Universidade de Lisboa

Faculdade de Farmácia

Modelling a fluidized wet granulation process

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Mestrado Integrado em Ciências Farmacêuticas

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Resumo

Tradicionalmente, a produção de medicamentos pela indústria farmacêutica é realizada em modo descontínuo sendo o produto acabado libertado após a sua verificação, também designado por *quality-by-testing*. Este fato decorre em parte devido ao elevado nível de regulação, o que, no passado, juntamente com outros fatores, dificultou a transição para processos contínuos e novos paradigmas de avaliação da qualidade. Atualmente, a transição para processos de produção em contínuo começou a ser incentivada pelas autoridades reguladoras, sendo que estes processos serão vantajosos não só para a indústria, por aumentar a eficiência dos processos de produção, mas também para os consumidores, fornecendo uma maior consistência na qualidade dos produtos fabricados. A *Food and Drug Administration* (FDA) e a *European Medicines Agency* (EMA), assim como as novas *guidelines* do Conselho Internacional para Harmonização de Requisitos Técnicos de Produtos Farmacêuticos para Uso Humano (ICH). incentivam agora o desenvolvimento de processos de produção de medicamentos baseados no conceito de *Quality-By-Design (QbD).* Permitindo implementar processos contínuos de produção baseando-se num conhecimento aprofundado das principais variáveis que influenciam o processo de fabrico, de forma a conceber um produto de qualidade e, tendo em conta que a qualidade não deve ser testada no produto final, mas sim desenvolvida desde a primeira etapa de produção. Com o conceito de QbD em mente, foi decidido, neste estudo, desenvolver um design space (DS) para um processo de granulação, uma vez que se trata de um processo importante na produção de várias formas farmacêuticas. Para isso, estudou-se uma combinação de variáveis e parâmetros do processo que demostram resultar num produto de qualidade, ou seja, dentro das especificações que foram estabelecidas. As variáveis escolhidas para este estudo incluíram a formulação e parâmetros identificados como críticos do processo. Para alcançar este objetivo, foi utilizado um método de delineamento experimental de forma a definir os ensaios a realizar. Os grânulos foram testados de acordo com vários parâmetros de qualidade de forma a estabelecer o DS. De modo a testar a influência do processo de granulação na forma farmacêutica final, foi decidido também proceder à produção de comprimidos, que foram também testados.

Palavras chave: Granulação; Quality-by-Design; Design space; Delineamento Experimental; Compressão.

Abstract

Traditionally the production of medicines by the pharmaceutical industry is done in batches with the finished product released after verification, also known as quality-by-testing. This is due to the fact that it is an industry with tight regulations that, in the past, together with other factors, made the transition to continuous processes, as well as quality control methods difficult. Currently, the transition to continuous processes has been encouraged by regulatory authorities as these processes will be advantageous not only for the industry, as it increases the efficiency of the processes, but also for the consumers, providing higher quality to the manufactured product. Food and Drug Administration (FDA) and the European Medicines Agency (EMA), as well as the new guidelines from the International Council for Harmonization of Technical Requirements for Pharmaceutical Products for Human Use (ICH) now encourage the development of drug manufacturing processes based on the concept of quality-by-design(QbD), with the opportunity of implementing continuous production processes based on an in-depth knowledge of the main variables that influence the manufacturing process, in order to design a quality product, with the notion that quality cannot be tested on a product but developed from the ground up starting with the first step of production. With the concept of QbD in mind, it was decided, in this study, to develop a design space (DS) for a granulation process, an important process in the production of various pharmaceutical forms, studying a combination of variables and process parameters that guarantee to result in a product with quality, that is, within the specifications that were decided. The variables chosen for this process included the formulation and critical parameters of the process. To achieve this objective, experimental design was used in order to establish the most important tests. The granules were tested in various experiments suitable to our variables in order to establish the DS. In order to test the influence of the granulation process on the final pharmaceutical form, it was also decided to proceed with the production of tablets, which were also tested.

Keywords: Granulation; Quality by design; Design space; Design of Experiments; Tabletting.

Acknowledgements

In memory of my loving mother who encouraged and supported me throughout all my life.

Abbreviations

ICH- International Council for Harmonization of Technical Requirements for Pharmaceutical Products for Human Use.

API- Active pharmaceutical ingredient.

DOE- Design of experiments.

PVP- Polyvinylpyrrolidone

MCC- Microcrystalline cellulose

Lac- Lactose

Pc- Paracetamol

MgSt- Magnesium stearate

AUC- Area under the curve

TImix- Inlet temperature AUC during the mixing stage

TIg- Inlet temperature AUC during the granulation stage

TIdry-Inlet temperature AUC during the drying stage

Vel- PVP addition rate

TOg- Outlet temperature AUC during the granulation stage

TOmix- Outlet temperature AUC during the mixing stage

TOdry- Outlet temperature AUC during the drying stage

Table of contents

Figure index:

Table index:

1.Introduction

Currently the production of medicines by the pharmaceutical industry is mostly conducted in batch mode. This type of production is still in use because it is an industry with tight regulations, which in the past, hindered changes to the process after the product entered the market as well as historical factors such as high profit margins that led to the cementation of batch manufacturing processes. Other industries such as food and chemistry have evolved to the adoption of the continuous production mode. (1,2) Recently, continuous production has gained great interest on the part of the pharmaceutical industry, with several companies implementing research and development groups dedicated to the implementation of continuous processes. (3)This shift to a focus on continuous production comes from an economic necessity and aims to increase profits by optimizing the process, since the proportion of generic drugs in the market, the competition and research and development costs are increasing. (3,4) In addition to economic factors, continuous production allows to satisfy a greater demand, which reduces the likelihood of a shortage of medicines and is also more flexible in its production capacity (2,5). Other advantages include a faster and more economical scale-up process, an increase in the consistency of the product quality and consistency of the process and a decrease in the dependence on cheap labor (6).

Currently, the transition to continuous manufacturing is encouraged by regulatory entities such as the FDA and EMA, being seen as a way to increase the quality and efficiency of production (7). The International Council for Harmonization of Technical Requirements for Pharmaceutical Products for Human Use (ICH) is developing specific guidelines for the use of continuous processes (guideline Q13). In the past, it has produced guidelines that allow and encourage the implementation of processes based on quality by design, an essential concept in continuous production, based on a systematic approach to the development of the manufacturing process, deepening the understanding and control of the processes, so that the quality is not tested into the medicines, but obtained by design and therefore allowing the implementation of Real Time Release Testing, a release system that ensures that the product has the desired quality at the end of production (3,8–10). These guidelines are important for advancing the implementation of continuous processes since the harmonization of regulatory processes allows the industry to avoid the need to produce differently for different markets. (6)

1.1 Pharmaceutical granules

Granulation is a process used in the pharmaceutical industry in which small particles are aggregated, to form a larger cohesive mass, called a granule, where the aggregated particles can still be distinguished. Granules can also be obtained from a higher mass, reducing the size of a compact material. (11,12)

The granules are used as a pharmaceutical form of several drugs, these dosage forms are aggregates of powders sufficiently robust to be able to be manipulated, with a diameter that typically varies between 1-4 mm. Granules are also used as intermediates in the preparation of tablets or for capsule filling, being this the main use of the granulation technique, these granules typically have a diameter that ranges from less than 0.2 to 0.5 mm. (13)

1.2 Motivation for granulation

There are several reasons for this process to be applied. The granulation step avoids the separation of the constituents of a mixture of powders since this phenomenon is mainly due to the difference of densities and sizes of the powders in a mixture, being that the denser particles will gather at the base of a container with the less dense stacked above. Since the granulate will consist of the mixture, the segregation of the individual components will not occur and therefore it allows handling of the granulate without loss of the quality of the mixture. Granulation makes it possible to decrease the total volume of the powders, increasing their density, allowing for better storage and transport. It also decreases the compaction of the powders with hygroscopic characteristics and allows an easier measurement of volumes and simpler administration in the case of the pharmaceutical form. (11–13) In production, this step decreases the amount of dust formed and improves the appearance of the medicine. Advantages of this step also include the increase in the flowability of the particles, due to the fact that, in relation to the powders, the granules have a larger dimension and are less irregular, thus being less cohesive, which allows them to flow more easily. Inadequate flowability will lead to variations in the mass of the produced drug since there is greater variability in the tablet die filling and the normal operation of compression and capsule filling machines requires good flowability of the raw material for a quality end result. (11–13) This process also improves the control of the uniformity of the particles and their shape, refining the compaction and compression. It is also possible to control the moisture and hardness of the granules. (11,13,14)

In general, the granulation step in the production of medicines allows better results, lower defects in the tablets, better productivity and reduced down times. (15)

In high-dose drugs, the quantity of excipients necessary to achieve the needed flow and compaction properties can result in a dosage form that is too heavy and bulky. In these cases, granulation is an often used solution as this process imparts two primary requisites to formulations: compatibility and flowability with less excipients needed. (15)

Even though there are several positive aspects that the granulation step can bring to the production of a medicine, the decision to include the granulation operation should take in consideration possible disadvantages associated with it. When the disadvantages outweigh the advantages of granulation, direct compression may be considered. (16)

1.3 Types of granulation

In the production of medicines, granulation is typically the most complex process and also the most difficult to control. The granules can be produced by different methods based on the properties of the drug's components. Granulation methods can be divided into dry granulation and wet granulation according to the use or not of liquids in the process although several new types of types granulation methods exist. (17)

The dry granulation methods are primarily utilized when the components of a mix are not compatible with moisture or if the utilization of a wet granulation method affects the tableting negatively. These methods are based primarily on the use of pressure to form the granulates. Examples of this method are slugging or roller compaction.

Wet granulation methods are used when such problems aren’t present and consists of wetting a powder mix with a granulation fluid for it to increase in mass. This granulation fluid can be used as a solvent for a binding agent which is used to increase particle adhesion once the granules are dry. This binding agent also has the ability to increase the mechanical strength of the final tablet by reducing the interparticle distances within the tablet and improving bond formation. (18)

The following table contains several granulation methods, wet and dry, as well as a small description of each method.(19–22)

Table 1.1 Granulation methods

Methods	Description
Roller compaction	Powders are agglomerated between the rollers of a compactor then milled to form granules.
High shear mixture granulation	A binder liquid is fed to the powder particles in a closed container with blending tools and a chopper
Fluid bed granulation	Granules are produced by spraying a binder solution onto a fluidized powder bed
Extrusion- Spheronization	Extrusion of a wet mass to form rod shaped particles and then rounding the particles in a spheronizer
Spray drying	Mixing of spray droplets with heated gas streams evaporating the liquid and leaving behind the dried solids.
Reverse wet granulation	Immersion of the dry powder formulation into the binder liquid followed by controlled breakage to form granules
Melt granulation	Binder that melts at low temperatures is used to achieve agglomeration of solid particles

Several other methods of granulation are also used in the pharmaceutical industry as the technology continues to change and evolve. Wet granulation methods are based on three principal fundamental processes: wetting and nucleation, consolidation and growth; and breakage and attrition. The wetting and nucleation are the first steps of the wet granulation

process and consist in the wetting of the powder mixture with the granulation fluid, attempting to distribute the liquid evenly. Nucleation happens when the binder begins to wet the powder, forming the initial clusters. A bad combination of powder and binder or an inefficient binder dispersion method will affect this stage of granulation creating a product that is difficult to control and reproduce.

The granule consolidation and growth happens when the mixture starts to collide and stick together. This process begins when the liquid is added to the powder mass and so is simultaneous with the wetting and nucleation stage and can continue after the liquid addition has seized. This process is affected by a range of factors such as the availability of liquid binder at or near the granule surfaces and average particle size which, if decreased, will cause less granule consolidation.

Breakage and attrition are divided and occur in different stages of granulation, with breakage happening to wet granules and attrition happening to the dried granules. Breakage of wet granules influences the final granule size distribution, attrition of dry granules leads to the generation of dusty fines and is generally to be avoided. (23)

The following figure shows the three fundamental processes described.(11)

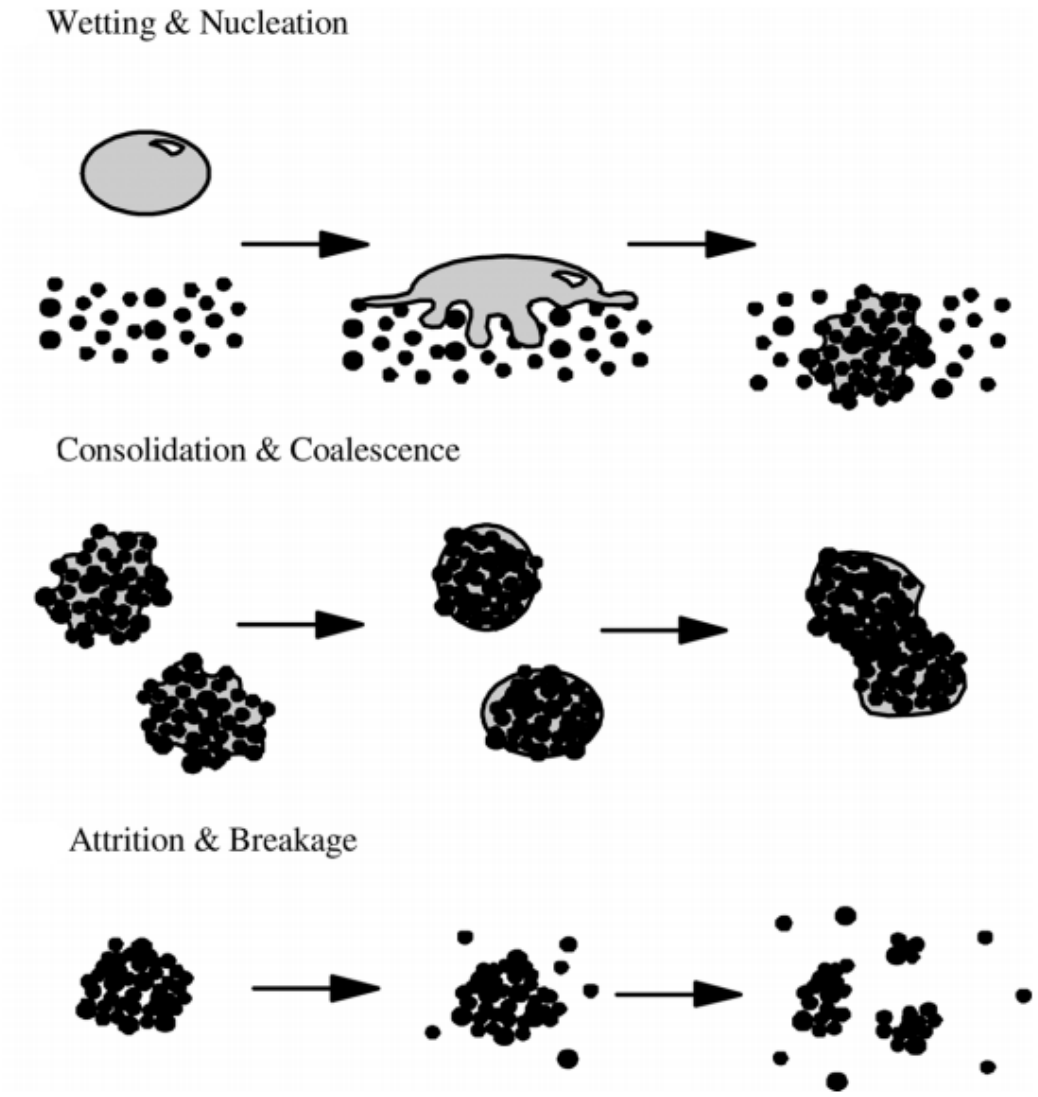

Figure 1.1 Wet granulation process

1.4 Fluid bed granulation

Different methods of wet granulation are used within the pharmaceutical industry, such as low and high shear granulation and fluid-bed granulation. Fluid bed granulation is a granulation method based on spraying a binder solution onto a fluidized powder bed, with the mixing, granulation and drying done in the same equipment, the fluid bed, saving labor costs, transfer losses and time, as well as simplifying the process and benefiting the GMP requirements. Fluidization is the state in which solids are transformed into a fluid-like state through contact with a gas. It is a behavior explained by a summation of various interaction and interparticle forces. When a gas is passed through a bed of particles at a certain velocity, the gas will support the weight of the particles leading them to become fluidized. The fluid bed is

a system comprised of an air handling unit that handles air filtering, heating, cooling and removal of humidity. This conditioned air is passed through a bed of solids in the container to achieve fluidization. The binder solution is sprayed onto the particles by a nozzle inside the container in the granulation phase. A spray is defined as a zone of liquid drops in a gas and spraying is the act of breaking up a liquid into a multitude of these droplets. The main purpose of spraying is to increase the surface area of a liquid so it can be better dispersed. The nozzle is an orifice through which liquid is forced through by compressed air. The spray pattern and angle are adjusted by the position of the cap surrounding the nozzle and the air pressure forcing the binder liquid out. Different types of fluid bed granulators have different properties according to where the nozzle is placed achieving different granule characteristics. The granulation fluid is pumped through a spray lance into the nozzle. After the air passes through the particles, it is filtered by filter bags which are shaken occasionally to reintroduce the collected particles into the fluidized bed. The air then leaves the system through an air filter system to the exhaust passing a blower or fan that keeps the system at a lower pressure than the surrounding atmosphere.(24)(11)

The following figure shows a fluid bed granulator similar to the one used in this work.(25)

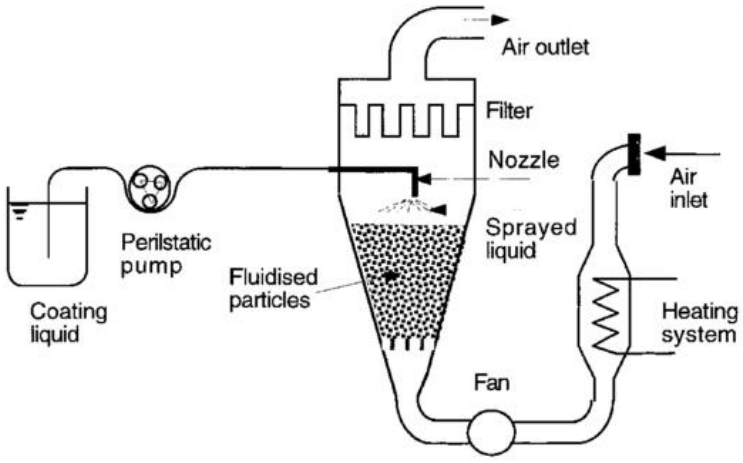

Figure 1.2 Fluid bed granulator

When compared to low and high shear granulation processes, the utilization of the fluidized bed leads to finer, free-flowing, less dense, and homogeneous granules that, after compression, produce harder and faster disintegrating tablets, requiring lower pressure to compress than the materials processed by conventional wet granulation methods.(24,26)

The typical fluidized bed process begins with the mixing of the dry components, which are loaded into the recipient. The mixing of powders is a key step in the manufacture of virtually

all solid dosage forms and is utilized in order to obtain a high-quality final product with an acceptable content uniformity of the API and the all components in the formulation. An ideal mixture is one in which any group of particles taken from any position within a mix contains the same proportions of each particle as the mixture as a whole. (15)(26) After the mixing stage, comes the wet granulation, and drying steps. The binder fluid is sprayed onto the bed of particles until the desired moisture content or granule size is achieved. Once the sprayed is stopped, the drying phase begins and continues until a predetermined product temperature is reached which concludes the granulation process.(26)

In addition to an increased uniformity in filling the tablet dies there are several advantages to granulation before compression. Direct compression of a mixture of powders is not always the most suitable approach since, in addition to flow problems that some raw materials or powder mixtures may have, there are also problems in the uniformity of the mixture, which have the biggest consequences in the case of low dose medicines. Another reason to granulate before compressing, in the case of some drugs, will be the properties that can be provided by the granulation, for example it may be advantageous to densify the mixture through the granulation step to decrease the size of the medicine. Other attributes that can be changed by granulation include friability, hardness and a more suitable dissolution profile. (11) The granulation process itself allows a migration of the solutes to the surface during the drying process and as such creates granules with a layer of binders on the surface that can allow an easier compaction compared to a mixture of powders with the same binder. (13)

1.5 Compression

The production of tablets involves the process of powder compaction with the objective of converting a loose mass of powder into a single solid tablet. A successful tableting process depends on interparticle interactions of powder particles, material properties, and compression process. When a low compressive force is applied to a powder it will lead to particle rearrangement until it attains bulk density and further densification is not possible without particle deformation. Further compression past this point will lead to elastic deformation. When the elastic limit is exceeded, there is a change in the rate of reduction in the bed volume as plastic deformation or brittle fracture of particles begins. Both these processes are necessary for the manufacturing of a tablet as plastic deformation increases contact areas between particles

irreversibly and fragmentation produces clean surfaces that bond strongly forming the tablet.(15,26)

A quality tablet will remain intact trough manufacturing, packaging and transportation processes and until it is consumed by the patient. A quality tablet will also disintegrate and dissolve after oral administration according to some expected profile and so it is important that it not excessively hard.(26)

1.6 Experimental design

Because experimentation typically takes time and resources it is practical to employ strategies to make it more efficient, thereby reducing the time and money expended. Most experiments consist of measuring the effect that a factor or multiple factors have on the outcomes of said experiments, being that the factors are the independent variables, and the outcomes are the dependent variables. (27) Experimental design is a technique used for exploring new processes, gaining insight into existing processes and optimizing these processes for achieving better performance. An example in the pharmaceutical industry are the challenges that surface in the production of a new medicine, such as the optimization of the excipient composition required to obtain a product with the desired characteristics.

Design of experiments (DOE) is defined as the process of planning, designing and analyzing the experiments. Multiple approaches for DOE exist, such as Plackett–Burman, Taguchi, mixture, Box– Behnken, surface, full and partial factorial design.(28,29)

2. Objective

The objective of the present study was to ascertain the feasibility to estimate a design space (DS) for a typical wet granulation process based on changes in the formulation and process variables that are known to affect the final properties of granules and indirectly the tableting process and the properties of such tablets.

3. Materials and Methods

3.1 Formulation

With the primary objective of finding the relationship between the process variables and the characteristics of the granules and tablets manufactured, a series of experiments were conducted varying the fractions of different components of our formulation. The center point of the formulation which was varied in the different experiments, was adapted from a previous in-house study developed in the University of Eastern Finland. This formulation was used because it successfully produced functional granules in the in-house study.

The formulation consists of paracetamol as the API, monohydrate lactose as a diluent and as a tablet binder, microcrystalline cellulose 101 as a diluent, with properties as a binder and disintegrant, polyvinylpyrrolidone dissolved in water and sprayed during the granulation phase as the main binder and magnesium stearate added after granulation as a lubricant for the tableting process. (30)

3.2 Design of experiments

This formulation was inputted into MODDE, a design of experiments software, with the central point of the experiment consisting in 13.7 % of paracetamol, 56.9% of MCC, 19.4% of lactose, 9.5% of PVP and 0.5% of magnesium stearate.

In MODDE, paracetamol and magnesium stearate were set as a constant percentage in each formulation 13.7% and 0.5% respectively, MCC was set to vary between 49.4% and 64.4%, PVP was set to vary between 4.5% and 14.5%. Lactose was set as a filler with the purpose of varying according to the other variables in order to complete the formulation. PVP addition rate was set to vary between 7 and 15 rpm in order to obtained the desired flow rate. The area under the curve of a plot of the temperature at each minute of each phase of the process was set as an uncontrollable variable.

The software was set to calculate a D-Optimal design with a total of 13 experiments. The results of the DOE are presented in table 3.1.

Table 3.1 DOE results, including run order and fractions (m/m) used for each batch.

Experiment number	Experiment Name	Run Order	Peristaltic pump speed(rpm)	Magnesium stearate	Microcrystalline cellulose	Lactose	PVP	Paracetamol
1	N1	3	7	0.005	0.494	0.319	0,045	0.137
2	N2	8	15	0.005	0.494	0.319	0,045	0,137
3	N3	5	7	0.005	0.644	0.169	0.045	0.137
4	N4	2	15	0.005	0.644	0.169	0.045	0.137
5	N5	7	7	0.005	0.494	0.219	0.145	0.137
6	N6	10	15	0.005	0.494	0.219	0.145	0.137
7	N7	9	7	0.005	0.644	0.069	0.145	0.137
8	N8	4	15	0.005	0.644	0.069	0.145	0.137
9	N9	12	11	0.005	0.494	0.319	0.045	0.137
10	N10	11	11	0.005	0.644	0.169	0.045	0.137
11	N11	6	11	0.005	0.644	0.069	0.145	0.137
12	N12	13	11	0.005	0.569	0.194	0.095	0.137
13	N13	1	11	0.005	0.569	0.194	0.095	0.137

The run order of the experiments was randomized by the software in order to reduce the chance of interference by unknown uncontrollable variables.

3.3 Granulation process conditions

In order to start the granulation process, the fractions of our API and all the excipients in the experiments generated by the DOE software, were converted from fractions to mass. To accomplish this, we set our batch size to 400g and multiplied this value by the fractions generated. In the case of PVP, it was decided to use a solution of 10% of PVP in water as our granulation fluid. As we set the rpm of our peristaltic pump (that pumps the granulation fluid into the fluid bed) as an independent variable, the amount of PVP added to the system had to be regulated based on time and speed of the spray. To find out how many ml of fluid per minute were pumped for 1 rpm set in the pump, a set of experiments were conducted in which

the speed of the pump was set to 10, 20 and 30 rpm and the fluid was sprayed into a measuring cylinder. After one minute the amount of liquid was read.

With the knowledge obtained in these experiments, the granulation time for each individual granulation was calculated by multiplying the fraction of PVP of each experiment with 400g. This value was then multiplied by 100 and divided by 10 (as the concentration of the binder solution is 10%) to acquire the volume of solution that was needed for the granulation. This value was then divided by the speed of the peristaltic pump in ml/min to know how many minutes of addition of PVP were necessary to end the granulation.

The mass of each excipient and API, plus the addition time of PVP are presented in the table 3.2.

Table 3.2 Formulation, peristaltic pump speed and granulation time for each batch.

Experiment Number	Experiment Name	Magnesium stearate(g)	Microcrystalline cellulose	Lactose (g)	Paracetamol(g)	PVP(g)	Peristaltic pump speed(ml/min)	Peristaltic pump speed (rpm)	Granulation Time(min)
1	N1	2	197,6	127,6	54,8	18	11,2	7	16:04
2	N2	2	197,6	127,6	54,8	18	24	15	07:04
3	N3	2	257,6	67,6	54,8	18	11,2	7	16:04
4	N4	2	257,6	67,6	54,8	18	24	15	07:30
5	N5	2	197,6	87,6	54,8	58	11,2	7	51:47
6	N6	2	197,6	87,6	54,8	58	24	15	24:10
7	N7	2	257,6	27,6	54,8	58	11,2	7	51:47
8	N8	2	257,6	27,6	54,8	58	24	15	24:10
9	N9	2	197,6	127,6	54,8	18	17,6	11	10:14
10	N10	2	257,6	67,6	54,8	18	17,6	11	10:14
11	N11	2	257,6	27,6	54,8	58	17,6	11	32:57
12	N12	2	227,6	77,6	54,8	38	17,6	11	21:35
13	N13	2	227,6	77,6	54,8	38	17,6	11	21:35

To start the granulation, the API and all the excipients except for magnesium stearate were weighted according to the table 3.2. The granulation solution was prepared, for a concertation of 10g/100ml and the peristaltic pump speed (rpm) was set differently for each experiment, according to the DOE. The hose which feeds the liquid into the granulation recipient, was filled the with the granulation liquid (so that when granulation step started, the liquid was sprayed immediately).

The equipment used in our experiments is a Glatt Gmbh fluidized bed system. The exhaust air flap was set to 75%, the filter shaking interval was set to 11 seconds and the inlet air temperature was set to 60 ºC. These conditions were maintained for all experiments. Because we selected the temperature as one of our variables, and the equipment could not maintain a steady 60ºC temperature, it was decided to monitor the inlet and outlet temperature of all stages of granulation, registering the temperature on a minute to minute basis.

After the weighted materials were introduced into the container, the granulation could begin, with the first step being the mixing stage. In all runs, the mixing time was set to 5 minutes. After 5 min the operation was stopped and the spray nozzle was adapted to the machine. The process was then restarted, beginning the granulation stage. During the granulation stage, the peristaltic pump was on, with the predetermined velocity and air at a pressure of 1.5 bar was conducted to the spray nozzle in order to spray the liquid. This pressure was maintained throughout all of the experiments. As said above, the time of granulation was calculated with the objective of spraying the quantity of PVP set in the DOE. After the preset time ended, the peristaltic pump as well as the air inputted into the nozzle were turned off and the drying stage begun. It was decided that the drying stage would continue until an outlet temperature of 34ºC was reached. At that time the air pump was turned off and the main container was removed. The granulate was then Sieved with a 1.00mm sieve. Larger granules than 1.0mm went to waste and the rest were collected and analyzed.

3.4 Mixing

After the granulation step, magnesium stearate was weighed and added to each batch as a lubricant, important for the tableting process. In order to mix the magnesium stearate into the batches of granulate a cube mixer was utilized. In our process an Erweka ar 400 fitted with a 3.5l cube mixer was used. The speed was set to 15 rpm and the mixing was set to 2 min for each batch. These cubic mixers work by being mounted in way that permits rotation on an axis. The resulting mixing happens primarily due to the container shape and is dependent on the number of revolutions essentially.(31)

3.5 Compression

After the process of granulation and the mixing with magnesium stearate, the granulate was then used for tableting. This process was conducted in a Lloyd Instruments

Ametek LR 50 Plus which is a tableting testing machine designed for quality control testing and for performing complex multi-stage tests. This machine consists of an upper punch that is driven by a hydraulic system and lower punch that remains static. The movement of the upper punch is controlled by a computer or can be programmed directly in the machine. The advantage of using these type of machine in our process is that it can be used to compress a single tablet at a time, only requiring small quantities of our granulate but simulating the conditions that may happen in a production tableting machine.(15,32)

For the tableting process we decided to utilize the same tableting properties for all batches. 150mg tablets were produced for each batch using a compression force of 5kN, a compression speed of 10mm/min and flat punches with a diameter of 7.5mm. These tableting conditions were chosen because they were believed to be capable of manufacturing tablets with the necessary properties for further assays and analyses.

3.6 Tablet hardness test

The hardness of tablets is a commonly used assay to characterize this pharmaceutical form. It is of importance as the hardness of a tablet needs to be optimized to allow handling but should still permit a fast disintegration and dissolution if that is the desirable specification. Ideally a tablet should have enough hardness and resistance to friability to resist the process of manufacturing, that includes mechanical forces, as well as the process of shipping and packaging. This is necessary in order to have a quality pharmaceutical form with content uniformity and is an important requirement for consumer acceptance.

The hardness of a tablet is described as the force necessary to crack it in a diametric compression test. In this type of test, the tablet is subjected to force between two anvils. The strength that causes the breakage of the tablet is recorded and is considered its hardness.(18)

The harness tests of our tablets were conducted in an Erweka tbh 20 tablet hardness tester, resourcing to a TA xt plus texture analyzer with the appropriate attachment to measure the hardness one of the tablets that was below the sensibility of the Erwka equipment (app. <40N). Three tablets were used for this assay.

3.7 Sieving

Sieving is a method of particle size characterization. Particle characterization is an important step in the development of a new formulation and as such it was selected as one of dependent variables. Particle size, size distribution, shape and texture all affect the

performance of the final pharmaceutical form. The particle size can have significant effects on the dissolution and tensile strength. (26,33–35)

There are different methods of particle characterization. Sieving permits determining the particle size distribution of a powder. It is often used because of its simplicity.(26)

The method used in our work, was adapted from the Portuguese pharmacopeia. Sieves of 125µm, 180µm, 250µm, 355µm, 500µm and 750µm were used. These sieves were mounted and the granulates from each experiment were made to transverse all the sieves. At the end the sieves were dismounted and the powder retained in each compartment was weighted. The results can be found in table 4.3.

The ideal size distribution for tableting varies according to the formulation and as such we did not possessed a value to input as a response in the plotting of our design space. To evaluate how our variables affected the particle size distribution we choose to use the standard deviation of the distribution, calculated according to the folk and ward method using the GRADISTAT tool.(36) The standard deviation was chosen as a dependent variable because it allows us to understand how wide the particle size distribution is. The Folk and Ward's method uses the standard deviation to explain how sorted are the particles analyzed with standard deviations of less than 1.27 being very well sorted; from 1.27 to 1.41 being considered well sorted; 1.41 to 1.62 being moderately well sorted. 1.62 to 2 moderately sorted; 2 to 4 poorly sorted, 4 to 16 very poorly sorted and above 16 extremely poorly sorted. In general, a granule batch with a wider particle size distribution will have more segregation problems and consequently, since the die is filled differently due to the segregation, it can induce a variation in compression force, tablet weights and content uniformity. For the specification of our design space we set the maximum value for the standard deviation as 2, to achieve at least a moderately sorted granule size distribution. (36–38)

3.8 Carr index

The density of a powder, or in our case granulate, is an important characteristic that has impact in the tableting and performance of the pharmaceutical form. It was decided to use the Carr index as a method of representing the density of our powder. The Carr index, or Carr compressibility index, is a measure used to predict the predisposition of a granulate to be compressed, and reflects the interactions between particles. This index is a function of the bulk density and the tapped density of a powder, which are defined as the volume of a loose powder bed and the volume occupied by the powder after it has been tapped a number of

times. We choose to employ the technique described in the ninth edition Portuguese pharmacopeia, which states that a sample with a volume between 50 and 250 ml should be taken from the granulate and weighted in a measuring cylinder. The volume before tapping should be noted. The measuring cylinder is then subjected to tapping in an apparatus similar to the one described in the pharmacopeia, in our case, the Stampfvolumeter STAV 2003 from JEL. The sample is subject to 10, 500 and then 1250 taps, the volumes are read, if the difference between the volume after the 500 tap and the 1250 is superior to 2 ml then the sample should be taped 1250 more times.

The Carr index is then calculated according to the equation 1.

$$\boldsymbol{Ci}(\%) = \mathbf{100} \times \frac{(\boldsymbol{V_0} \times \boldsymbol{V_f})}{\boldsymbol{V_0}} \qquad \mathbf{(1)}$$

In this equation V_0 corresponds to the untapped volume and V_f symbolizes the tapped volume after 1250 or 2500 taps.(26,39,40) The Carr index has a correlation with the flow of the powder, Values lower than 15 are considered good flow for tableting. Values in the range of 25 to 30 are considered best for capsule filling, with the general rule being that the higher the Carr index value, the poorer is the flowability which in turn correlates directly with the compressibility of the tablets. (11) Even though this method should not be used as the only measure of powder flowability, it has the advantage of being simple to calculate and execute. (26)

3.9 MODDE software

MODDE software, version 12.1, manufactured by Sartorius Stedim data Analytics, allows the user to generate an experimental design by planning a set of experiments that vary all the relevant factors and then connect the results of these experiments by means of a mathematical model. This model is then used for interpretation, predictions, optimization and identifying a design space. (41)

For a proper investigation it is important to identify the independent variables that have a relevant influence on the responses and which variables have significant interactions between each other. This analysis is needed to understand what are the best settings for the independent variables to achieve optimal conditions for best performance of a process, in this case the granulation process, and what are the predicted values of the responses (results) for a given combination of values for the independent variables. (41)

For this analysis MODDE software has a series of tools that facilitate the comprehension of the interaction between the factors (independent variables) and responses. (41)

3.9.1 Summary of fit plot

One of these tools is the summary of fit plot that presents four parameters: R2, Q2, model validity, and reproducibility. (41) R2 shows the mathematical model fit and, as such, is a measure of how significant the model is. A model with R2 of 0.5 is a model with a low significance. Q2 represents how well the model can predict the future behavior of the interaction between the independent and depended variables. Q2 should be greater than 0.1 for a significant model and greater than 0.5 for an accurate model. The difference between R2 and Q2 should also be smaller than 0.3 for an acceptable model, being Q2 the most sensitive indicator. (41)

Reproducibility and model validity evaluate the model based on replicated runs. These runs were not conducted during the development of our experiments due to time constrains but are key to understanding the overall variability of the model and other significant model problems. (41)

The Q2 value can be improved after the model is tuned, that is, set to only use the most relevant factors.(41)

3.9.2 Coefficients plot

The coefficients plot is another tool offered by MODDE software. It allows the user to understand how significant the variables inputted into the model are in relation to the dependent variables. In this plot the displayed model terms (independent variables as well as interaction between them) are represented for each of the dependent variables and plotted according to their relevance. Bars that are away from y=0 with uncertainty ranges that do not cross y=0 are indicative of a relevant model term, signifying that the model term has an effect on the dependent variable. Non-significant model terms have smaller bars with their uncertainty range crossing zero. The coefficients plot provides support for tuning of the model by adding or removing model terms.(41)

3.9.3 Design Space

The design space is the region where all set specifications are fulfilled for a given product at a given probability level and has the objective of assuring the quality of the manufactured medicine. This software uses the model created in the previous steps to plot the design space according to the specifications set for the optimal results. (41)

The specifications set for the design space are represented in the table below.

Table 3.3 Design space specifications

Dependent Variable	units	min	target	max
Carr Index		5		15
Hardness	N	50	70	90
Weight	mg	130	150	160
Standard deviation of the particle size distribution				2

These specifications are further explained in the discussion of each dependent variable.

The design space created by this software only allows up to four independent variables to be showed in the graph at a time, the others are set to a static value. In order to have the best possible value for all variables of the process, MODDE software has an optimizer tool that tests every combination and proposes the values for each variable that will be suited for the best results.(41)

4.Results

4.1 Granulation

4.1.1 Peristaltic pump

The assay to determine the peristaltic pump speed corresponded to a value of 1.6 ml/min for each rpm.

4.1.2 Granules

Overall, all the granulation batches with the exception of N5, produced granulates with good macroscopic characteristics that later were analyzed and used to produce tablets.

Experiments N1, N2, N3, N6, N7, N9, N10, N12 and N13 produced dry and loose granules of smaller dimensions and easily passed the 1.00 mm sieve, originating a high yield. In contrast, granulations N4, N8 and N11 formed loose granules, as well as big masses of granules which remained humid in the center and were retained by the 1.00 mm sieve, being discarded and as such leading to smaller yields.

4.2 Compression

Table 4.1 shows the weight of each of the three tablets manufactured for each batch and the average weight in the last column.

Table 4.1 Weight of the manufactured tablets.

	Tablet 1(g)	Tablet 2(g)	Tablet 3(g)	Average
N1	0.139	0.138	0.137	0.138
N2	0.14	0.135	0.137	0.137
N3	0.14	0.135	0.135	0.137
N4	0.136	0.139	0.139	0.138
N5	0.135	0.14	0.143	0.139
N6	0.138	0.135	0.138	0.137
N7	0.132	0.138	0.137	0.136
N8	0.127	0.131	0.13	0.129
N9	0.136	0.136	0.139	0.137
N10	0.141	0.14	0.135	0.139
N11	0.133	0.135	0.136	0.135
N12	0.14	0.136	0.127	0.134
N13	0.136	0.137	0.137	0.137

4.3 Tablet hardness test

Table 4.2 shows the results of the hardness test. Three tablets from each batch were tested. The average hardness of the tablets was calculated for a more representative result of the produced batches.

Table 4.2 Hardness of the produced tablets.

	Tablet 1(N)	Tablet 2(N)	Tablet 3(N)	Average
N1	71	74	68	71
N2	53	55	62	57
N3	84	81	86	84
N4	64	65	61	63
N5	66	64	84	71
N6	86	109	49	81
N7	98	89	95	94
N8	49	138	122	103
N9	64	76	147	96
N10	82	66	71	73
N11	25	27	27	27
N12	67	58	55	60
N13	87	53	57	66

4.4 Sieving

The results from this assay can be displayed as a percentage of the sample retained on each sieve (histogram) or a cumulative distribution as a function of sieve size.(26)

Table 4.3 Particle size distribution for each granulation batch(m/m).

	Batch												
Sieve	N1	N2	N3	N4	N5	N6	N7	N8	N9	N10	N11	N12	N13
710	0.05	1.35	0.13	0.44	2.08	21.57	7.00	55.64	0.44	0.24	44.3	1.72	1.11
500	0.32	1.59	0.07	0.93	14.21	39.02	9.14	35.46	1.23	1.08	41.56	15.49	4.18
355	2.65	2.67	0.68	1.26	26.84	27.27	11.59	7.89	3.12	2.15	12.35	46.17	15.03
250	22.93	10.71	16.87	4.78	26.67	9.95	15.97	0.79	20.15	7.47	1.76	26.50	37.17
180	43.02	32	43.21	42.48	16.77	1.56	17.72	0.03	45.80	22.41	0.02	7.47	39.77
125	20.19	27.74	20.17	37.83	7.74	0.48	15.96	0.02	8.97	26.25	0	0.952	0.3
Base	10.84	23.95	18.87	12.28	5.69	0.15	22.62	0.17	20.30	40.40	0	1.7	2.45

The figure 4.1 was plotted from the data in table 4.3 and shows the particle size distribution obtained from sieving the different batches. The y axis shows the percentage of the total mass trapped in each sieve. The sieves are color coded and are represented in order from 710µm to the base. In table 4.3 it's also displayed the calculated standard deviation of each assay.

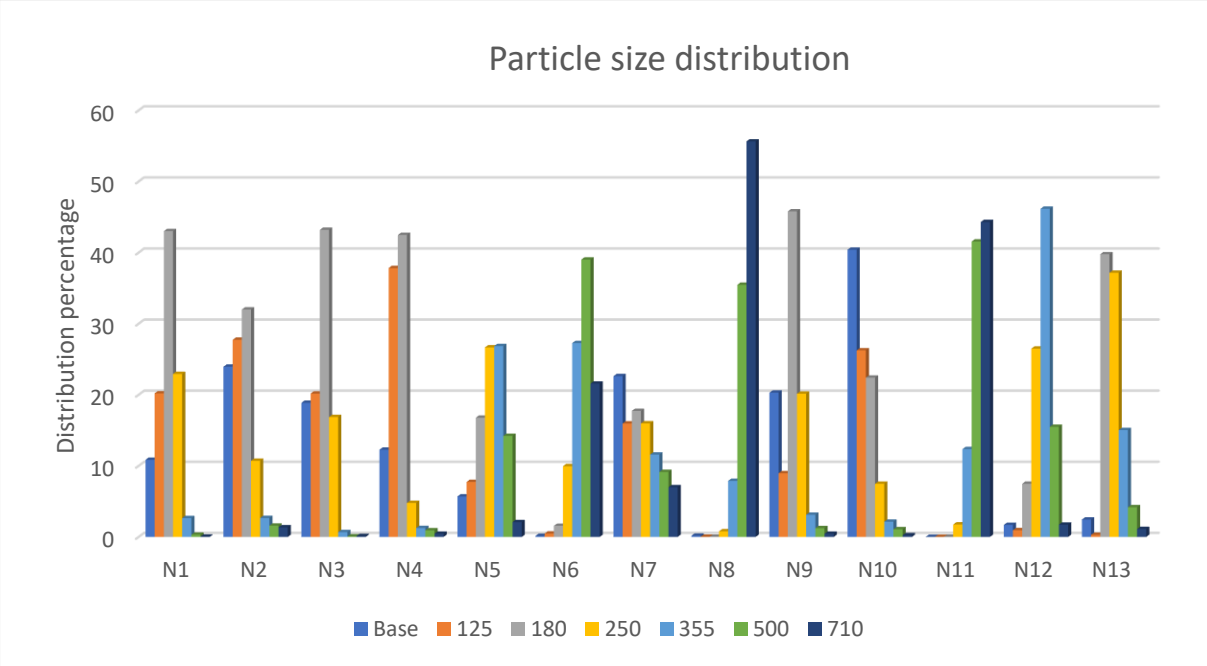

Figure 4.1 Particle size distribution for each batch.

4.5 Carr index

Figure 4.2 contains the Carr index values of each batch of granules. The blue line in the y axis indicates a Carr index of 15, with the values below being considered a good flow for tableting. Two orange lines demark the region between 25 and 30 which is considered the ideal Carr index values for capsule filling.

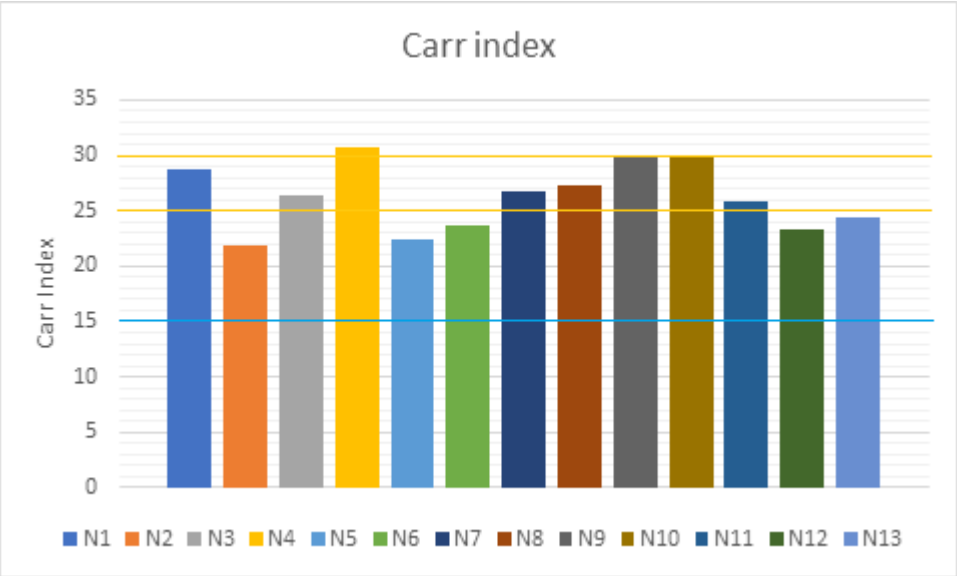

Figure 4.2 Carr index of each batch.

4.6. Regression Model

The figure 4.3 shows the fitting parameters obtained from the four developed regression models. Green represents the R2 value and blue represents the Q2 value. These models were refined with the optimization tool of MODDE, which removes the less relevant factors in order to obtain the highest Q2 and R2 values. The linear factors selected for each model as well as the interaction between the factors are represented in table X.

Table 4.4 Factors selected for each model

Carr Index	Hardness	Weight	Standard deviation
Timix	Timix	Timix	Timix
TIG	TIG	TIG	TIG
Tidry	Tidry	Tidry	Tidry
vel	TODry	Tog	Tomix
Tog	TIg*TODry	TOmix	PVP
TODry	TIdry*TODry	TODry	TIg*TIdry
Microcrystaline cellulose		TImix*TIg	TIg*TOmix
PVP		TImix*TIdry	
TImix*TOg		TImix*TOg	
TIdry*vel		TImix*TOmix	
		TImix*TODry	

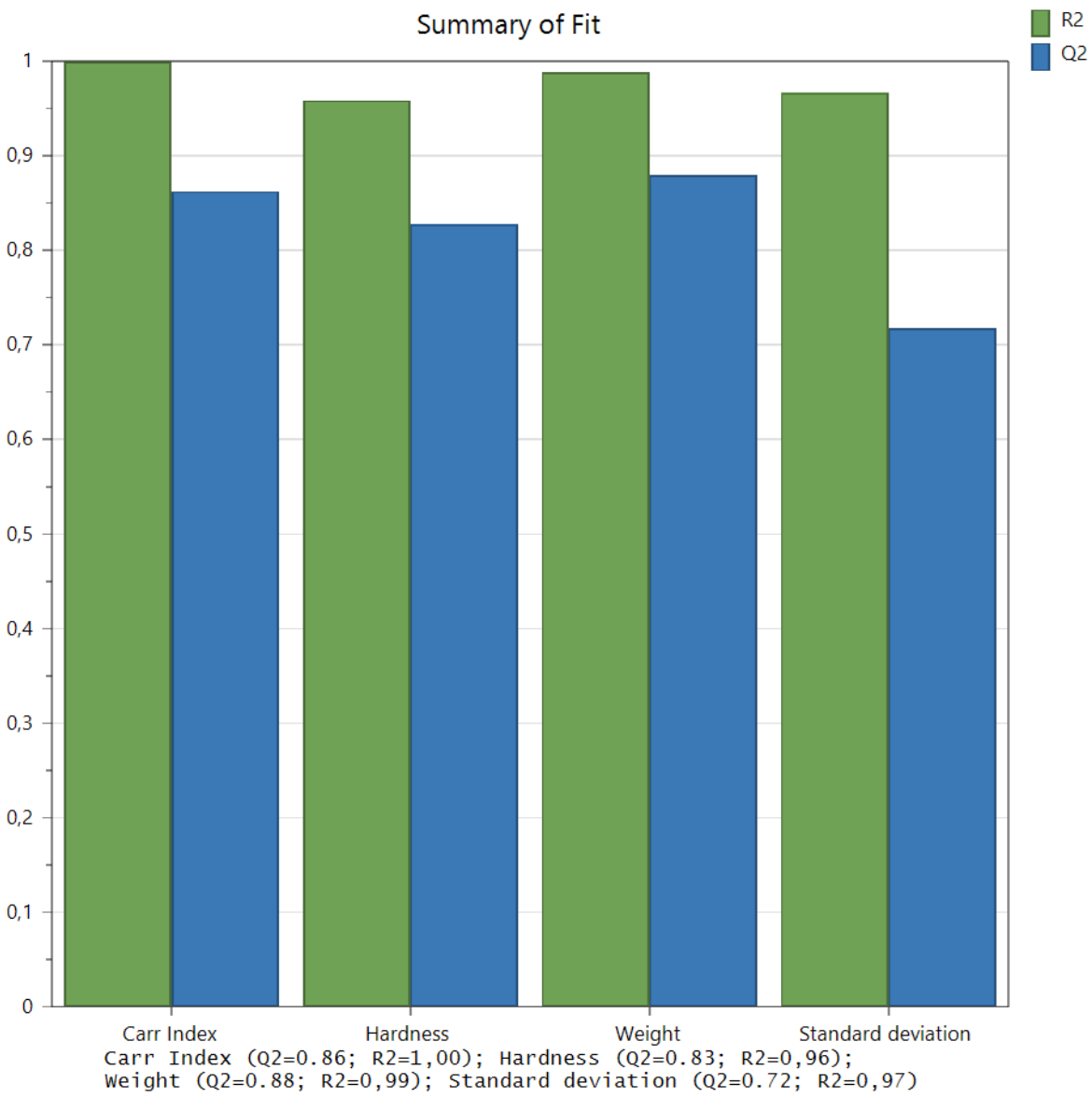

Figure 4.3 Summary of fit plot.

The Carr index shows a difference between R2 and Q2 of 0.14, the difference between these values for the hardness of the tablets is of 0.13, for the weight is of 0.11 and for the standard deviation is of 0.25.

Figure 4.4 shows the coefficients obtained for each model after refining the inputs based on their statistical significance. These factors are represented under each graph with the

interaction between factors being represented by an asterisk between them.

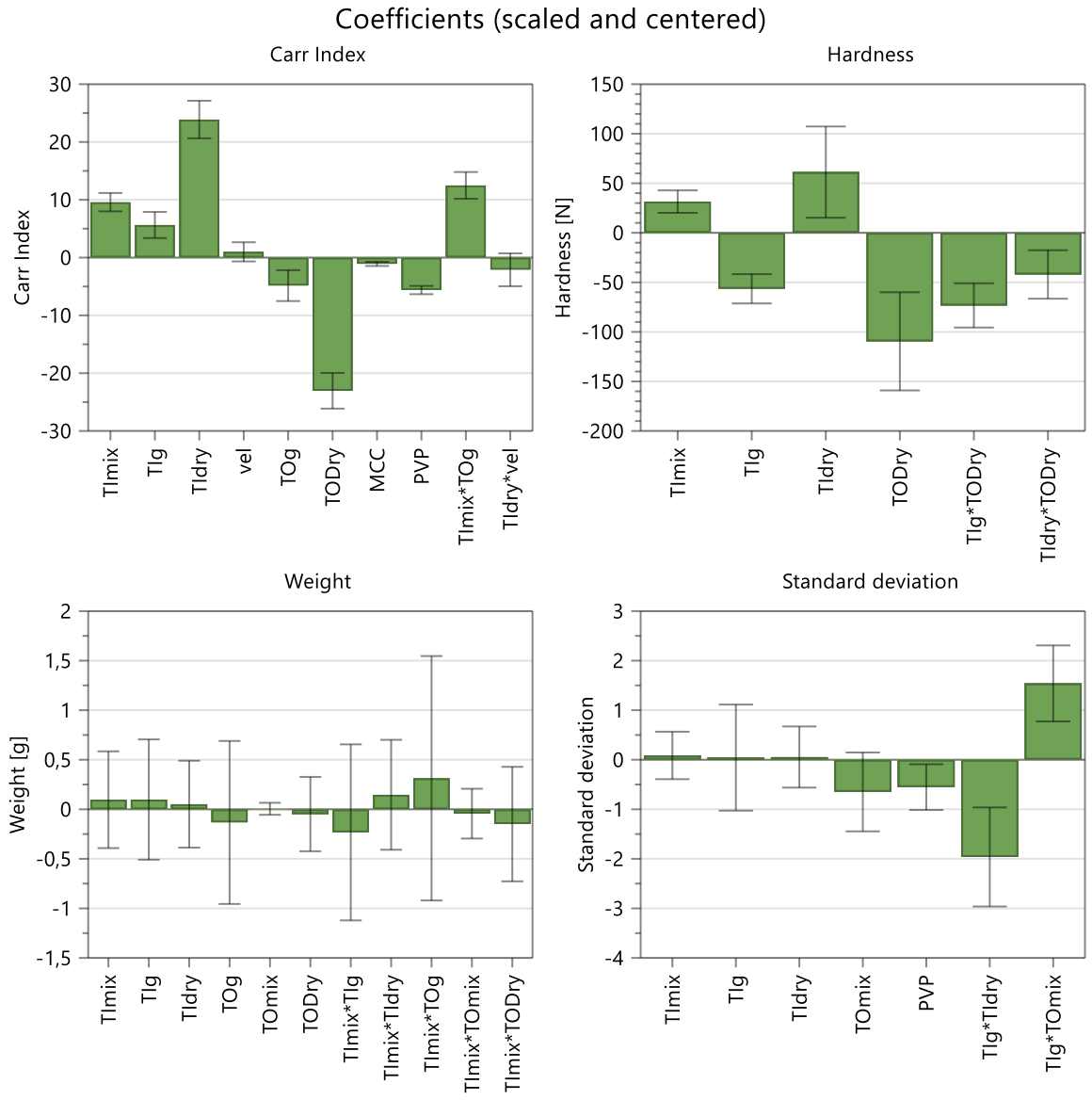

Figure 4.4 Coefficients plot

Figure 4.5 Design space, including the weight of the tablets as a response.

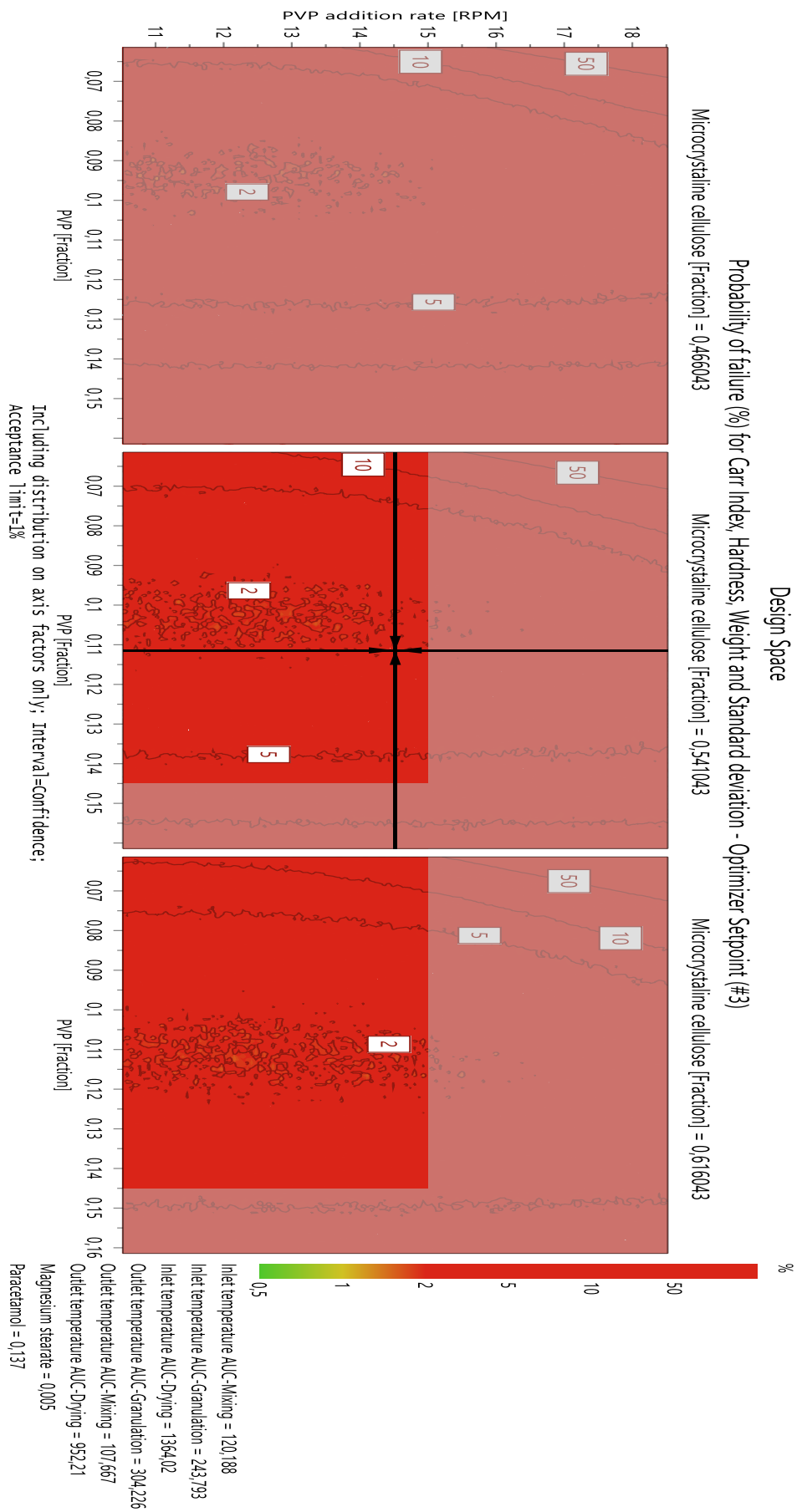

Figure 4.6 Design space, excluding the weight of the tablets as a response.

Both plots display the design space with the arrows pointing to the optimal point at which there is the lowest probability of failure percentage. In the design space the probability of failure is displayed inside the graph with the delineations and color grating representing different probabilities of failure percentages. It was chosen to represent in these graphs the controllable independent variables with the PVP addition rate and PVP fraction as the y and x axis respectively and three variations of MCC fractions represented in each graph. The values for the other independent variables are also displayed, in the bottom right of the graph. In figure 4.6 the model for the weigh of the tablets were removed as no variable was found statistically significant.

5. Discussion

5.1 Formulation and experimental design

Like other operations, many variables can impact the manufacture of the granules and tablets. To develop a robust process, it is necessary to evaluate how these variables affect the final product. Some of the main variables that can be controlled, and are critical for the quality of the process are the excipients used and the quantity of the excipients added to the formulation.(26)

The role of excipients in a formulation is to guaranty that the manufacturing process is successful, with a final product that is of a consistent quality. In our formulation, lactose was used as a diluent. Lactose is a commonly used diluent that is added to increase the bulk of a pharmaceutical form to help with handling and processing. As it is used in our formulation primarily as a diluent, we choose to set it as the filler in our DOE, and so the percentage of lactose in our formulation varied according to the other independent variables.(18) Although lactose is used as the filler, it still can play an important role in granulation, as it was shown in the past, in a study with a formulation containing only crystalline cellulose, lactose and starch, that when a higher lactose content was used, larger granulates were manufactured.(26)

Microcrystalline cellulose is also used as a diluent in our formulation. It was decided to set it as an independent variable because it also acts as a disintegrant in tablet formulations and has properties as a binder, and so we wanted to analyze how those properties would affect

our granules and tablets. Disintegrants are used in formulations to facilitate the breakup of the tablet once it enters the body, with the objective of increasing the dissolution by increasing the surface area of the pharmaceutical dosage form. In case of microcrystalline cellulose, this disintegrant property is believed to be a combination between the disruption of particle-particle bonds and wicking, that is defined as the process of liquid entry by capillarity action into the microstructure crevices within the tablet. Because of this property it was thought that it would affect the dissolution assay, and as such, if it wasn't for time constrains, this assay might have been useful to understand the extent of influence that this excipient has in a formulation.

PVP was used in our formulation as the main binder that was sprayed onto the bed of solids to initiate and complete the granulation. We choose to dissolve it in water in a concentration of 10% and vary the amount of PVP added by controlling the time and speed of addition, which were also independent variables. We choose not to vary the concentration of the solution of PVP, as we would have a harder time dissolving PVP in higher concentrations.

The amount of PVP is a key variable in a formulation as binders are added to formulations to promote cohesiveness within powders. Because the concentration of the granulation solution was set to 10%w/w, the amount of PVP also carried with it an increase or decrease in liquid addition and an increase or decrease of granulation time which played an important role in the characteristics of our granules and tablets.(18)

The formulation that was chosen has paracetamol as the API. Paracetamol is one of the most important drugs used in the treatment of mild to moderate pain when an anti-inflammatory effect is not necessary.(42) Because it is our formulation API, it was set not to vary in the design of experiment, in order to emulate a formulation that would be used in a real scenario, as in a real scenario the amount of API in a pharmaceutical form could not be varied if the mass of the tablet was set.

As was the case for paracetamol, magnesium stearate was also set to not to vary. We choose to keep it at a stable fraction of our formulation, as it would not affect the granulation process, because it was added after the granulation was completed. We choose to add magnesium stearate because it has properties as a lubricant, and lubricants are an important excipients for tableting since they can reduce friction between the tablet and the die wall during compression and ejection and, as such, help to ensure that the tablet is cleanly ejected without cracking or breakage.(18,43)

The mathematical model chosen for our DOE was D-Optimal, primarily because we had time constrains that only allowed 13 granulations, and this method of DOE allowed us to set the number of experiments desired and generated the experiments that gave the most information about how our independent variables affect our responses.

5.2 Granulation

The results obtained relative to the properties of the batches N8, N11 and N4 might be explained by the quantity of PVP added to the mixture in the case of N8 and N11 and in the case of N4 might be explained by the speed at which the granulation fluid was added, although other factors could have an influence in this results, such as a high microcrystalline cellulose content.

During the experiment N2, the inlet air heating component of the fluid bed granulator was turned off and as such it was decided to stop the granulation process when the inlet temperature matched the outlet temperature. The granulate produced was dry and loose.

Experiment N5 had to be repeated as the primary filter was clogged in the granulation before, and as such the fluid bed could not impart fluidization to the particles, which lead to them sitting at the bottom of the granulator being sprayed by the granulation fluid, which in part generated a liquid mass at the bottom of the granulator, that could not be dried. After the filter change the repeated granulation was successful. Although all the granulations before the N5 batch were successful, a partially clogged filter could have an effect on the results, and as such remains as an uncontrollable variable that is partially mitigated by the randomization of the run order. If time constrains weren't a limiting factor, repeated experiments might be advised.

5.3 Compression

All of the granulation batches were successfully tableted. In can be seen in table 4.1 that the weight of all the tablets was below 150 mg which was the target set for this assay. A weight close to specification is important for a tablet as it is required to deliver the therapeutic amount of API. A small mass would also affect the results of the hardness test. Overall, the tableting process had mixed results with tablets that were not brittle and were capable of being handled but weights that were below the target.

Between the tableting process and the hardness test manufactured tablets were stored for 24h, as the process of tablet formation continues after tableting. It has been proven in the

past that changes in the material can take place up to 24 h after tableting caused by the elastic properties of the granulated materials. (44)

5.4 Tablet hardness test

The hardness of tablets is described as being a function of the force used for tableting as well as the die fill. It is considered that the harder the pressure applied during tableting, the harder the tablets manufactured will be. Although this is the general rule, the formulation also plays an important part, as well as the process of granulation, as can be seen from the results obtained, none of the batches had the same hardness.

For the N11 assay, a different equipment had to be used as the Erweka had a threshold of 40 N. The tablets of this batch were less hard than the rest of the tablets tested from the other batches. Results from the sieving test and the Carr index test were similar to the other formulations. This may be explained by the humidity of granules from this batch.

The hardness specification interval for this assay was adapted from a study that evaluated the hardness of various paracetamol tablets in the Bangladesh market. We set the specification for our design space between 50 and 90 N with a target of 70N. We choose these specification values so that the tablets manufactured according to the design space could end up comparable to commercialized tablets. (45)

5.5 Sieving

The data obtained from the sieving process was primarily used as a response in MODDE, although some conclusions can be drawn from this data alone. The histogram plotted from the obtained data, presented in figure 4.1, shows that the granules manufactured in experiments N8 and N11 had their highest percentage of mass distribution in the 710 µm sieve. These results are explained by the fact that these assays ended with large granules and clumps of wet granules sticking together. After the clumps were discarded by passing through the 1mm sieve, the remaining granules were still larger than those manufactured in the other batches and as such most were retained in the top sieve. The production of granules of this size might be related to the quantity of PVP added to the mixture in theses batches. Experiment N4 had similar clumps of large granules but the material was drier than the batches N8 and N11 and the granules that were capable of traversing the 1mm sieve were smaller and looser compared to the batches of the experiments N8 and N11. Batches N1, N2, N3, N4, N9 and N13 had their main percentage of distribution in the 180 nn sieve. All the other batches had variable results.

5.6 Carr index

All of the batches had higher Carr index values than the ideal described as a good flow for tableting. It is generally believed that a higher Carr index correlates with worst flow capabilities. With that in mind, the N2 batch had the lowest Carr index value and as such may have a better flow than the batches manufactured in the other experiments. N2 and N4 had similar granulation conditions, with the only difference between both these assays being the microcrystalline cellulose value and because of that, the lactose value, with the experiment N4 having the maximum microcrystalline cellulose value that was attributed and the N2 experiment having the lowest microcrystalline cellulose value, which could correlate with more favorable granulate although other variables could be affecting the results. N1, N3, N7, N8, N9, N10 and N11 all sat in the region that is considered a good flow for capsuling, and although we did not plan to include a capsuling operation, the primary objective of this study was to identify how the variables in the granulation stage would affect the characteristics of the granules and the final dosage form, and as such it is important to note that multiple experiments had good flow attributes for capsuling. In regards to our design space we set the target for our granules as a maximum of 15, even though none of our batches achieved these specifications. A value of 15 was considered as the maximum for our design space because values under 15 are considered ideal for tableting, having a good flow and compressibility. The lower limit for this response was set at 5 because powders with a Carr index above 5 have better properties for tableting.

5.7 Regression Models

After obtaining all the results from the previously described assays, all of the models, now with the inputted results, were analyzed with the tools that the MODDE software offers.

The summary of fit plot appeared to indicate the creation of a significant and predicative models for each of our variables, with the values of R2 being close to 1 and the values of Q2 also being close to 1 in all models. The difference between R2 and Q2 is also smaller than 0.3 in all models.

Even though these values appear positive results, the lack of reproducibility and model validity testing leave some unsureness about the quality of the models and, as will be discussed, the mathematical models of some of the dependent variables are misleading. The analysis of the summary of fit plot is incomplete without tuning the models and understanding

the key factors that influence the responses. As such, it is important to use the coefficients plot.

The presented coefficients plot in figure 4.4 was achieved after testing all model terms and interactions and using the auto tune function of MODDE to select only the most relevant terms that gave the highest Q2 and R2 values for the model, these terms are present in table 4.4. Although high values of Q2 and R2 were achieved, no model term was found relevant for the weight of the compressed tablets, this might be explained by the fact that the weight of the produced tablets may be influenced mainly by human errors during the weighting of the granules and the loading of the granules into the tableting machine.

Results for the standard deviation shown that the terms that have the most relevant weight on the standard deviation of the granulometric distribution are the interactions between less relevant independent variables. Both carr index and hardness had good coefficients plots, with multiple relevant terms.

It was decided to plot a design space graph using the controllable variables of our process in order to find a design space usable for a percentage of probability of failure of at most 1%. Previous to the plotting of the design space graph, the optimizer tool of MODDE was utilized to find the optimal value of each variable so the ideal design space could be created. Even though the optimizer tool was used, the best possible combination of variables using our models still had a percentage of failure of 50%, as can be seen in figure 4.4, that is not compatible with the objective set. It was thought that this high percentage of probability of failure might be due to the model created for the weight of the compressed tablets, as this model, when evaluated in the coefficients plot, showed that none of the variables that were chosen had an effect on the weigh and that the best explanation for the weight fluctuations and for missing the target weight was due to human error. With this in mind, a new design space, displayed in figure 4.5, was plotted using as responses only the hardness, the standard deviation and Carr index. In this new design space, although impossible to choose a region where the percentage probability of failure is less than 1% with the current model, the optimal point is situated in a percentage of probability of failure of 2 %.

Even after removing the weight of the tablets from the design space and achieving this more favorable result it is important to note that the conditions presented in this plotted design space are only possible to replicate if the temperature conditions could be reliably set to match the suggestion given by the optimizer tool and it is also to note that the measure used to

represent the temperatures that occurred during the process was the area under the curve of the graph plotted between the temperature at each minute for all stages of granulation and as such it is difficult to match the conditions used for a given area under curve temperature.

6. Conclusion

Granulation is a step of great importance in the production of various pharmaceutical forms, being considered by some authors as the most complex and difficult to control step in the manufacturing of medicines. As such we set out to conduct a study that aimed to acquire a deeper understanding of the granulation process. For this, it was set as an objective the devolvement of a design space using the data collected from this study.

An important step of this study, was the design of the experiments, that we successfully created with MODDE software. This software was also used for the analysis of the results and permitted a better understanding of how the variables we set out to test affected the final product.

The assays used for the characterization of the granulate batches, were successfully conducted.

Although the study conducted was planned and designed around the variables described along this dissertation, the final result of the plotted design space was unfavorable for a tool that could be used to predict the quality of a future manufactured medicine. Several explanations could be offered for the results obtained, including the sheer complexity of the granulation step, the exclusion of replicated runs, several problems with the fluid bed granulator including an impossibility to set a constant controllable temperature for the process and problems with the filters for the process. It is important to note that these results can still be used to understand how some of the variables interact with the quality of the granules and that these results could be further explored in future research using replicated runs and a different equipment, as well as other assays that could potentially further represent the quality of the manufactured granules.

For a further study, a continuous process, controlled by PAT would be beneficiary to the understating of the importance of the numerous variables of the granulation step in the

manufacturing of the tables and as such would be of interest to conduct using the same experiments designed for the present study.

7.Bibliography

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