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A QUALITY BY DESIGN APPROACH ON PHARMACEUTICAL DEVELOPMENT OF ORALLY DISINTEGRATING TABLET OF DIAZEPAM

Thesis submitted to the Faculty of Pharmacy, University of Coimbra
in partial fulfillment of the requirements for the degree of
Master of Science in Medicine Technologies

July 2014

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ABSTRACT

The purpose of this study was to develop an orally disintegrating tablet (ODT) of diazepam, taken Quality by Design (QbD) approach to achieve it.

Pharmaceutical development of ODT of diazepam started with the definition of the target quality attributes that it was expected for the final product. These QTPP formed the basis of the CQAs, which were identified consequently and used for all experiments.

The experimental part were divided in two parts: drug product development and manufacturing process development.

In drug product development study, an initial risk assessment was performed in order to identify the formulation variables that impact the CQAs. A feasibility study was performed and revealed the acceptable compression parameters and the importance of the binder on drug product. The factors identified on risk assessment, type and amount of disintegrant were analyzed and the results indicated crospovidone as the better superdisintegrant, allowing better ODT characteristics. Therefore, crospovidone was used in the next studies.

For manufacturing process development, an initial assessment of each unit operation was made using a Fishbone diagram, to identify potential variables of the process impact product quality. A risk assessment was undertaken to identify the process variables (CPPs) that that impact on product quality. The manufacturing process development was conducted in two studies. The first study evaluated impact of the scaling-up on the compression machine, and settled the amount of crospovidone at 30%. A 3^2 full factorial Design of Experiment (DoE) design was used in the second study in order to understand the relationship between the compression machine speed and compression force with the drug product quality attributes. Results indicated that compression force was the most critical compression process factor affecting hardness, disintegration time, wetting time and dissolution.

In summary, it was possible to development an ODT of diazepam through QbD.

Keywords: Orally Disintegrating Tablet, Quality by Design; Design of Experiment; superdisintegrant.

RESUMO

O objetivo deste estudo foi desenvolver comprimidos orodispersíveis de diazepam, numa abordagem *Quality by Design* (QbD).

O desenvolvimento farmacêutico dos comprimidos orodispersíveis de diazepam começou com a definição dos atributos de qualidade pretendidos para o produto final. A partir destes atributos de qualidade definiram-se os atributos de qualidade críticos.

A parte experimental foi dividida em duas partes: desenvolvimento da formulação e desenvolvimento do processo de fabrico.

O estudo de desenvolvimento da formulação, iniciou-se por uma avaliação de risco com o objectivo de identificar as variáveis da formulação que impactam os atributos de qualidade críticos. Foi efetuado um estudo prévio de viabilidade de processo que revelou os parâmetros de compressão e a importância da presença do agente aglutinante. Os fatores identificados na avaliação de risco, tipo e quantidade de desagregante foram analisados e os resultados indicaram a crospovidona como o melhor superdesagregante, permitindo melhores características num comprimido orodispersível. Deste modo, a crospovidona foi usada nos estudos seguintes.

Para o desenvolvimento do processo de fabrico, foi feita uma avaliação inicial de cada operação da unidade usando um diagrama de *Fishbone*, para identificar possíveis variáveis do processo que afetam a qualidade do produto. Foi efetuada uma avaliação de risco para identificar as variáveis do processo que impactam na qualidade do produto. O desenvolvimento do processo de fabrico foi realizado em dois estudos. O primeiro estudo avaliou o impacto do *scale-up* da máquina de compressão, e estabeleceu-se a quantidade de crospovidona em 30%. No segundo estudo foi delineada uma experiência 3^2 *full factorial*, a fim de compreender a relação entre a velocidade e força de compressão e os atributos de qualidade. Os resultados indicaram que a força de compressão foi o fator crítico processo de compressão afetando a dureza, tempo de desagregação, dissolução e tempo de molhagem.

Em resumo, estes resultados demonstram que foi possível desenvolver comprimidos orodispersíveis de diazepam através QbD.

Palavras-chave: Comprimidos orodispersíveis, *Quality by Design*; *Design of Experiments*; superdesagregante.

ACKNOWLEDGMENTS

Firstly, I would like to express my thanks to my supervisor at BIAL, Teófilo Vasconcelos for all confidence, motivation, precious advice and support given. Also, I would thanks to Prof. Dr. João José Sousa, supervisor at FFUC, for all helping, guidance and invaluable comments during the research. Them support give me more confidence, professional experience and it was particularly essential to the progress of this experience.

A special thanks to Prof Dr. Alberto Pais for all scientific helping and support on Design of Experiments analysis.

I would like to acknowledge Quality Control Laboratory and Quality Department of BIAL in name of José Carlos Ferreira and Paula Teixeira, and Pharmaceutical Development Laboratory in name of Ricardo Lima for all consideration and to BIAL for providing the opportunity to perform and develop all the research work in its facilities.

Special tanks go to colleagues at Quality Control Laboratory and Pharmaceutical Development Laboratory, for all kind of help. All of those were essential to the development of the project.

I am also grateful to all of my friends for giving me a helping hand during this whole research.

Lastly, I would like to thank my parents and my family for encouragement and unconditional support.

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CHAPTER I – INTRODUCTION

1. Orally Disintegration Tablets

1.1. History

Despite the remarkable development in drug delivery technology, orally drug delivery remains the preferred route for administration of drugs due the accurate dosage, low-cost of therapy, ease of administration and patient compliance.[1] In this case, tablets and capsules represents the most popular forms among oral drug delivery systems, occupying a large portion of oral dosage forms that are presently available. However, traditional tablets and capsules may have some inconvenient for patients with swallowing difficulties, especially paediatric and geriatric patients, people with conditions related to impaired swallowing, and for treatment of patients when compliance may be difficult (e.g., for psychiatric disorders). Moreover, orally administered conventional tablets or capsules can be a problem for travelling patient with limited access to water. To overcome these difficulties, a large number of solid oral dosage forms have been developed, as the orally disintegration tablets (ODTs).

Orally disintegrating tablets, classification assumed by United States Food and Drug Administration (FDA), is the general form of nomenclature for tablets that disintegrate rapidly or instantly in the oral cavity. In its turn, European Pharmacopoeia (Ph. Eur.) adopted the term orodispersible tablets. Despite the similarity between the names, they have owns its definition. The earliest United States regulatory definition for an ODT consisted in "a solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds when placed upon the tongue".[2] More recently, FDA approved a new guideline which recommend an *in vitro* disintegration time less than 30 seconds, when examined by the disintegration test or an alternative method, on United States Pharmacopeia (USP).[3] Also, it suggests a tablet weight not more than 500 mg, although the combined influence of tablet weight, size, and component solubility all factor into the acceptability of an ODT for both patients and regulators.[4] According to Ph. Eur., "orodispersible tablets are uncoated tablets intended to be placed in the mouth where they disperse rapidly before being swallowed". It also, should disintegrate within 3 minutes, when based on Ph. Eur. disintegration test method for tablets or capsules.[5]

Historically, Claritine (loratidine) was the first ODT form of a drug to get approval from the FDA in 1996. It was followed by Klonopin (clonazepam) in 1997, Maxalt (rizatriptan) in 1998. Today, there are several pharmaceutical companies present ODTs in their portfolio, as shown in Table I.

Product	Company	Indication
Zomig ZMT	AstraZeneca	Migraine
Zofran ODT	Glaxo SmithKline	Reactions to surgery, chemotherapy, radiation
Maxalt-MLT	Merck	Migraine
Claritan RadiTabs	Schering-Plough	Antihistamine
Aricept ODT	Eisai	Alzheimer's disease
Zyprexa Zydis	Eli Lilly	Schizophrenia, bipolar disorder
Benadryl Fastmelt products	Johnson & Johnson	Allergy, cold, sinus
Remeron SolTab	Organon	Depression

Table 1 – ODTs commercially available.

The first generation of ODT technologies revealed certain limitations. Despite these technologies produce tablets that dissolve rapidly in the mouth, provide convenience and ease of swallowing, they lack the ability to effectively mask poor-tasting active pharmaceutical ingredients and accommodate high doses. As a result, these technologies limited their application to non-bitter APIs and the therapeutic application to low dose drugs.[6] Furthermore, first generation ODTs are commonly characterized by high porosity, low density, and low hardness, making them brittle and difficult to handle.[6]

Today, the available generation of ODT technologies overcome the first generation of ODTs problems and offer unique applications. In fact, these new technologies combine a process to improve taste masking, allow a modified-release profile, and enhance bioavailability.[7-9] Consequently, new generation of ODT technologies provide higher API loading, more effective taste masking, low friability, cost-effective development, and more packaging options, expanding the range of therapeutic applications.[7-9] As a result, new generation ODTs exhibit excellent physical robustness, a pleasant taste in mouth and tremendous disintegration properties.

1.2. Ideal properties of ODTs

The performance of ODTs depends on its formulation and manufacturing and the most necessary property is the ability of rapidly disintegrating and dispersing or dissolving in the saliva. ODTs should show some characteristics to distinguish them from traditional conventional dosage forms. Ideal appropriate characteristics of these dosage forms include:[10-12]

- Require no water for oral administration, but it should dissolve or disintegrate in the mouth usually within few seconds
- Allow high drug loading

- Provide pleasant feeling in the mouth
- Be compatible with taste masking and other excipients
- Leave minimal or no residue in the mouth after oral administration
- Should be harder and less friable.

1.3. Advantages and Limitations of ODTs

The ODTs show the following advantages, in comparison to the traditional oral formulations:[13-16]

- Ease of administration to geriatric, paediatric, psychiatric and disabled patients who are unable or have difficulty in swallowing
- Does not require water for oral administration, being useful for patients who are travelling or do not have immediate access to water
- Easy manufacturing, accurate dosing, good physical and chemical stability as a solid dosage form
- Adaptable to conventional processing and packaging machinery, allowing the manufacturing of tablets at low cost
- Possibility of improved bioavailability due to rapid absorption and faster onset of therapeutic action, improving clinical performance and providing rapid drug therapy intervention. Also, it helps avoids hepatic metabolism by allowing pre-gastric drug absorption thus reducing the dose of drug required
- Can be designed to leave minimal or no residue in the mouth after administration and also to provide a pleasant mouth feel
- Provide new business opportunities in the form of product differentiation, patent-life extension, line extension, and life cycle management, and exclusivity of product promotion.

Despite the numerous benefits, this fast dissolving tablets may have some limitations, including:[17-21]

- The tablets usually have insufficient mechanical strength and therefore careful handling is required
- It may leave unpleasant taste in mouth if not formulated properly
- Drugs with relatively large doses are difficult to formulate into ODTs
- Requires special packaging for properly stabilization and safety of stable product
- It is hygroscopic in nature, so must kept in dry place.

1.4. Challenges in formulating ODTs

Despite the recent advances, formulation and manufacturing of ODTs still possess a great challenge for the formulation scientist, since they have a number of problems in the manufacturing and quality control.

A critical challenge and characteristic in oral drug delivery systems is palatability and mouth feel, affecting patient compliance. Many active pharmaceutical ingredients (API) have an offensive or bitter taste and require flavoring and sweeteners to overcome the unpleasant flavor. Other techniques are available for masking the bitter taste, which includes taste masking by ion-exchange resins, by coating with hydrophilic vehicles or using lipophilic vehicles.[22] Also, ODTs should disintegrate into fine particles in the oral cavity in order to leave minimal or no residue in mouth after oral administration. The addition of flavoring and cooling agents like menthol improves the mouth feel.[23]

For allowing disintegration of tablets in the oral cavity, ODTs should have a porous matrices or be compressed with very low compression force. These could result in soft, friable tablets with a weak mechanical strength. In other hand, tablets with high mechanical strength leads to a larger disintegrating time. Therefore, it is required a proper balance between the compression pressure and disintegrating time to get the quality ODT.[24]

The hygroscopicity of ODT excipients is other challenge to overcome during pharmaceutical development. Most of these excipients are highly soluble in water in order to enhance fast dissolving properties as well to create good mouth feel. To overcome this challenge and protect ODT from humidity a good packaging should be provided.[25]

The technology used for ODTs should be acceptable in terms of cost of the final product. Also, the special and specific packaging that they may need, could increase the cost to a remarkable extent.

1.5. Formulation aspects of ODTs

Important ingredients that are used in the formulation of ODTs should allow quick release of the drug, resulting in faster dissolution, promote a good taste and mouth feel, support mechanical strength of tablets, allows a good bioavaibility, keep the stability and exhibit swalloability properties. Excipients balance the properties of the active pharmaceutical ingredient in ODTs. This demands a thorough understanding of the chemistry of these excipients to prevent interaction with the actives.

For drug selection, several factors may be considered for development of ODTs. The

critical characteristics of a drug for dissolution in mouth and pregastric absorption orally disintegration dosage forms include: [26,27]

- Ability to permeate through the oral mucosa
- At least partially non-ionized at the oral cavity
- Have the ability to diffuse and partition into the epithelium of the upper gastrointestinal tract (log P > 1 or preferably >2)
- Small to moderate molecular weight (< 300)
- Low dose drugs preferably less than 50 mg
- Good stability in saliva and water
- No bitter or unacceptable taste and odour.

In contrast, the following characteristics may be unsuitable for drug delivery as an ODTs: [28]

- Short half-life and frequent dosing
- Very bitter or otherwise unacceptable taste
- Required controlled or sustained release
- Combination with anticholinergics.

Category	Examples
Anti-diabetics	Glipizide, Tolbutamide, Glibenclamide, Tolazamide, Gliclazide, Chlorpropamide
Anti-hypertensive	Minoxidil, Nimodipine, Amlodipine, Terazosine, Prazosin, Diltiazem
Anti-arrhythmics	Quinidine, Amiodarone, Disopyramide
Anti-histaminics	Loratadine, Cetrizine, Cinnarizine, Triprolidine, Texofenadine
Diuretics	Acetazolamide, Spironolactone, Furosemide, Amiloride
Analgesics	Ibuprofen, Ketoprofen, Diclofenac, Mefenamic acid, Piroxicam, Indomethacin
Antibacterial agents	Penincillin, Rifampicin, Trimethroprim, Cirpofloxacin, Tetracyclin, Doxycyclin
Anxiolytics, sedatives, hypnotics, neuroleptics	Diazepam, Alprazolam, Clozapine, Mylobarbitone, Lorazepam, Haloperidol, Nitrazepam , Midazolam, Phenobarbitone, Thioridazine, Oxazepam
Corticosteroids	Hydrocortisone, Betamethasone, Beclomethasone, Prednisolone
Gastro-intestinal agents	Ranitidine, Famotidine, Cimitidine, Omeprazole, Ondansteron, Domperidone

Table 2 – API used in ODT formulation.[29,30]

Researchers have formulated ODT for various categories of drugs, as shown in Table 2. These include cardiovascular agents, antiallergic, diuretics, analgesics, antibacterial agents, anxiolytics, sedatives, hypnotics, neuroleptics, corticosteroids and gastro-intestinal agents. In this work, it will be used diazepam as active pharmaceutical compound.

Concerning to excipient selection, the most used in orally disintegration dosage forms includes at least a disintegrant, a diluent, a lubricant, and optionally, a swelling agent, sweeteners, and flavoring agents. Excipients to be used for the preparation of ODTs should

disperse and dissolve in the mouth within a few seconds without leaving any residue, masks the taste of drug and offers a pleasant mouth feel, enables sufficient drug loading and remains relatively unaffected by changes in humidity or temperature. Therefore, excipients has an important role in the formulation of ODTs. These excipients, when incorporated in the formulation, offers the desired organoleptic properties and product efficacy. In formulation of ODTs, it can be used:

- Flavoring agents to increase product acceptability and patient compliance. Its intent to produce pleasant taste and mouth feel. Examples of flavors used are vanilla, citrus oil, fruit essence, eucalyptus oil and peppermint oil.
- Sweeteners, which can be natural or artificial and it act as bulking agents. They exhibit a good aqueous solubility and sweetness and have an important taste masking property. Typical sweeteners used in ODT formulation are aspartame, dextrose, fructose, mannitol, sorbitol and maltose.
- Fillers or diluents, which are added to formulations to enhance bulk of dosage form. It also improve cohesion, enhance flow properties of the powder and allow direct compression manufacturing. Mannitol, sorbitol, xylitol, calcium carbonate, magnesium carbonate, calcium sulfate, magnesium trisilicate are the fillers most used for formulating ODTs.
- Surface active agents, which reduce interfacial tension and thus enhances solubilization of ODTs. Examples of surface active agents are sodiumlaurlysulfate, sodiumdoecylsulfate, polyoxyethylene sorbitan fatty acid esters and polyoxyethylene stearate.
- Lubricants, which are incorporated into dosage forms to support the manufacturing process. It help to reduce friction and wear by introducing a lubricating film. Lubricants include calcium and magnesium stearate, polyethylene glycol, stearic acid and talc.
- Coloring agents, which help with product identification and are also used for consistency with flavors, particularly in children's formulations. Its enhance appearance and organoleptic properties of dosage form. Coloring agents include sunset yellow, red iron oxide and amaranth.
- Binders or adhesives, which are the substances that promotes cohesiveness. It maintains integrity of dosage form. Some common binders are povidone, PVP, Polyvinylalchol, Hydroxy propyl methylcellulose.
- Disintegrants, which increase the rate of disintegration and dissolution. For the

success of orally disintegrating tablet, the tablet having quick dissolving property which is achieved by superdisintegrants. The most common superdisintegrants are crospovidone, croscarmellose sodium, sodium starch glycolate, carboxymethylcellulose and modified corn starch. The next point details the most important aspects of superdisintegrants.

1.6. Superdisintegrants

As seen before, disintegrants are agents added to tablet formulations to promote the breakup of the tablet into smaller fragments in presence of water and the dispersion of the tablet matrix. This phenomenon increases the available surface area and promotes a more rapid release of the drug substance. Disintegrants have the important purpose to compete against the efficiency of the binder and the physical forces that act in tableting. In its turn, superdisintegrant refers to a substance which achieves disintegration faster than the disintegrants conventionally used, resulting in higher rates of drug dissolution.[31] In fact, disintegration has received a significant consideration as an critical step in obtaining faster drug release, improving the availability of the drug.[32] Therefore, the proper choice of superdisintegrants have a primary role in ODT formulation. Ideally, superdisintegrant should exhibit poor solubility, leads to poor gel formation, have good hydration capacity, compressibility and flow properties and no tendency to form complexes with the drugs.

The mechanism for tablet disintegration affects decisively the rate and extent of tablet disintegration and drug release, and depends on the type disintegrant used. There are some mechanisms responsible for the breaking of tablets into small particles, including:

- Swelling
- Porosity and capillary action (Wicking)
- Deformation Recovery
- Particle Repulsive Forces
- Heat of wetting
- Chemical reaction
- Enzymatic reaction

Swelling is the most widely accepted and principal mechanism for tablet disintegration. In this situation, superdisintegrants particles swells when they come in contact with water, resulting in loss of adhesiveness of the tablet components. In consequence the matrix breaks up into fine particles. It is important to note that tablets with high porosity show poor disintegration due to lack of adequate swelling force. The same result are

presented in tablets with very low porosity: water has troubles in penetrates into matrix, and so, superdisintegrants do not swells.[33,34]

Capillary action is the mechanism by which the water penetrates into the tablets and replace the air adsorbed on the particles. Tablet porosity provides pathways for the penetration and as result, intramolecular bonds break and the tablet disintegrates into smaller particles. The water penetration depends on hydrophilicity of the tablet components and on the porous structure of the tablet.[33,34]

In deformation recovery, the deformed particles get into their normal structure when they are exposed to aqueous environment. These deformed particles are result from the high compaction force during tableting. The energy potential of the particle size increasing causes a breaking up of the tablet.[33,34]

The particle repulsion mechanism is based on the electric repulsive forces between particles, in presence of water, resulting in tablet disintegration. This mechanism is secondary to wicking.[33,34]

Another mechanism of disintegration is the chemical reaction between tartaric acid and citric acid (acids) with alkali metal carbonates or bicarbonates (bases) in presence of water. This reaction release CO_2 in gas form, and creates a pressure within the tablet, promoting the tablet disintegration. These disintegrants are highly sensitive to humidity level and temperature, requiring a strict control environment during manufacturing and good packaging material.[33,34]

In heat of wetting, disintegrants exhibit exothermic properties, and when wetted, a stress is generated, which helps the disintegration of tablet.[33,34]

Enzymes can also act as disintegrants. This substances, through enzymatic reaction, disrupt the binding action of binder and facilitates the disintegration. The water absorption and swelling mechanism are enhanced. Amylase, protease and cellulase are some examples of disintegrating enzymes.[33,34]

Despite all mechanisms described, swelling, wicking and deformation are the three major mechanisms observed for tablet disintegration. Also, it is noted that a combination action of mechanisms occurs for a large number of superdisintegrants.[35]

Superdisintegrants can be classified into 2 classes, based on its origin:

- Natural
- Synthetic

Natural superdisintegrants are original from Nature and in comparison to synthetic superdisintegrants, are comparatively cheaper, abundantly accessible, non-irritating and

nontoxic.[36] These superdisintegrants are bio-acceptable, eco-friendly and come from a renewable source. Also, based on their molecular structures, they are capable of chemical modifications, generating superdisintegrants with different properties.[37] Mucilages and gums are the most explored substances as natural superdisintegrants. Table 3 shows the most common natural superdisintegrants used in ODT formulation.

Superdisintegrant	Mechanism
Alginate (Alginic acid)	It has affinity for water absorption and high sorption
Soy polysaccharides	Rapid swelling in aqueous medium or wicking action
Gums (Guar gums, gum Karaya, Agar, Gellan gum)	Swells in water
Chitin and Chitosan	Moisture sorption and water uptake
Smecta	It has a large specific area and high affinity for water makes it good disintegrant
Isapghula Husk	It has high swellability and gives uniform and rapid disintegration

Table 3 – Natural superdisintegrants.

The group of synthetic superdisintegrants integrates a variety of compounds, being modified cellulose, crosslinked polyvinyl-pyrrolidone and modified starch the classes of superdisintegrants most commonly used in ODT formulation. These fast working disintegrants are chemically modified polymeric molecules, typically by crosslinking the organic chains. Synthetic superdisintegrants are more effective in lower concentrations than standard disintegrants and the compressibility and flowability are less affect in the presence of these substances.[38] However, they have a hygroscopic nature, which can affect moisture sensitive drugs, and some of them are anionic and may cause, *in vitro*, some slight binding with cationic drugs.[39] The most common synthetic superdisintegrants used are sodium starch glycolate, crospovidone and croscarmellose sodium and they will be subject of study in this work.

Sodium starch glycolate is, chemically, a sodium salt of carboxymethyl ether of starch. It is white to off white tasteless, odorless, relatively free flowing powder, and it can be used in direct compression and wet-granulation processes. Figure 1 shows the structure of sodium starch glycolate. The mechanism by which disintegration occurs is by rapid water absorption and swell leading to a huge increase in volume which result in rapid and uniform tablet disintegration. However, sodium starch glycolate gels on prolonged exposure to water and at high concentration.[39]The extent of crosslinking and the degree of substitution are important factors in disintegration properties of this substance.[40] In fact, crosslinking allows the reduction of the water soluble fraction of the polymer and the viscosity of dispersion in

water. In addition, the inclusion of large hydrophilic carboxymethyl groups disrupt the hydrogen bonding within the polymer structure, allowing water penetration into molecule. A good balance between the degree of substitution and the extent of cross-linking allows for rapid water uptake by the polymer without the formation of a viscous gel that might hinder dissolution.[41] For instance, natural pre-dried starches swell in water to the extent of 10-20 percent and the modified starches increase in volume by 200-300 percent in water.[42] Sodium starch glycolate is commercially available as Explotab® and Primogel® among others.

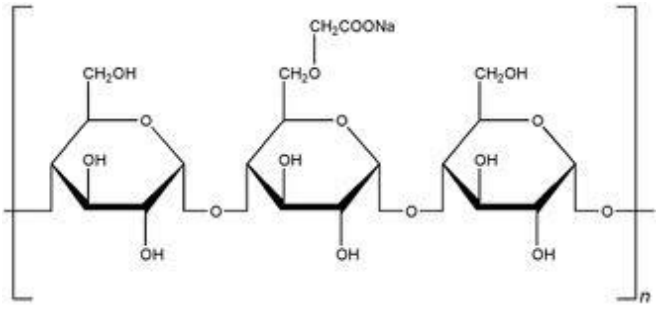

Figure 1 – Basic chemical structure of sodium starch glycolate.

Croscarmellose sodium is a cross-linked polymer of carboxymethylcellulose and it may be used in tablets prepared by direct compression and wet granulation processes. Crosslinking makes it insoluble, hydrophilic, highly absorbent material. Thus, croscarmellose sodium swells in a large extent in aqueous medium, with minimal gel formation, resulting in rapid disintegration.[43] Also, the fibrous structure of croscarmellose particles allows intra and extraparticulate wicking, results in rapid disintegration.[44] Figure 2 shows the chemical structure of croscarmellose sodium. This modified cellulose substance reveals a degree of substitution higher than that of sodium starch glycolate. Furthermore, the mechanism of cross-linking is different, where the carboxymethyl groups are themselves used to crosslink the cellulose chains. Croscarmellose sodium swells 4-8 folds in less than 10 seconds.[45] Ac-Di-Sol® or Primellose® are examples of croscarmellose sodium commercially available.

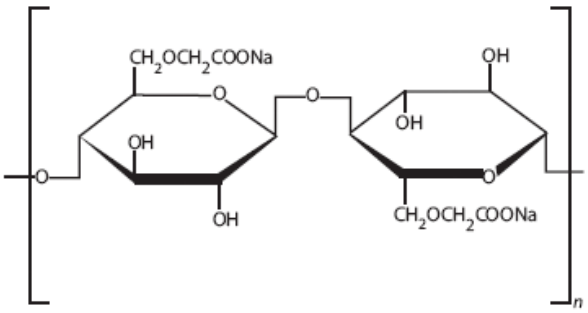

Figure 2 – Basic chemical structure of croscarmellose sodium.

Crospovidone is a synthetic homopolymer of cross-linked N-vinyl pyrrolidinone and it

is a white, free flowing, compressible powder and hygroscopic in nature. Direct compression, wet and dry granulation processes can be used to prepared tablets with crospovidone. Besides the rapid swelling capacity in water, without gel formation, crospovidone use deformation and wicking action as mechanism for tablet disintegration. The basic chemical structure of crospovidone is represented in Figure 3. In fact, unlike other superdisintegrants which have a lower crosslink density and, as a result, form gels when fully hydrated, particularly at the higher use levels in ODT formulations, crospovidone has a higher degree of crosslinking, providing rapid swelling and dispersion in water, with no gel formation even after prolonged exposure. Also, the granular and highly porous morphology of crospovidone particles facilitates water absorption by capillary action and excellent compressible properties, unlike other superdisintegrants which are poorly or non-compressible, resulting in extremely deformed crospovidone particles. Therefore, crospovidone uses a combination of deformation, wicking and swelling actions to tablet disintegration: when the water contacts the deformed crospovidone particles, being wicked into the tablet, the particles recuperate their normal structure and then swell, resulting in rapid volume expansion and high hydrostatic pressures that cause tablet disintegration.[36,39] Crospovidone is commercially available as Polyplasdone™ or Kollidon® among others.

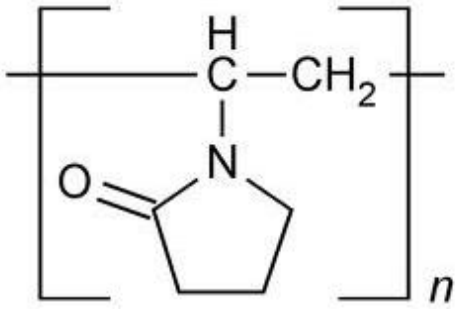

Figure 3 – Basic chemical structure of crospovidone.

Table 4 resumes the characteristics and properties of the superdisintegrants used in the work.

Superdisintegrant	Chemical structure	Mechanism
Sodium Starch Glycolate	Sodium salt of carboxymethyl ether of starch	Water uptake followed by rapid and enormous swelling
Croscarmellose Sodium	Crosslinked from sodium carboxymethylcellulose	Swelling with minimal gelling and wicking
Crospovidone	Synthetic homopolymer of cross-linked N-vinyl-2-pyrrolidone	Combination of deformation, wicking and swelling actions

Table 4 – Characteristics and properties of superdisintegrants.

1.7. Technology used in ODT formulation

The performance of ODTs depends on the technologies used in their manufacturing. A number of different techniques such as direct compression, freeze drying/lyophilization, moulding, mass extrusion or spray drying are used for manufacturing ODTs.

The three conventional technologies most commonly used are direct compression, freeze drying, and molding.[46-48] Direct compression is the favorite method since it uses conventional equipment, commonly available excipients and a limited number of processing steps that minimizing manufacturing costs, and provides strong tablets that can be handled without disintegrating. Freeze drying or lyophilization is the process in which water is sublimed from the product after it is frozen. The resulted tablets have an amorphous porous structure and are fragile, requiring a special blister pack, and a higher cost for equipment and packaging. Freeze drying also requires longer processing time. The tablets prepared by lyophilization disintegrate rapidly in less than 5 seconds due to quick penetration of saliva. Also, lyophilization is useful for heat sensitive drugs. Tablets prepared by moulding are solid dispersions. The major advantage of this technique is that as the dispersion matrix is made from water soluble sugars, moulded tablets disintegrate more rapidly and offer improved taste Molded tablets are typically soft and can break during handling or when blister packets are opened. Others conventional technologies included: mass extrusion, sublimation, spray drying, cotton candy process and nanonization.[49-52]

The new generation of ODT technologies overcomes many of conventional technologies problems and offers unique applications. Some can be combined with other drug delivery technologies for enhanced therapeutic benefits. Some patented formulation technologies, used to formulate the fast disintegrating tablets are described in Table 5.[53]

Patented technology	Company	Commercially available products
AdvaTab™	Eurand	AdvaTab Cetrizine, AdvaTab Paracetamol
Durasolv	Cima Labs Inc.	NuLev, Zomig ZMT
Flashtab	Prographarm	Nurofen®, Flashtab®
Lyoc™	Cephalon-France, Inc.	Sermion®, Paralyoc®, Seglor®
Orasolv	Cima Labs Inc.	Remeron Soltab, Tempra FirstTabs
Quicksolv	Janssen Pharmaceutica	Risperdal Quicklet™, Propulsid®
Oraquick	KV Pharmaceutical Co., Inc.	Hyoscyamine Sulfate ODT
Wowtab	Pfizer/Yamanouchi Pharma	Benadryl Allergy, Sinus Fastmelt
Zydis	Catalent	Ativan®, Claritin, Imodium®, Feldene melt, Zyprexa®

Table 5 – Patented formulation technologies for ODTs.

2. Quality by Design

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.[54]

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, Food and Drug Administration (FDA) announced the "cGMP for the 21st Century: A Risk based Approach" Initiative.[55] 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).[56] 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.[54,57-59]

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".[54] 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".[57]

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 6 compares the current state to the desired QbD state.

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; postapproval changes needed	Continual improvement enabled within design space

Table 6 – Comparison between the current state and the desired QbD state.

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 4. 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 4 – Quality by Design concept.

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 5 presents the guidelines that explain QbD.

Figure 5 – ICH Q8/Q9/Q10 triangle in QbD paradigm.

The application of QbD presents several advantages and can be summarized as:[60]

- 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 analyzed
- It offers robust method or process
- Business benefits are also driving force to adopt QbD

2.2. Elements of Quality 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

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".[57] 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".[3] 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.[58] 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.

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.[58]

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.[58] 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:[58]

- 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, Active Pharmaceutical Ingredient (API), starting materials, APIs, 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.[58] Additionally, the pharmaceutical industry can evaluate the risk using recognized risk management tools. Some of these tools are:[58]

- Basic risk management facilitation methods (flowcharts, check sheets, cause and effect diagram, etc.)
- Failure Mode Effects Analysis (FMEA)
- Failure Mode, Effects and Criticality Analysis (FMECA)
- Fault Tree Analysis (FTA)
- Hazard Analysis and Critical Control Points (HACCP)
- Hazard Operability Analysis (HAZOP)
- Preliminary Hazard Analysis (PHA)
- Risk ranking and filtering.

These tools might be adapted for use in specific areas to drug substance and drug product quality. Also, quality risk management methods and some supporting statistical tools can be used in combination. Combined use provides flexibility that can facilitate the application of quality risk management principles.[58]

The statistical tools can support and facilitate quality risk management. They can enable effective data assessment, aid in determining the significance of the data set(s), and facilitate more reliable decision making. Example of statistical tool are Design of Experiments, Control Charts, Histograms, etc.

2.2.2.1. 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.

Created by Sir Ronal A. Fisher in the 1920s and 1930s, DoE is defined as a structured and efficient statistical method for planning experiments, so that the data obtained can be analyzed to yield valid and objective conclusions and for determining the relationships among the factors affecting a process and its output.[57]

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 6. The measured responses describe the properties of the investigated system. By changing the most influential factors (e.g. amount of disintegrant, time of mixture, force of compression) the features of the system might be altered according to a response (e.g. disintegration time, content uniformity, hardness).

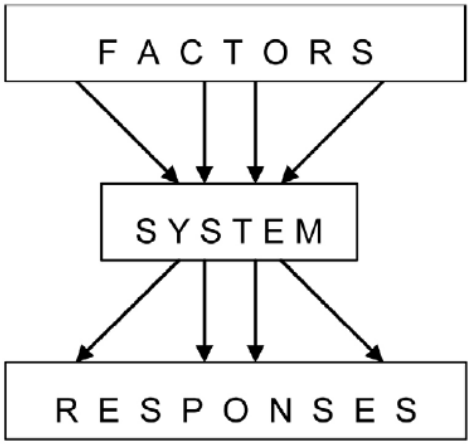

Figure 6 – A "Black Box" Process Model Schematic.

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 humidity.

Once factors have been chosen and responses measured, it is desirable to get an understanding of the relationship between them, that is, linking the changes in the factors to the changes in the responses 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 100% 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.[61]

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).[61] 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

2.2.3. 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."[57]

A Design Space is a way to represent the product and process understanding which will be establish (Figure 7). 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.

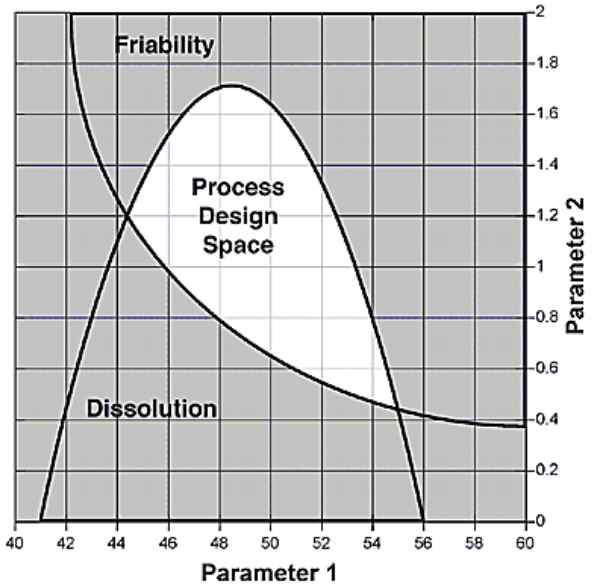

Figure 7 – Potential process design space, comprised of the overlap region of design ranges for friability and or dissolution.[58]

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 8 shows how Control Strategy are connected and interact with Design Space and Knowledge Space.

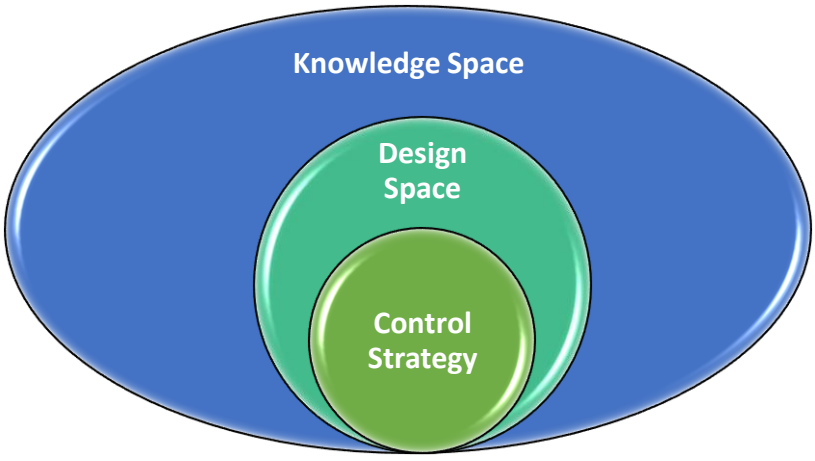

Figure 8 – Linkage between Knowledge Space, Design Space, and Control Strategy.

Control Strategy is defined as "a planned set of controls, derived from current product and process understanding that ensures process performance and product quality. The 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."[57]

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. This 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.[57]

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

1.2.5. 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.[59] In fact, PQS facilitate continual improvement, helping the identification and implementation of appropriate product and process quality improvements, reducing the variability, and identifying and prioritizing areas for continual 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. Linkages among the Design Space, Control Strategy, CQA and QTPP are an important part of this shared knowledge.[59]

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.[57]

3. Diazepam as Model

Diazepam, the most representative benzodiazepine, is widely used as sedative, anxiolytic and anticonvulsant agent.[62] For rapid onset action, diazepam is very useful in suppressing epileptic convulsions, epileptic seizures, anxiety attacks and panic attacks.[63]

Chemically, diazepam is 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one. It is a colorless to light yellow crystalline compound, insoluble in water. The empirical formula is $C_{16}H_{13}ClN_2O$ and the molecular weight is 284.75. The structural formula is represented in Figure 9.

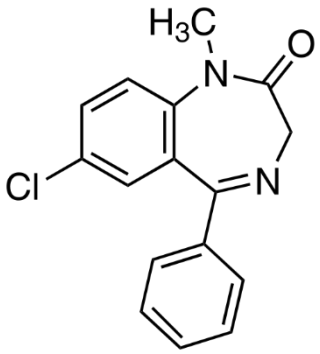

Figure 9 – Structural formula of diazepam.

As benzodiazepines, diazepam is a positive allosteric modulator of the GABA type A receptors ($GABA_A$). The binding of diazepam to the $GABA_A$ receptor increases the affinity of gamma amino butyric acid (GABA) and its receptor, thereby increasing the opening frequency of $GABA_A$ receptor. As a consequence of this diazepam potentiate GABAergic neurotransmission: the binding of GABA to the site opens the chloride channel, resulting in a hyperpolarized cell membrane that prevents further excitation of the cell. The excitability of the neurons is therefore diminished.

Although intravenous therapy is the most rapid way to get a rapid action, this route of drug administration shows some inconvenient to the patient, such as the pain, the syringe manager, the risk of needle infection, etc., carrying discomfort and poor patient compliance. Oral immediate-release dosage forms can be a good alternative to intravenous therapy. However, diazepam exhibits poor aqueous solubility that produces erratic and delayed absorption when administered orally. In fact, diazepam is a poorly soluble, highly permeable Biopharmaceutics Classification System (BCS) Class II compound.[64]

The drugs of class II have a high absorption but a low dissolution number. Therefore, a faster absorption of diazepam requires rapid dissolution from the tablet, being *in vivo* drug dissolution the rate-limiting step for absorption.

Other characteristics make diazepam a good model to develop an orally disintegrating tablet:[65,66]

- log P: 2.82
- pKa: 3.4

4. Objectives

The main objective of this work was the development of ODTs of diazepam and studying effect of formulation and process variables on formulations, 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. On the basis of this information, the first aim of the project was define the QTPP and identify the quality attributes that impact directly the product quality.

A key objective of risk assessment in pharmaceutical development was 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, namely composition (binder presence and disintegrant type and amount) and process parameters (compression force).

As a third objective, it was intended to provide approaches to the rational development of a Design Space for the current process. In consequence, DoE was used to understand the interaction between critical formulation and process variables and the quality attributes identified as critical. Particularly, it was studied the impact of disintegrant and compression force parameters on CQAs of an orally disintegrating diazepam tablet.

CHAPTER II – MATERIALS AND METHODS

1. Material

Diazepam, lactose, povidone, magnesium stearate, croscarmellose sodium, sodium starch glycolate, crospovidone were used in the manufacture of diazepam ODT tablet and were provided by BIAL.

Hydrochloride acid 35-37% (Sigma-Aldrich, Germany), sodium phosphate dibasic (Merck KGaA, Germany), potassium phosphate monobasic (Merck KGaA, Germany), sodium chloride (Merck KGaA, Germany), diazepam reference standard (USP, USA).

2. Methods

2.1. Batch Manufacturing

The manufacturing process consisted in a direct compression. Where, diazepam, lactose, disintegrant and povidone were blended for 15 minutes. Magnesium stearate was then added to the previous blend and mixed for 5 minutes more, and the obtained blend was compressed.

2.2. Analytical Techniques

2.2.1. Weight variation

Randomly, twenty tablets were selected after compression and the mean weight was determinated (METTLER XS205 Balance, USA). None of the tablets deviated from the average weight by more than ± 7.5%.

2.2.2. Dissolution

In vitro drug release was performed for diazepam ODT according to the USP30-NF25 "Dissolution procedure" for immediate release dosage forms. A minimum of 6 tablets of each formula were tested. The dissolution of oral disintegrating tablets was executed using USP 30 (apparatus 2) paddle method (Vankel VK700 Dissolutor, USA). Dissolution was carried out in 900 ml of HCl 0.1M medium for 15 minutes. The paddle was rotated at 100 rpm at 37±0.5 °C.

Samples were filtered through a 0.45 µm pore size membrane filter (Millipore Co., USA) and analyzed spectrophotometrically (Shimadzu UV2101PC UV-Vis Spectrophotometer, Japan) at 284 nm.

2.2.3. Disintegration

In vitro disintegration test was assessed according to the USP30-NF25 requirements. One dosage unit was put in each of the six tubes of the basket. The apparatus was operated, using distilled water as the immersion fluid, maintained at 37°C±2°C. Time for complete disintegration of each tablet, standard deviation and relative standard deviation were calculated.

2.2.4. Hardness

Tablet hardness was determined using the Hardness Tester (Pharmatest PTB311 Hardness Tester, Germany) for 10 tablets of each batch; the average hardness, standard deviation and relative standard variation were reported.

2.2.5. Wetting Time

Five circular tissue paper of 10 cm diameter were placed in a Petri dish. 10 ml of simulated saliva pH (pH 6.8 phosphate buffer) was poured into the tissue paper placed in the Petri dish. Few drops of crystal violet solution were added to the Petri dish. A tablet was placed carefully on the surface of the tissue paper. The time required for the solution to reach upper surface of the tablet was noted as the wetting time.[67]

2.2.6. Water Absorption Ratio

The weight of the tablet before keeping in the Petri dish was noted (W_2). Fully wetted tablet from the Petri dish was taken and reweighed (W_1).[67]

The water absorption ratio can be determined according to the following formula:

$$Water\ Absorption\ Ratio = \frac{W_1 - W_2}{W_2} \times 100$$

2.3. Quality by Design Tools

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 the level of risk based on our improved product and process understanding. The relative risk that each attribute was ranked as high, medium, or low, as shown in Table 7. 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.

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.

Table 7 – Overview of relative risk ranking system.

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

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 lead improvement 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 disciplined 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 causation. Finally, it can help the team answer the question of where to begin the process of improvement.

2.3.3. Design of Experiment

For DoE, a two factors three variables (level) (3^2) factorial was used in first and second steps which requires 9 experiments in each step. In the first step, the two factors X_1, type of disintegrant and X_2, level of disintegrant are represented by –1, 0, and +1, corresponding to the low, middle and high values respectively.

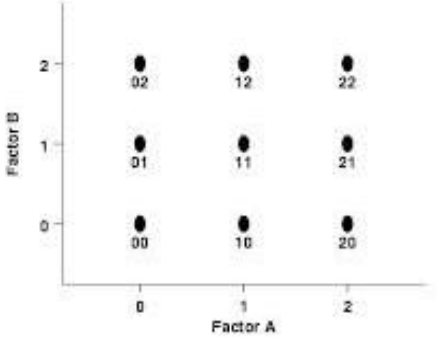

Figure 10 – 3^2 full factorial design.

The following quadratic model was built to describe the response:

$$Y_i = b_0 + b_1X_1 + b_2X_2 + b_{11}X_1^2 + b_{12}X_2^2 + b_{13}X_1X_2$$

Y_i is the dependent variable or the response, b_0 is the arithmetic mean response of the nine runs, and b_1 and b_2 is the estimated coefficient for the factor X_1 and X_2, respectively. The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value. The interaction terms (X_1X_2) show how the response changes when two factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate non-linearity.

In the second step, the two factors X_1, press speed and X_2, compression force are represented by –1, 0, and +1, corresponding to the low, middle and high values respectively.

2.4. Statistical Data Analysis

The mean ± standard deviation of the experiments results were analyzed using Mann-Whitney test. Differences were considered significant if the associated probability level (p) was lower than 0.05.

The statistical analysis of the factorial design batches was performed by multiple linear regression analysis carried out in Microsoft Excel 2013.

CHAPTER III – EXPERIMENTAL DESIGN

1. Quality Target Product Profile and Critical Quality Attributes

The pharmaceutical development of diazepam ODTs begins with identification of the desired dosage form and performance attributes through the target product profile. Diazepam ODTs are being developed for the treatment of epileptic convulsions, epileptic seizures, anxiety attacks and panic attacks. The pharmaceutical target profile for diazepam is a safe efficacious ODT that will facilitate patient compliance and promotes a rapid onset action. The manufacturing process for the tablet should be robust and reproducible, and should result in a product that meets the appropriate drug product critical quality attributes. The drug product should be packaged in a container closure system that will provide adequate protection from moisture, protection through distribution and use as well as convenience of use for the patient.

Table 8 summarizes the expected quality profile for drug product.

QTPP elements	Target
Dosage form	Orally Disintegrating Tablet
Route of administration	Oral
Dosage strength	5 mg
Pharmacokinetics	T_{max} in 2 hours or less
Palatability	Minimum bitter taste intensity and duration, absence of gritty texture desirable
Appearance	Tablet conforming to description shape and size
Identity	Positive for diazepam
Assay	95 – 105%
Impurities	Known impurity: NMT 0.5%, Any unknown impurity: NMT 0.2%, Total impurities: NMT 1.0%
Water	NMT 1%
Content Uniformity	Meets UPS criteria
Hardness	NLT 10 N
Friability	NMT 1,0%
Dissolution	NLT 80 % (Q) at 15 minutes
Disintegration	NMT 30 seconds
Microbiology	Meets USP criteria

Table 8 – QTPP elements expected.

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 CQAs definition were based on empirical evidence derived from previous experimentation as well as similar experiences with other products. Table 9 indicates which quality attributes were classified as CQAs.

CQA	Justification
Hardness	Hardness will affect friability, disintegration and dissolution which can impact the bioavailability. Both formulation and process variables affect the hardness.
Disintegration	Disintegration will affect dissolution, and therefore can impact the bioavailability. Both formulation and process variables affect the disintegration.
Friability	Friability should be sufficient to ensure physical integrity during packaging, transport and patient handling. Both formulation and process variables affect the friability.
Assay	Assay variability will affect safety and efficacy. Process variables may affect the assay of the drug product.
Impurities	Degradation products can impact safety and must be controlled based on compendial/ICH requirements.
Content Uniformity	Variability in content uniformity will affect safety and efficacy. Both formulation and process variables impact content uniformity.
Dissolution	Failure to meet the dissolution specification can impact bioavailability. Both formulation and process variables affect the dissolution profile.
Palatability	Palatability influence decisively the patient compliance and should be appropriate for target patient population.

Table 9 – Critical Quality Attributes.

2. Formulation and Manufacturing Process Selection

Table 10 lists the composition of diazepam ODT. This formulation was composed by Diazepam, a filler, a binder, superdisintegrant and a lubricant.

Lactose is a widely used excipient and was selected as filler due to its water solubility and acceptable compressibility properties. A direct compression grade of lactose was selected and its amount varied accordingly to the superdisintegrant content. A binder was included in the formulation in a very small amount in order to improve the mechanical properties of the tablets. Povidone was selected due to its acceptable compressibility in a dry from and due to its water solubility. Magnesium stearate which is the most used lubricant was selected due to its good compressibility properties in a relatively low concentration. Moreover, the level provided for each excipient is consistent with previous experience and based on literature. The formulation has a final mass of 220 mg.

Ingredient	Function	Quantity (mg)
Diazepam	Active Pharmaceutical Compound	5
Lactose 80 M	Filler	139.0 - 183.0
Povidone	Binder	0 - 5.6
Superdisintegrant	Disintegrant	22 – 66
Magnesium stearate	Lubrificant	4.4

Table 10 – Formulation composition of diazepam ODT.

A direct compression process was chosen based on prior scientific knowledge of products with similar physical and chemical properties, advantages of the process and available technologies and equipment. Figure 11 shows the flowchart of the manufacturing process of diazepam ODT.

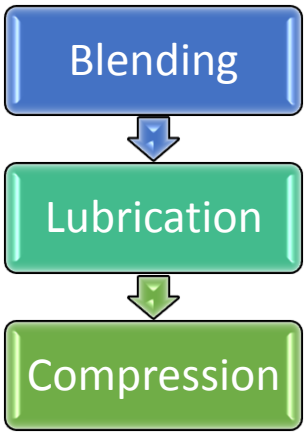

Figure 11 – Flowchart of manufacturing process.

Diazepam, lactose, disintegrant and povidone were blended for 15 minutes at 25 rpm. Then, magnesium stearate was added to the previous blend and mixed for 5 minutes more at

25 rpm. Finally, the obtained blend was compressed.

A risk analysis, in accordance with ICH Q9, was used to establish which variables and unit operations were likely to have the greatest impact on product quality. This initial risk assessment is shown in Table 11.

CQA	Variables			
	Formulation	**Blending**	**Lubrication**	**Compression**
Hardness	High	Low	Medium	High
Disintegration	High	Low	Medium	High
Friability	High	Low	Low	High
Assay	Low	High	Low	High
Impurities	High	Low	Low	Low
Content Uniformity	High	High	Low	Low
Dissolution	High	Medium	Low	High
Palatability	High	Low	Low	Low

Table 11 – Risk assessment to identify variables potentially impacting product quality.

From the perspective of the project purposes, it was investigated the CQAs of the drug product that has a high potential to be impacted by the formulation and the manufacturing process:

- Hardness
- Disintegration
- Dissolution

3. Drug Product Formulation Development

3.1. Initial risk assessment

In this initial risk assessment for formulation development, the manufacturing process has not been established in detail. The study was conducted in a laboratory scale, using a hydraulic press for the compression step. The use of the hydraulic compression press would allow a better control of the compression force applied as well as the compression time. Therefore, risks were rated assuming a similar behavior between the equipment used in the formulation development and in the manufacturing process development.

CQA	Formulation Variables				
	Diazepam	Lactose M80	Povidone	Disintegrant	Magnesium stearate
Hardness	Low	Low	Medium	Medium	Low
Disintegration	Low	Low	Low	High	Low
Dissolution	High	Low	Medium	High	Medium

Table 12 – Initial risk assessment of the formulation variables.

The physical and chemical properties of diazepam have some impact in the CQAs, particularly in dissolution. The drug substance is a BCS class II compound and therefore, it was considered that the diazepam particle size is a critical variable affecting dissolution.

Lactose 80 M, as filler, is not expected to have a decisive influence over the CQAs defined, especially because its grade is defined as 80M which is the most adequate for direct compression. As a consequence, the risk is considered low for all CQAs.

Povidone, as binder, affects directly tablet cohesiveness and breaking force, but can be controlled during compression. Therefore its risk is considered medium for hardness. In a less extension it can also affect dissolution and disintegration, which can be managed by the type and amount of disintegrant. Therefore, both quality attributes have a medium and low risk, respectably.

Regarding the defined CQAs, the disintegrant is considered as a critical variable and was subject of study. Disintegrant level impact the disintegration time and, ultimately, dissolution. Since achieving rapid disintegration is important for an ODT containing a BCS class II compound, the risk is high. Therefore, three disintegrants were studied, sodium starch glycolate, croscarmellose sodium and crospovidone, at different level.

As lubricant, magnesium stearate may have an influence in dissolution since lubrication due to excessive lubricant may retard the drug release. It can also have some impact in the tablet hardness due to over-blending. However this risk is minimized by the use of a brittle

filler (lactose). Consequently, it is considered a medium risk variable.

The risk assessment also indicates that hardness and disintegration time should be used as the response variables. Additionally, to predict the behavior of the tablet in the mouth, the wetting time was tested. As well, water absorption ratio were tested to understand the mechanism of disintegration of the different disintegrant used.

3.2. Study Design

Formulation development was focused on evaluation of the high risk formulation variables as identified in the initial risk assessment shown in Table 12.

The formulation development was conducted in two studies: the first formulation study was a feasibility study of the compression step and also studied the impact of the binder on the drug product CQAs and the second formulation study was conducted to allow the selection of the disintegrant and it level. Formulation development studies were conducted at laboratory scale.

3.2.1. Feasibility Studies

The first formulation study evaluated the feasibility of the manufacturing process and studied the impact of the binder on the drug product CQAs. In order to understand the properties of the initial formulation and the compression parameters to produce tablets by direct compression, four formulations were prepared with varying the superdisintegrant and the presence of binder as shows Table 13. All four formulations were prepared without the drug substance.

Formulation code	**A1**	**B1**	**A1'**	**B1'**
Superdisintegrant	Sodium starch glycolate at 10 %	Croscarmellose sodium at 10 %	Sodium starch glycolate at 10 %	Croscarmellose sodium at 10 %
Binder	Povidone	Povidone	Absent	Absent

Table 13 – Formulation code characterization.

Crospovidone has some binder properties, therefore the study was performed only in sodium starch glycolate and croscarmellose sodium at 10%, assuming the worst case for both disintegrants.

All four formulation were tested for two different compression parameters. Table 14 details the equipment and the associated process parameters used in these studies.

Process step	Equipment	Process parameters
Blending	V Blender coupled to ERWEKA Rotor AR402	375 revolutions for blending (15 min at 25 rpm)
Lubrication	V Blender coupled to ERWEKA Rotor AR402	125 revolutions for blending (5 min at 25 rpm)
Compression	SPECAC Hydraulic Press	2 tonnes during 10 seconds or 5 tonnes during 5 seconds

Table 14 – Equipment and fixed process parameters used in formulation development studies.

Tablets were analyzed regarding hardness, disintegration and wetting time. The compression parameters showing the higher hardness without compromise the disintegration time was selected for the following experiments. The same study was performed for the effect of the presence of the binder in the formulation.

3.2.2. Selection of Disintegrant

To evaluate the influence of the disintegrant and it level a second set of experiments was designed. Therefore, batches differing in the disintegrant type and disintegrant level were prepared. The study is described in detail in Table 15.

Factor	Level		
Disintegrant	-1	0	1
Type of Disintegrant	Sodium starch glycolate	Croscarmellose sodium	Crospovidone
Disintegrant level (%)	10	20	30

Table 15 – Design of the selection of the disintegrant study.

The superdisintegrants croscarmellose sodium, sodium starch glycolate, crospovidone were challenged at 3 different levels, 10%, 20% and 30%.

The results obtained from de previous study allowed the selection of the compression parameters for this study. Additionally, the presence or absence of the binder in formulation was concluded in the feasibility study. Table 14 details the equipment and the associated process parameters for blending and lubrication.

Tablets were analyzed regarding hardness, disintegration and wetting time. Additionally, it was studied the water absorption capacity for the obtained tablets. The disintegrant showing the lowest disintegration time and good physical properties was selected for the following experiments.

3.3. Results and Discussion

3.3.1. Feasibility Studies

In order to understand the properties of the initial formulation, the compression parameters and the presence of binder, four formulations were prepared with two different disintegrants and with and without binder, as shown in Table 15. These four formulations were compressed with different compression parameters values.

The powder blend was compressed using a hydraulic press, and the compression parameters were predefined. Initially, it was tested a compression force of 10 tonnes during 2 seconds and the obtained tablets exhibited a fragile consistence. Due to the weak physical properties, none of the four formulations were tested. Then, it was changed the compression force for 5 tonnes during 5 seconds and the tablets showed good mechanical properties. Therefore, the selected compression parameters were a force compression of 5 tonnes with a duration of 5 seconds.

For the selected compression parameter, the obtained tablets were evaluated for weight, thickness, diameter, hardness, disintegration time and wetting time.

Formulations A1 and B1 were successfully compressed, resulting in flat, white, uniform tablets. The tablets manufactured from formulations A1' and B1' exhibit a weaker consistence due the absence of binder. Table 16 summarizes the results of weight, thickness, diameter and hardness.

Formulation code	Weight[a] (mg)	Thickness[b] (mm)	Diameter[b] (mm)	Hardness[b] (N)
A1	217.1 ± 1.6	1.15 ± 0.02	12.77 ± 0.04	19.4 ± 2.2
A1'	213.3 ± 1.9	1.18 ± 0.01	12.12 ± 0.82	7.0 ± 0.7
B1	217.1 ± 2.7	1.14 ± 0.01	13.08 ± 0.01	20.9 ± 1.2
B1'	215.1 ± 3.3	1.16 ± 0.02	13.07 ± 0.01	14.8 ± 2.4

Table 16 – Mean weight, thickness, diameter and hardness results of tablets. The results are mean ± SD of [a] 10 tablets; [b] 3 tablets.

All the batches of tablets passed the uniformity of weight test, showing a low weight variation, regardless of the type of the disintegrants used and the presence of binder. The thickness of the tablets ranged from 1.15 to 1.18 mm and the diameter ranged from 12.12 mm to 13.08 mm. The hardness of the tablets was particularly affected by the presence of binder, which ranged from 7.0 to 20.9 N. Tablets formulated with binder exhibited the highest breaking force. In fact, the presence of binder helps with the formation of interparticle bonds, promoting cohesiveness and maintaining integrity of the tablets. This results in higher hardness values. However, strong interparticle bond strength correlates to bad disintegrability of tablets, being important examine the effect of binder on disintegration time test.[68]

The results of disintegration and wetting time are given in Table 17.

Formulation code	Disintegration time (s)	Wetting time (s)
A1	19.8 ± 2.6	92.4 ± 5.7
A1'	14.6 ± 2.2	14.4 ± 1.3
B1	30.0 ± 4.6	44.8 ± 4.3
B1'	12.8 ± 0.8	13.3 ± 1.5

Table 17 – Disintegration time and wetting time results of tablets. The results are mean ± SD of 3 tablets.

Disintegration time is an important criterion for selecting an optimum orally disintegrating tablet formulation. In the present study, the lowest disintegrating time it was observed for formulations without binder (A1' and B1'), as it was expected. For formulations with binder, it was seen that the lowest disintegration time (19.8 seconds) was found when sodium starch glycolate was used as disintegrant and the highest disintegration time (30.0 seconds) was found with croscarmellose sodium. However, all formulations complies the specification expected. The measurement of wetting time may be used as another test to predict the disintegration of tablets. Wetting time is closely related to the inner structure of the tablets and to the hydrophilicity of the excipients.[69] In the wetting time study, the wetting time was faster in formulations without povidone (formulation A1' and B1'). The presence of povidone, which acts as binder, increases the time taken for wetting. Also, it was observed that the formulation A1 required a larger time for the solution reach upper surface of the tablets.

The presence of binder enhanced the tablets consistence but affected considerably its disintegration time. Several studies have been referring that selecting an appropriate binder content is extremely important in designing ODTs.[68] Disintegration time can be reduced by increasing the amount of disintegrant, which was evaluated in the second study. The selected compression parameters were a force compression of 5 tonnes with a duration of 5 seconds.

3.3.2. Selection of Disintegrant

The goal of this formulation study was to select the type of disintegrant and disintegrant level. In fact, although sodium starch glycolate, croscarmellose sodium and crospovidone are used to provide the same function within the formulation, they differ in their chemical structure, particle morphology, and powder properties, which influence the characteristics of the tablets. Also, the amount of disintegrant in the formulation has an important role in ODT formulation design. Therefore, to study the impact of these two formulation factors on the response variables, a set of experiments were performed, as shown Table 18.

Factor	Experiment								
	#1	#2	#3	#4	#5	#6	#7	#8	#9
Type of Disintegrant	SSG	SSG	SSG	CS	CS	CS	CP	CP	CP
Disintegrant level (%)	10	20	30	10	20	30	10	20	30

Table 18 – DoE design for the selection of disintegrant.

This results in the manufacturing of 9 batches, according to Table 19, obtained by direct compression. The compression parameters, selected in the previous study, was a force compression of 5 tonnes with a duration of 5 seconds.

Ingredient (mg)	Formula code								
	A1	A2	A3	B1	B2	B3	C1	C2	C3
Diazepam	5	5	5	5	5	5	5	5	5
Lactose 80 M	183.4	161.4	139.4	183.4	161.4	139.4	183.4	161.4	139.4
Povidone	5.2	5.2	5.2	5.2	5.2	5.2	5.2	5.2	5.2
Sodium starch glycolate	22	44	66	-	-	-	-	-	-
Croscarmellose sodium	-	-	-	22	44	66	-	-	-
Crospovidone	-	-	-	-	-	-	22	44	66
Magnesium stearate	4.4	4.4	4.4	4.4	4.4	4.4	4.4	4.4	4.4
Total	220	220	220	220	220	220	220	220	220

Table 19 – Tablet formulation. All the quantities expressed are in mg / tablet.

The obtained tablets were evaluated for weight, thickness, diameter, hardness, disintegration time, wetting time and water absorption ratio.

All formulations were successfully compressed, resulting in flat, white, uniform tablets, showing good consistence. The results of weight, thickness and diameter are given in Table 20.

Formulation code	Weight[a] (mg)	Thickness[b] (mm)	Diameter[b] (mm)
A1	222.1 ± 1.4	1.18 ± 0.02	13.07 ± 0.02
A2	222.3 ± 1.5	1.22 ± 0.02	13.10 ± 0.04
A3	222.0 ± 1.3	1.23 ± 0.02	13.14 ± 0.05
B1	220.5 ± 1.6	1.23 ± 0.03	13.14 ± 0.02
B2	222.2 ± 2.0	1.25 ± 0.03	13.25 ± 0.03
B3	225.0 ± 1.3	1.23 ± 0.02	13.24 ± 0.05
C1	223.1 ± 1.7	1.25 ± 0.03	13.11 ± 0.02
C2	222.6 ± 2.3	1.38 ± 0.05	13.12 ± 0.03
C3	228.2 ± 1.8	1.46 ± 0.03	13.33 ± 0.11

Table 20 – Mean weight, thickness and diameter results of tablets. The results are mean ± SD of [a] 20 tablets; [b] 10 tablets.

All the batches of tablets passed the uniformity of weight test, showing a low weight variation, regardless of the type of the disintegrants used and its level. The thickness of the tablets ranged from 1.18 to 1.46 mm and the diameter ranged from 13.07 mm to 13.33 mm.

Since mechanical integrity is crucial in successful formulation of ODTs, hence the hardness of tablets were determined and were found to be in the range of 9.8-15.5 N. Figure 12 summarizes the results obtained in hardness test.

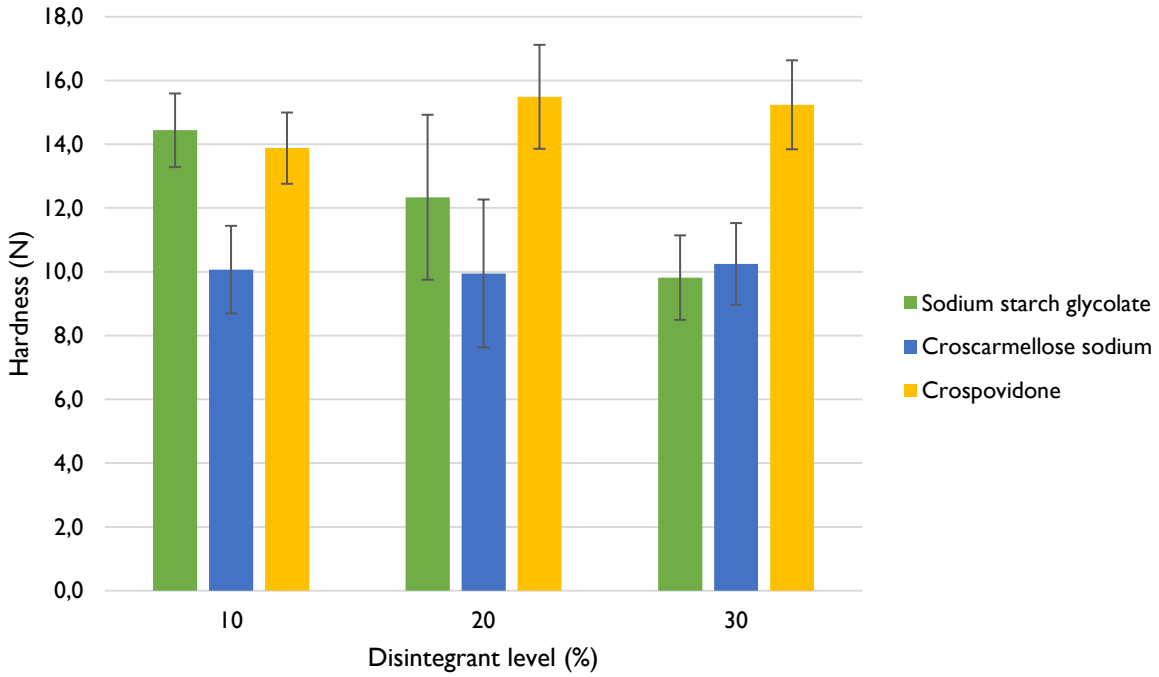

Figure 12 – Hardness results of tablets. The results are mean ± SD of 10 tablets.

Tablets prepared using crospovidone showed higher breaking force values compared to sodium starch glycolate and croscarmellose sodium. For formulations prepared with sodium starch glycolate, it was observed a decrease in hardness values as the amount of disintegrant increase, while no significant variations were observed for croscarmellose sodium and crospovidone, as its levels increase.

Table 21 summarizes the results obtained for disintegration time, wetting time and water absorption ratio. Figure 13 shows the relation between disintegration time and wetting time.

Disintegration time is a crucial parameter that needs to be optimized in the development of ODTs. The disintegration times for all nine formulation were found to be ranged from 10.5 seconds (A3) to 33.7 seconds (B2). In this study, it was observed that the disintegration time of the tablets decreased with increasing level of crospovidone and sodium starch glycolate.

Formulation code	Disintegration time[a] (s)	Wetting time[a] (s)	Water absorption ratio[b] (%)
A1	14.8 ± 2.5	40.5 ± 5.7	131.2 ± 6.4
A2	13.2 ± 1.7	72.8 ± 3.1	235.4 ± 3.1
A3	10.5 ± 1.7	94.7 ± 3.1	370.7 ± 5.9
B1	29.0 ± 3.3	24.2 ± 2.5	108.0 ± 6.1
B2	33.7 ± 2.3	46.9 ± 2.8	185.2 ± 8.2
B3	31.7 ± 2.6	87.9 ± 8.2	253.0 ± 15.1
C1	19.4 ± 1.5	20.6 ± 1.5	61.5 ± 2.1
C2	18.3 ± 1.5	17.2 ± 1.2	91.1 ± 0.5
C3	15.6 ± 2.2	12.3 ± 1.5	103.8 ± 1.4

Table 21 – Disintegration time, wetting time and water absorption ratio results of tablets. The results are mean ± SD of [a] 6 tablets; [b] 3 tablets.

Also, no differences were observed in the disintegration time when it was used croscarmellose sodium. Theoretically, as the concentration of superdisintegrant increased, the disintegration time should decrease. This fact is easily explained by the fact that superdisintegrants may sorb liquid and cause swelling of the tablet in proportion to the amount added.[70] However, there is a sufficient amount of disintegrant that expose particles to the perfect wetting and therefore, there is stagnancy in the disintegration time after this perfect amount.[70] In other hand, few disintegrant particles do not expose particles to the wetting and it may lead to the production of larger aggregates, which will have difficulty in disaggregate.[70]

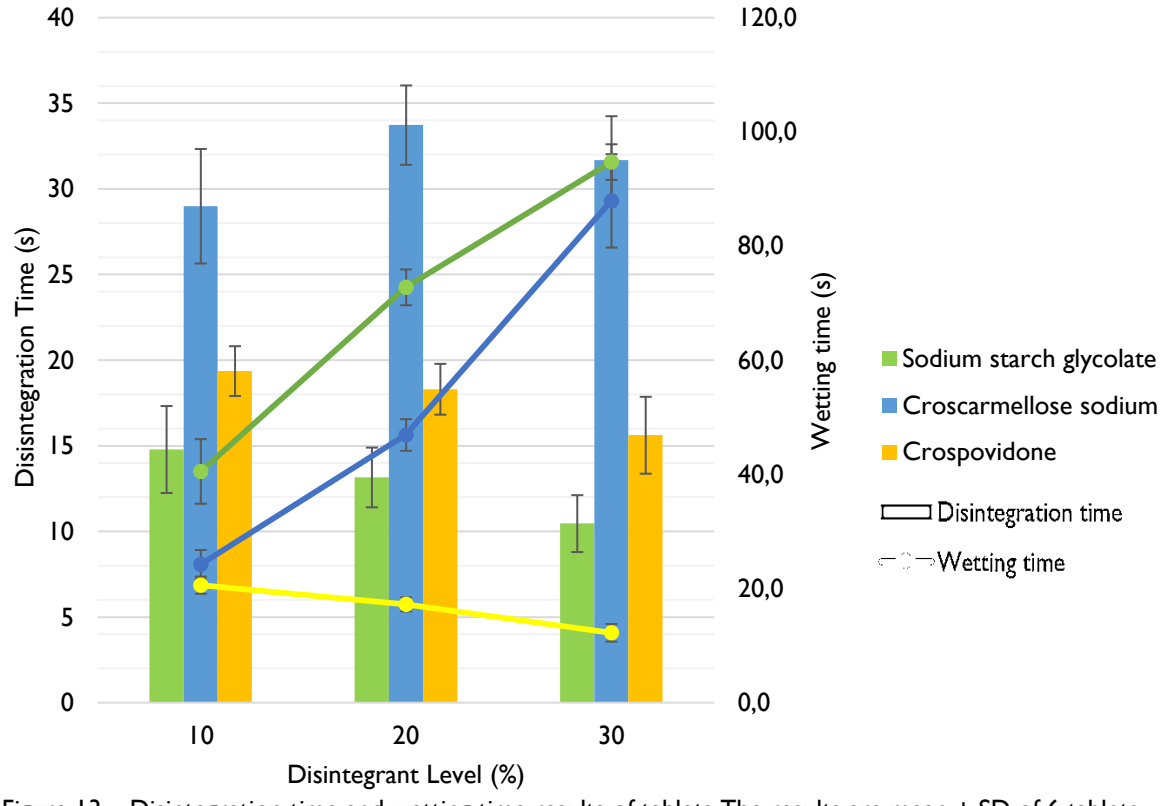

Figure 13 – Disintegration time and wetting time results of tablets. The results are mean ± SD of 6 tablets.

Among the superdisintegrants used, sodium starch glycolate showed better performance in disintegration time when compared to croscarmellose sodium. This fact may be explained by the mechanism by which disintegration occurs, which is by rapid water uptake that leads to a huge increase in volume which result in rapid and uniform tablet disintegration.[35,36] Crospovidone shows a disintegration time closer to the sodium starch glycolate, reflecting the combining mechanism of swelling, deformation and wicking for tablet disintegration. [35,36]

As seen in the previous study, wetting time is closely related to the inner structure of the tablets and to the hydrophilicity of the excipients and it is used as an indicator from the ease of the tablet disintegration in buccal cavity and indicates penetration velocity of water into the tablets. The wetting time study showed that the time required for the solution to reach the upper surface of the tablet was shorter in formulas using crospovidone followed by croscarmellose sodium and sodium starch glycolate, at equivalent concentration. Remya *et al.* and Bi *et al* reported a high wetting time for tablet formulations containing sodium starch glycolate and croscarmellose sodium.[71,72] Also, it was observed that the wetting time of the tablets increased with increasing level of sodium starch glycolate and croscarmellose sodium. This is explained by the fact of sodium starch glycolate and croscarmellose sodium gels on exposure to water. Consequently, increasing the level of disintegrants, the gel formation increases and may act as an obstacle to solution uptake into the tablet and thus the wetting time is delayed. [73,74] The larger extent of gel formation in sodium starch glycolate may explain the larger time required for tablet wetting, compared to croscarmellose sodium. In disintegration test this phenomenon did not occurs, because the gel formed by contact with water is always removed from the tablet, due to the equipment agitation. Consequently, the water has access to tablet permanently. In the case of tablets prepared with crospovidone, due to the combination of deformation, wicking and swelling actions, without gel formation, the wetting time was shorter. [35,36]

Figure 14 shows the appearance of ODTs containing sodium starch glycolate, croscarmellose sodium and crospovidone at 30% before wetting, during and after wetting time experiment. For tablets containing sodium starch glycolate and croscarmellose sodium was observed a huge increase of tablet volume, explaining the mechanism of action of these disintegrants. For tablets containing crospovidone was observed a small increase of volume, and a distortion in the circular shape of the tablet, reflecting the deformation action as mechanism for tablet disintegration. [35,36]

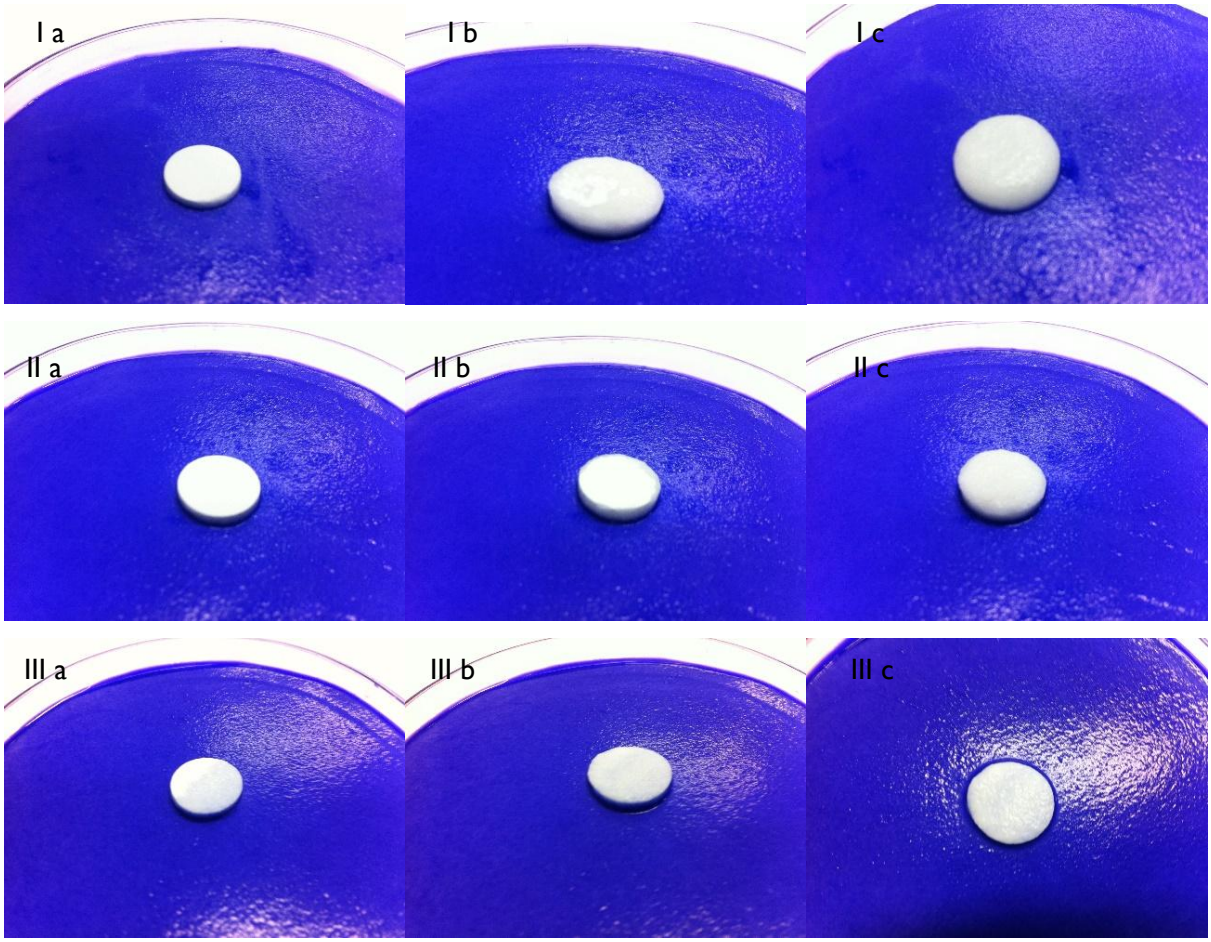

Figure 14 – Appearance of ODTs containing I) sodium starch glycolate, II) croscarmellose sodium and III) crospovidone at 30% a) before wetting, b) during and c) after wetting time experiment.

The increasing of volume due to water intake is a very important phenomenon in disintegration of ODTs. The water absorption ratio reflects the capacity of the tablet to take the water from the outside to the inner structure.

The water absorption ratio ranged from 131.2 to 370.7% for sodium starch glycolate formulation, 108.0 to 253.0% for ODTs containing croscarmellose sodium and 61.5 to 103.8% for ODTs with crospovidone, increasing as the superdisintegrant concentration increase, in a proportional relationship ($R^2 > 0.95$), as shown in Figure 15. Also, at the same amount of superdisintegrant, the water absorption ratio of sodium starch glycolate has greater values compared to croscarmellose sodium and crospovidone. This results confirm the differences between the superdisintegrants properties. The water uptake ability is extremely high for sodium starch glycolate, generating a greater volume expansion in the tablet. This creates a hydrostatic pressure inside the tablet leading to disintegration. Croscarmellose sodium shows a similar behavior, but with less extension compared to sodium starch glycolate.

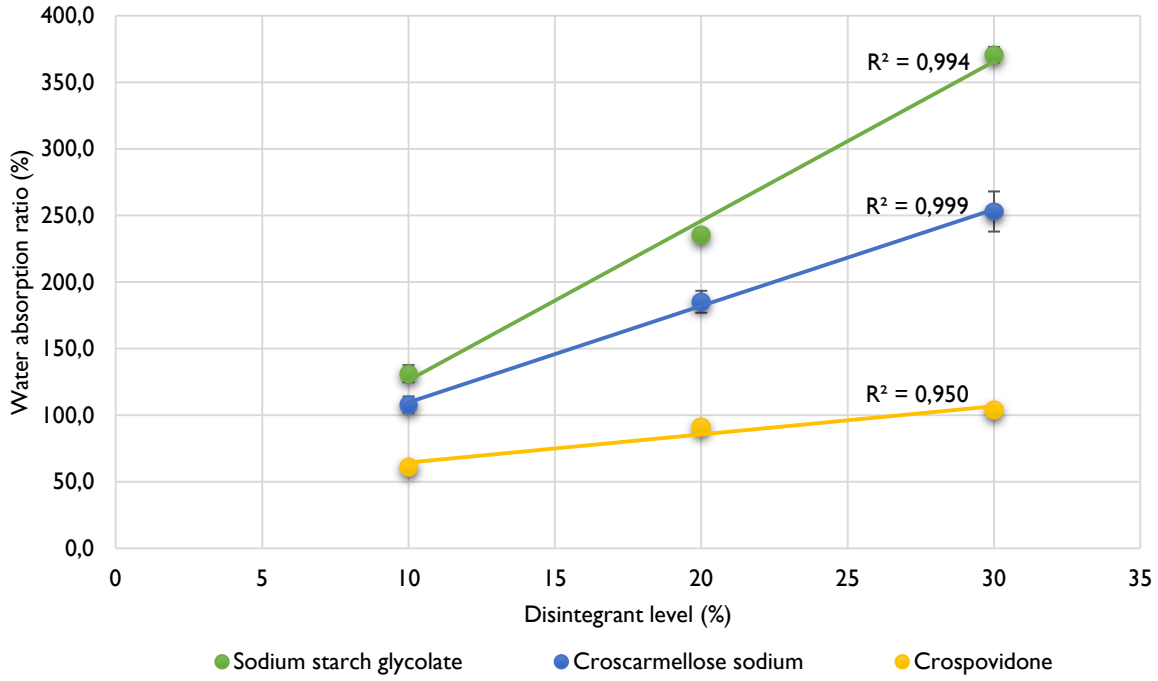

Figure 15 – Correlation between amount of disintegrant and water absorption ratio. The results are mean ± SD of 3 tablets.

The wetting time of the ODTs was found to be directly related to the water absorption ratio of the tablets. Linear regression analysis of wetting time and water absorption ratio of all tablets formulated showed a coefficient of determination (R^2) value of 0.911, as shown in Figure 16. A similar phenomenon was observed for different swellable and no-swellable disintegrants by Pabari et *al.*[75]

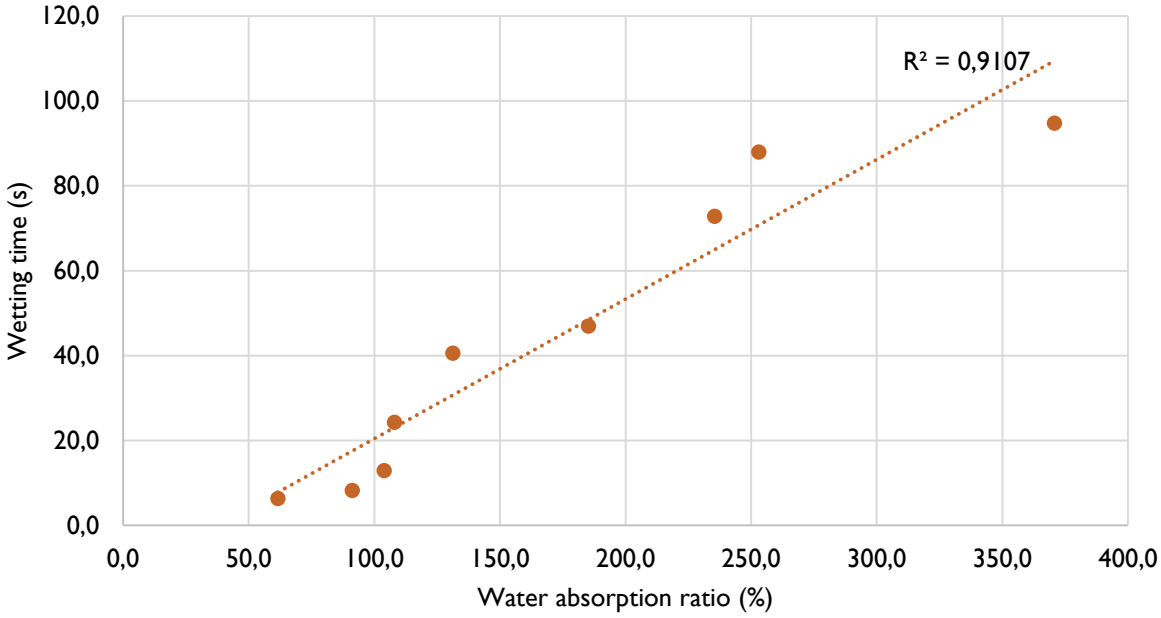

Figure 16 – Correlation between water absorption ratio and wetting time.

Taken together, all data show that crospovidone is very effective at wetting the tablet matrix, requiring low amount of water to promote tablet disintegration. These characteristics are fundamental in ODT formulation development. Furthermore, crospovidone provides good mechanical strength, essential to maintain integrity of dosage form.

3.4. Conclusion

The formulation composition was finalized based on formulation development studies. Direct compression technique was a suitable method to produce ODT tablets. Based on the results of the formulation development studies, the risk assessment of the formulation variables was updated as given in Table 22.

CQA	Formulation Variables				
	Diazepam	Lactose M80	Povidone	Disintegrant	Magnesium stearate
Hardness	Low	Low	Low	Low	Low
Disintegration	Low	Low	Low	Low	Low
Dissolution	High	Low	Low	Low	Medium

Table 22 – Updated risk assessment of the formulation variables.

The presence of povidone, evaluated in first study, was crucial to enhance the tablets consistence but affects its disintegration time. Therefore, the risk of the quality attribute hardness was reduced to low, and the disintegration time remained in the pre-defined target, lowering it risk as well.

In the second study, it was concluded that the disintegrant crospovidone leads to acceptable ODTs. Tablet with crospovidone shows excellent disintegration times, and therefore the risk was reduced to low. Consequently, being dissolution depending on the disintegration time, the risk was reduced to low too.

From the study it can be concluded the formulation for drug product manufacturing process study, as shows Table 23.

Ingredient	Quantity (mg)
Diazepam	5
Lactose 80 M	139.0 - 183.0
Povidone	5.6
Crospovidone	22 – 66
Magnesium stearate	4.4

Table 23 – Formulation selected for diazepam ODT.

4. Manufacturing Process Development

4.1. Initial risk assessment

A risk assessment of the overall 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 equipment trains.

An Ishikawa diagram was used to identify all potential variables on direct compression technique, such as raw materials, compression parameters, and environmental factors, which can have an impact. Figure 17 represents the Ishikawa diagram of direct compression, identifying the potential variables that can affect the CQAs.

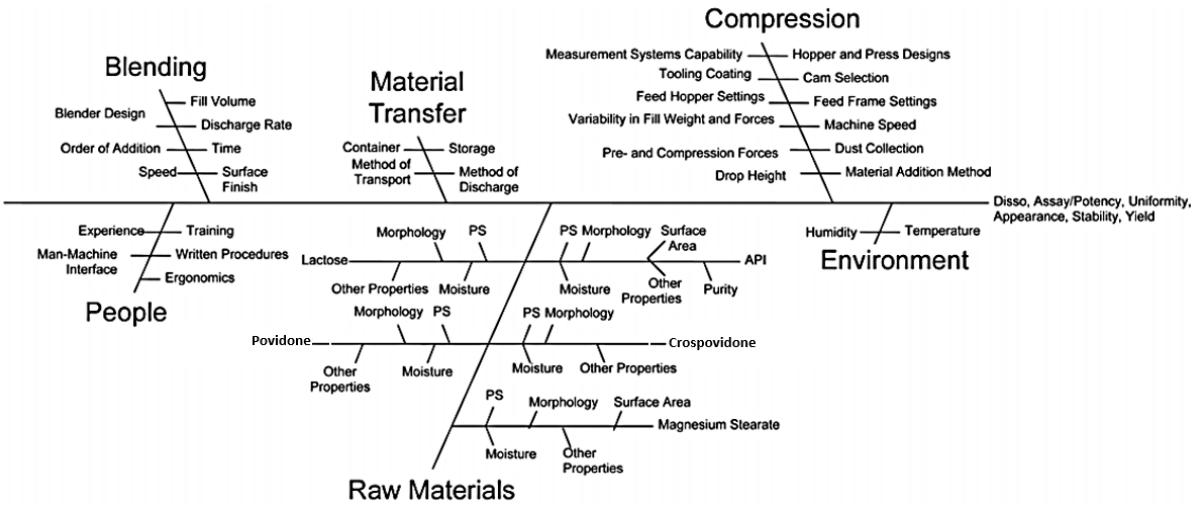

Figure 17 – Ishikawa diagram for direct compression technique.

Ishikawa diagram helped to assess the risk in manufacturing process steps.

A risk assessment for the manufacturing process was performed and result is depicted in table 24. This identifies the unit operations which require further investigation to determine the appropriate control strategy.

CQA	Process Step		
	Blending	**Lubrication**	**Compression**
Hardness	Low	Low	High
Disintegration	Low	Medium	High
Dissolution	Low	Medium	High

Table 24 – Initial risk assessment of the manufacturing process development.

Blending step may impact the distribution of crospovidone in the blend which could impact disintegration of the tablets and, ultimately, its dissolution. Nevertheless, blending is considered a low risk variable.

Over-lubrication due to an excessive number of revolutions may impact disintegration and, ultimately, dissolution of the tablets. The risk is medium for both CQAs.

Tablet hardness is impacted by compression force and in consequence, compression is considered a high risk variable. Since tablet hardness affects directly the disintegration time, and consequently dissolution, compression is also a high risk variable for these quality attributes.

The risk assessment also indicates that hardness and disintegration time should be used as the response variables. Additionally, it was tested the wetting time and drug release profile of the diazepam ODTs.

4.2. Study Design

Manufacturing process development was focused on evaluation of the high risk process variables, or CPP, as identified in the initial risk assessment.

The manufacturing process development was conducted in two studies: the first study evaluated impact of the scaling-up on the compression machine and allowed to settle the amount of crospovidone and the second study was conducted to allow the selection of the ideal compression parameters.

4.2.1. Feasibility Study

In this study it was evaluated the impact of a laboratory scale manufacturing and the behavior of a new type of tablet on tablet quality attributes. Furthermore, this study allowed the selection of the amount of crospovidone for the last study. Crospovidone, was challenged at different level and different compression forces. Table 25 summarizes the set of experiments performed.

Factor	Level		
	-1	**0**	**1**
Disintegrant level (%)	10	20	30
Compression Force	-	+	++

Table 25 – Design for the selection of disintegrant.

Table 26 details the equipment and the associated process parameters used in these studies.

Process step	Equipment	Process parameters
Blending	V Blender coupled to ERWEKA Rotor AR402	375 revolutions for blending (15 min at 25 rpm)
Lubrication	V Blender coupled to ERWEKA Rotor AR402	125 revolutions for blending (5 min at 25 rpm)
Compression	KILLIAN Compressing Machine (eccentric)	At three compression forces

Table 26 – Equipment and process parameters used in manufacturing process development studies – feasibility study.

Tablets were analyzed regarding hardness, disintegration and wetting time. The amount of crospovidone showing the higher hardness and the lower disintegration time was selected for the following and final experiment.

4.2.2. Selection of the Compression Parameters

In the final study, a series of experiments were undertaken to investigate the relationship between the process parameters related to compression and the drug product quality attributes. The compression variables were tested using 3^2 full factorial experiment DoE. Compression force varied between 15 and 25 kN and the velocity of compression varied between 5000 to 20000 tablets per hour. Table 27 presents the study design.

Factor / Process parameters	Level -1	Level 0	Level 1
Compression Force (kN)	15	20	25
Velocity (x 1000 tablets/hour)	5	10	20

Table 27 – Design of the full factorial DoE to study the compression parameters.

Table 28 details the equipment and the associated process parameters used for compression step, in these study. For blending and lubrication, the equipment and process parameters are shown in Table 26.

Process step	Equipment	Process parameters
Compression	Fette 1200i Compression machine (rotative)	According to DoE

Table 28 – Equipment and process parameters used in manufacturing process development studies.

Tablets manufactured were tested regarding hardness, disintegration, wetting time and dissolution rate.

The compression condition showing the lowest disintegration time and highest dissolution rate, maintaining acceptable hardness was considered the ideal conditions to manufacturing process.

4.3. Results and Discussion

4.3.1. Feasibility Studies

In order to comprehend the effects of a laboratory scale manufacturing and the behavior of a tablet shape, a preliminary study was performed. The disintegrant selected in the previous work was challenged at different level (10, 20 and 30%) and different compression forces (Table 29). The compression force was selected by the changing the distance between the rollers, since the compression machine did not allow the selection of a specific compression force. To schematize the different compression forces used, it was used the symbols (-), (+) and (++) to express the lower, medium and higher compression force, respectively.

Factor	Experiment								
	#1	#2	#3	#4	#5	#6	#7	#8	#9
Formulation code	**C1-**	**C2-**	**C3-**	**C1+**	**C2+**	**C3+**	**C1++**	**C2++**	**C3++**
Disintegrant level (%)	10	20	30	10	20	30	10	20	30
Compression force	-	-	-	+	+	+	++	++	++

Table 29 – Design for the selection of disintegrant.

All formulations were successfully compressed, by direct compression, resulting in oblong, white, uniform tablets, exhibiting a good consistence, with the exception of formulations with the lower compression force, which showed a weak consistence (C1-, C2- and C3-).

Formulation code	Weight[a] (mg)	Length[b] (mm)	Width[b] (mm)	Thickness[b] (mm)
C1-	209.6 ± 4.4	11.28 ± 0.03	5.91 ± 0.03	4.24 ± 0.02
C1+	213.6 ± 2.7	11.14 ± 0.02	5.82 ± 0.01	4.11 ± 0.03
C1++	207.6 ± 3.6	11.08 ± 0.02	5.78 ± 0.02	3.88 ± 0.09
C2-	206.1 ± 2.5	11.39 ± 0.05	5.94 ± 0.03	4.48 ± 0.02
C2+	208.5 ± 3.8	11.15 ± 0.03	5.80 ± 0.02	4.28 ± 0.06
C2++	214.9 ± 5.0	11.18 ± 0.03	5.81 ± 0.01	4.00 ± 0.04
C3-	210.4 ± 5.7	11.41 ± 0.05	5.95 ± 0.04	4.82 ± 0.07
C3+	212.2 ± 4.8	11.15 ± 0.01	5.79 ± 0.01	4.36 ± 0.07
C3++	211.2 ± 5.0	11.13 ± 0.02	5.79 ± 0.01	4.26 ± 0.05

Table 30 – Mean weight, length, width and thickness results of tablets. The results are mean ± SD of [a] 20 tablets; [b] 10 tablets.

The prepared tablets were evaluated for physical parameters. The results of weight, length, width and height are given in Table 30.

As expected, the results obtained for weight, width and thickness were similar in all formulations. The thickness results showed variances, which can be attributed to the

compressibility and cohesion of the tablets.

The results of hardness, disintegration time and wetting time are given in Table 31.

Formulation code	Hardness[a] (N)	Disintegration time[b] (s)	Wetting time[b] (s)
C1-	< LD	9.9 ± 0.7	64.5 ± 3.1
C1+	28.2 ± 2.8	9.4 ± 0.4	76.2 ± 2.7
C1++	32.4 ± 1.7	9.5 ± 0.5	85.5 ± 2.2
C2-	< LD	9.6 ± 0.7	58.3 ± 3.6
C2+	35.9 ± 3.5	11.5 ± 0.7	62.4 ± 2.1
C2++	37.0 ± 3.5	12.8 ± 0.3	69.4 ± 1.6
C3-	< LD	9.4 ± 0.4	60.9 ± 3.6
C3+	44.1 ± 1.8	11.4 ± 0.7	60.9 ± 3.0
C3++	46.2± 4.3	11.8 ± 0.8	86.6 ± 3.8

Table 31 – Hardness, disintegration time and wetting time results of tablets. The results are mean ± SD of [a] 10 tablets; [b] 6 tablets. LD: limit of detection.

Concerning the hardness results, tablets compressed with the lower compression force showed not enough breaking force as a hardness tester can detect. The remaining formulas showed a good breaking force (28.2 N – 46.2 N).

The disintegration time test revealed that all formulations disintegrates less than13 seconds. For wetting time, it was observed that the time required for the solution to reach the upper surface of the tablet was greater than 60 seconds.

Based on the results, the formulation containing crospovidone at 30% exhibited a good performance as ODT formulation.

4.3.2. Selection of the Compression Parameters

Compression parameters have a crucial impact in ODTs properties and quality. The objective of the this manufacturing development study was to select the optimum compression parameters that leads to the tablets manufacturing with the quality attributes assessed in the beginning of the experimental work.

The unit operations that require more investigation were assessed and it was identified the compression step as the top priority operation to study. In this step, the parameters: compression force and press speed were identified as the critical parameters and therefore the experimental design explores these two CPPs and established the relationship between these parameters and the critical drug product quality attributes.

A 3^2 full factorial experiment DoE was performed, varying the compression force between 15 and 25 kN and the velocity of compression between 5000 and 20000 tablets per hour. Table 34 summarizes the experiment number performed in the study.

Factor	Experiment								
	#1	#2	#3	#4	#5	#6	#7	#8	#9
Formulation code	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Compression force (kN))	15	15	15	20	20	20	25	25	25
Press speed (x 1000 tablets/hour)	5	10	20	5	10	20	5	10	20

Table 32 – Experimental design for the compression parameters study.

The obtained tablets were evaluated for weight, thickness, diameter, hardness, disintegration time, wetting time and dissolution.

All formulations were successfully compressed, resulting in oblong, white, uniform tablets. Table 33 shows the results of weight, length, width and thickness.

Formulation code	Weight[a] (mg)	Length[b] (mm)	Width[b] (mm)	Thickness[b] (mm)
F1	232.7 ± 2.6	11.28 ± 0.03	5.91 ± 0.03	4.63 ± 0.03
F2	226.3 ± 1.1	11.39 ± 0.05	5.82 ± 0.01	4.65 ± 0.02
F3	220.2 ± 1.6	11.41 ± 0.05	5.78 ± 0.02	4.68 ± 0.03
F4	232.3 ± 1.1	11.14 ± 0.02	5.94 ± 0.03	4.50 ± 0.02
F5	226.5 ± 1.1	11.24 ± 0.02	5.80 ± 0.02	4.47 ± 0.02
F6	219.3 ± 1.3	11.28 ± 0.03	5.81 ± 0.01	4.51 ± 0.02
F7	229.6 ± 3.4	11.25 ± 0.02	5.95 ± 0.04	4.34 ± 0.02
F8	226.2 ± 1.5	11.23 ± 0.01	5.79 ± 0.01	4.35 ± 0.02
F9	222.1 ± 3.0	11.13 ± 0.02	5.79 ± 0.01	4.41 ± 0.02

Table 33 – Mean weight, length, width and thickness results of tablets. The results are mean ± SD of [a] 20 tablets; [b] 10 tablets.

The tablets showed a low weight variation, irrespective of the compression force and press speed used. The thickness of the tablets ranged from 4.34 to 4.68 mm and was related to the compression force applied. Also, it can be observed a slightly effect of the press speed in the tablet thickness. As the press speed increases, tablet thickness tends to increase, reflecting the decreasing of the dwell time.

Table 34 summarizes the results obtained for hardness, disintegration time and wetting time.

Formulation code	Hardness[a] (N)	Disintegration time[b] (s)	Wetting time[b] (s)
F1	5.5 ± 0.7	44.0 ± 1.8	48.2 ± 3.3
F2	5.8 ± 0.6	43.8 ± 0.9	47.1 ± 2.7
F3	5.0 ± 0.7	41.8 ± 2.0	47.8 ± 1.4
F4	8.0 ± 0.7	57.7 ± 1.8	55.4 ± 3.8
F5	8.3 ± 0.7	55.3 ± 2.9	53.8 ± 4.4
F6	6.8 ± 0.5	47.5 ± 1.6	51.9 ± 3.4
F7	10.2 ± 0.5	61.0 ± 1.4	67.4 ± 4.4
F8	9.7 ± 0.7	56.8 ± 1.3	62.8 ± 4.7
F9	7.7 ± 0.6	54.3 ± 1.9	58.3 ± 4.5

Table 34 – Hardness, disintegration time and wetting time results of tablets. The results are mean ± SD of [a] 10 tablets; [b] 6 tablets.

The summary of DoE results for hardness show that a very good model (R^2 = 0.996, Figure 20) was obtained and are present on Table 35. Figures 18 and 19 portray the response surface plot and the contour plot for hardness test, respectively, showing the influence of press speed and compression force.

Compression force is the most important factor impacting tablet hardness, indicated by a high coefficient value of b_2.

In fact, hardness is directly related to the compression force. As the compression force increases, it is expected that the tablet breaking force increases too. That observation was detected in the hardness test, showing the higher hardness values for higher compression forces, as depicted in Table 34 and Table 35. As the compression force increases, the bulk volume is reduced and the particle interaction is increased, resulting in higher tensile strength of tablets.

Coefficient	Value
b_0	8,200
b_1	-0,697
b_2	1,860
b_{12}	-0,510
b_{11}	-0,710
b_{22}	-0,430

Table 35 – Coefficient values obtained for hardness.

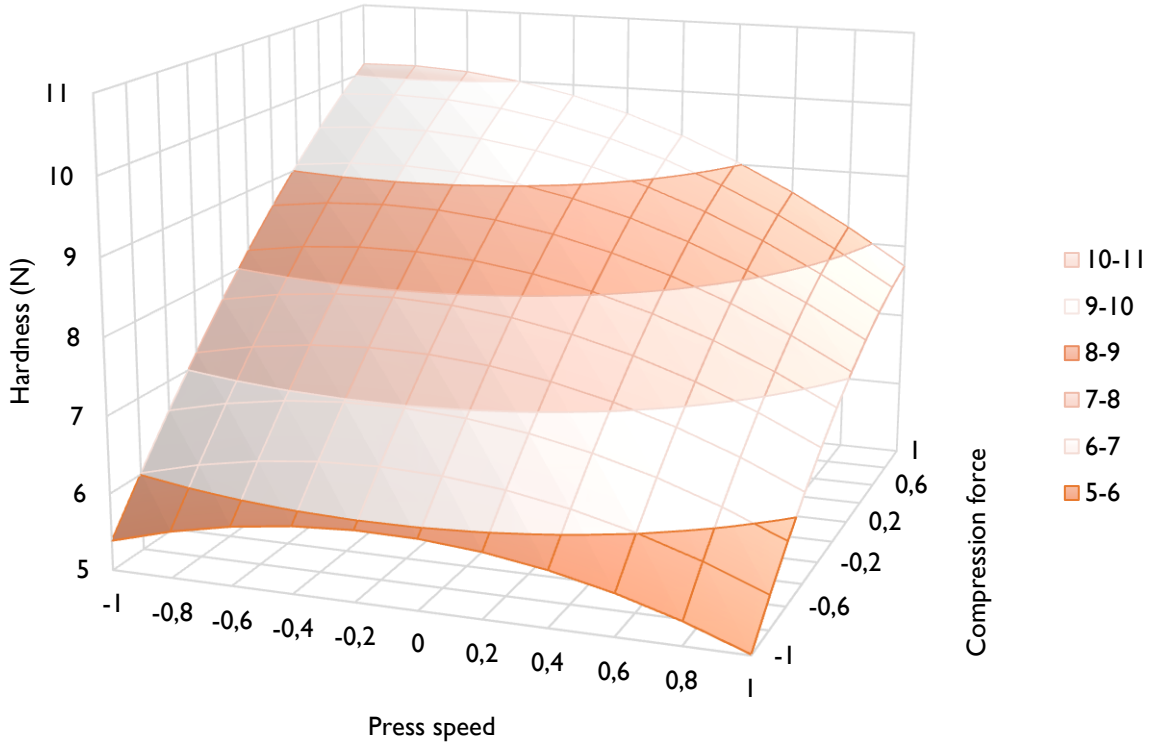

Figure 18 – Response surface plot showing the influence of compression force and press speed on the hardness.

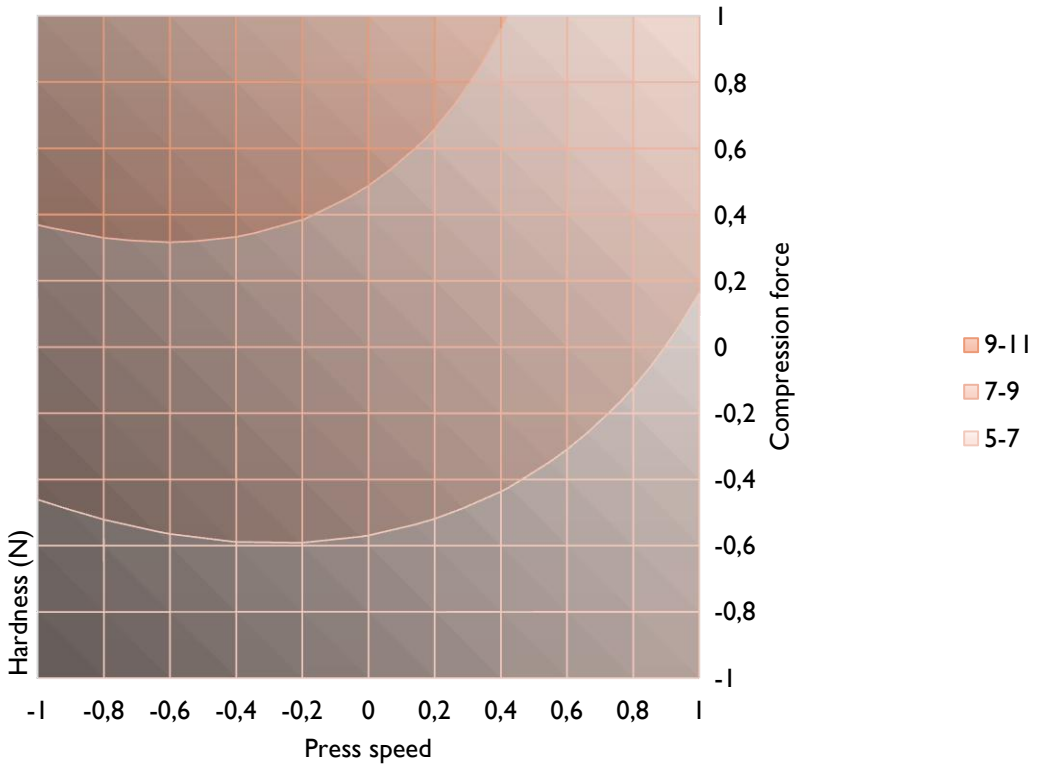

Figure 19 – Contour plot showing the influence of compression force and press speed on the hardness.

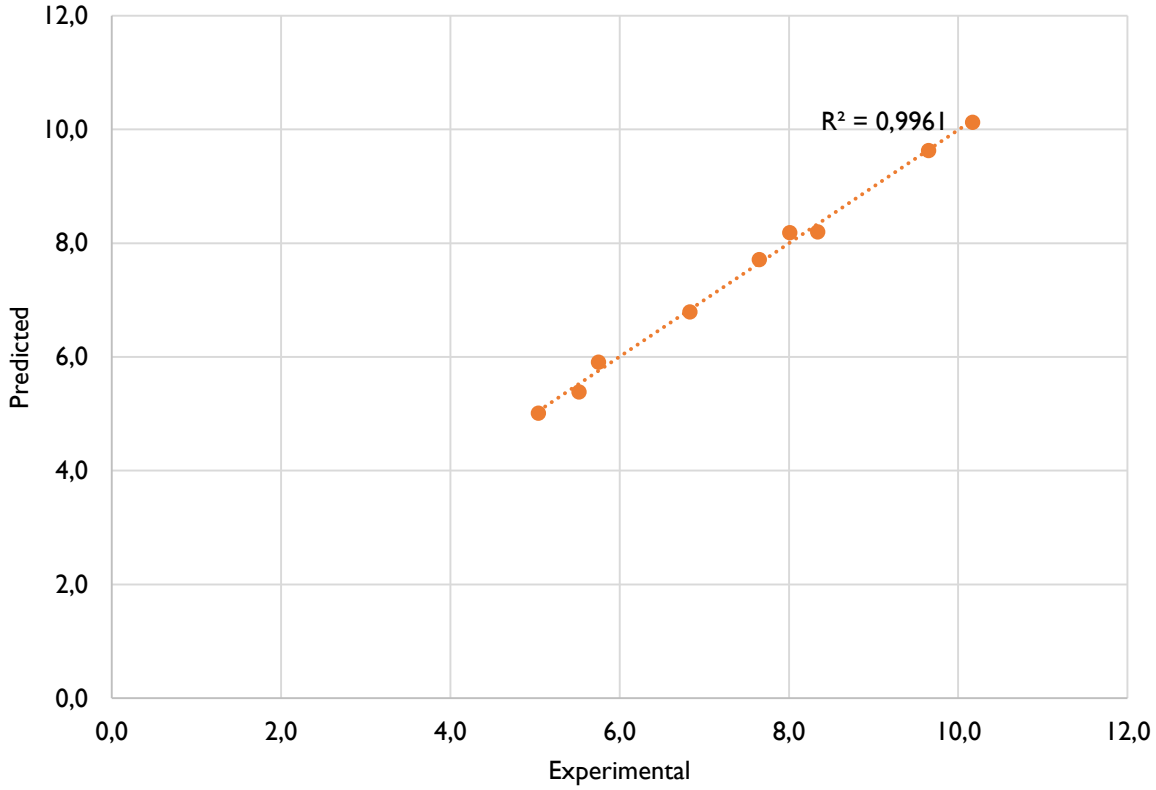

Figure 20 – Correlation between the experimental and the predicted values on hardness.

Press speed reveals also to be an important factor, affecting negatively the CQA hardness, with a coefficient value of -0.697. The reason for that is that as the punch speed increases, the length of time the punches are under pressure, also called as dwell time, decreases, and the tensile strength of compacts tends to decrease. This phenomenon especially happens for materials such as lactose, which initially shows some fragmentation, but then may exhibit plastic flow under increased pressure.[76]

The interactive coefficient reveals that effect of press speed is bigger at higher compression force values, affecting negatively the hardness values. At lower compression force, the effect of press speed is almost insignificant. Also, the results show that the effect of compression force is bigger at lowers press speeds rather than high press speed, but both with a positive significant impact on hardness.

Schiermeier *et al* and Late *et al* studies show the key influence of the compression force in tablet hardness.[77,78] The tensile strength at different compression pressures and at different dwell times has also been studied by Tye *et al*. The tablet hardness increased with the increase in compaction pressure. The dwell time also affected the tensile strength, being higher at low dwell time, in general.[79]

For disintegration studies, the value of the correlation coefficient indicate a good fit, suggesting a good model (R^2 = 0.963), as shown in Figure 23. The summary results of DoE are

presented on Table 36. Figures 21 and 22 depict the response surface plot and the contour plot of the impact of press speed and compression force on disintegration time.

The results for disintegration time showed a similar behavior compared to the effect of the compression parameters studied on tablet hardness. It was observed a major impact of the compression force in comparison to press speed on disintegration time, but both with an important impact. This fact is directly related to the hardness values obtained, as depicted in Figure 27. A linear correlation between disintegration time and hardness was observed, showing a coefficient of determination (R^2) value of 0.913. Schiermeier *et al* and Late *et al* refer the key role of the compression force in disintegration time.[77,78] Both studies concluded that by increasing compression force, disintegration time of tablets increased. The increase of compression force, the tablet density and tablet strength increase as well, decreasing the space between the tablet particles. This situation hinders the liquid penetration into the tablet structure, and delays the action of the disintegrant particle, leading to an increasing in disintegration time.[80]

The interactive coefficient reveals that effect of press speed is bigger at higher compression force values, affecting negatively the time to tablet disintegration. At lowers compression forces, the impact of press speed decrease. Also, the results show that at lowers press speeds, the effect of compression force increase. On the other hand, the effect of compression force has a slight decrease at faster compression speed.

Coefficient	Value
b_0	54,087
b_1	-3,175
b_2	7,105
b_{12}	-1,140
b_{11}	-0,925
b_{22}	-3,185

Table 36 – Coefficient values for disintegration time.

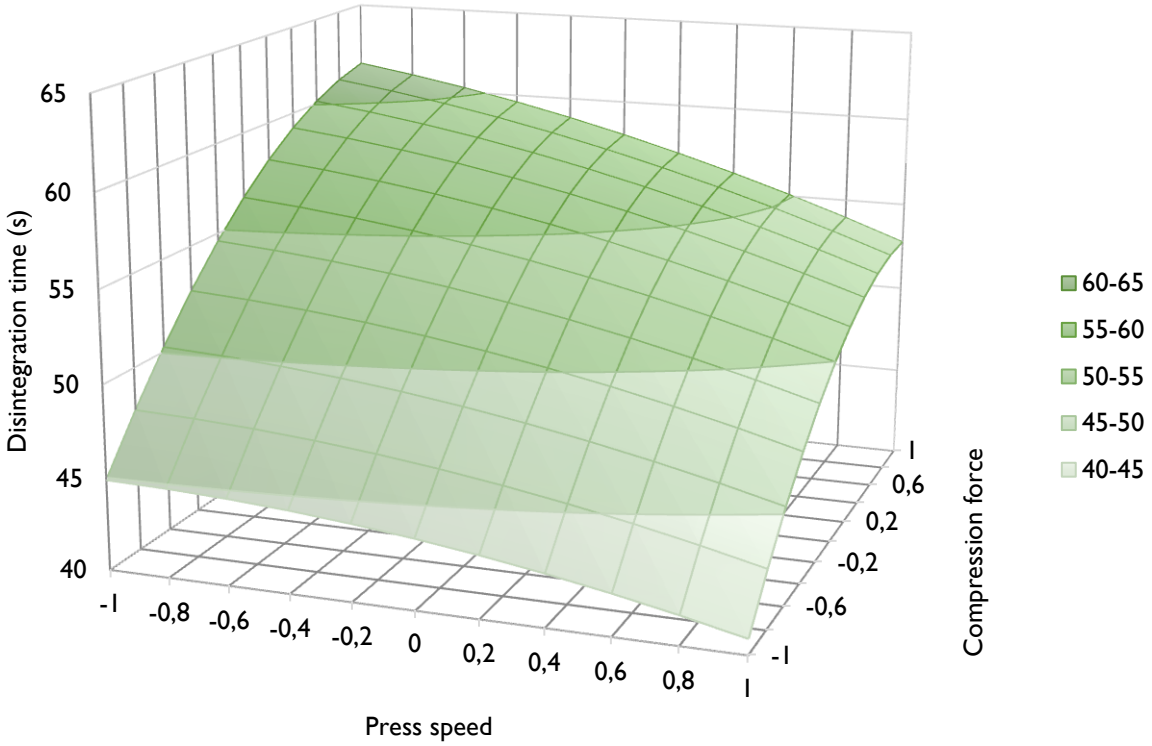

Figure 21 – Response surface plot showing the influence of compression force and press speed on disintegration time.

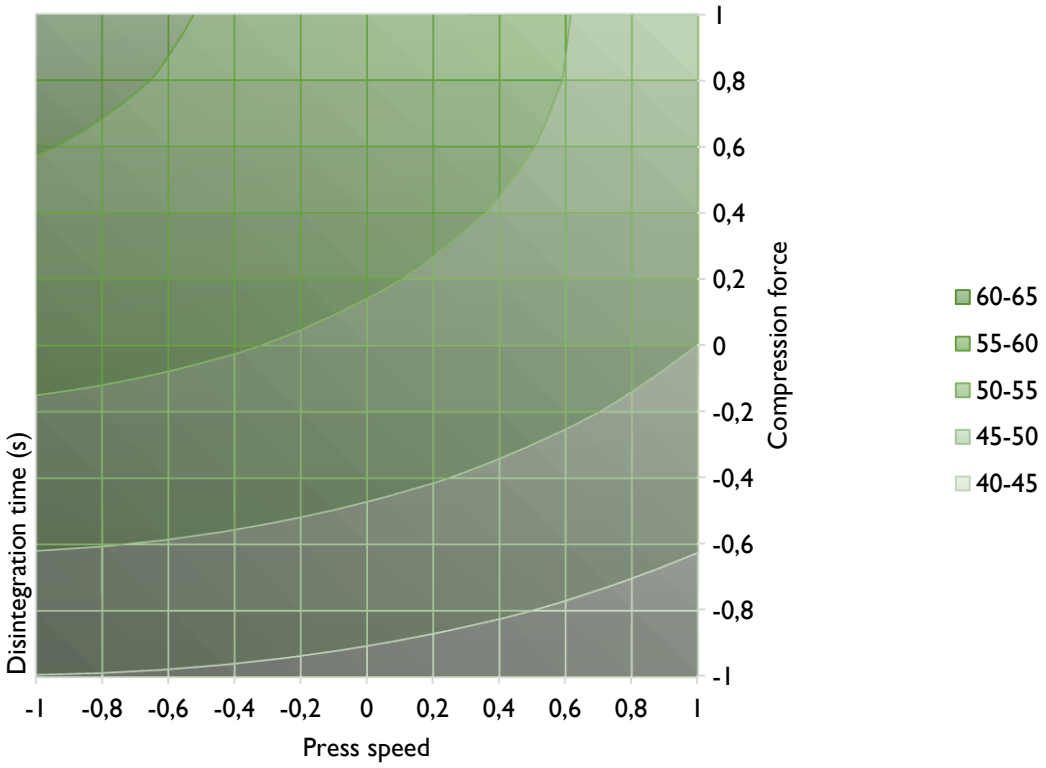

Figure 22 – Contour plot showing the influence of compression force and press speed on disintegration time.

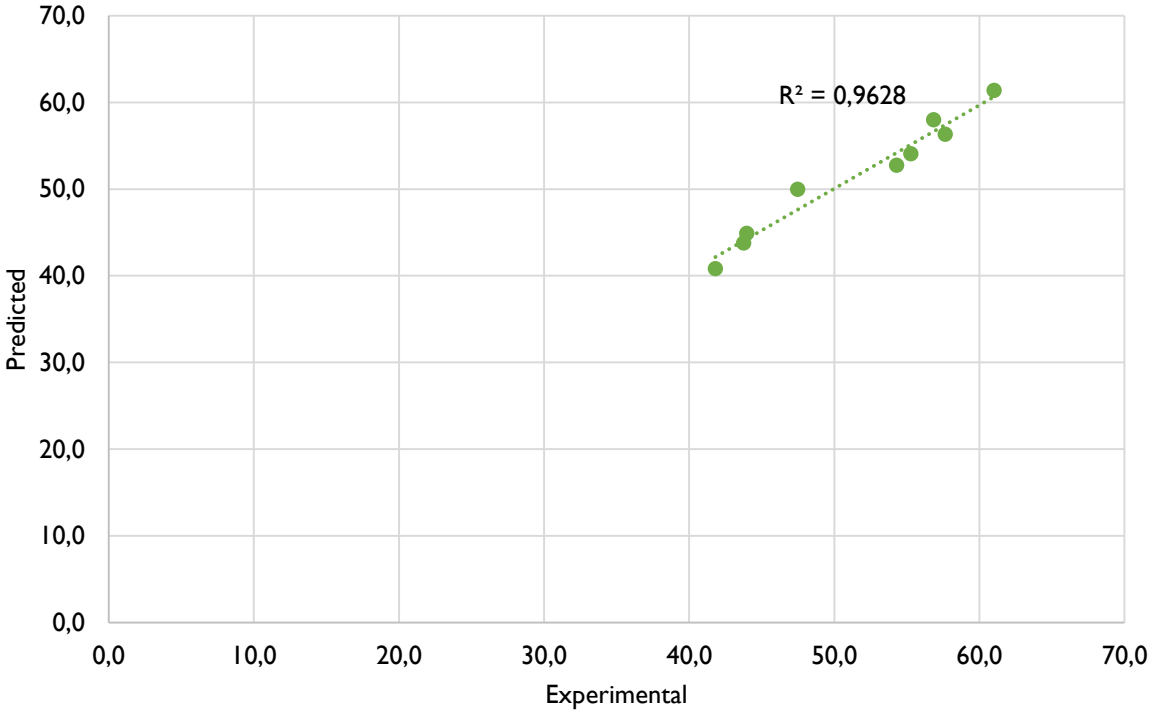

Figure 23 – Correlation between the experimental and the predicted values on disintegration time.

A confirmative test to disintegration study was performed and reveals a similar performance of the wettability of the tablets.

A good model was found to describing the effect of compression parameters on wetting time, with a R^2 value of 0.998, as shown in Figure 26. The coefficient values obtained for wetting time are presented on Table 37. Figures 24 and 25 show influence of compression force and press speed on wetting time, represented in a response surface plot and in a contour plot, respectively.

Coefficient	Value
b_0	53,522
b_1	-2,167
b_2	7,567
b_{12}	-2,175
b_{11}	0,267
b_{22}	1,567

Table 37 – Coefficient values obtained for wetting time.

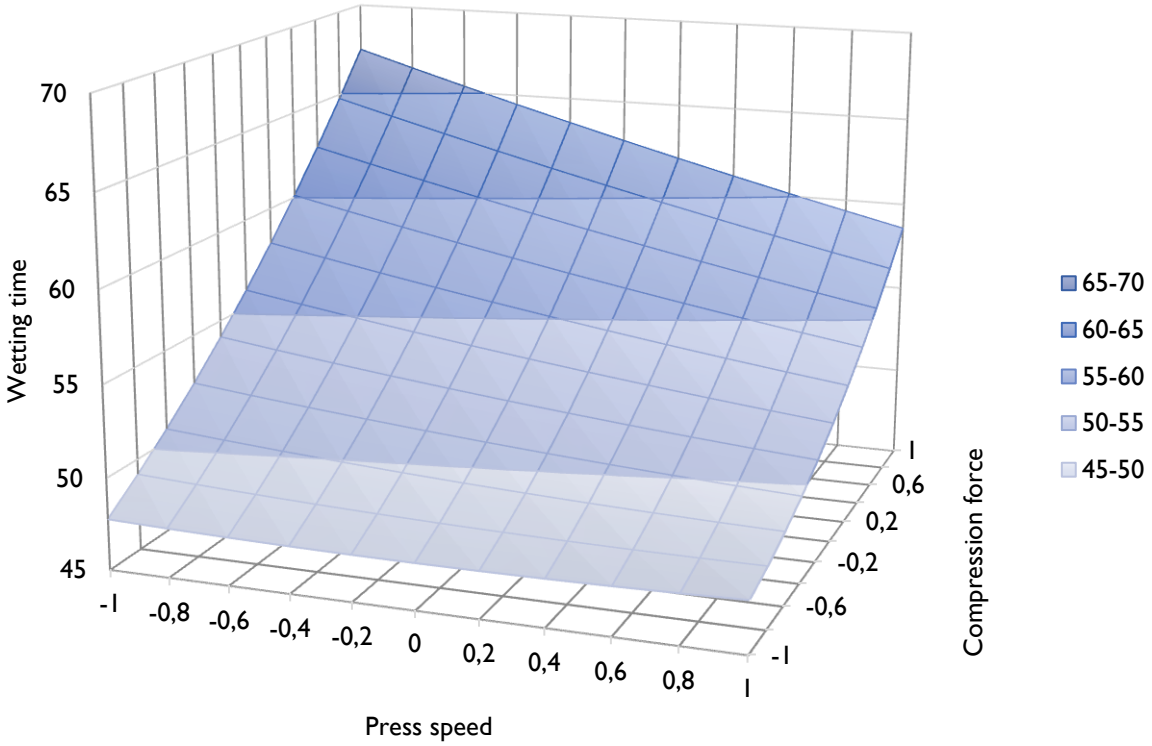

Figure 24 – Response surface plot showing the influence of compression force and press speed on wetting time.

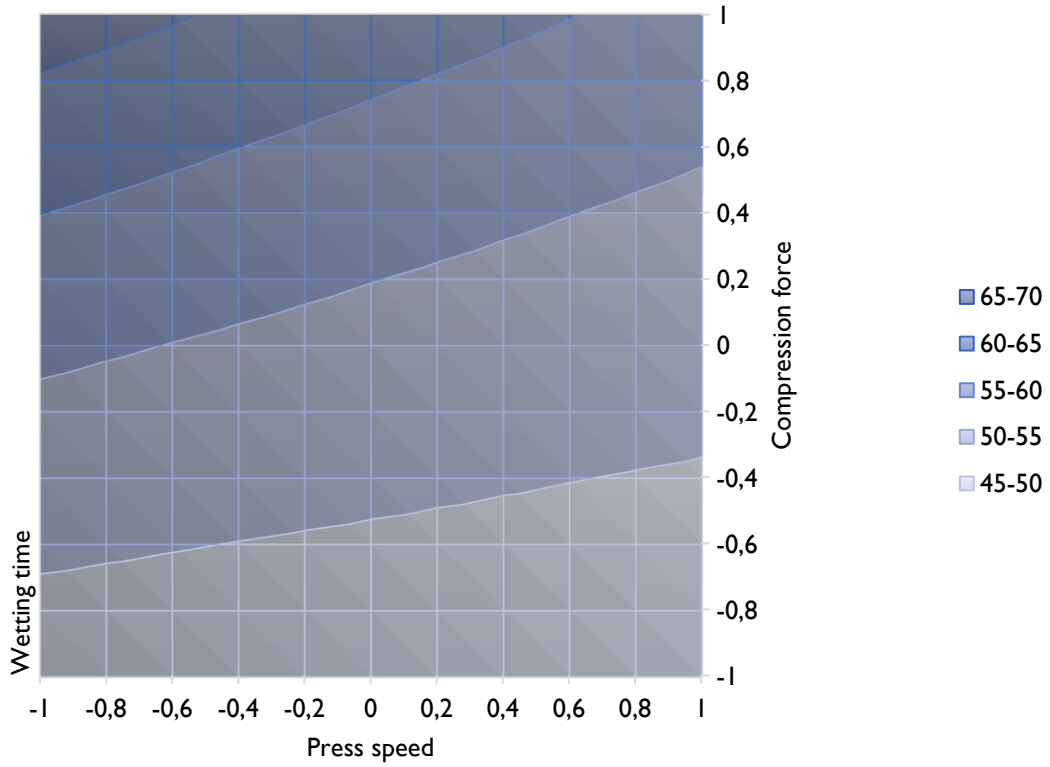

Figure 25 – Contour plot showing the influence of compression force and press speed on wetting time.

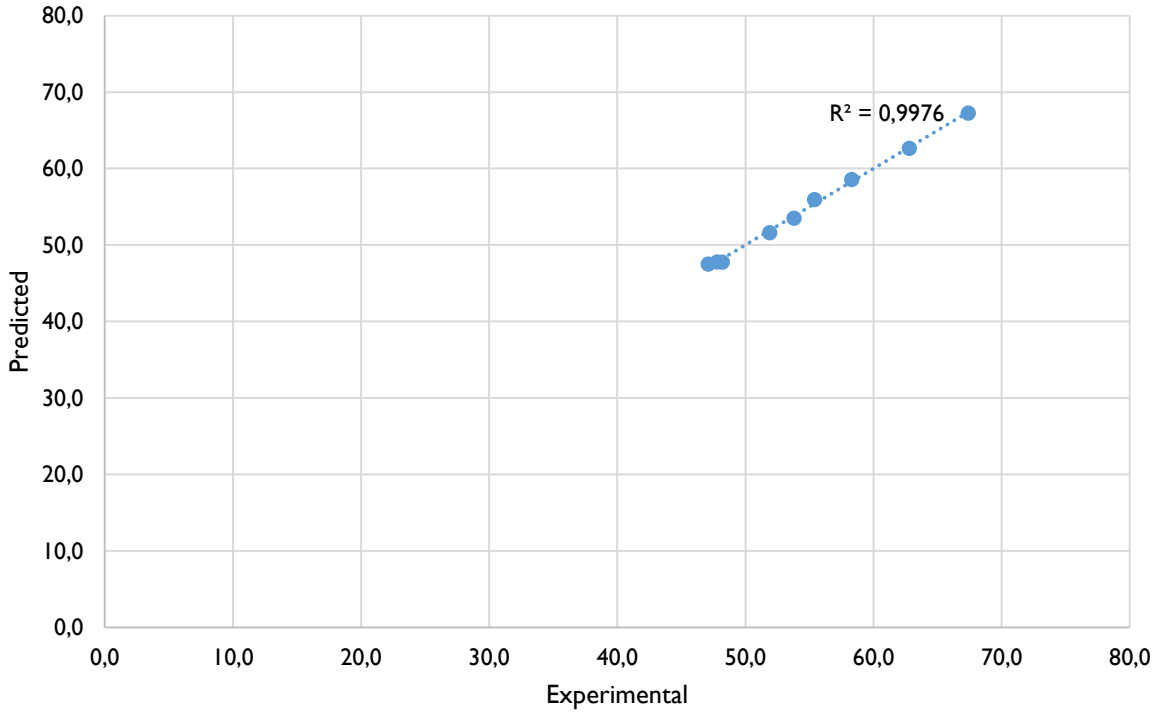

Figure 26 – Correlation between the experimental and the predicted values on wetting time.

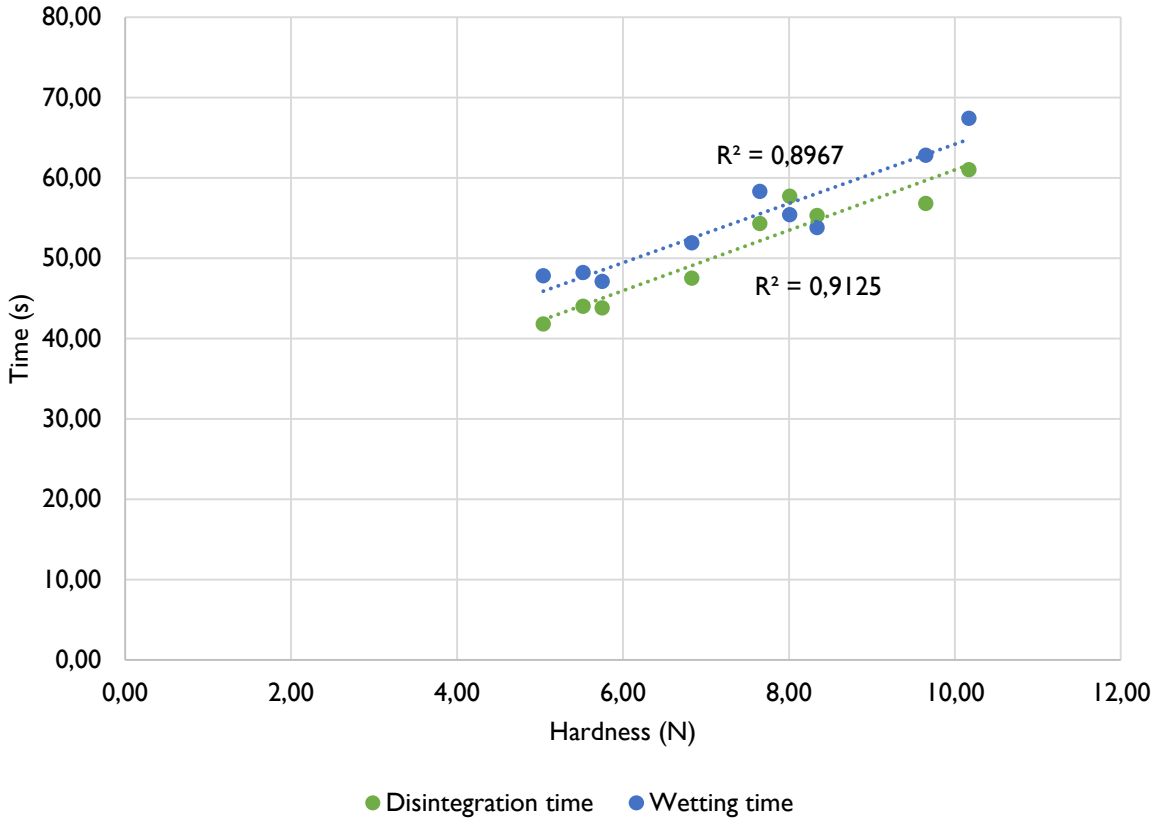

Figure 27 – Correlation between hardness and disintegration time and hardness and wetting time.

As predicted, compression force exercised a much higher influence on wetting time, compared to press speed. This is directly related to the hardness values obtained. A linear relationship observed between wetting time and hardness values (R^2 = 0.897, Figure 27), reflecting the importance of the hardness, and ultimately of compression force, in water intake into tablet matrix.

The increasing of tablet hardness, as a result of higher compression force mostly, become the space between the tablet particles smaller, which delays the liquid penetration into the tablet structure. Consequently, the time to water required for the solution to reach the upper surface of the tablet will increase.

The interactive coefficient reveals that effect of press speed is bigger at higher compression force values, affecting negatively the wetting time values. At lower compression force, there is no effect of press speed. Also, the effect of compression force increases as the press speed increases too.

The *in vitro* dissolution profiles of the tablets are shown in Table 38 and Figure 28. The results obtained clearly indicate that the values of drug release on 1st minute, 2nd minute and 5th minute, are dependent on the independent variable in study, the press speed and the compression force. That observation and the magnitude of the effect of each process parameter studied on dissolution are shown in the statistical analysis of the factorial design.

Figures 29 to 34 portray the 3-dimensional response surface plots and the correspondent contour plots for the drug release studies at 1 minute, 2 minutes and 5 minutes. Table 39 summarizes the DoE results obtained for dissolution testing.

	Dissolution		
Formulation code	**1st minute**	**2nd minute**	**5th minute**
F1	56.8 ± 3.3	82.4 ± 1.7	93.1 ± 1.1
F2	62.6 ± 6.0	85.9 ± 2.6	97.2 ± 0.3
F3	65.6 ± 2.6	88.2 ± 1.2	98.9 ± 1.7
F4	69.0 ± 3.8	88.0 ± 3.0	96.1 ± 1.8
F5	80.6 ± 4.2	90.6 ± 1.1	98.0 ± 0.4
F6	77.4 ± 3.4	90.3 ± 2.2	98.3 ± 2.0
F7	76.6 ± 2.4	88.4 ± 0.7	94.2 ± 1.0
F8	73.6 ±3.5	91.5 ± 2.3	94.9 ± 1.4
F9	76.2 ± 6.5	94.7 ± 3.5	98.9 ± 1.8

Table 38 – *In vitro* drug release results obtained on 1st, 2nd and 5th minute.

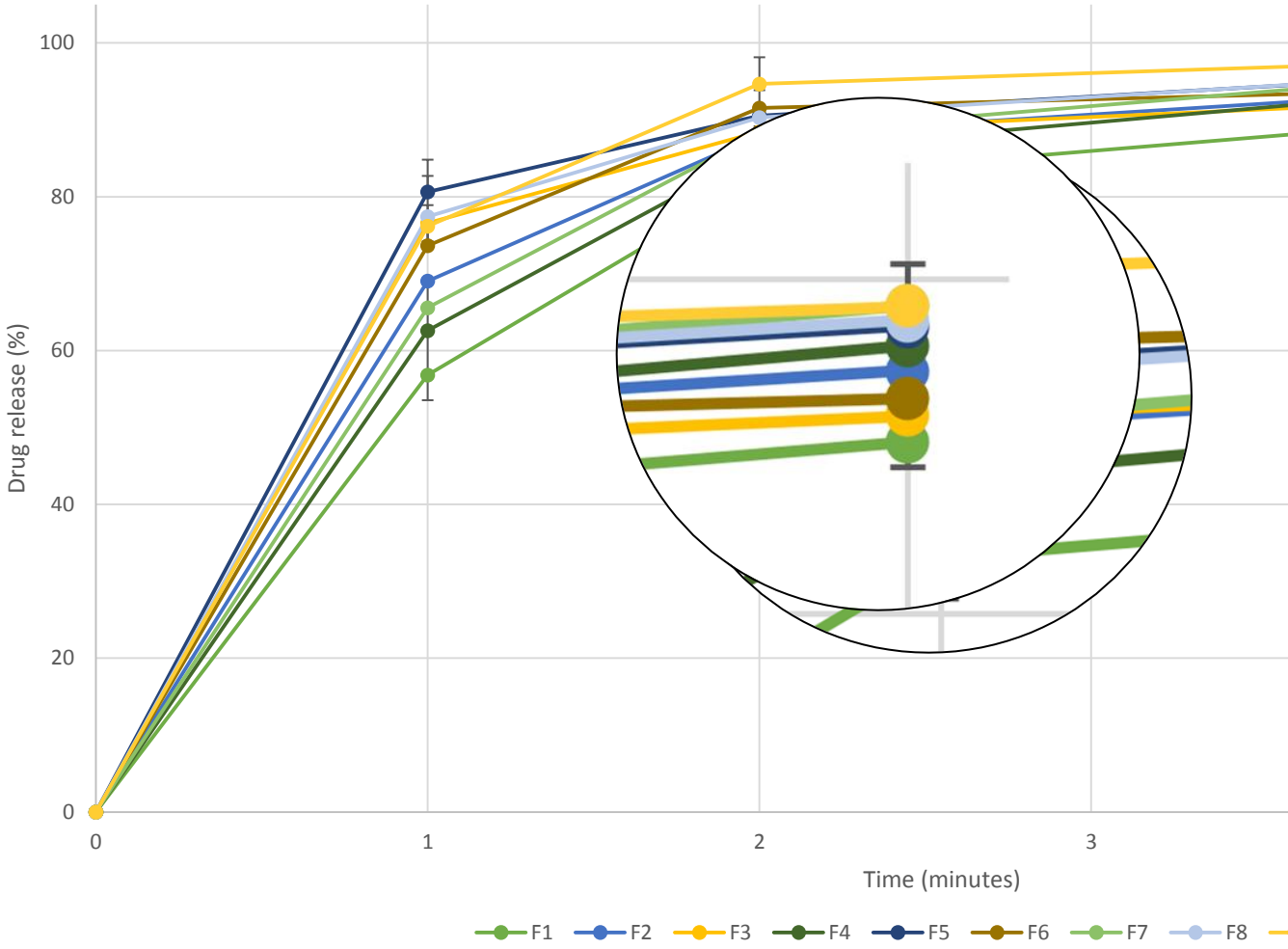

Figure 28 – *In vitro* dissolution profile of diazepam from tablet formulation F1 to F9. The results are mean ± SD of 3 tablets.

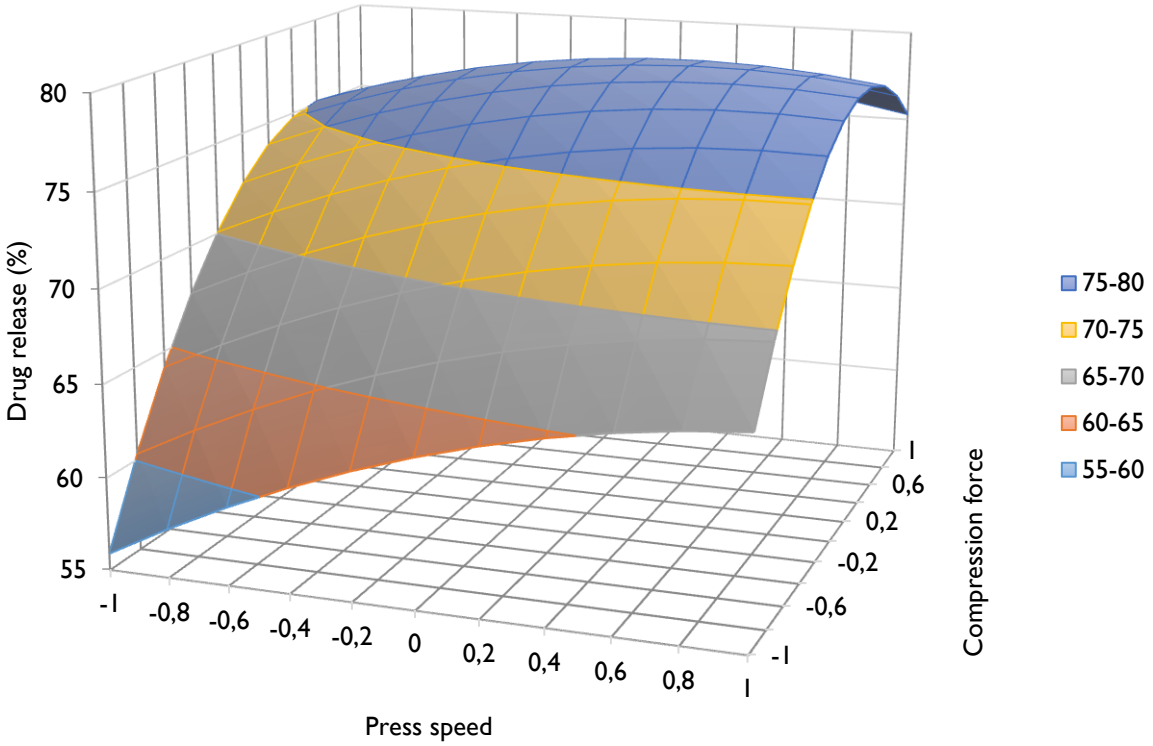

Figure 29 – Response surface plot showing the influence of compression force and press speed on drug release on 1st minute.

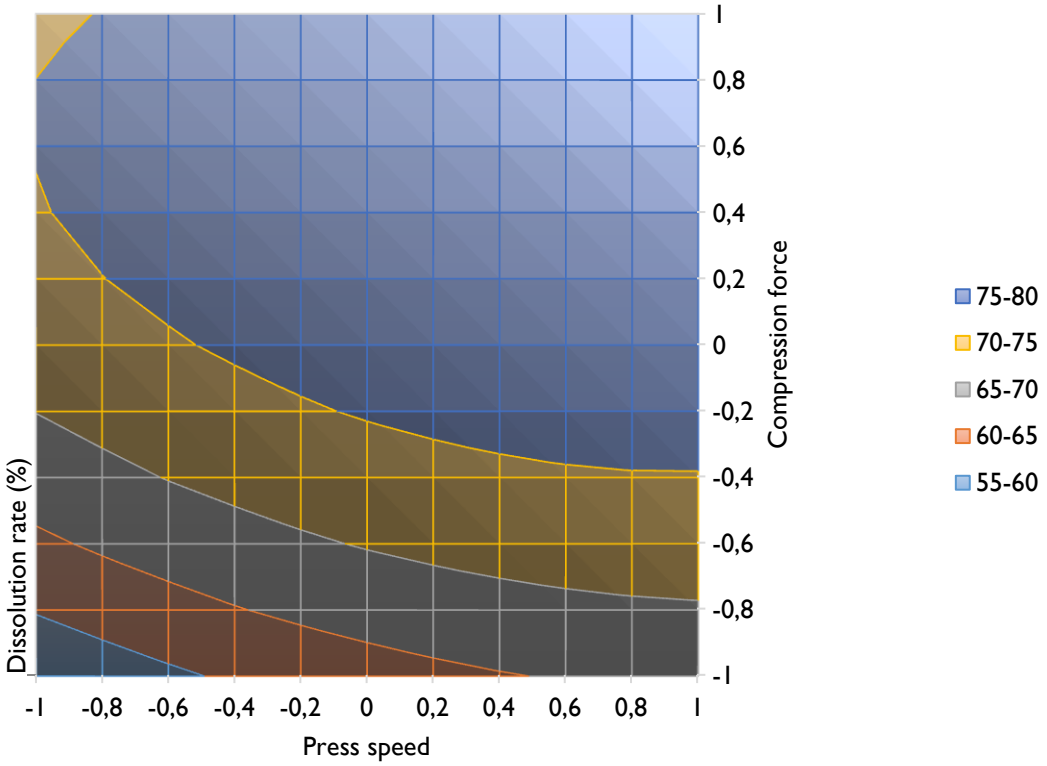

Figure 30 – Contour plot showing the influence of compression force and press speed on drug release on 1st minute.

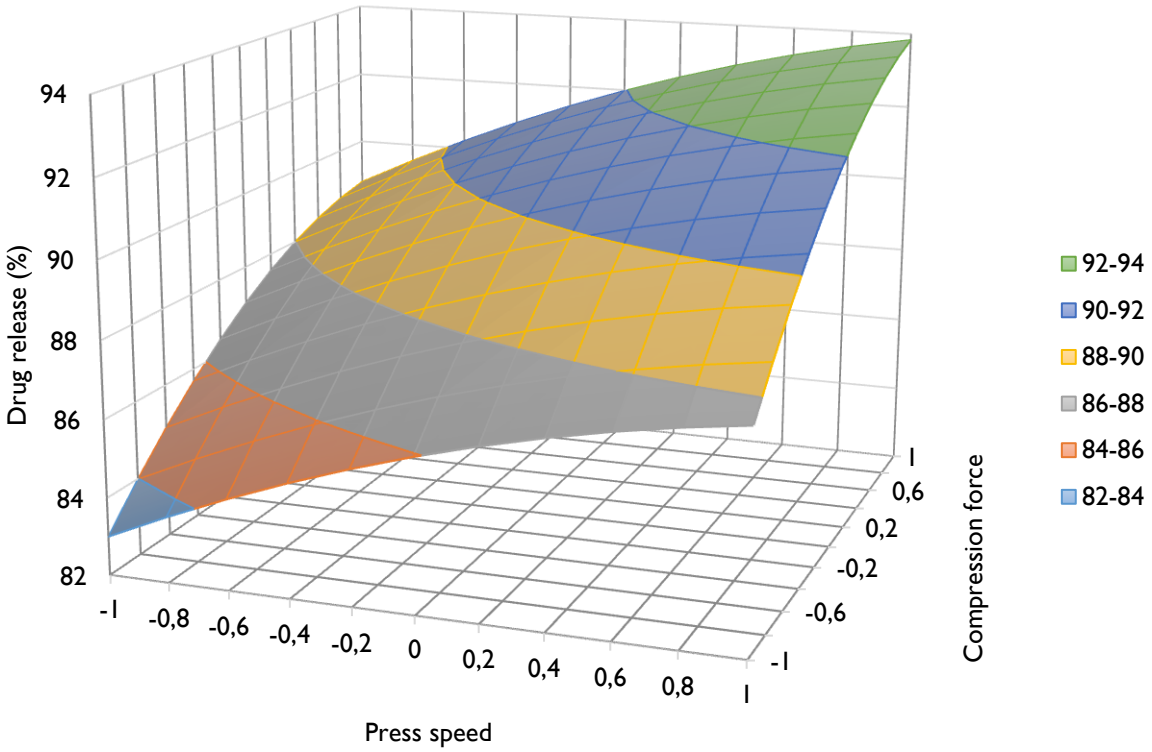

Figure 31 – Response surface plot showing the influence of compression force and press speed on drug release on 2nd minute.

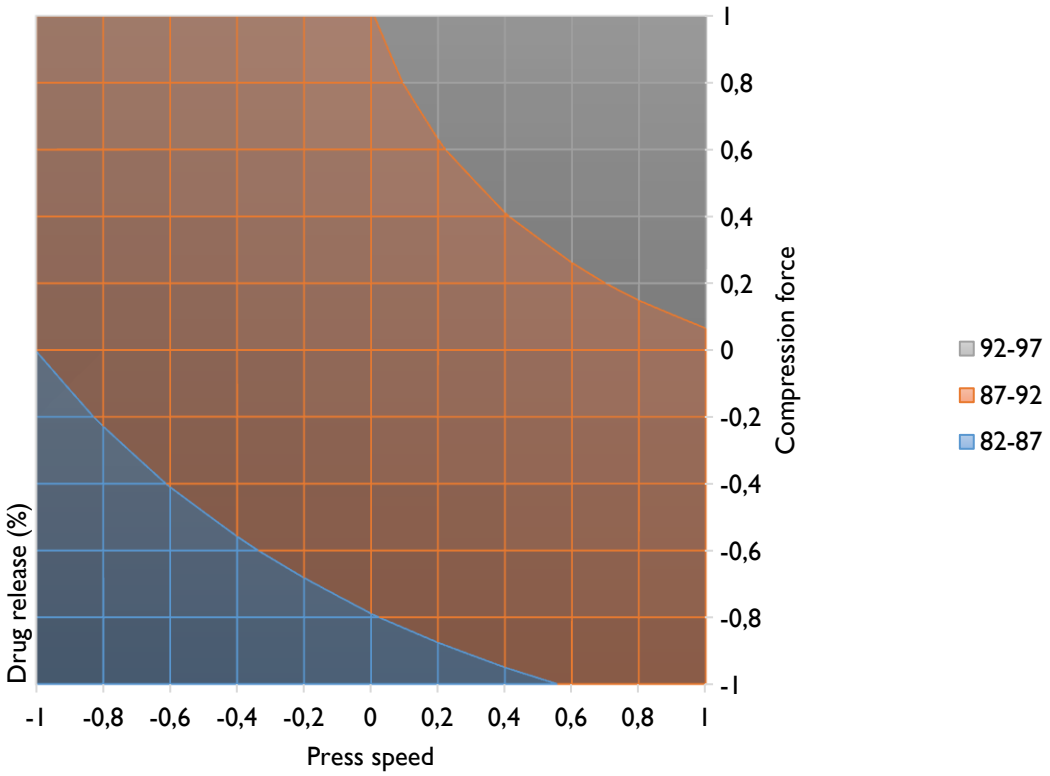

Figure 32 – Contour plot showing the influence of compression force and press speed on drug release on 2nd minute.

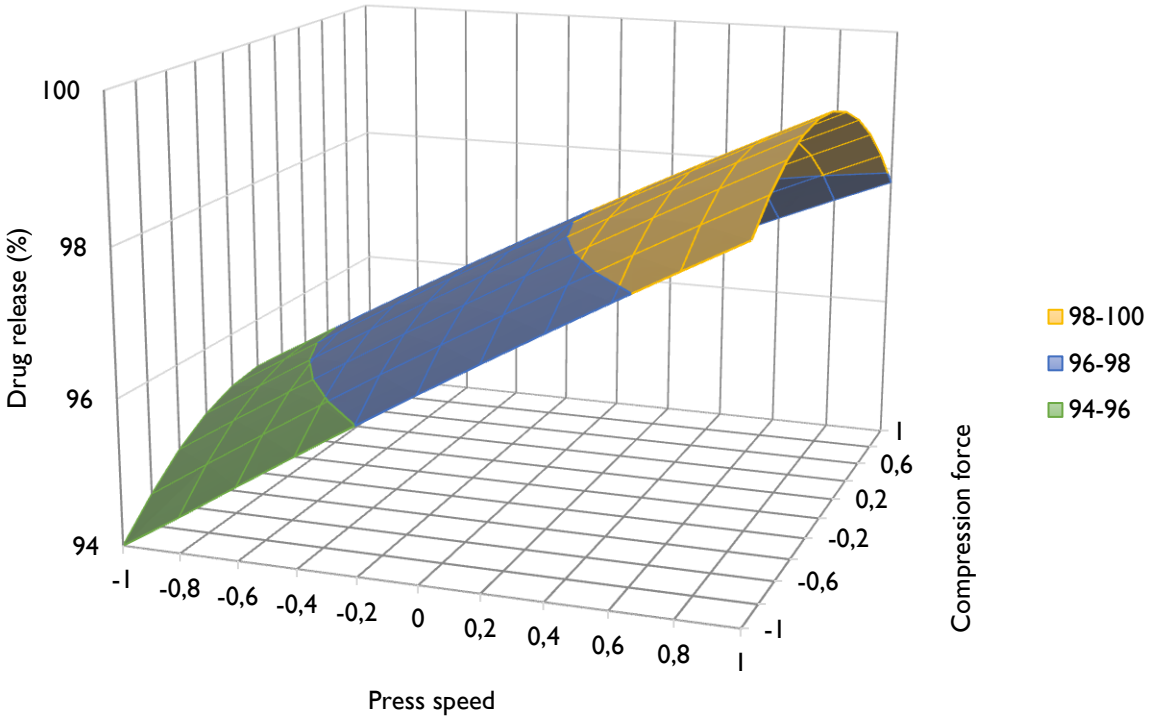

Figure 33 – Response surface plot showing the influence of compression force and press speed on drug release on 5th minute.

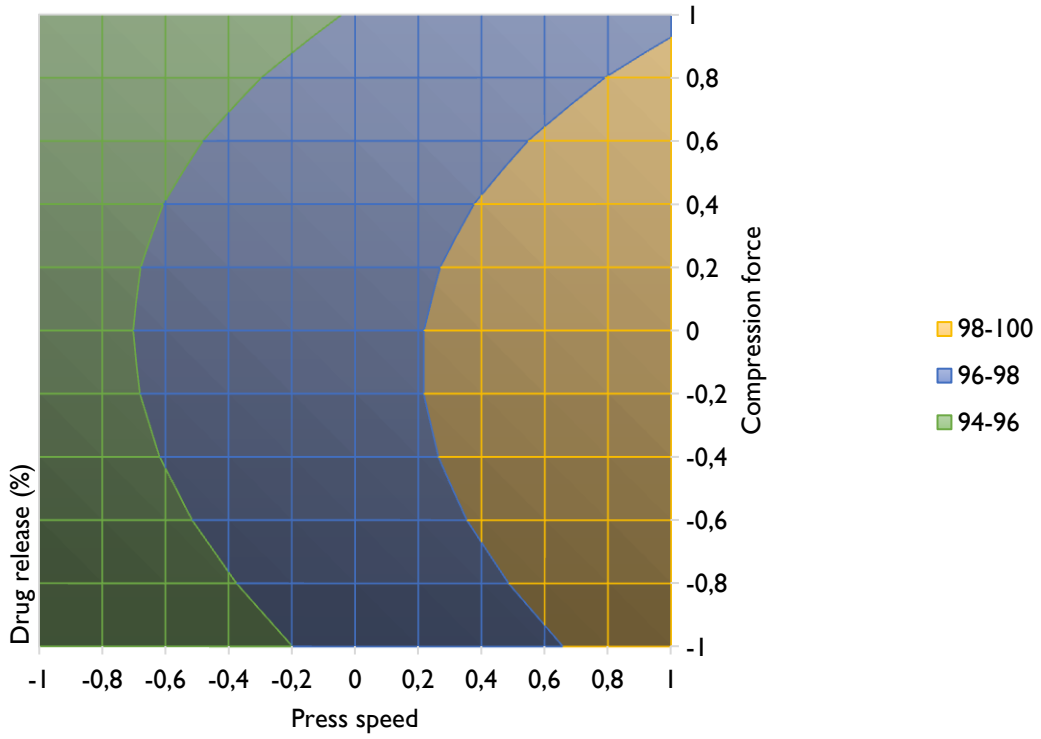

Figure 34 – Contour plot showing the influence of compression force and press speed on drug release on 5th minute.

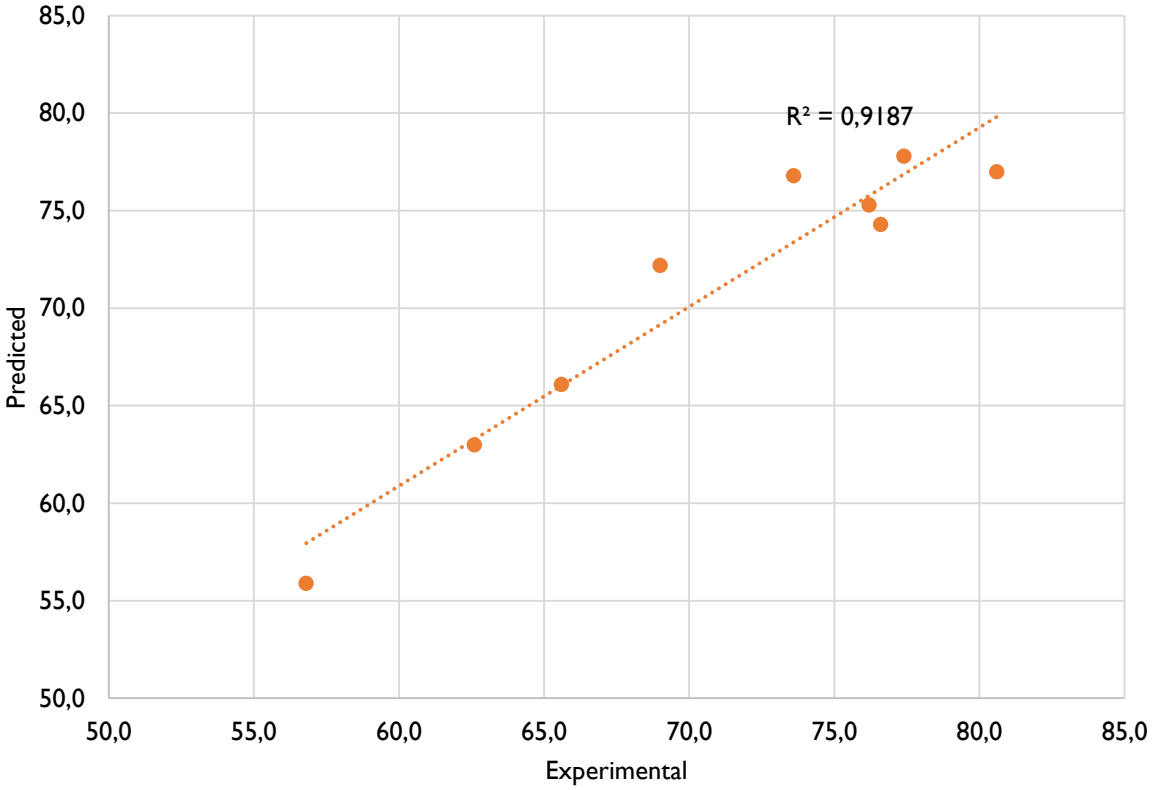

Figure 35 – Correlation between the experimental and the predicted values on dissolution at 1st minute.

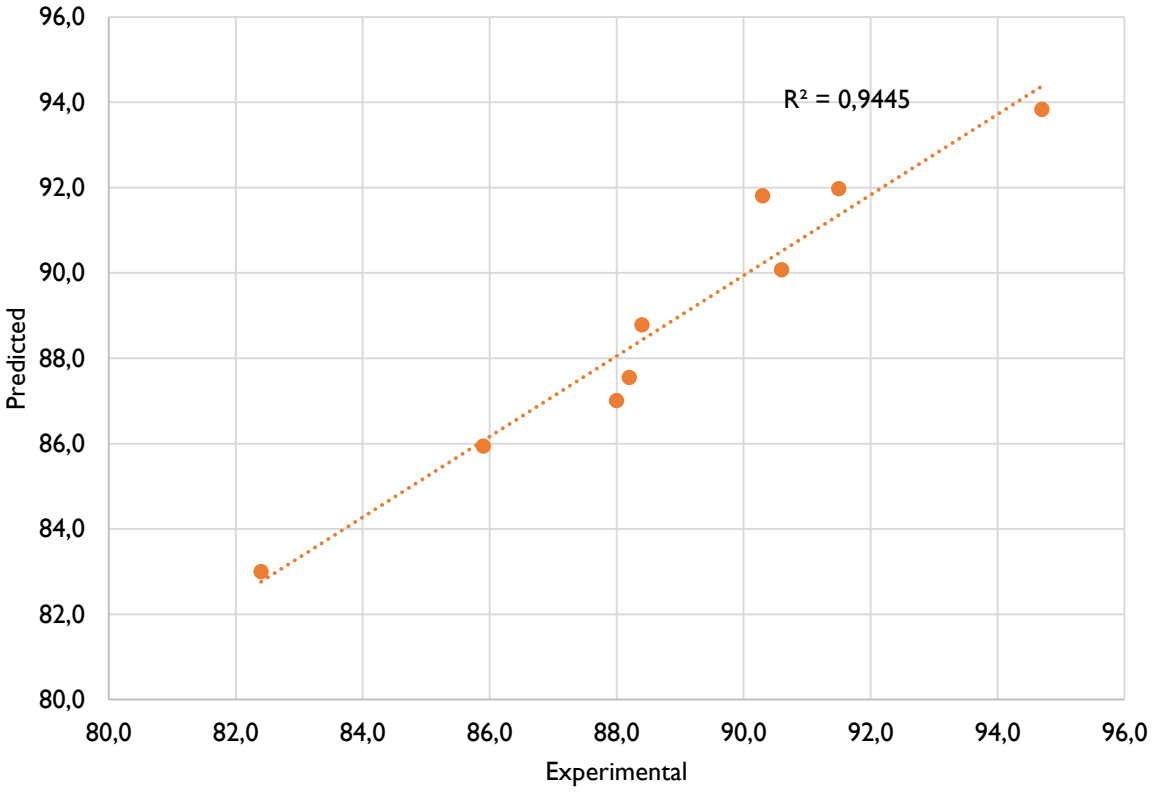

Figure 36 – Correlation between the experimental and the predicted values on dissolution at 2nd minute.

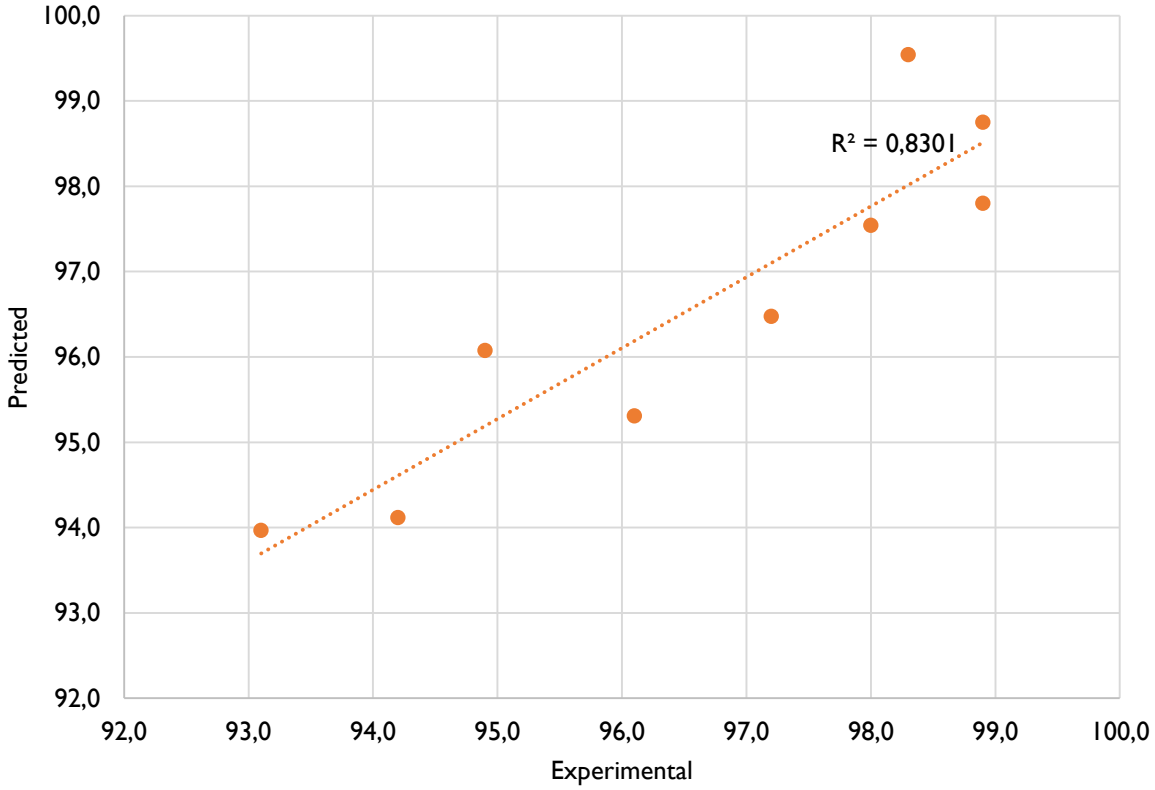

Figure 37 – Correlation between the experimental and the predicted values on dissolution at 5th minute.

Coefficient	1st minute	2nd minute	5th minute
b_0	77,000	90,078	97,544
b_1	2,800	2,400	2,117
b_2	6,900	3,017	-0,200
b_{12}	-2,300	0,125	-0,275
b_{11}	-2,000	-0,667	-0,117
b_{22}	-7,100	-1,117	-1,267

Table 39 – Coefficient values obtained for dissolution testing.

The values of R^2 of the multiple linear regression analysis coefficients for all 3 time points ranging between 0.830 and 0.944, assuring good models on the description of the results obtained on dissolution testing, as depicted in Figures 35 to 37.

On the first minute, the drug release was mostly affected by compression force in a positive way. Press speed also influences positively the drug release, but in a lesser extent. At the second minute the effect of compression force is reduced and becomes quite similar to the effect of press speed on dissolution. Both processes parameters maintain a positive effect on drug release. At the fifth minute, the compression force has no impact on drug release, being the effect of drug release mediated by the press speed, decreasing in magnitude compared to the first and second minutes. This is due to the fact that almost every drug is

released from the tablets, influencing the obtained model and reducing the effect of both variables.

Other studies suggest that hardness has an important role on dissolution profile, promoting a faster dissolution if tablet presents lower breaking forces.[80,81] As seen before, higher hardness values increase the tablet disintegration and wettability being expected, for this reason, a delay on the drug release. Logically, as hardness values fairly depend on the compression force, it should be expected that, as the compression force increases, the drug released from the tablet decreases. Although with a minor impact, it is similarly expected that the growth of press speed will affect positively the dissolution due to the lower harness values found at higher press speeds.

A positive effect of press speed is found in dissolution study at all three time-points. That means that with an increasing of press speed, the release of the drug from the tablet increases as well, which corroborates the role of hardness on dissolution.

Au contraire, a positive effect was also found for compression force on time-points 1st minute and 2nd minute, which means that, increasing the compression force, increases the drug release. The prediction that higher compressions forces leads to lower drug releases via higher hardness tablet values was not found, suggesting others factors for the obtained results.

These data suggest that a good balance between press speed and compression force is needed in order to obtain a fast release. That means that there is a range of hardness values that allow rapid drug release from tablets.

4.4. Conclusion

In manufacturing process development, the identified high risks for compression process step were assessed. Experimental studies were defined and executed in order to establish additional scientific knowledge and understanding, reducing the risks to an acceptable level. Finalized the experimentation, the initial manufacturing process risk assessment was updated with the current process understanding. Table 40 presents updated risk assessment of the manufacturing process.

The manufacturing process studies, involving the process parameters considered as critical in compression step, show, in general, a higher influence of compression force in comparison to press speed, on CQAs studied.

CQA	Process Steps		
	Pre-Blending	Blending	Compression
Hardness	Low	Low	Medium
Disintegration	Low	Medium	Low
Dissolution	Low	Medium	Low

Table 40 – Updated risk assessment of the manufacturing process development.

From the QTPP, it was initially expected diazepam ODT with hardness values not less than 10N, with a disintegration time not more than 30 seconds and with not less than 80% (Q) of diazepam released from the tablet at 15 minutes, in dissolution test.

The risk of the quality attribute hardness was considered high in the beginning of the study, due to the influence of compression force. Also, hardness affects directly the disintegration time and dissolution and consequently it was studied in detail. From the obtained results, it can be seen that formula F7 and F8 present hardness values within the acceptable range. Therefore, the risk was reduced to medium by using these compression parameters.

Formula F7 and F8 present disintegration times of 61.0 and 56.8 seconds respectively, failing the desired value. Furthermore, the DoE results obtained for disintegration time show that none of the formulas achieved the pre-defined target of not more than 30 seconds. Despite that, the risk was updated to low risk due to the results obtained in dissolution test, where it was observed that disintegration had no impact on dissolution.

In dissolution test, the amount of diazepam released from the tablets were more than 80% (Q) at 5 minutes for all batches prepared. Consequently, dissolution risk was reduced to low too.

From the study it can be concluded that using the following manufacturing process conditions to prepared ODTs of diazepam (Table 41) we have a controlled process and a product with the desired quality.

Process step	Equipment	Process parameters
Blending	V Blender	375 revolutions for blending (15 min at 25 rpm)
Lubrication	V Blender	100 revolutions for blending (5 min at 25 rpm)
Compression	Fette 1200i Compression machine (rotative)	25 kN, 5000 tablets/hour

Table 41 – Manufacturing process parameters selected for diazepam ODT.

CHAPTER IV – CONCLUSION

ODT technology offers significant advantages for lifecycle management, patient convenience and market share and should be considered, being a growing trend in pharmaceutical dosage forms.

In this project, ODTs of diazepam were successfully prepared on a QbD approach, using a direct compression method.

In formulation study, sodium starch glycolate, croscarmellose sodium and crospovidone were challenged in accordance with an experimental design. The study concluded that crospovidone allowed better quality attributes for ODT of diazepam, at 30% in formulation. Also, the presence of binder was crucial to enhance the tablets consistence but affects its disintegration time.

For manufacturing process development, compression was considered as the most important step, and therefore a multivariate analysis was used to understand the relationship between the critical compression variables and the drug product quality attributes. The study showed a higher influence of compression force on hardness, disintegration time, wetting time and dissolution, over press speed.

Additional work should be planned in order to investigate the impact of others formulation and process variables on properties on the ODT.

QbD proves to be an excellent method to develop pharmaceutical systems, providing several tools that increase a much better understanding of the formulation and manufacturing process.

ANNEXES

Solutions and Buffers

Dissolution medium

Hydrochloridric acid at 0.1M solution: 83 mL of Hydrochloridric acid 35-37% in 10L of distilled water

Simulated saliva

pH 6.8 phosphate buffer (Wetting time and Water Absorption Ratio): 2.38 g Na_2HPO_4 and 0.19 g KH_2PO_4 and 8.00 g NaCl per liter of distilled water adjusted with phosphoric acid to pH 6 .8±0.05

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