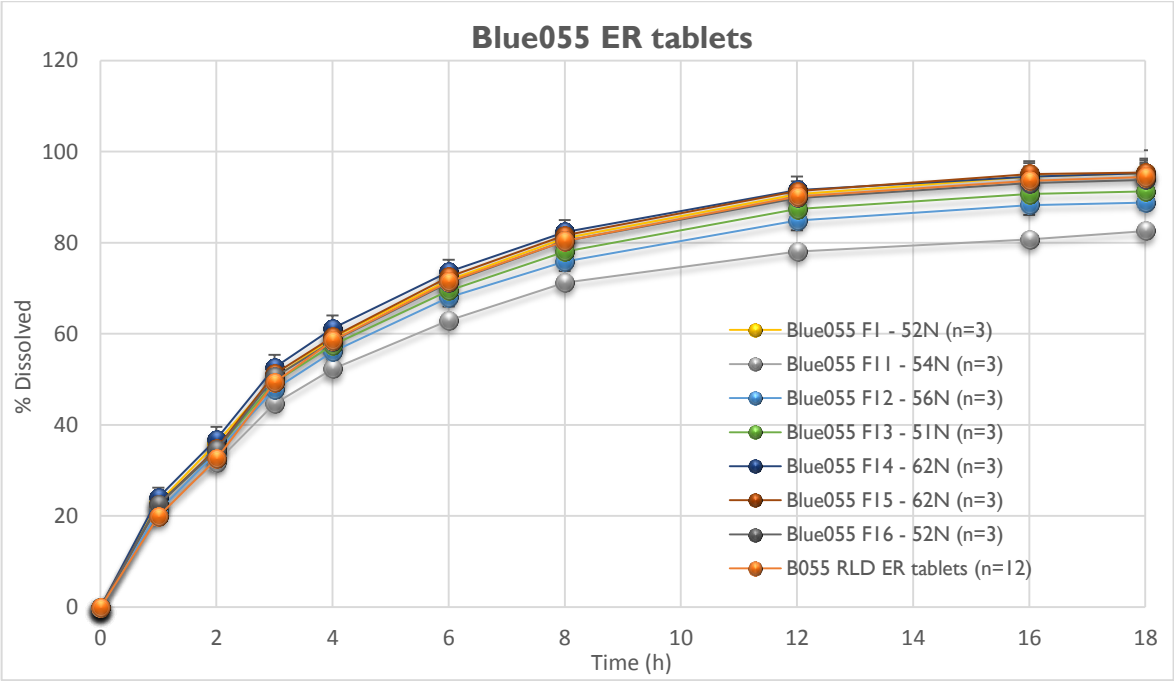

Figure 20 Dissolution profiles of F11-F16 *versus* F1 *versus* RLD, in OGD medium.

The results for the comparison of the tests with the RLD are presented below (Table 28):

Table 28 Results of the statistical analysis and f2 of the tests compared to RLD

Test		Assay SPEC 95-105% RSD NMT 5.0%	Dissolution SPEC 18 hours: NLT 80% (Q)	Assay t-test	Hardness t-test	Dissolution t-test	Dissolution f2
HPMC Supplier A	F1	C	C	I	0	0	85.64
	F11	NC	C	0	0	I	53.04
	F12	C	C	I	0	I	70.18
	F13	C	C	I	0	0	80.18
	F14	C	C	I	0	0	76.80
	F15	C	C	I	0	0	86.15
	F16	C	C	I	0	0	90.34

C – Complies with Specification; NC – Does not Comply with Specification; 0 – not significantly different; I – significantly different.

The results of BU for the comparison of the tests with the F1 are presented below (Table 29):

Table 29 Results of the statistical analysis of the BU compared to F1.

Test		SPEC Blend Uniformity SPEC 95-105% RSD NMT 5.0%	t-test
DS PSD	F11	NC	I
	F12	NC	0
	F13	C	0
	F14	C	0
	F15	C	0
	F16	C	0

C – Complies with Specification; NC – Does not Comply with Specification; 0 – not significantly different; I – significantly different.

Regarding the HPMC critical attributes (Viscosity, PSD and hydroxypropyl content) from Supplier A, test F11 led to lower blend uniformity and the highest tablet assay, both out of the defined specification (QTPP).

Dissolution results were found to be similar to RLD, with the exception of test F11. This indicates that the viscosity is a crucial parameter that has to be monitored.

Nevertheless, the product is robust to changes in what concerns the HPMC PSD and hydroxypropyl content. Hydroxypropyl groups are of relatively hydrophilic nature, contributing significantly to the rate of hydration of the polymer, unlike the methoxyl groups, which are relatively hydrophobic.

Thus, viscosity seems to be the attribute with higher impact, with an intermediate level resulting in dissolution profiles closer to the RLD. In turn, PSD and hrydroxypropyl content were not discriminatory variables.

HPMC - Properties from Supplier B

To study the impact of the of HPMC critical attributes (viscosity, PSD and hydroxypropyl content) provided by the Supplier B on the DP performance, seven tests were performed using the same formulation and manufacturing process of the previous Leading formulation, with the exception of HPMC batch (Table 30). These tests are also meant to be compared with the Leading formulation (F1).

Table 30 Critical parameters of HPMC used in F17-F23.

Test	HPMC Supplier B			
	Viscosity (mPa.s)	**PSD (d_{90})**	**Hydroxypropyl content (%)**	**Attribute**
F17	66400	89	9.5	Low Viscosity
F18	122000	113	9.5	High Viscosity
F19	80000	94	9.5	Low PSD
F20	93800	149	9.5	High PSD
F21	101000	89	7.9	Low Hydroxypropyl
F22	94200	100	10.6	High Hydroxypropyl
F23	89800	107	9.5	Central Point
F1	121894	109	10.2	-

The summary of the results obtained is presented below:

Table 31 Blue055 ER tablets, F17-F23 analytical results with comparison to F1 and RLD.

Test		F17	F18	F19	F20	F21	F22	F23	F1	RLD
Hardness (Mean, N)		61	74	65	45	53	52	47	52	55
Blend Uniformity (Mean±%RSD)		99.9 ±1.0	96.9 ±0.8	97.4 ±0.1	102.4 ±1.6	97.2 ±1.4	97.0 ±0.9	96.6 ±0.7	93.1±2.0	-
Assay (%)		104.4	105.7	106.5	104.7	99.1	99.6	100.1	101.3	99.2
Degradation products (Total Imp., %)		≤0.1	≤0.1	≤0.1	≤0.1	≤0.1	≤0.1	≤0.1	ND	0.12
Dissolution (%dissolved)	**2h**	37	38	37	36	34	37	36	36.1	32.2
	4h	60	62	58	60	58	60	61	59.2	59.7
	8h	82	84	81	83	80	83	84	81.0	81.8
	18h	99	100	95	99	94	98	99	95.4	95.4

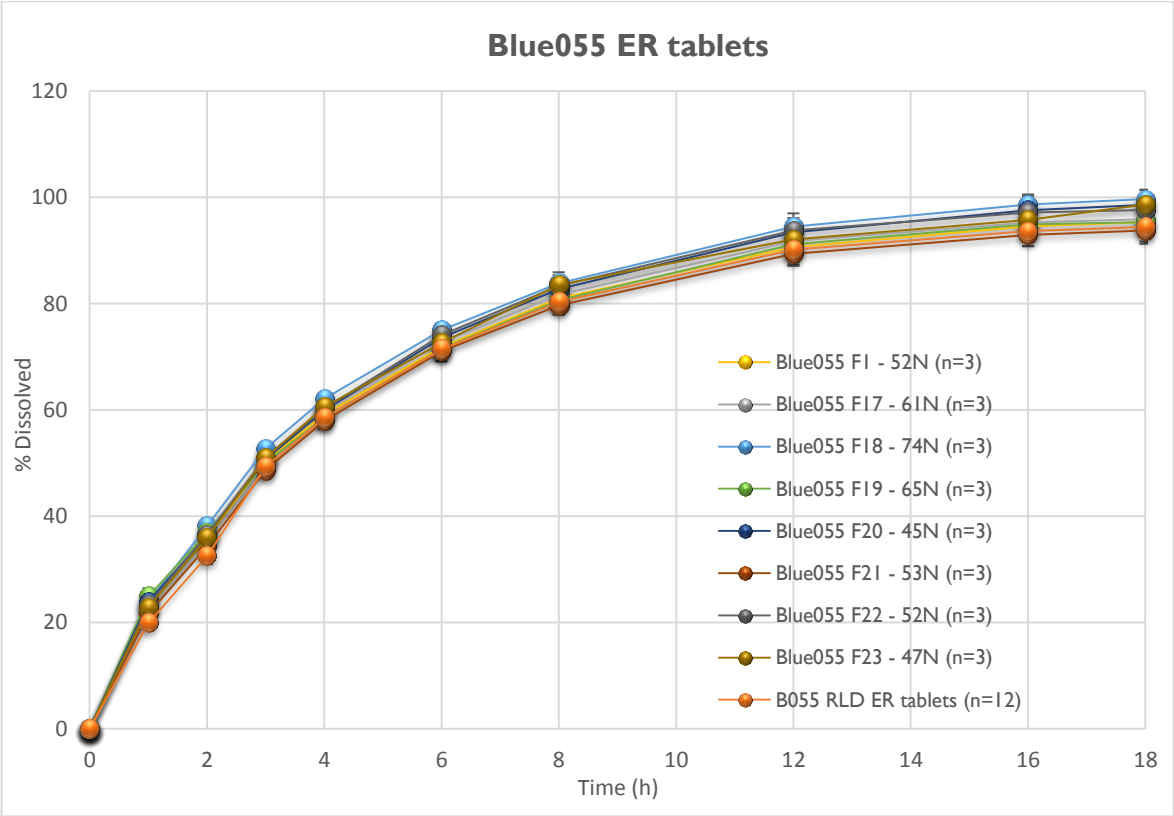

Figure 21 Dissolution profiles of F17-F23 *versus* F1 *versus* RLD, in OGD medium

The results for the comparison of the tests with the RLD are presented below (Table 32):

Table 32 Results of the statistical analysis and f2 of the tests compared to RLD

Test		Assay SPEC 95-105% RSD NMT 5.0%	Dissolution SPEC 18 hours: NLT 80% (Q)	Assay t-test	Hardness t-test	Dissolution t-test	Dissolution f2
HPMC Supplier B	F1	C	C	I	0	0	85.64
	F17	C	C	I	0	0	81.53
	F18	NC	C	I	I	I	67.59
	F19	NC	C	I	0	0	79.83
	F20	C	C	I	0	0	74.04
	F21	C	C	0	0	0	92.46
	F22	C	C	0	0	0	74.52
	F23	C	C	0	0	0	77.13

C – Complies with Specification; NC – Does not Comply with Specification; 0 – not significantly different; I – significantly different.

The results of BU for the comparison of the tests with the F1 are presented below (Table 33):

Table 33 Results of the statistical analysis of the BU compared to F1.

Test		SPEC Blend Uniformity SPEC 95-105% RSD NMT 5.0%	t-test
HPMC Supplier B	F17	C	I
	F18	C	0
	F19	C	0
	F20	C	I
	F21	C	0
	F22	C	0
	F23	C	0

C – Complies with Specification; NC – Does not Comply with Specification; 0 – not significantly different; I – significantly different.

Regarding the HPMC critical attributes (Viscosity, PSD and hydroxypropyl content) from Supplier B, all tests lead to adequate blend uniformity and test F18 and F19 resulted in a higher tablet assay, also out of specification.

Dissolution results were found to be very similar to RLD, with the exception of F18, which correspond to higher HPMC viscosity.

Hardness values were found to be between 45-74N, showing more heterogeneity than in the tests performed with the HPMC from Supplier A.

3.7.2.3 Impact of Proportions of the Major Excipients

In order to study the impact of different diluent, disintegrant and HPMC proportions on the DP performance, six tests were performed using the same formulation and manufacturing process of the previous Leading formulation, with the exception of diluent, disintegrant and HPMC (diluent was used to compensate for the other excipients in formulation). These tests are meant to be also compared with the Leading formulation (F1).

For the DoE, the type of design chosen was a Custom Design in a single block and the list of experiments to be performed was made using the JMP® software and is shown in Table 34. For this design, different amount ranges for each excipient (%/tablet) were considered, according to Table 14 (section 3.3). These comprised: %Diluent: between 20-40; %Disintegrant: between 20-40 and %HPMC: between 30-50.

Table 34 Custom design experiments retrieved from JMP.

Test	Diluent: %	Disintegrant: %	HPMC %
F24	40.00	20.00	40.00
F25	20.00	40.00	40.00
F26	40.00	30.00	30.00
F27	30.00	20.00	50.00
F28	30.00	40.00	30.00
F29	20.00	30.00	50.00

The summary of the results obtained is presented below:

Table 35 Blue055 ER tablets, F24-F29 analytical results with comparison to F1 and RLD.

Test		F24	F25	F26	F27	F28	F29	F1	RLD
Hardness (Mean, N)		63	38	48	56	37	43	52	55
Blend Uniformity (Mean±%RSD)		96.2±1.0	92.0±1.7	95.7±1.2	95.2±0.8	95.5±1.8	96.1±2.5	93.1±2.0	-
Assay (%)		101.6	98.7	104.4	99.4	103.7	102.2	101.3	99.2
Degradation products (Total Imp., %)		ND	≤0.1	≤0.1	≤0.1	≤0.1	ND	ND	0.12
Dissolution (%dissolved)	**2h**	34.1	32.9	36.4	33.7	39.8	34.2	36.1	32.2
	4h	55.3	56.7	61.3	53.6	62.1	57.5	59.2	59.7
	8h	79.3	77.7	86.8	72.3	81.3	77.8	81.0	81.8
	18h	97.3	90.4	99.3	86.4	90.3	94.9	95.4	95.4

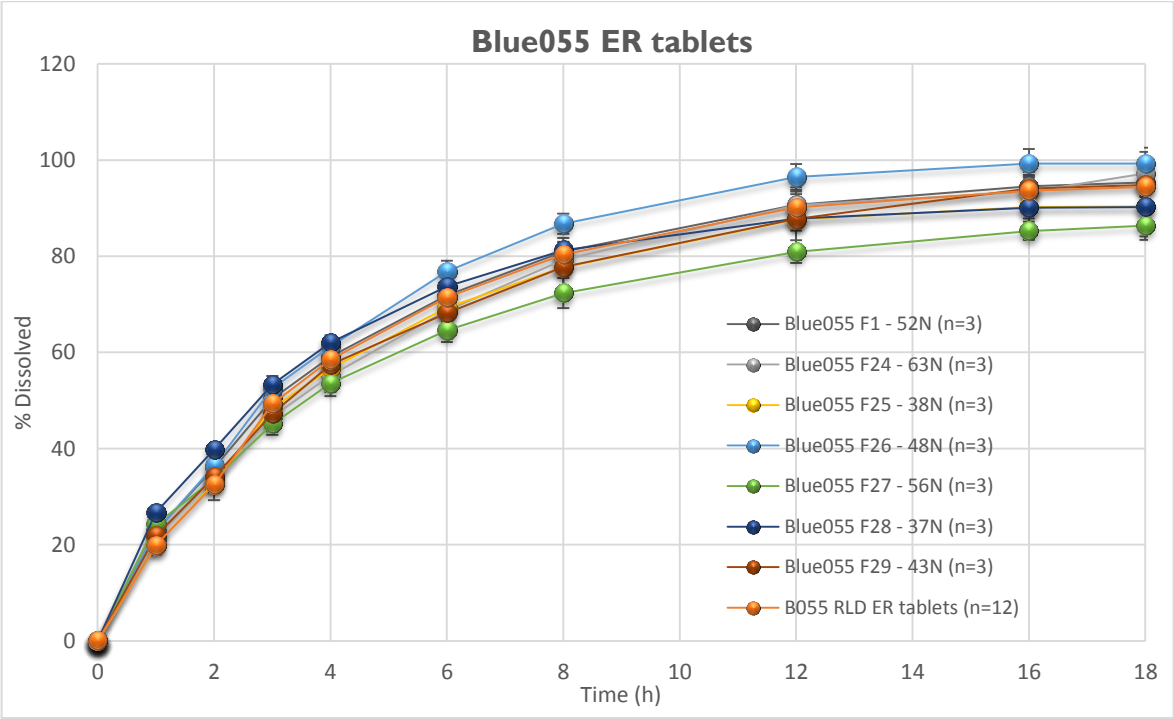

Figure 22 Dissolution profiles of F24-F29 *versus* F1 *versus* RLD, in OGD medium.

The results for the comparison of the tests with the RLD are presented below (Table 36):

Table 36 Results of the statistical analysis and f2 of the tests compared to RLD

Test		Assay SPEC 95-105% RSD NMT 5.0%	Dissolution SPEC 18 hours: NLT 80% (Q)	Assay t-test	Hardness t-test	Dissolution f2	
Major Excipients amount	F1	C	C	I	0	0	85.64
	F24	C	C	I	0	0	81.89
	F25	C	C	I	I	0	79.58
	F26	C	C	0	I	0	65.50
	F27	C	C	I	0	I	58.75
	F28	C	C	I	I	0	67.60
	F29	C	C	0	I	0	82.80

C – Complies with Specification; NC – Does not Comply with Specification; 0 - not significantly different; I - significantly different.

Regarding the impact of major excipients amount, all tests lead to adequate tablet assay.

Hardness data are generally statistically different, exhibiting lower values when compared to RLD. F24 and F27, the formulations with the lower amount of disintegrant are an exception, presenting higher values than RLD and F1.

In general, dissolution results were found to be similar to RLD, with the exception of tests F26 (slightly faster) and F27 (slightly slower). This behaviour may be due to the minimum and maximal amount of HPMC, respectively.

3.7.2.3.1 Design of Experiments (DOE) for the Impact of Proportions of Major Excipients

To better understand the combined effect of the major excipients on the DP performance, a design of experiments (DoE) was performed, using JMP® software (Version 13.1.0).

The DOE models were used to establish acceptable ranges for the studied factors. Figure 23 shows the overlay plot for response (Hardness) for Diluent% and HPMC%. The white zone indicates where the response is achieved (design space). From the analysis of the contour profilers, it can be stated that the chosen working settings lead to responses inside the design space.

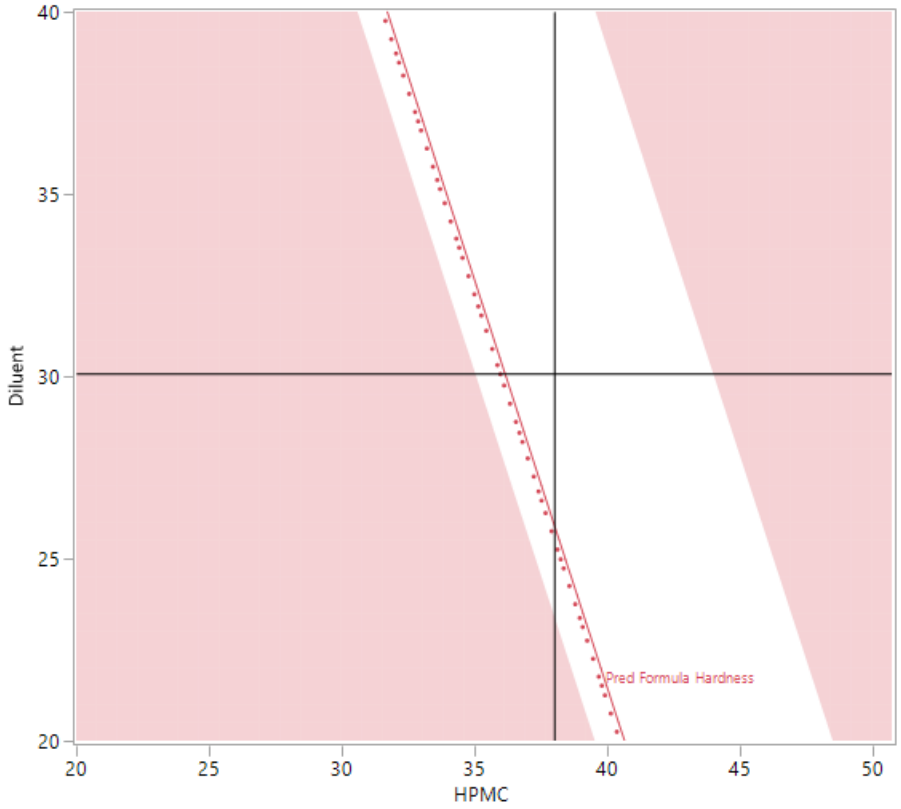

Figure 23 Overlay contour profiler plots (Diluent% versus HPMC%).

Studied response was applied to fit the appropriate model. The model for response was tested for goodness of fit, with an obtained value R^2=0.95 and their significances were obtained by an F-test (p-value=0.0193).

3.7.2.4 Impact of Proportions of Minor Excipients

With the purpose of studying the impact of different surfactant, glidant and lubricant proportions on the DP performance, eight tests were performed using the same formulation and manufacturing process of the previous Leading formulation (with the exception of diluent to compensate for the previous excipients). These tests are also meant to be compared with the Leading formulation and RLD (F1). The amount of each excipient used in different tests is provided in Table 37 (JMP® software). The analysis was consubstantiated by a DoE analysis.

Table 37 Percentage per tablet of the major excipients used in F30-F37.

Test	Surfactant	Glidant	Lubricant
	%	%	%
F30	2.00	0.00	3.00
F31	0.00	1.00	0.25
F32	0.00	0.00	0.25
F33	0.00	0.00	3.00
F34	2.00	1.00	0.25
F35	2.00	0.00	0.25
F36	2.00	1.00	3.00
F37	0.00	1.00	3.00
F1	1.67	0.17	1.00

The summary of the results obtained is presented below:

Table 38 Blue055 ER tablets, F30-F37 analytical results with comparison to F1 and RLD.

Test		F30	F31	F32	F33	F34	F35	F36	F37	F1	RLD
Hardness (Mean, N)		20	120	115	27	101	63	34	37	52	55
Blend Uniformity (Mean±%RSD)		94.8 ±1.1	96.1 ±1.9	97.5 ±0.6	95.4 ±2.0	95.1 ±0.4	91.8 ±5.1	94.8 ±0.4	98.4 ±3.0	93.1 ±2.0	-
Assay (%)		105.1	103.5	103.1	105.4	107.5	105.4	104.6	105.2	101.3	99.2
Degradation products (Total Imp., %)		0.15	ND	ND	0.15	ND	0.16	ND	ND	ND	0.12
Dissolution (%dissolved)	**2h**	36	49	50	54	32	29	35	49	36.1	32.2
	4h	56	69	70	74	55	51	54	67	59.2	59.7
	8h	78	85	87	92	79	79	74	81	81.0	81.8
	18h	96	90	92	98	98	88	91	86	95.4	95.4

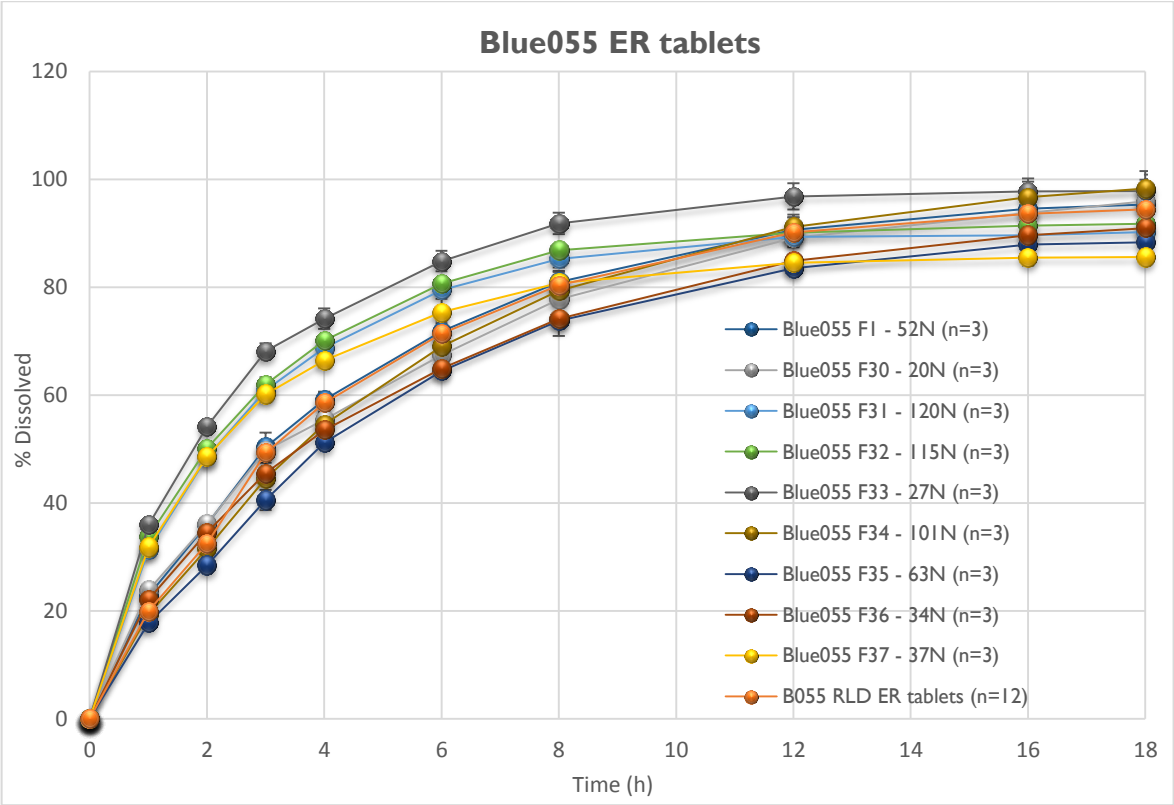

Figure 24 Dissolution profiles of F30-F37 versus F1 versus RLD, in OGD medium.

For the DoE, the type of design chosen was a full factorial, 2^k, k=3, yielding to 8 different experiments, according to the levels defined in Table 39. The coefficients of the following equation $Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_{12} X_1 X_2 + \beta_{23} X_2 X_3 + \beta_{13} X_1 X_3$ were estimated and are presented in Table 40.

Table 39 Experimental design independent variables and respective codification.

Formulation variable	Independent variables	Level -1	Level +1
Surfactant (%)	X_1	0	2
Glidant (%)	X_2	0	1
Lubricant (%)	X_3	0.25	3

Table 40 Parameters of the response surfaces for size obtained from 2^3 factorial planning in the indicated formulations and results of Student's t-test analysis.

Formulation variable	β_0	β_1	β_2	β_3	β_{12}	β_{23}	β_{13}
Dissolution (t=18hours)	92.394	1.016	-1.101	0.201	2.351	-0.151	-3.203
Significance Level	100.00	99.29	99.59	44.55	100.00	34.16	100.00
t value	277.93	3.06	-3.31	0.60	7.07	-0.45	-9.64
Hardness	64.625	-10.125	8.375	-35.125	4.625	7.625	-2.375
Significance Level	100.00	100.00	100.00	100.00	99.91	100.00	95.34
t value	57.43	-9.12	7.46	-31.28	4.03	6.87	-2.15

The influence of each variable and their respective interaction can be evaluated from the magnitude of the obtained polynomial coefficients. A higher magnitude corresponds to the major influencing factor upon the system, while a negative signal indicates that an increase in the factor level leads to a decrease in the respective dependent variable.

For the analysis of the magnitude of each coefficient obtained, dissolution (t=18h) was not significantly affected by the system variables. In turn, a greater influence of the variables tested was obtained for the Hardness. Accordingly, the percentage of lubricant was the tested variable with higher impact, followed by the percentage of surfactant and glidant. A higher concentration of the lubricant-surfactant yielded lower hardness values, while for glidant the opposite behavior was observed. This trend is somewhat reinforced by the interaction term (β_{13}).

The results for the comparison of the tests with the RLD are presented below (Table 41):

Table 41 Results of the statistical analysis and f2 of the tests compared to RLD

Test		Assay SPEC 95-105% RSD NMT 5.0%	Dissolution SPEC 18 hours: NLT 80% (Q)	Assay t-test	Hardness t-test	Dissolution f2	
Minor Excipients amount	F1	C	C	I	0	0	85.64
	F30	C	C	I	I	0	77.31
	F31	C	C	I	I	0	51.88
	F32	C	C	0	I	0	49.48
	F33	C	C	I	I	0	42.99
	F34	NC	C	I	I	0	76.08
	F35	C	C	I	0	I	59.76
	F36	C	C	0	I	0	66.70
	F37	C	C	I	I	I	51.55

C – Complies with Specification; NC – Does not Comply with Specification; 0 – not significantly different; I – significantly different.

The results of BU for the comparison of the tests with the F1 are presented below (Table 42):

Table 42 Results of the statistical analysis of the BU compared to F1.

Test		SPEC Blend Uniformity SPEC 95-105% RSD NMT 5.0%	t-test
Minor Excipients amount	F30	C	0
	F31	C	0
	F32	C	I
	F33	C	0
	F34	C	0
	F35	NC	0
	F36	C	0
	F37	C	0

C – Complies with Specification; NC – Does not Comply with Specification; 0 – not significantly different; I – significantly different.

Regarding the minor excipients amount, all tests lead to similar blend content, with the exception of test F35. This might be explained by the higher surfactant amount and the absence of glidant, which may compromise the mixture homogeneity, needing a lubricant to promote DS distribution.

All assay results are similar (103.1-105.4%), with the exception of the test F34 (107.5%, OoS).

Hardness values obtained present some differences, with trials F31, F32 and F34 presenting higher hardness achievable (120, 115 and 101N, respectively), and this may be explained, by the minimum amount of Lubricant used. Lower hardness is obtained when higher amount of lubricant is used, being this overlubrication phenomenon known from the literature.

In what concerns dissolution results, there is a clear distinction between the trials without surfactant (F31, F32, F33 and F37) and those containing 2% of surfactant (F30, F34, F35 and F36). The former exhibit a significantly faster release when compared to the latter and the Leading formulation.

In dosage systems that contain polymer, it can be explained by the interactions between polymers and surfactants in aqueous media giving rise to the formation of association structures, thereby modifying the solution and interfacial properties. The morphologies of association complexes depend on the molecular properties of the polymer and the surfactant. The presence of a polymer lowers the critical micellar concentration (CMC) and reduces the size of spherical micelles (Benrraou, 2003; Nagarajan, 2001). The

solubility of drug can be enhanced by ensuring that the surfactant concentration is at least above the critical micellar concentration (CMC).

As a conclusion, the formula is sensitive to overlubrication, considering resistance to crushing. Moreover, the formula responds to the amount of surfactant, evidencing a higher dissolution rate when no surfactant is used.

3.7.2.4.1 Design of Experiments (DOE) for the Impact of Proportions of Minor Excipients

To better understand the combined effect of the minor excipients variables on the DP performance, a design of experiments (DoE) was performed, using JMP® software (Version 13.1.0).

Response contour diagram was generated to interpret the process domains. The DOE models were used to establish acceptable ranges for the studied factors. Figure 25 shows the overlay plot of response Hardness for Surfactant% and Lubricant%. The white zone indicates where the response is achieved (design space). From the analysis of the contour profilers, it can be stated that the chosen working settings lead to responses inside the design space.

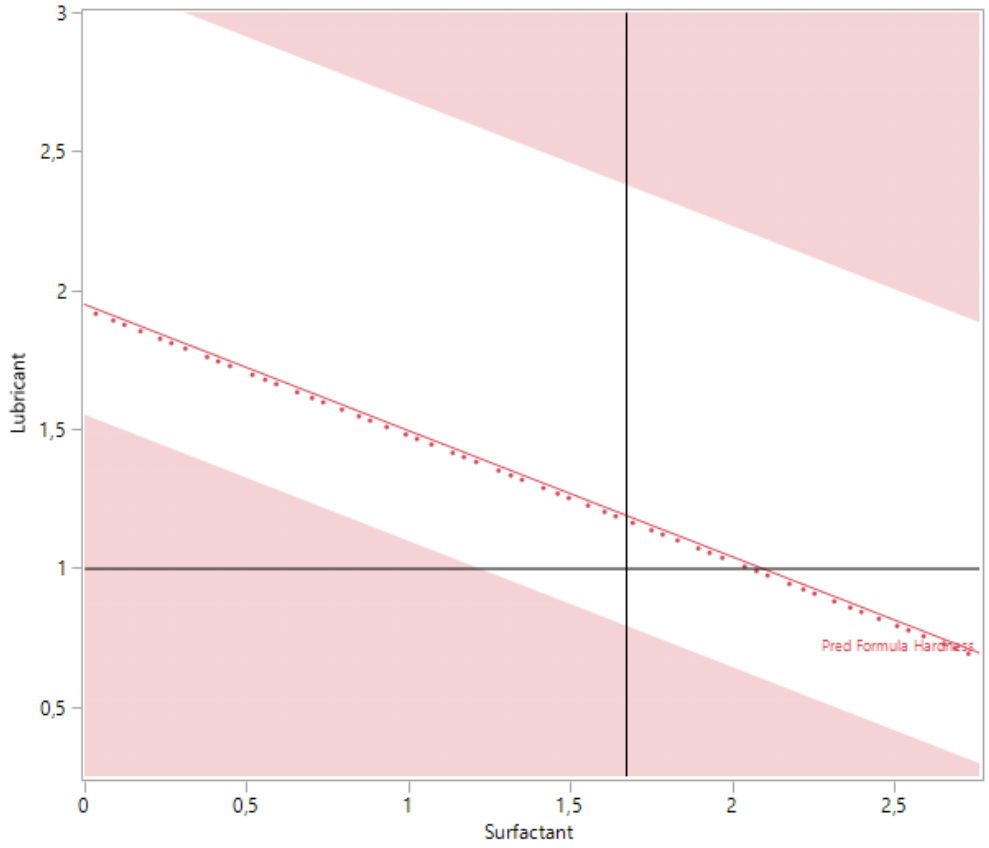

Figure 25 Overlay contour profiler plots (Lubricant% versus Surfactant%).

Studied response was applied to fit the appropriate model. The model for response was tested for goodness of fit, with an obtained value R^2=0.92 and their significances were obtained by an F-test (p-value=0.0035).

3.7.3 Formulation development overall conclusions

- DS particle size has a great impact on blend uniformity and assay, but not on the dissolution profile. PSD should be monitored in order to guarantee an adequate blend uniformity.
- Regarding the diluent grade, the milled grade showed better results when compared with spray dried grade. Moreover, it is advisable to use diluent with smaller particle size distribution leading to better homogeneity and higher resistance to crushing of tablets.
- HPMC physical properties are critical to the DP performance. Lower viscosities lead to faster dissolution profiles. This indicates that the viscosity is a crucial parameter that has to be monitored. Nevertheless, within the Grade X, the product is robust to changes in HPMC viscosity, PSD and Hydroxypropyl content.
- Major amount excipients proportions are also relevant for the DP performance. In this case, faster dissolution profiles are achieved when using the minimum amount of HPMC and the maximum amount of disintegrant, simultaneously. Nevertheless, the formula seems to be robust to changes on formulation.
- Minor amount excipients also interfere with the DP behaviour, mainly on dissolution profiles. In this case, the greater the surfactant amount is, the slower the dissolution profiles are. It seems to be sensitive to overlubrication considering resistance to crushing.

3.8 Drug Product Manufacturing Process Development

For the studies performed on the formulation development addressed and taking into consideration the obtained conclusion, it was considered also critical to study the manufacturing process parameters, namely the roller compaction parameters, the addition order of the excipients, the blending and lubrication times and lubrication time of the intra-granular phase.

3.8.1 Excipients order of Addition

To further investigate the impact of the presence of the excipients either on the internal or external phases of the granulation process on the DP performance, nine tests were performed using the same formulation of the Leading formulation. These tests are also meant to be compared with the RLD and Leading formulation (F1).

For the planning of experiments, the type of design chosen was a Custom Design in a single block and the list of experiments to be performed was made using the JMP® software and is shown in Table 43. In the table shown, the value 0 corresponds to the addition of the excipient in the extragranular phase, the value 0.5 corresponds to the addition of the excipient, half in the extragranular phase and the other half in the intragranular phase, and the value 1 corresponds to the addition of excipient in the intragranular phase.

Table 43 Custom design experiments retrieved from JMP®.

Test	HPMC	Surfactant	Glidant
FI_A	0	1	0
FI_B	0.5	1	1
FI_C	1	0	0
FI_D	0	0	1
FI_E	1	1	1
FI_F	0.5	0	0
FI_G	1	1	0
FI_H	0	1	1
FI_I	1	0	1
FI	1	1	1

The summary of the results obtained is presented below (Table 44):

Table 44 Blue055 ER tablets, FI_A - FI_I analytical results with comparison to FI and RLD.

Test		FI_A	FI_B	FI_C	FI_D	FI_E	FI_F	FI_G	FI_H	FI_I	FI	RLD
Hardness (Mean, N)		56	62	49	59	62	63	65	54	57	52	55
Blend Uniformity (Mean±%RSD)		101.1 ±1.8	99.4 ±0.1	88.5 ±1.5	102.9 ±1.6	98.5 ±2.6	97.8 ±1.7	96.0 ±2.6	104.9 ±2.1	89.6 ±1.2	93.1 ±2.0	-
Assay (%)		102.5	102.6	86.5	102.5	101.3	95.7	97.9	105.5	90.1	101.3	99.2
Degradation products (Total Imp., %)		≤0.1	ND	ND	ND	ND	ND	ND	0.35	ND	ND	0.12
Dissolution (%dissolved)	**2h**	36	41	35	38	42	34	35	37	33	36.1	32.2
	4h	59	65	54	61	64	56	57	61	55	59.2	59.7
	8h	81	87	72	83	85	79	79	83	74	81.0	81.8
	18h	97	97	84	97	95	92	93	101	84	95.4	95.4

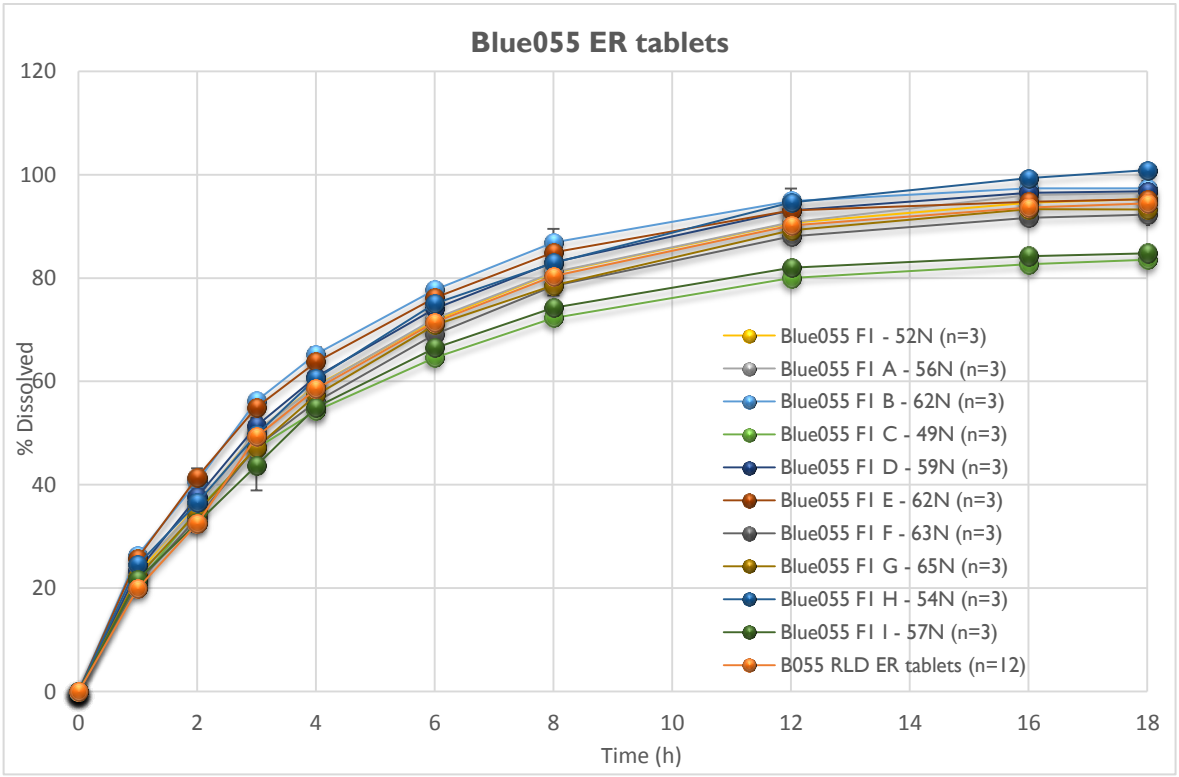

Figure 26 Dissolution profiles of FI_A-FI_I versus FI versus RLD, in OGD medium.

The results for the comparison of the tests with the RLD are presented below (Table 45):

Table 45 Results of the statistical analysis and f2 of the tests compared to RLD

Test		Assay SPEC 95-105% RSD NMT 5.0%	Dissolution SPEC 18 hours: NLT 80% (Q)	Assay t-test	Hardness t-test	Dissolution t-test	Dissolution f2
Excipients Order of Addition	F1	C	C	I	0	0	85.64
	$F1_A$	C	C	I	0	0	82.67
	$F1_B$	C	C	I	0	0	60.70
	$F1_C$	NC	C	I	0	I	56.51
	$F1_D$	C	C	I	0	0	74.75
	$F1_E$	C	C	I	0	0	64.50
	$F1_F$	C	C	I	0	0	83.01
	$F1_G$	C	C	0	0	0	86.81
	$F1_H$	NC	C	I	0	I	68.48
	$F1_I$	NC	C	I	0	I	59.77

C – Complies with Specification; NC – Does not Comply with Specification; 0 – not significantly different; I – significantly different.

The results of BU for the comparison of the tests with the F1 are presented below (Table 46):

Table 46 Results of the statistical analysis of the BU compared to F1.

Test		SPEC Blend Uniformity SPEC 95-105% RSD NMT 5.0%	t-test
Excipients Order of Addition	$F1_A$	C	I
	$F1_B$	C	0
	$F1_C$	NC	0
	$F1_D$	C	I
	$F1_E$	C	0
	$F1_F$	C	0
	$F1_G$	C	0
	$F1_H$	C	I
	$F1_I$	NC	0

C – Complies with Specification; NC – Does not Comply with Specification; 0 – not significantly different; I – significantly different.

Hardness values obtained are very similar when compared to Leading formulation.

During the study of the excipients order of addition (inside the granules or external to the granules), a clear trend was noticed. All the tests that presented low content results ($F1_C$ and $F1_I$) were manufactured using HPMC in the extragranular phase. So, it is crucial to always use this excipient in the intragranular phase. However, the effect is not as noticeable when half of the HPMC is added in the intragranular phase and the other half in the extra-granular phase ($F1_B$ and $F1_F$).

Dissolution results were found to be similar to Leading formulation, with the exception of tests $F1_B$ and $F1_E$, which presented slightly faster dissolution profiles. This fact may be due to the presence of HPMC, surfactant and glidant in the extra-granular phase.

3.8.2 Dry Granulation Process

In order to study the impact of the dry granulation critical process parameters (roller pressure, roller gap and net sieve size) on the DP performance, eight tests were performed using the same formulation of the Leading formulation. The settings of each studied parameter in different experimental runs are provided in Table 36. These tests are also meant to be compared with the Leading formulation (F1).

Ribbon density is directly related to roller pressure and inversely related to the roller gap, which may impact the PSD, flowability, uniformity and compressibility of the milled granules. The mill screen orifice size directly impacts PSD of the DP, which may potentially have an impact on granule uniformity and dissolution profile.

For the DoE, the type of design chosen was a full factorial, 2^k, k=3, in a single block and the list of experiments to be performed was made using the JMP® software and is shown in Table 47.

Table 47 Table of full factorial obtained with the experiments performed.

Parameters / Test	Roller gap (mm)	Roller pressure (bar)	Final net sieve (mm)
FI_J	1	50	0.63
FI_K	2	34	0.63
FI_L	3	18	0.63
FI_M	3	50	0.63
FI_N	1	18	1.0
FI_O	1	50	1.0
FI_P	3	18	1.0
FI_Q	3	50	1.0
FI	1.5	20	0.63

The summary of the results obtained is presented below (Table 50):

Table 48 Blue055 ER tablets, FI_J - FI_Q analytical results with comparison to FI and RLD.

Test		FI_J	FI_K	FI_L	FI_M	FI_N	FI_O	FI_P	FI_Q	FI	RLD
Hardness (Mean, N)		31	35	40	30	30	21	39	25	52	55
Blend Uniformity (Mean±%RSD)		95.4 ±1.3	95.1 ±0.9	94.1 ±1.0	95.4 ±0.9	94.0 ±1.2	97.3 ±7.6	98.3 ±2.8	93.9 ±2.0	93.1 ±2.0	-
Assay (%)		105.9	103.7	100.7	103.1	101.6	103.2	97.2	101.0	101.3	99.2
Degradation products (Total Imp., %)		≤0.1	ND	≤0.1	ND	≤0.1	ND	≤0.1	ND	ND	0.12
Dissolution (%dissolved)	**2h**	36	35	35	36	34	35	33	37	36.1	32.2
	4h	59	59	58	61	57	57	55	61	59.2	59.7
	8h	80	81	82	84	77	77	74	84	81.0	81.8
	18h	92	98	97	100	91	89	86	99	95.4	95.4

ND: not detected.

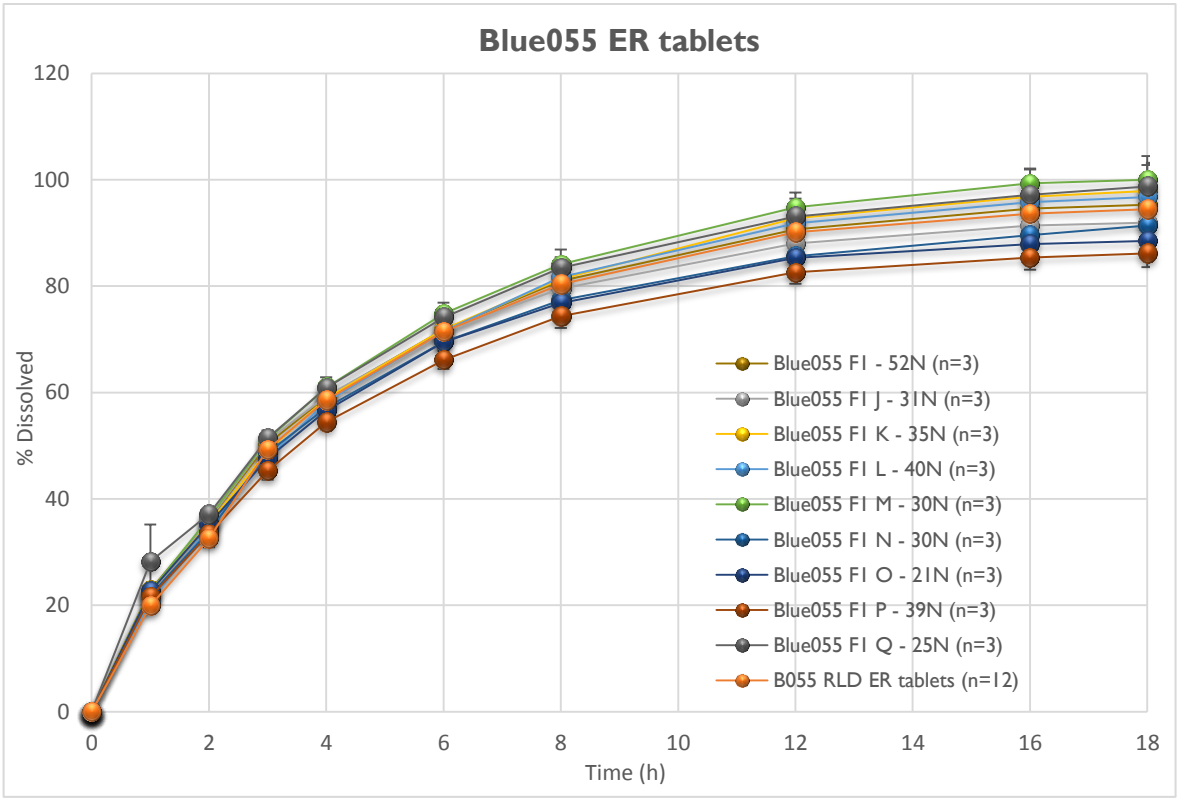

Figure 27 Dissolution profiles of FI_J-FI_Q versus FI versus RLD, in OGD medium.

For the DoE, the type of design chosen was a full factorial, 2^k, k=3, yielding to 8 different experiments, according to the levels defined in Table 49. The coefficients of the following equation $Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_{12} X_1 X_2 + \beta_{23} X_2 X_3 + \beta_{13} X_1 X_3$ were estimated are presented in Table 50.

Table 49 Experimental design independent variables and respective codification.

Process parameters	Independent variables	Level -1	Level +1
Roller Gap (mm)	X_1	1	3
Roller Pressure (bar)	X_2	18	50
Sieve size (mm)	X_3	0.63	1

Table 50 Parameters of the response surfaces for size obtained from 2^3 factorial planning in the indicated formulations and results of Student's t-test analysis.

Formulation variable	β_0	β_1	β_2	β_3	β_{12}	β_{23}	β_{13}
Dissolution (t=18hours)	94.715	0.7075	0.085	-3.5025	3.8575	0.54	2.3475
t value	100.00	61.09	8.57	99.96	99.98	48.92	99.06
Significance Level	118.19	0.88	0.11	-4.37	4.81	0.67	2.93
Hardness	31.5	2	-4.75	-2.75	-1.25	1.25	-1
t value	93.37	4.88	-14.33	-7.91	-3.55	4.46	-1.86
Significance Level	100.00	99.99	100.00	100.00	99.75	99.97	91.96

As previously discussed (*section 3.7.2.4*), the influence of each variable, and the respective interaction in the response term, can be rationalized by the polynomial equation coefficients.

In what concerns the isolated terms, dissolution seems to be mainly affected by sieve size, with an increase of this setting yielding a decrease in the dissolution rate. Taking into account the interaction coefficients, there seems to be some influence when combined higher roller gap values and roller pressure on dissolution variable.

For hardness, the coefficient with greater magnitude obtained was the roller pressure parameter, -4.75, a negative coefficient signal indicates that a decrease in the parameter level leads to a decrease in hardness.

The results for the comparison of the tests with the RLD are presented below (Table 51):

Table 51 Results of the statistical analysis and f2 of the tests compared to RLD

Test		Assay SPEC 95-105% RSD NMT 5.0%	Dissolution SPEC 18 hours: NLT 80% (Q)	Assay t-test	Hardness t-test	Dissolution t-test	Dissolution f2
Dry Granulation Process	FI	C	C	I	0	0	85.64
	FI_J	NC	C	I	I	0	82.10
	FI_K	C	C	I	I	0	80.49
	FI_L	C	C	I	I	0	86.23
	FI_M	C	C	I	I	I	69.42
	FI_N	C	C	I	I	0	76.82
	FI_O	C	C	I	I	I	70.38
	FI_P	C	C	0	I	I	61.75
	FI_Q	C	C	I	I	0	68.40

C – Complies with Specification; NC – Does not Comply with Specification; 0 - not significantly different; I - significantly different.

It was found that only when using extreme granulation conditions (higher roller pressure and thinner gap, tests FI_O and FI_P) there is a risk of heterogeneity on mixture (higher RSD>3%) and less accurate assay results.

Hardness values obtained are slightly lower when compared to Leading formulation, although similar to each other.

Dissolution results showed some significant differences, namely in tests FI_J, FI_M, FI_N, FI_O, FI_P and FI_Q, where the most extreme pressure setting were applied.

3.8.2.1 Design of Experiments (DOE) for the Dry Granulation Process

To better understand the effect of roller compaction process variables on the DP performance, a design of experiments (DoE) was performed, using JMP® software (Version 13.1.0).

Response contour diagram was generated to interpret the process domains. The DOE models were used to establish acceptable ranges for the studied factors. Figure 26 show the overlay plot of responses (Hardness and Dissolution for 18h) for Roller gap and Roller pressure. The white zone indicates where all of the responses are achieved simultaneously (design space). From the analysis of the contour profilers, it can be stated that the chosen working settings lead to responses inside the design space.

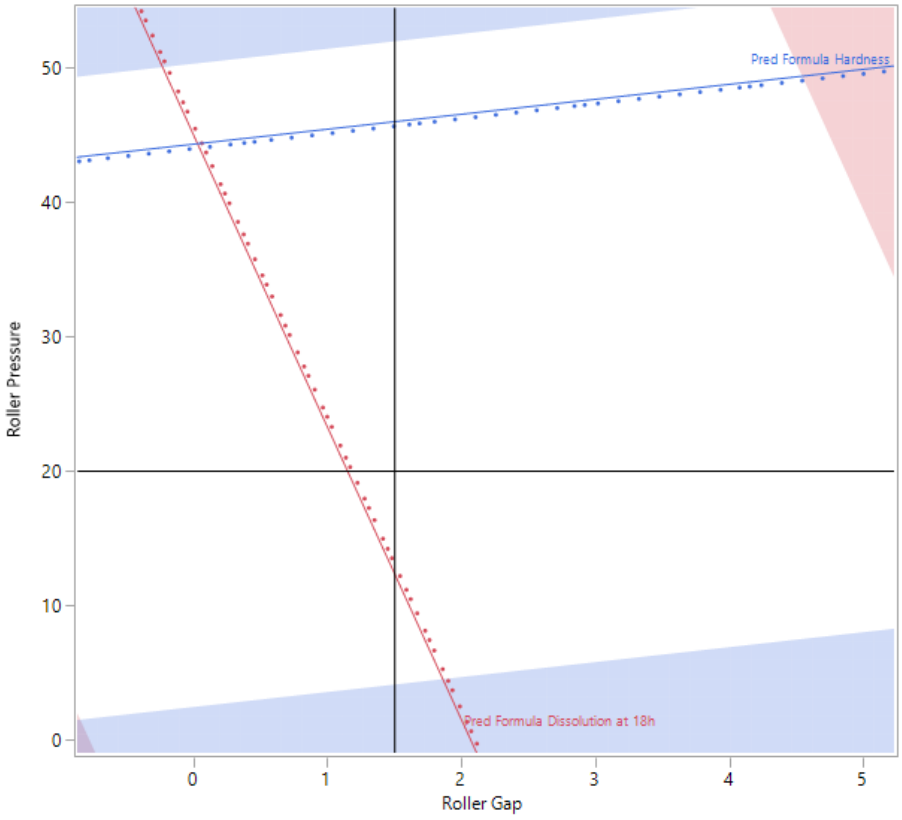

Figure 28 Overlay contour profiler plots (Roller gap *versus* Roller pressure; Sieve size: 0.63 mm).

Studied responses were applied to fit the appropriate model. The model for each response was tested for goodness of fit, with an obtained value R^2=0.56 and their significances were obtained by an F-test (p-value=0.2154).

3.8.3 Mixing Times

3.8.3.1 Blending and Lubrication Time

In order to investigate the impact of the granular phase blending and lubrication time on the DP performance, four tests were performed using the same formulation of the Leading formulation (Table 52). These tests are also meant to be compared with the Leading formulation (F1). The formulation and manufacturing processes are presented hereafter.

Table 52 Blending and Lubrication Time used for $F1_R$-$F1_U$.

Test	$F1_R$	$F1_S$	$F1_T$	$F1_U$	F1
Blending Time (minutes)	10	10	5	20	10
Lubrication Time (minutes)	3	10	5	5	5

The summary of the results obtained is presented below (Table 53):

Table 53 Blue055 ER tablets, $F1_R$ - $F1_U$ analytical results with comparison to F1 and RLD.

Test		$F1_R$	$F1_S$	$F1_T$	$F1_U$	F1	RLD
Hardness (N)		58	54	55	54	52	55
Blend Uniformity (Mean±%RSD)		96.4±0.7	97.8±2.0	100.6±1.7	98.4±0.9	93.1±2.0	-
Assay (%)		98.1	98.2	97.0	97.8	101.3	99.2
Degradation products (Total Impurities, %)		ND	ND	ND	ND	ND	0.12
Dissolution (%dissolved)	**2h**	35	35	36	35	36.1	32.2
	4h	60	60	61	58	59.2	59.7
	8h	81	81	83	79	81.0	81.8
	18h	94	93	96	92	95.4	95.4

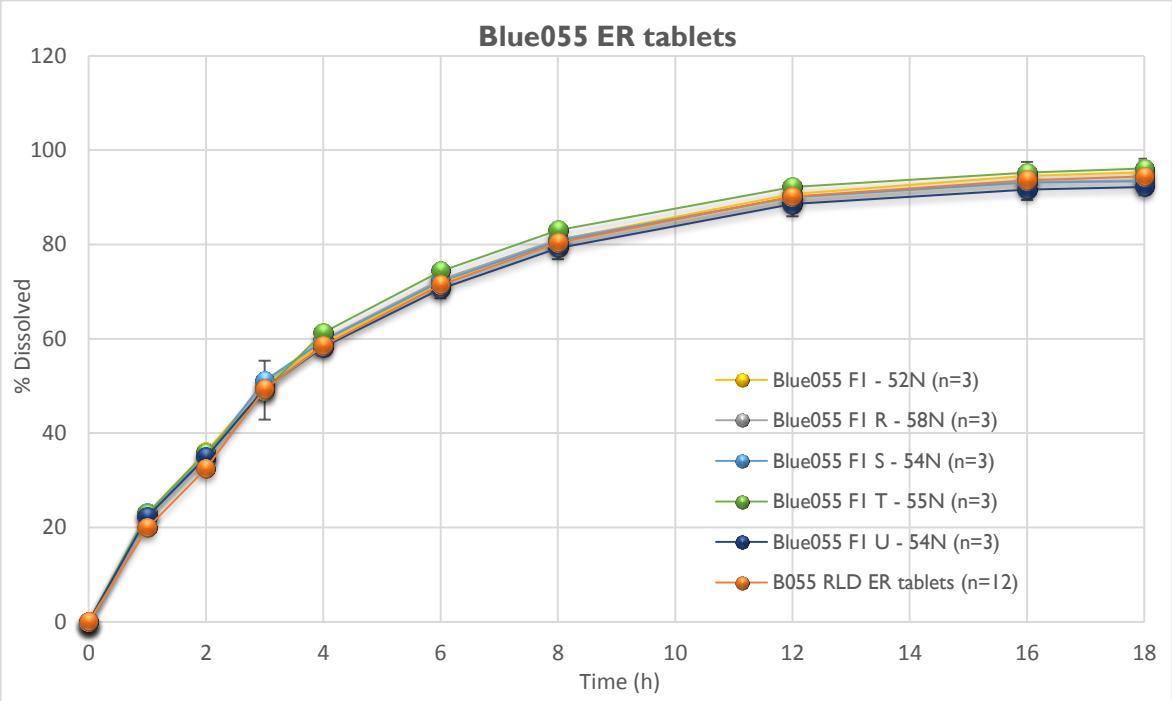

Figure 29 Dissolution profiles of FI_R-FI_U versus FI versus RLD, in OGD medium.

The results for the comparison of the tests with the RLD are presented below (Table 54):

Table 54 Results of the statistical analysis and f2 of the tests compared to RLD

Test		Assay SPEC 95-105% RSD NMT 5.0%	Dissolution SPEC 18 hours: NLT 80% (Q)	Assay	Hardness t-test	Dissolution t-test	f2
Mixing times	FI	C	C	I	0	0	85.64
	FI_R	C	C	I	0	0	88.43
	FI_S	C	C	0	0	0	86.33
	FI_T	C	C	0	0	0	78.87
	FI_U	C	C	0	0	0	85.51

Key: C – Comply with Specification; NC – Not Comply with Specification; 0 – not significantly different; I – significantly different

The results of BU for the comparison of the tests with the F1 are presented below (Table 33):

Table 55 Results of the statistical analysis of the BU compared to F1.

Test		SPEC Blend Uniformity SPEC 95-105% RSD NMT 5.0%	t-test
Mixing times	FI_R	C	0
	FI_S	C	0
	FI_T	C	I
	FI_U	C	I

Key: C – Comply with Specification; NC – Not Comply with Specification; 0 – not significantly different; I – significantly different

Blending time did not have a substantial impact on the blend uniformity content or the tablets assay, as low RSD (<3.0%) is obtained independently of blending times, and adequate assay results are obtained (always between 97% and 103%).

Hardness values obtained are very similar to Leading formulation.

Dissolution results were found to be very similar to Leading formulation, leading to conclude that the blending times are not influencing this parameter.

3.8.3. Lubrication Time of the Intra-Granular Phase

In order to study the impact of the intra-granular phase lubrication time on the DP performance, two tests were performed using the same formulation and manufacturing process of the Leading formulation, with exception of lubrication time of the intragranular phase (Table 56). These tests are also meant to be compared with the RLD and Leading formulation (F1).

Table 56 Lubrication time of the intra-granular phase used for F1v-F1x.

Test	$F1_V$	$F1_X$	F1
Lubrication time of the intra-granular phase (minutes)	3	10	5

The summary of the results obtained is presented below (Table 57):

Table 57 Blue055 ER tablets, F1v - F1x analytical results with comparison to F1 and RLD.

Test		Test $F1_V$	Test $F1_X$	F1	RLD
Hardness (N)		52	55	52	55
Blend Uniformity (Mean±%RSD)		96.8±1.6	97.6±1.2	93.1±2.0	-
Assay (%)		97.8	97.6	101.3	99.2
Degradation products (Total Impurities, %)		ND	ND	ND	0.12
Dissolution (%dissolved)	**2h**	34	34	36.1	32.2
	4h	58	58	59.2	59.7
	8h	79	80	81.0	81.8
	18h	94	95	95.4	95.4

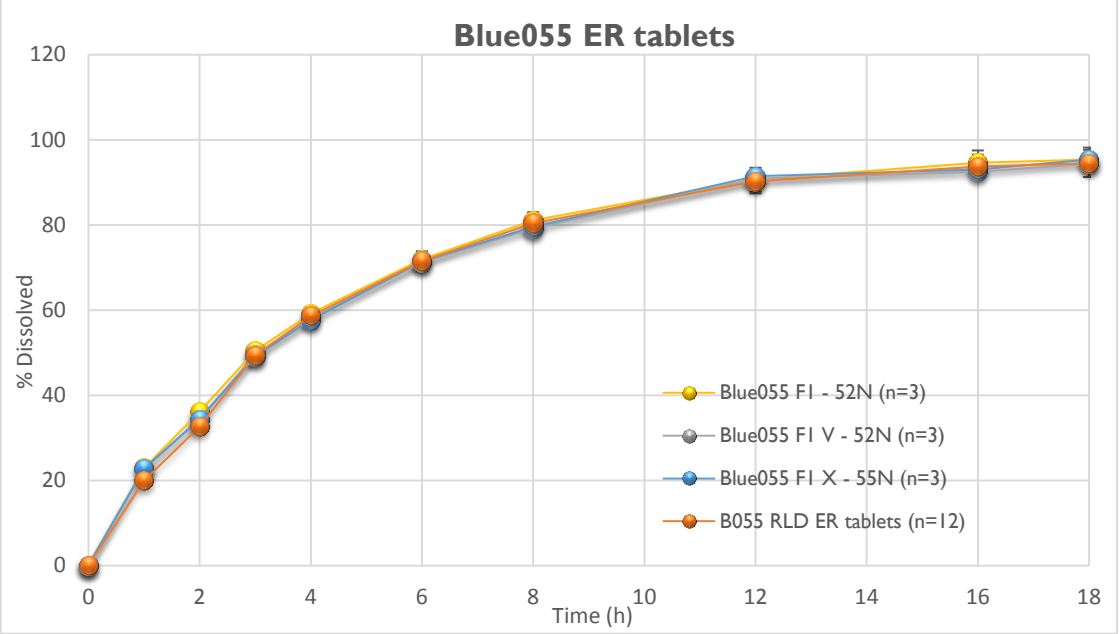

Figure 30 Dissolution profiles of F1v - F1x versus F1 versus RLD, in OGD medium.

The results for the comparison of the tests with the RLD are presented below (Table 58):

Table 58 Results of the statistical analysis and f2 of the tests compared to RLD

Test		Assay SPEC 95-105% RSD NMT 5.0%	Dissolution SPEC 18 hours: NLT 80% (Q)	Assay t-test	Hardness t-test	Dissolution t-test	Dissolution f2
Lubrication time IGP	FI	C	C	I	0	0	85.64
	FI_V	C	C	0	0	0	89.91
	FI_X	C	C	0	0	0	89.10

C – Complies with Specification; NC – Does not Comply with Specification; 0 - not significantly different; I - significantly different.

Intragranular phase lubrication time did not have a substantial impact on the blend uniformity content or the tablets assay, as low RSD (<3.0%) and adequate assay results, are obtained (always between 97% and 103%).

Hardness values obtained were very similar to Leading formulation.

Dissolution results were found to be very similar to Leading formulation, with the conclusion that the lubrication times are not influencing this parameter.

3.8.4 Manufacturing process development overall conclusion

- Regarding the roller compaction settings, it was found that extreme granulation conditions (higher roller pressure and smaller gap) lead to blend heterogeneity and less accurate assay results. Dissolution results corroborate these data, showing some significant differences in relation to the prototype, mainly when the most extreme pressure setting was applied.
- During the study of the excipients order of addition (inside the granules or external to the granules), a clear trend was noticed. It is crucial to always use HPMC in the intra-granular phase. In what concerns dissolution results, it was found that the presence of HPMC, surfactant and glidant in the extra-granular phase led to faster dissolution rates. Hence, it is mandatory to use these excipients in the intra-granular phase.
- No impact was observed in blending or lubrication times on the DP performance. Intra-granular phase lubrication time may vary between 3 and 10 minutes. Final blending and lubrication times are acceptable between 5 – 20 minutes and 3 – 10 minutes, respectively.

3.9 Updated Risk Assessment

During development, the medium and high risk formulation and process variables have been defined and the identified risks for each process step were addressed and studied. Based on the experimental data generated, scientific knowledge and understanding, appropriate controls were developed and implemented to reduce the risk to an acceptable level. After detailed experimentation, and applying the mentioned controls, the initial risk assessment was updated, in line with the current process understanding and presented in Table 59.

Table 59 Updated risk assessment of formulation and manufacturing process variables.

			Drug Product Quality Attributes (CQA)				
		Material Attributes	Assay	BU	Degradation Products	Dissolution	Hardness
Drug Substance		Solid State Form	Low	Low	Low	Low	Low
		Particle Size Distribution	High	High	Low	Medium	Low
		Hygroscopicity	Low	Low	Low	Low	Low
		Solubility	Low	Low	Low	Low	Low
		Moisture Content	Low	Low	Medium	Low	Low
		Residual Solvent	Low	Low	Low	Low	Low
		Process Impurities	Low	Low	Low	Low	Low
		Chemical Stability	Low	Low	Medium	Low	Low
		Flow Properties	Low	Low	Low	Low	Low
Formulation Variables	**Diluent**	Amount	Low	Low	Low	Low	Low
		Grade and PSD	Low	Low	Low	Low	Low
	HPMC	Amount	Low	Low	Low	Low	Low
		Grade	Low	Low	Low	Low	Low
		PSD	Low	Low	Low	Low	Low
		% Hydroxypropyl	Low	Low	Low	Medium	Low
		Supplier	Medium	Medium	Low	Medium	Low
	Disintegrant	Amount	Medium	Medium	Low	Medium	Low
	Surfactant	Amount	Low	Low	Low	Low	Low
	Glidant	Amount	Low	Low	Low	Low	Low
	Lubricant	Amount	Low	Low	Low	Low	Low
Manufacturing Process Variables	**Sifting of Raw Materials**	Mesh Size	Low	Low	Low	Low	Low
	Intragranular Phase Blending	Blender Occupancy	Low	Low	Low	Low	Low
		Blending Time	Low	Low	Low	Low	Low
	Intragranular Lubrication	Blending Time	Low	Low	Low	Low	Low
	Dry Granulation	Screw feeder speed	Low	Low	Low	Low	Low
		Roller speed	Low	Low	Low	Medium	Low
		Hydraulic pressure	Medium	Medium	Low	Medium	Low
		Roller gap	Medium	Medium	Low	Medium	Low
		Mesh size	Low	Low	Low	Low	Low
		Milling Speed	Low	Low	Low	Low	Low
	Blending	Blending time	Low	Low	Low	Low	Low
	Lubrication	Blending time	Low	Low	Low	Low	Low
	Compression	Compression speed	Low	Medium	Low	Low	Low
		Compression force	Low	Low	Low	Medium	Low

3.10 Classification of the type of release mechanism

For the classification of the type of mechanism involved during the release process, only the test formulations exhibiting closer similarity with the RLD (higher f2 values) were considered.

3.10.1 Korsmeyer-Peppas Model

In the diffusion process of a penetrant through a viscoelastic material, as for example a polymer, two main phenomena must be considered: the rate of diffusion of the fluid and the change in the internal structure of the material. If the rate of penetrant diffusion is much smaller or much bigger than the rate of relaxation of the polymer-solvent system, the transport is properly described by Fick's law. Conversely, if the rate of penetrant diffusion is of the same order of the relaxation process, Fick's law does not represent an accurate description of the phenomenon. The explanation lies in the fact that the diffusing penetrant causes a deformation, which induces a stress that interacts with the Brownian motion of the fluid molecule (Ferreira *et al.*, 2015).

Korsmeyer *et al.* (1983) derived a simple relationship, which describes drug release from a polymeric system. As previously described in section 1.1.4, drug transport mechanism can be classified as displayed in Table 60.

Table 60 Interpretation of Korsmeyer-Peppas power release exponent. (Baneja, 1986).

Release exponent (c2)	**Drug transport mechanism**	**Rate as a function of time**
0.5	Fickian diffusion	$t^{-0.5}$
0.5<n<1.0	Anomalous transport	t^{n-1}
1.0	Case-II transport	Zero order release
Higher than 1.0	Super Case-II transport	t^{n-1}

The results obtained from the application of this mathematical model to the formulations previously identified are shown in Table 61.

Table 61 Drug release kinetics parameters derived from Korsmeyer-Peppas model equation.

Test	**Formulations**	**c1**	**c2**	**R^2**
Kormeyer-Peppas $c_1 t^{c2}$	F1	22.808±1.027	0.696±0.039	0.99856
	F16	22.141±1.746	0.710±0.068	0.99572
	F21	21.413±0.997	0.724±0.040	0.99855
	$F1_V$	22.023±1.424	0.705±0.056	0.99708
	$F1_X$	22.181±1.331	0.694±0.052	0.99743
	RLD	19.611±1.562	0.800±0.068	0.99638

Note: c1 is the release rate constant; c2 is the release exponent. Data are presented as mean± standard deviation.

The c2 value is used to characterize different release mechanisms for cylindrical shaped matrices, e.g. tablets. Usually c2 value is referred to as n value.

The values obtained of the release exponent for the different formulations and RLD of B055 ER tablets were between 0.694-0.800. For n values between 0.5 and 1, non-Fickian diffusion is often observed as a result of the combined contribution of drug diffusion and polymer erosion, which supports the use of matrix tablets as an extended release pharmaceutical dosage form.

CHAPTER IV

CONCLUSIONS

4. Conclusions

In the present work, the main objective was the development of a generic extended release drug product in the pharmaceutical form of tablets.

Development work was supported on the quality by design principles, which allowed the study and understanding of the effect of formulation/process parameters on the DP quality attributes.

The main effects observed from formulation parameters were:

- DS particle size has a large impact on blend uniformity and assay, not on dissolution performance.
- Regarding the diluent grade, it is advisable to use diluent with smaller particle size distribution and milled grade, leading to better homogeneity and higher resistance to crushing of tablets.
- HPMC physical properties are critical to the DP performance. Lower viscosities lead to faster dissolution profiles. This indicates that the viscosity is a crucial parameter that has to be monitored. Nevertheless, the product is robust to changes in HPMC PSD and hydroxypropyl content.
- Major excipients proportions are also relevant for the DP performance. In this case, faster dissolution profiles are achieved when using the minimum amount of HPMC and the maximum amount of disintegrant, simultaneously.
- Minor excipients amount also interferes with the DP behaviour, mainly on dissolution profiles. In this case, the drug substance release showed slower when the surfactant amount is higher.

The main effects observed on process parameters were:

- During the study of the excipients order of addition (inside the granules or external to the granules), a clear trend was noticed. It is crucial to always use HPMC in the intra-granular phase. In what concerns dissolution results, it was found that the presence of HPMC, surfactant and glidant in the extra-granular phase led to faster dissolution profile.
- Regarding the roller compaction settings, it was found that extreme granulation conditions (higher roller pressure and smaller gap) lead to blend heterogeneity and less accurate assay results. Dissolution results corroborate these data, showing some

significant differences when compared with the Leading formulation, mainly when the most extreme pressure setting was applied.

Control Strategy

The control strategy for Blue055 ER tablets is built upon the outcome of extensive product and process understanding studies. These studies enabled to investigate the material attributes and process parameters that were deemed high/medium risk to the CQAs of the drug product during the initial risk assessment. Through these systematic approaches, the CMAs and CPPs were successfully identified and the acceptable operating ranges established.

The control strategy is an integrated overview of how quality is assured based on current process and product knowledge. Nevertheless, it may be further refined based on continuous improvement and additional experience gained during the commercial lifecycle of the product.

REFERENCES

REFERENCES

ALDERMAN, D.A. - A review of cellulose ethers in hydrophilic matrixes for oral controlled-release dosage forms, Int. J. Pharm. Tech. Prod. Mfr., 5, 1-9, 1984.

AMIDON, G.L., et al- A Theoretical Basis for a Biopharmaceutics Drug Classification: The Correlation of In Vitro Drug Product Dissolution and In Vivo Bioavailability. Pharm. Res., 12, 413-420, 1995.

ANAL, Anil - Controlled-Release Dosage Forms. ISBN 9780470259818.

BENRRAOU, M.; BALES, B.; ZANA, R. - Effect of the nature of the counterion on the interaction between cesium and tetraalkylammonium dodecylsulfates and poly(ethylene oxide) or poly(vinylpyrolidone). J. Colloid Interface Sci. 2003, 267 (2), 519-523.

BERNER, B.; DINH, S. - Fundamental concepts in controlled release. In Treatise on Controlled Drug Delivery; Fundamentals, Optimization, Applications, Kydonieus, A., Ed.; Mercel Dekker: New York, 1992. p. 1- 35.

BETTINI R.; et al. - Influence of layer position on release kinetics of levodopamethyl ester and carbidopa from three-layer matrix tablets. EurJ Pharm Biopharm. 53:227-232. 2002. doi:10.1016/S0939-6411(01)00238-7.

BETTINI R.; et al. - Translocation of drug particles in HPMC matrix gel layer: effect of drug solubility and influence on release rate, J. Control. Release, 70 (3), 383-391, 2001.

BETTINI, R., et al. -. Swelling and drug release in hydrogel matrices: polymer viscosity and matrix porosity effects. Eur. J. Pharm. Sci. 2. 1994. p. 213-219.

BETTINI, R. et al. - Drug Release Kinetics and Front Movement in Matrix Tablets Containing Diltiazem or Metoprolol -Carrageenan Complexes. 2014. doi: 10.1155/2014/671532.

BONDERONI, M.C. et al. - Rheological behaviour of hydrophilic polymers and drug release from erodible matrices, J. Controlled Release, 18, 205-212, 1992.

BRANNON, P. L., PEPPAS N.A. - Solute and penetrant diffusion in swellable polymers: IX. The mechanisms of drug release from pH-sensitive swelling-controlled systems. J. Controlled Release, 8. 1989. p.267-274.

BRUSCHI, Marcos - Strategies to Modify the Drug Release From Pharmaceutical Systems. [S.l.] : Elsevier, 2015. ISBN 9781420044355. p.87-96.

BURI, P.; DOELKER, E. - Formulation des comprimés à libération prolongée II. Matrices hydrophiles. Pharm. Acta Helv. 55. 1980. p.189-197.

CAMPOS-ALDRETE, M.E. e VILLAFUERTE-ROBLES, L. - Influence of the viscosity degree and the particle size of HPMC on metronidazole release from matrix tablets. Eur. J. Pharm. Biopharm. 43.1997. p.173-178.

CARAMELLA, C.; et al. - Rheological properties and diffusion dissolution behaviour of hydrophilic polymers, Boll. Chim. Farmaceutico, 128. 1989. p.298-301.

CHEBLI, C.; CARTILIER, L. - Effect of some physical parameters on the sustained drug-release properties of substituted amylose matrices. Int. J. Pharm. 193 (2000) 167-173.

CHEONG, L.W.S. et al. - Relationship between polymer viscosity and drug release from a matrix system, Pharm. Res., 9 (11), 1510-1514, 1992.

COLOMBO, P., et al. - Drug diffusion front movement is important in drug release control from swellable matrix tablets. J. Pharm. Sci. 84. 1995. p.991-997.

COLOMBO, P., et al. - In vitro programmable zero-order release drug delivery system. Acta Pharm. Technol. 33. 1987. p.15-20.

COLOMBO, P. et al. - Swellable matrices for controlled drug delivery : gel-layer behaviour , mechanisms and optimal performance. 3:6. 2000.

COLOMBO, P. et al. - Swellable and Rigid Matrices: Controlled Release Matrices with Cellulose Ethers. In L. L. Augsburger, and S. W. Hoag (eds.), Pharmaceutical Dosage Forms: Tablets, Vol. 2, Informa Healthcare USA, Inc., New York, 2008, p. 433-468.

DOW COMMERCIAL INFORMATION - Dow Pharmaceutical Excipients - An Expanding World of Solutions Through Science and Polymer Technology. The Dow Chemical Company. 2002.

DOW COMMERCIAL INFORMATION - Effects of PEO Particle Size Distribution on CR Tablets by Direct Compression Method. The Dow Chemical Company. 2002.

DOW COMMERCIAL INFORMATION - HPMC Handbook. The Dow Chemical Company. 2000.

DOW COMMERCIAL INFORMATION - Pharmaceutical Excipients from Dow Water Soluble Polymers. The Dow Chemical Company. 2002.

DOW COMMERCIAL INFORMATION - POLYOX Water-Soluble Resins NF Patents Related to Pharmaceutical Applications. The Dow Chemical Company. 2002.

DOW COMMERCIAL INFORMATION - Using METHOCEL Cellulose Ethers for Controlled Release of Drugs in Hydrophilic Matrix Systems. The Dow Chemical Company. 2002.

DOW COMMERCIAL INFORMATION - Methocel Cellulose Ethers in Technical. The Dow Chemical Company, 2002. p:1-30.

EBUBE, N.K. e JONES, A.B. - Sustained release of acetaminophen from a heterogeneous mixture of two hydrophilic non-ionic cellulose ether polymers. Int. J. Pharm. 272 (2004) 19-27.

EMA - Guideline on process validation for finished products. 2014.

ENGELHARDT, J. - General Introduction on cellulose: sources, industest derivatives and commercial application of cellulose. Carbohydr. Eur. 12. 1995. p.5-14.

EUROPEAN PHARMACOPOEIA (Eur. Ph.) - 9th edition. Council of Europe, Strasbourg, 2017.

FAO/WHO - Evaluation of certain food additives and contaminants. Thirty-fifth report of the joint FAO/WHO expert committee on food additives., World Health Organ. Tech. Rep. Ser., 789. 1990.

FERREIRA, J. A. et al. - A new look to non-Fickian diffusion. Applied Mathematical Modelling. ISSN 0307904X. 39:1 (2015) 194-204.

FOOD AND DRUG ADMINISTRATION CDER, Guidance for Industry Q10 Pharmaceutical Development, Rockville, 2008.

FOOD AND DRUG ADMINISTRATION CDER, Guidance for Industry Q8 (R2)

Pharmaceutical Development, Rockville, 2009.

FOOD AND DRUG ADMINISTRATION CDER, Guidance for Industry Q8 Pharmaceutical Development, Rockville, 2006.

FOOD AND DRUG ADMINISTRATION CDER, Guidance for Industry Q9 Pharmaceutical Development, Rockville, 2006.

FOOD AND DRUG ADMINISTRATION. Final Report on Pharmaceutical cGMPs for the 21st Century – A Risk Based Approach, Rockville, 2004.

FOOD AND DRUG ADMINISTRATION. Guidance for Industry. PAT - A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance. Pharmaceutical cGMPs. Rockville, 2004.

FOOD AND DRUG ADMNISTRATION - Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System, 2000.

FORD, J.L. et al. - Importance of drug type, tablet shape and added diluents on drug release kinetics from hydroxypropyl-methylcellulose matrix tablets, Int. J. Pharm., 40, 223-234, 1987

FORD, J.L.; RUBINSTEIN, M.H.; HOGAN, J.E. - Dissolution of a poorly water soluble drug, indomethacin, from HPMC controlled release tablets, J. Pharm. Pharm., 37 (Supp.), 37, 1985.

FORD, J.L.; RUBINSTEIN, M.H.; HOGAN, J.E. - Formulation of sustained-release promethazine hydrochloride tablets using hydroxypropyl methyl cellulose matrixes, Int. J. Pharm., 24, 327-338; 1985.

GUSTAFSSON, C. et al. - Characterisation of particle properties and compaction behaviour of hydroxypropylmethylcellulose with different degrees of methoxy/hydroxypropyl substitution. Eur. J. Pharm. Sci. 9 (1999) 171-184.

HAMID A., et al. - Natural and synthetic polymers as drug carriers for delivery of therapeutic proteins. Polymer Reviews. . ISSN 15583716. 55:3 (2015) 371–406. doi: 10.1080/15583724.2014.995806.

HIGUCHI, T. - Mechanism of sustained-action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J. Pharm. Sci. 52 (1963) 1145-1149.

HIGUCHI, T. - Rate of release of medicaments from ointment bases containing drugs in suspension. J. Pharm. Sci. 50 (1961) 874-875.

ICH - International Conference on Harmonization - Quality of prolonged release oral solid dosage forms, Guidelines Eudra/Q/91/025/, 1991. p: 89-93.

KEARY, C.M. - Characterization of METHOCEL cellulose ethers by aqueous SEC with multiple detectors. Carbohydr. Polym. 45 (2001) 239-303.

KÖRNER, Anna et al. - Influence of different polymer types on the overall release mechanism in hydrophilic matrix tablets. Molecules. . ISSN 14203049. 14:8 (2009) 2699–2716. doi: 10.3390/molecules14082699.

KORSMEYER, R.W., et al. -. Mechanisms of solute release from. porous hydrophilic polymers. Int J Pharm. 15. 1983. p.25-35.

LEE, P.I. -Controlled drug release from polymeric matrices involving moving boundaries. In: Levis, D.H. (Ed.), Controlled Release of Pesticides and Pharmaceuticals, Plenum, New York. 1981. p. 30-48.

LI, C.L. et al. - The use of HPMC in oral drug delivery. J. Pharm. Pharmacol. 57 (2005) 533-546.

LOFTSSON, Thorsteinn - Essential Pharmacokinetics: A Primer for Pharmaceutical Scientists. USA: Elsevier Inc., 201. ISBN: 978-0-12-801411-0. p. 85-103.

LONGER, M.A. e ROBINSON, S. - Sustained release drug delivery systems: In Remington´s Pharmaceutical Sciences; 18th Ed.; Mark Easton: New York, 1990. p.1676-1693.

MALFROID, F. e BENTEJAC, R. - Formulation des comprimés à libération prolongée de type matrice hydro- phile étude de dérivés cellulosiques. Labo-Pharma-Probl. Techn. 30 (1982) 727-734.

MITCHELL, K., et al. - The influence of additives on the cloud point, disintegration and dissolution of hydroxypropyl methylcellulose gels and matrix tablets, Int. J. Pharm., 66, 233-242, 1990.

MITCHELL, K., et al. - The influence of the particle size of hydroxypropylmethylcellulose K15M on its hydration and performance in matrix tablets, Int. J. Pharm., 100, 175-179, 1993.

MOHAMED, Faiezah A. A. *et al.* - The effect of HPMC particle size on the drug release rate and the percolation threshold in extended-release mini-tablets. Drug Development and Industrial Pharmacy. . ISSN 0363-9045. 41:1 (2015) 70–78. doi: 10.3109/03639045.2013.845843.

MOLLER, H.; SIEWERT, M. - FIP Guidelines for dissolution testing of solid oral products. Pharm. Ind. 57 (1996) 362-369.

MONTGOMERY, D.C. - Design and Analysis of Experiments. 5th Edition. New York: John Wiley & Sons, Inc., 2004 ISBN: 0471316490.

NAGARAJAN, R. - Polymer–Surfactant Interactions. In Detergents for the New Millennium, Proceeding of New Horizons Conference, American Oil Chemists Society and Consumer Specialty Products Association, Fort Myers, FL, Oct 14–17, 2001.

ORLANDINI, S. [et. al] - Application of quality by design to the development of analytical separation methods. Anal. Bioanal. Chem. (2012).

PARK, H., et al. - Mucoadhesive hydrogels effective at neutral pH. Proc. Int. Symp. Control. Release Bioact. Mater. 16 (1989) 217-218.

PARK, H. e ROBINSON, J.R. - Mechanisms of mucoadhesion of poly(acrylic acid) hydrogels. Pharm. Res. 4 (1987) 457-464.

PEPPAS N.A., GURNY R. - Relation between the structure of polymers and the controlled release of active ingredients. Pharm Acta Helv.58: 1983. p.2-8.

PEPPAS N.A., LUSTING S.R. - Solute Diffusion in Hydrophilic Network Structures – Hydrogel in Medicine and Pharmacy, CRC Press, 1986.

PEPPAS N.A., SHALIN J.J. - A simple equation for the description of solute release. III. Coupling of diffusion and relaxation. Int. J. Pharm. Amsterdam, 57. 1989. p.169-172.

PEPPAS, N. A. et al. - Hydrogels in pharmaceutical formulations. European Journal of Pharmaceutics and Biopharmaceutics. . ISSN 09396411. 50:1 (2000) 27–46. doi: 10.1016/S0939-6411(00)00090-4.

PEPPAS, N.A.; BURI, P.A. - Surface, interfacial and molecular aspects of polymer bioadhesion on soft tissues. J. Control. Rel. 2 (1985) 257-275.

PEPPAS, N.A.; SÉGOT-CHICQ, S. - Les dispositifs à libération contrôlée pour la delivrance des princips actifs médicamenteux. II: Aspects fondamentaux de la diffusion des actifs dans des polymères. STP Pharma 1 (1985) 121-127.

PRAMOD K, et al. - Pharmaceutical product development: A quality by design approach. International Journal of Pharmaceutical Investigation. 2016;6(3):129-138. doi:10.4103/2230-973X.187350.

PRISTA, L.N. et al. - Tecnologia Farmacêutica. Lisboa: Fundação Calouste Gulbenkian. Volume I. 6ª Edição. 2002. p:325-478.

QIU, Y.; ZHANG, G. - Research and developmental aspects of oral controlled-release dosage forms. In Handbook of Pharmaceutical Controlled-Release Technology, New York: Marcel Dekker Inc. 2000. p:465-503.

QIU, Y., et al. –. Developing solid oral dosage forms: Pharmaceutical Theory & Practice. 2nd edition. Academic Press: New York. 2016. p: 519.

RAJABI-SIAHBOOMI. et al. - Structure and behaviour in hydrophilic matrix sustained release dosage forms: 4. Studies of water mobility and diffusion coefficients in the gel layer of HPMC tablets using NMR imaging, Pharm. Res., 13, p:376-380, 1996.

RANGA RAO, K.V.; et al. - Studies on factors affecting the release of drugs through cellulose matrices, Proc. Int. Symp. Cntr. Rel. Bioact. Mater., 15, p:101-102, 1988.

REINHART, C.T.; KORSMEYER R.W.; PEPPAS N.A. - Macromolecular network structure and its effects on drug and protein diffusion. Int. J. Pharm. Tech. & Prod. Mfr., 2. 1981. p.9–16.

RODRIGUEZ, C.F., et al. - Hydrophilic cellulose derivatives as drug delivery carriers. In Handbook of Pharmaceutical Controlled Release Technology; New York, Wise, D.L., Ed.; Marcel Dekker Inc. 2000. p: 1-30.

ROWE, R.C.; SHESKEY, P.J.; QUINN, M.E. - Handbook of pharmaceutical excipients - 6th Ed., Pharm. Press Ed., 2009.

SANGSHETTI, J.N., et al. - Quality by design approach: Regulatory need. Arab J Chem. In Press. 2014.

SINGH, D. R. L.; SHARMA, V. - Quality by Design (QbD) Approach in Pharmaceuticals: Status, Challenges and Next Steps. 2014.

SHESKEY, P.J., et al. - Effect of lubricant level, method of mixing, and duration of mixing on a controlled release matrix tablet containing hydroxypropyl methyl cellulose, Drug Dev. Ind. Pharm., 21 (19), 2151-2165, 1995.

SIEPMANN, J. e PEPPAS, N.A. - Modelling the drug release of delivery systems based on hydroxypropylmethylcellulose (HPMC). Adv. Drug Deliv. Rev. 48 (2001) 139-157.

SOLOMONIDOU, D., et al. - Effect of carbomer concentration and degree of neutralization on the mucoadhesive properties of polymers films. J. Biomater. Sci. Polym. Ed. 12 (2001) 1191-1205.

USP XXXVI - The National Formulary 31. 36th edition. Rockville: United States Pharmacopoeial Convention, Inc., 2013.

VEIGA, F. - Medicamentos orais de libertação controlada. Comprimidos matriciais hidrofilicos. Coimbra [s.n]. Provas de aptidão Pedagógica Cientifica apresentadas à Faculdade de Farmácia da Universidade de Coimbra. 1989. p:19-38.

VELASCO, M.V. et al. - Influence of drug: hydroxypropylmethylcellulose ratio, drug and polymer particle size and compression force on the release of diclofenac sodium from HPMC tablets. J. Control. Rel. 57 (1999) 75-85.

VILA JATO J.L. (Ed) - Tecnologia Farmaceutica I Vol, Ed. Sintesis, 2000.

VILA JATO, J.L. (Ed) - Tecnologia Farmaceutica II Vol, Ed. Sintesis, 2000.

VIRTANEN, S.; TALJA, R.; VUOTI, S. - Synthesis and melt processing of cellulose esters for preparation of thermoforming materials and extended drug release tablets. Carbohydrate Polymers. . ISSN 01448617. 177:August (2017) 105-115. doi: 10.1016/j.carbpol.2017.08.095.

WALLACE, J.W. - Cellulose derivatives and natural products utilized in pharmaceutics. Cellulose chemistry. In Swarbrick, J. and Boylan, J.C. Encyclopaedia of Pharmaceutical Technology. New York: Marcel Dekker, Vol. 2, 1990, pp. 319-337.

WELLING, P.G. Absorption of drugs. - In Encyclopaedia of Pharmaceutical Technology Swarbrick, New York, J. & Boylan, J.C. Ed.; Marcel Dekker Inc. 2002, Vol. 1, p:8-22.