A Quality by Design approach on pharmaceutical development of magnesium dosage forms: Tablet and Oral Solution

Ana Rita da Cruz Cipriano
anacruzcipriano@tecnico.ulisboa.pt

Instituto Superior Técnico, Lisboa, Portugal

November 2019

Abstract

Different approaches can be applied to the development of pharmaceutical dosage forms. However, recently, a systematic approach to pharmaceutical development, known as Quality by Design (QbD), has been strongly recommend and analyzed by the European Medicines Agency (EMA) and Food and Drug Administration (FDA). QbD promotion began with the recognition by the regulatory agencies that quality must be built into the pharmaceutical product, and that increased testing does not imply the improvement of product quality. The overall aim of this work was to develop magnesium dosage forms, tablets and oral solutions, taking in consideration the QbD approach. Therefore several concepts and tools of QbD approach were applied, such as definition of the Quality Target Product Profile (QTPP), risk assessment and Design of Experiments (DoE). DoE was performed in order to evaluate the effect of formulation factors variation on the products Critical Quality Attributes (CQAs). Regarding tablets development, it was studied the impact of glidant, lubricant and superdisintegrant level variation on the appearance, friability and disintegration time attributes. In addition, response surface analysis was applied in order to predict and establish optimal formulation settings, culminating in a immediate release tablet complying with QTPP criteria. Concerning the oral solution development, a DoE was applied in order to select the combination of excipients that enable an oral solution complying with the appearance, taste and pH quality targets.

Keywords: Quality by design, Design of experiments, Immediate release tablet, Oral solution, Food supplement development.

1. Introduction

The aim of pharmaceutical development is to design quality products and their manufacturing process, in order to consistently achieve the desired performance of the pharmaceutical product [1]. Until recently, the approach of pharmaceutical development was based on the quality by test method. This method comprises a process in which the quality of the product is assured, alone, by testing raw materials, drug substances and the manufacturing process [2]. Quality by test relies on the idea that raw materials and drug substances can only be introduced in the manufacturing process when all the specifications and criteria defined by the several regulatory agencies, such as the EMA and the FDA, are fulfilled. In a scenario where those specifications and criteria are not complied, a re-processing of the raw materials, drug substances and formulations is needed. The fundamental causes of failure are usually not well understood, due to poor understanding of the process or of the relation between raw material and product quality attributes [3]. Consequently, in order to better understand them, the development procedure has to be restarted [3]. Summarizing, quality by test development may lead to product variation, resulting in low drug safety, and poor cost-efficiency [3, 2].

Recently, a new approach - QbD - has been strongly suggested and analyzed by both regulatory agencies, EMA and FDA [2, 4]. In September of 2004, the FDA published the final report on its new initiative: "The Pharmaceutical Current Good Manufacturing Practices for the 21^{st} century - A Risk-Based Approach". In this document, the American agency encourages the pharmaceutical industry to adopt risk-based approaches, and to apply QbD principles in pharmaceutical development, manufacturing process and quality assurance [5, 6]. Moreover, the QbD promotion began with the recognition by FDA and EMA that quality must be built into the pharmaceutical product, and that increased testing does not imply the improvement of product quality [6]. The concept of QbD has been gaining importance along the years in the pharmaceutical industry panorama. In particular, due to the publishing of the International

Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines Q8 (R2) (Pharmaceutical Development) and Q9 (Quality Risk Management) [6]. In the ICH Q8 guideline, it is stated that the manufactures may choose between two different approaches to pharmaceutical development: an empirical approach or a more systematic approach (also mentioned as QbD). Finally, in the same document, the ICH defines QbD 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." [1].

Nowadays, it is possible to notice an increasing tendency in the scientific and commercial interest in food supplements, consequently, the research and development in this field has been growing. In the past few years, several pharmaceutical companies have started to develop and manufacture food supplements. Unlike pharmaceutical development, there are no guidelines suggesting or recommending the application of different approaches to the development of food supplements. Moreover, the food supplements regulation is significantly less strict than the pharmaceuticals regulation. Thus, food supplements are easier to marketing and its development is, by far, cheaper than pharmaceutical development [7, 8, 9]. Nevertheless, food supplements can interact with drug substances or nutrition substances normally absorbed in the daily diet. In addition, some nutritional substances when consumed in high doses can cause adverse reactions, e.g., magnesium can cause diarrhea [7, 10]. Regardless of the mentioned before, currently, there is no post-market monitoring system for food supplements that, similarly to the pharmacovigilance system, manage adverse reactions after the product is introduced in the market [7].

QbD is not a new concept in the food industry, but there seems to be a limited number of studies concerning the application of QbD approach to food supplements development. These may be to the lack of guidelines suggesting its application but, it can not be discarded that, food supplements are marketed in dosage forms similar to pharmaceutical products and that a certain level of quality and safety is expected from these products. Nevertheless, there are nutritional substances that, depending on the dosage, can be considered as medicines, e.g., magnesium [7, 10, 11, 8]. Concluding, it seems to be relevant to understand the potential of QbD as an approach to the development of food supplements.

The overall aim of this work is to develop safe, stable and effective magnesium oral solutions and tablets, that fall under the classification of food supplements. Thereby, it is suggested the application of QbD approach to the development of both dosage forms. In particular, it is purposed that the oral solution development culminate in a pleasant solution with a composition free of sugar and low in sodium, indicated for diabetic and hypertensive patients. The tablet development process must culminate in an immediate release tablet produced through direct compression.

2. Materials and methods

2.1. Tablets materials

Magnesium oxide was supplied by MAGNESIA (Luneburg, Germany). Magnesium chloride, also mentioned as magnesium chloride hexahidrate, was supplied by Laborspirit (Loures, Portugal). Magnesium citrate was supplied by Dr. Paul Lohmann (Emmerthal, Germany). Pyridoxine Chloride (vitamin B6) was supplied by Farmalabor - Produtos Farmacêuticos, S.A. (Condeixa-a-Nova, Portugal). Regarding excipients, the product Prosolv EASYtab Nutra CM, also mentioned as Prosolv Nutra, was supplied by JRS PHARMA (Rosenberg, Germany). Additionally, the excipients colloidal silicon dioxide (Aerosil 200), Sodium Stearyl Fumarate (SSF), croscarmellose sodium (croscarmellose) and Soidum Starch Glycolate (SSG) were kindly supplied by Farmalabor - Produtos Farmacêuticos, S.A. (Condeixa-a-Nova, Portugal).

2.2. Oral solution materials

Magnesium citrate, magnesium chloride (magnesium chloride hexahidrate), pyridoxine chloride (vitamin B6), sodium cyclamate, ponceau Dye, acesulfame, sodium benzoate, potassium sorbate, sodium saccharin, citric acid, neohesperidina were kindly supplied by Farmalabor - Produtos Farmacêuticos, S.A. (Condeixa-a-Nova, Portugal). Additionally, magnesium L-pidolate and sodium gluconate were supplied by MAGNESIA (Luneburg, Germany). Mango flavour was supplied by Mane (Bar-sur-Loup, France). Sodium glutamate was supplied by Ajinomoto (Tokyo, Japan). Stevia (Rebaudiose A 97 %) was supplied by Herboveda (Noida; India).

2.3. Tablets batch manufacturing

The manufacturing process consisted of direct compression of $100\,g$ batches. First, all the batches components were separately weighted. A precision Mettler Toledo scale (d= $0.1\,g$; maximum weight = $3100\,g$) was used for amounts $\geq 10\,g$, while a Mettler Toledo AG204 analytical scale (d = $0.0001\,g$; maximum weight = $210\,g$) was used for amounts $\leq 10\,g$. Following, the components were blended using a cube mixer, model AR 402 from ERWEKA at 30 rpm of speed during 15 minutes. For batches consisting of lubricant (SSF) an extra mixing cycle was performed at the same speed for 5 minutes.

The blend was transferred to the single station press machine model EK 0, brand Korsch and the compression process initiated. The compression parameters were adjusted accordingly to the hardness and weight of the produced tablets.

2.4. **Tablets design of experiments**

To study the effect of different excipient levels on disintegration time and friability several DoE were performed. The parameters considered as factors for each DoE were varied at two levels: maximum and minimum. All the other formulation and manufacturing parameters were kept invariant, except Prosolv Nutra level. The level of this excipient varied with the amount of excipients added to each experiment. From the performed DoE resulted experiments corresponding to a different formulation, i.e., to a different $100\,g$ batch. Disintegration time and friability were considered as responses, and tested accordingly to what is described in the sub-chapter 2.6 and 2.7, respectively. The experimental design, mathematical models, Pareto plots of main effects, interaction plots and the response contour plots were obtained through Minitab 19 software.

2.5. **Weight and harness testing**

In order to perform weight and hardness tests, a sample of 6 tablets was collected for each manufactured formulation. A Mettler Toledo AG204 analytical scale (maximum weight = $210\,g$; d = $0.0001\,g$) was used to individually weight each tablet and a Vanderkamp VK 200 tablet hardness tester was used to individually test each tablet breaking force. Finally, the average and standard deviation of the mentioned values were calculated using Microsoft Excel software.

2.6. **Disintegration testing**

The disintegration time was determined by placing a sample of 6 tablets in a disintegration apparatus (Venkel VK 100). Each tablet was placed in a different basket with one disc, the set of baskets was then submerged in 900 mL of water at $37^o\,C$ $\pm 0.5^o\,C$. The test was consider complete when all the tablets were completely disintegrated and the time was registered in minutes.

2.7. **Friability testing**

For each formulation, it was collected a sample of 10 whole tablets and each tablet was gently swept. The sample was then accurately weighted, using a Mettler Toledo AG204 analytical scale (d = $0.0001\,g$), and the initial weight - W_i - registered considering six significant figures. Following, the tablets were placed in a Vankel friability drum and rotate 100 times. Then, the sample was cleaned and weighted as before; the final weight - W_f - was registered considering six significant figures and the percentage of mass lost by friability - M_L - was calculated, applying the following expression,

$$M_L = \frac{W_i - W_f}{W_i} \times 100\,\%. \tag{1}$$

3. Results and discussion

The development process of both dosage forms was initiated with the establishment of a QTPP (not shown). This quality profile was used as a support for the identification of the products CQAs. Following, a simple risk assessment tool, most known as risk matrix, was used to qualitatively assess the risk (as high, medium or low) that process and formulation variables may encompass for the accomplishment of the identified product CQAs. The variables encompassing high risk for the product CQAs were selected for further investigation and understanding. In particular, main importance was given to the source of magnesium, therefore, different magnesium salts were initially studied, culminating in the selection of magnesium citrate as the nutritional source of tablets and magnesium L-pidolate as the nutritional source of oral solutions. The mentioned magnesium salts were selected based on its bioavailability, solubility, magnesium weight percentage and formulation behaviour.

Regarding the formulation design of tablets, it was given special attention to the variation of disintegrant level on the formulation. Disintegrant level variation was identified as a factor of high risk for the accomplishment of the CQAs disintegration, friability and dissolution. Thereby, the impact of level variation of croscarmellose sodium in the tablets performance was study regarding disintegration and friability. On the other hand, during the oral solution development special importance was given to palatability, considering that the formulation composition was assessed as a high risk factor for this product attribute.

3.1. **Tablet formulation and process design**

The process of tablet formulation design was initiated with the selection of a suitable magnesium source and, as mentioned before, magnesium citrate was the chosen salt. In order to fulfill the desired magnesium dosage, 77% of the tablet weight (1.5g) must correspond to magnesium citrate. Therefore, only 23% of tablet weight is available for the incorporation of excipients. During the manufacture of magnesium citrate tablets it was found that the incorporation of Aerosil 200 (glidant) and SSF (lubricant) was crucial for the accomplishment of the appearance QTPP criteria, thereby both this excipients were added to the formulation in a level of 4% and 0.7%, respectively. The remaining tablet weight being fulfilled by Prosolv Nutra (co-processed excipient). However, the incorporation of glidant and lubricant in the formulation affected the tablet disintegration time negatively, by increasing

it above the European Pharmacopoeia specification (15 minutes). Consequently the incorporation of superdisintegrants in formulation was considered and its effect studied as shown below.

3.1.1 Effect of superdisintegrant level and hardness on disintegration time

Considering that the immediate realise tablets initially produced exhibit disintegration times not complying with the European Pharmacopoeia 8^th edition, it was decided to study the impact of disintegrant level variation on the performance of the tablet. Two superdisintegrants were selected based on a literature review (ref. [12, 13]) and on prior knowledge: croscarmellose sodium and SSG. The aim of this study was to select one of this excipients based on the outup disintegration time and friability values. Thus, two DoE, one considering SSG and another considering croscarmellose as factors, were separately performed and the resulting models compared. Disintegration time and friability were considered as responses. Herein the results of the DoE considering croscarmellose sodium are shown.

The study of the effect of croscarmellose sodium variation on the formulation performance was performed through a DoE. The DoE was performed considering 2 factors, croscarmellose sodium percentage (Z_1) and hardness (Z_2), varying between two levels. Croscarmellose level was varied between 0.5 and 2.75 % (w/w) and tablet hardness between 10 and 18 kp. There were considered 2 center points corresponding to 2.75 % (w/w) of croscarmellose and 14 kp of tablet hardness. Each experiment was repeated once, resulting in a total of 11 experiments, i.e., 11 formulations. The resulting formulations were tested for disintegration time and friability.

Two response surface designs were applied and analyzed in order to fit the experimental data, one for disintegration time data and another for friability data. The croscarmellose model for disintegration time (DT) in uncoded units is given by,

$$DT = 12.48 - 2.69Z_1 + 0.325Z_2 + 0.252Z_1^2 + 0.0081Z_1Z_2, \quad (2)$$

while the croscarmellose model for friability (FRI) corresponds to,

$$FRI = -0.122 + 0.0602Z_2 + 0.6053Z_1 - 0,00174Z_2^2, \quad (3)$$

where DT and FRI represent the measured responses related to each factor-level combination. The terms Z_1 and Z_2 represent the main effects of each factor on the response (croscarmellose level and tablet hardness, respectively). The term Z_1Z_2 represents the interaction effect and the polynomial terms Z_1^2 and Z_2^2 represent curvature. The terms significance was evaluated through the Pareto charts of the standardized effects (presented elsewhere), in which was always considered a significance level of $\alpha = 0.05$. First, it will be presented the disintegration time model analysis and further the analysis of the friability model.

The disintegration time model obtained presented a good predictive ability, having $R^2_{(pred)}$ equals to 65.57 %. Considering the Pareto chart presented in the Figure 1, it is possible to conclude that disintegration time is mainly impacted by croscarmellose level (B). In order to better understand the relationship between the factors and disintegration variability, a contour plot is presented in Figure 2. As illustrated, disintegration time variability is mainly impacted by croscarmellose level variation. Moreover, it is possible to conclude that if croscarmellose level is $\geq$ 2 % (w/w) and tablet hardness is $\leq 16\,kp$ then the European Pharmacopoeia (EP) specification for disintegration time will always be fulfilled.

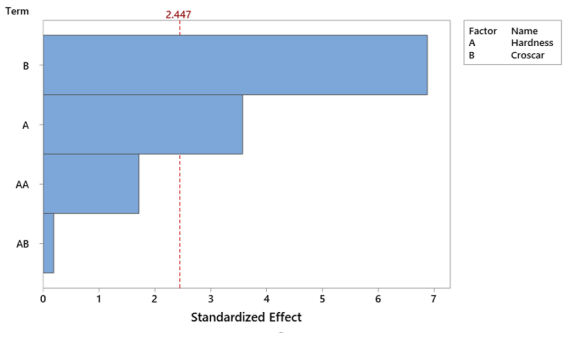

Figure 1: Pareto chart of standardized effects of croscarmellose level and hardness on disintegration time. Croscar: Croscarmellose level.

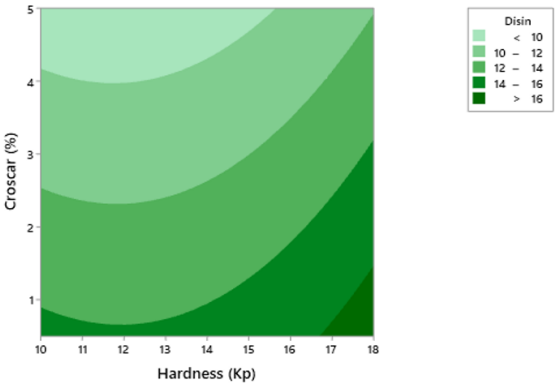

Figure 2: Contour plot regarding disintegration time as function of croscarmellose sodium level and hardness variation. Disin: Disintegration time. Note: consider disintegration time in minutes.

Taking in consideration the model of friability as

function of croscarmellose level, a $R^2_{(pred)}$ equals to 96.84 % was obtained, meaning that the model has an adequate predictive ability. The factor that mainly impacts friability seems to be croscarmellose level, as illustrated in the Pareto chart presented in the Figure 3. As illustrated in the contour plot presented in Figure 4, all the formulations tend to friability values $\leq 0.75\,\% \, w/w$ at hardness values $\geq 17\,kp$. Indicating that high values of tablet hardness enable low friability values, regardless the croscarmellose level considered. On the other hand, high levels of croscarmellose lead to an increment on friability mass losses. Concluding, high tablet hardness values are crucial in order to accomplish acceptable values of friability mass.

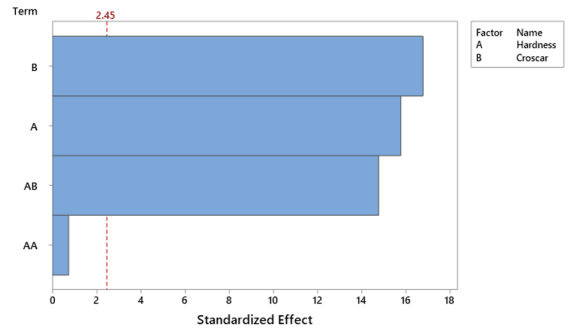

Figure 3: Pareto chart of standardized effects of croscarmellose level and hardness on friability mass losses. Croscar: Croscarmellose level.

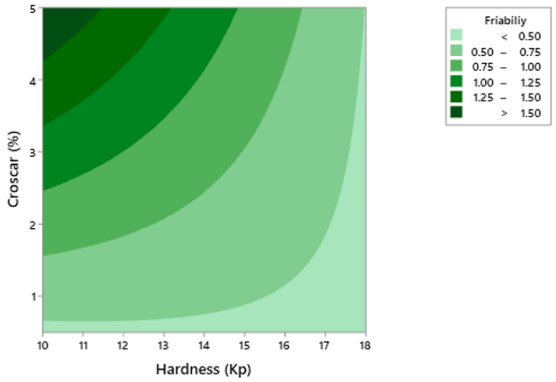

Figure 4: Contour plot regarding friability as function of croscarmellose sodium level and hardness. Croscar: croscarmellose. Note: consider friability mass losses in % (w/w).

Finally, with both croscarmellose data models analyzed, it is possible to define formulation settings that enable optimal disintegration and friability responses. With that purpose, a response optimization was performed considering two targets: i. disintegration time equals to 10 minutes and ii. friability mass losses equals to 0.6% w/w. As shown in Table 1, it was found that a combination of the target responses is not possible. Specifically, the disintegration time target can not be met, the nearest predicted value corresponding to 11.30 minutes. Subsequently, the suggested formulation settings were experimental tested. The batch was produced accordingly to what is described in the sub-chapter 2.3. The resulting tablets were tested for disintegration time and friability. It was found that the observed results differed from the predicted values. The observed disintegration time is 0.60 minutes less than its predicted value. On the other hand, the experimental friability is superior to its predicted value by 0.06 % w/w. Similarly, the tablet hardness observed (mean value of 6 tablets) is inferior to the required optimization setting. It is important to notice that this difference is not significant, nevertheless, the observed Standard Deviation (SD) value is considerable, indicating reasonable tablet hardness variance. Such variance has an impact on the output responses. Concluding, given that the disintegration time and friability values comply with the target criteria, this formulation (CO4) was considered adequate. Moreover, all the produced tablets complied with the appearance targets described in the QTPP.

Taking in consideration the results obtained so far, it is possible to conclude that the tablets disintegration time decreased with increasing levels croscarmellose sodium. This behavior was expected as it is largely described in literature [12]. The explanation for this behavior relays on the superdisintegrants mechanism of action. Superdisintegrants act mainly through swelling mechanisms. Swelling happens as a consequence of the hydrophilic nature of superdisintegrants. Particularly, superdisintegrants are insoluble hydrophilic colloids, therefore, they will absorb water from the tablet surrounding and as the water enters the tablet matrix the superdisintegrant particles will tend to swell [12, 13]. The swelling will break-up the tablet matrix and culminate in tablet disintegration. The tablet swelling tends to be proportional to the superdisintegrant level, in the sense that, the more disintegrant particles available in the tablet matrix the greater quantity of water will be absorbed [12, 13]. In literature it is also described a process of disintegration time stagnancy. This process happens for a given threshold disintegrant concentration, above which the disintegration time stagnates [12]. However, during the performance of this study this process was not observed.

Regarding the superdisintegrant performance, croscarmellose sodium seemed to have a greater impact on disintegration. In the sense that, croscarmellose appears to be effective at lower formulation levels. Taking in consideration the

Table 1: Optimal magnesium citrate formulation containing croscarmellose sodium. Cros_{level} – Croscramellose level, H_{exp} – Hardness expected, H_{obs} – Hardness observed, DT_{pred} – Disintegration time predicted, DT_{obs} – Disintegration time observed, FRI_{pred} – Friability predicted, FRI_{obs} – Friability observed.

ID	Cros_{level} (% w/w)	H_{exp} (kp)	H_{obs} (kp) $\pm SD$	DT_{pred} (min)	DT_{obs} (min)	FRI_{pred} (% w/w)	FRI_{obs} (% w/w)
CO4	5	17.36	17.20 $\pm$0.53	11.30	10.70	0.60	0.692

disintegration time contour plot for croscarmellose (Figures 2), it is possible to notice that the minimal disintegration time predicted for 2 % w/w of croscarmellose is 10 minutes. On the other hand, for the same level of SSG the disintegration time increased for 13 minutes (results not shown). This fact may be explained by the differences found between the mechanisms of action of SSG and croscarmellose. Specifically, SSG acts mainly through swelling, while, croscarmellose seems to work partly by swelling and, additionally, by wicking and recovery of energy of elastic deformation [12, 13]. Nevertheless, it is notable that the optimal disintegration time (10 minutes) was not accomplished, regardless the superdisintegrant used. Moreover, the addition of small amounts of superdisintegrants was not sufficient to significantly reduce disintegration time. Actually, significant disintegration time reductions were only observed at high values of superdisintegrant. This behaviour may be a consequence of the high level of magnesium citrate per tablet (77% w/w) and its considerable water solubility. It has been strongly suggested in literature that superdisintegrants have a worse disintegration performance in tablet formulations that contain significant amounts of soluble substances [12, 14]. The explanation of this relays on the fact that superdisintegrants function mainly by breaking the tablet matrix. When a soluble substance is part of the tablet matrix, the matrix starts dissolving instead of disintegrating in smaller parts. As the matrix dissolves the superdisintegrant is no longer in contact with solid particles to physical force breaking, consequently reducing disintegration [12, 14]. This may be an explanation why low disintegration time values were never accomplished.

Regarding the friability studies, it was possible to conclude that increasing levels of both superdisintegrants caused increasing friability mass losses. However, it appeared that croscarmellose sodium had a less negative impact on friability when compared with SSG. Moreover, it was found that tablet hardness had an important impact on friability. For both disintegrants it was observed a decreasing effect on tablet friability caused by increasing tablet hardness. These results were found before in several studies [15, 16]. It was also found that friability is significantly impacted by the interaction of tablet hardness and superdisintegrant level.

In conclusion, croscarmellose sodium appears to be the superdisintegrant that allows a better formulation performance. As shown in the Figures 5 and 6, the range of croscarmellose level and hardness values that comply with the disintegration time and friability requirements is much wider than the same SSG range. This fact indicates that croscarmellose variance is a less significant risk factor for the accomplishment of the CQAs, disintegration time and friability, than SSG variance. Therefore, the formulation presented in the Table 1 was considered the final formulation and proposed for further studies, mostly importantly process understanding studies.

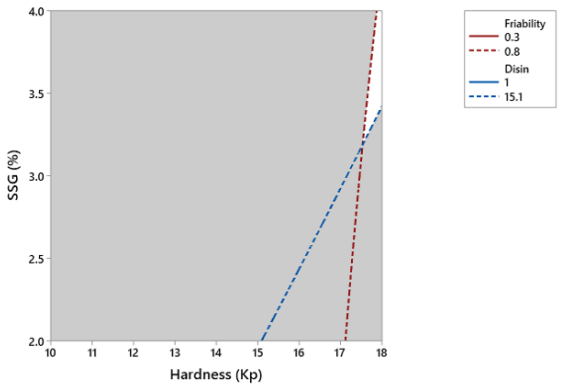

Figure 5: Overlaid contour plot regarding disintegration time and friability as function of sodium starch glycolate level and hardness. Note: consider friability mass losses in % (w/w).

3.2. Oral solution formulation and process design

The manufacturing process of oral solutions is simple, encompassing a limited number of equipment and unit operations. The equipment necessary includes a vessel with a suitable capacity, an agitation system and a filtration system. The last, only being necessary to ensure the solution clarity [17, 18, 19]. The manufacture process consists of the addition

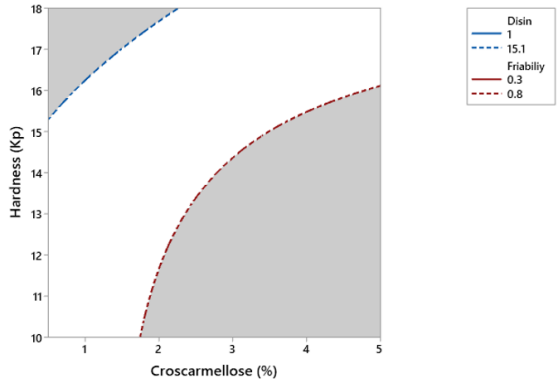

Figure 6: Overlaid contour plot regarding disintegration time and friability as function of sodium croscarmellose level and hardness. Note: consider friability mass losses in % (w/w).

of solid solutes to the solvent, while the system is constantly agitated.

The formulation design studies were carried in order to identify the combination of excipients and magnesium salt that result in a formulation that meets all the QTPP criteria. As mentioned before, three magnesium salts were considered and tested: trimagnesium citrate, magnesium chloride and magnesium L-pidolate. Culminating in the selection of magnesium L-pidolate as the magnesium source of oral solutions. Regarding the excipients selection, a literature review (ref. [17, 18]) was performed in order to understand which excipients are commonly used in oral solutions. It is important to highlight that the final formulation is expected to be composed by three sweeteners, two antimicrobial preservatives and one flavoring agent. Therefore, through formulation design studies, the best combination of sweeteners, antimicrobial preservative and flavoring agents will be selected form a defined list of excipients. In order to select the best combination of excipients to constitute the final oral solution formulation, two QbD tools were initially used: risk assessment and DoE. The risk assessment performed showed that variation in the majority of the formulation variables represented high or medium risk for the accomplishment of the product CQAs palatability. Thus, and given that it was found that no other CQAs may be affected in same extend by the formulation variables, palatability was chosen as a selection attribute. As describe above, another QbD tool was employed during the excipients selection process: DoE. The DoE was performed in order to establish different formulations and palatability was considered as the main response. From this process resulted twelve different formulations, each with a different combination of sweeteners, antimicrobial preservatives and flavoring agents. Thereby, each formulation was initially tested for palatability. For this test, ten volunteers were asked to blind taste each formulation and score it for sweet and sour taste. The scores were independent, in the sweet score 7 represents the most pleasant sweet taste and 1 the absence of this taste, in the sour score 1 represents the most sour taste and 7 the absence of sour taste. The results are presented as mean values in the Chart illustrated at Figure 7. As shown, there are six formulations that scored 5 or higher in both taste evaluations: 2.A, 2.B, 5.A, 5.B, 6.A and 6.B. From this set of formulations, the formulations 6.A and 6.B were discarded, given that both have sodium saccharin in its composition. It is a company expectation to develop a product free of caloric sweeteners, therefore no further studies were performed on the solutions 6.A and 6.B. Another aspect demonstrated in Figure 7, is the constant score superiority of the solutions A when compared with the solutions B. The difference between A and B solutions is only one excipient, the flavoring agent. Solutions A have sodium gluconate, while solutions B have monosodium glutamate in its composition. The flavoring agents were added with the intention to mask the typical sour taste of magnesium salts and given the results obtained, sodium gluconate seems to have a superior masking taste capacity than monosodium glutamate. Concluding, from the previous set of formulation the formulations B where discarded, remaining the solutions 2.A and 5.A. An important factor to consider regarding the solutions 2.A and 5.A is their similarity in sweeteners composition. Both formulations contain sodium cyclamate and aspartame, this may suggest that this combination of sweeteners have a synergistic action that improves the sweet feeling caused by the formulation. On the other hand, the solutions 1.B and 3.B were the solutions with the lowest scores, as the Figure 7 shows. This formulation have sodium saccharin and acesulfame potassium in its composition, suggesting that this combination of sweeteners is not sufficiently efficient.

Summarizing the formulations 2.A and 5.A complied with the palatability targets. Therefore pH measurements were performed in both formulations. The formulations presented, at t = 0 months and ambience conditions, pH values of 4.86, complying with the pH target. Thus, no pH adjustments procedures were needed. Following, such formulation were placed under stability conditions (real time storage conditions, i.e., $25^o\,C$ and 60 % of relative humidity and accelerated conditions, i.e., $40^o\,C$ and 75 % of relative humidity). After 30 days one sample from each condition was taken and tested for pH and palatability. No significant changes were found, suggesting that both formulations are stable

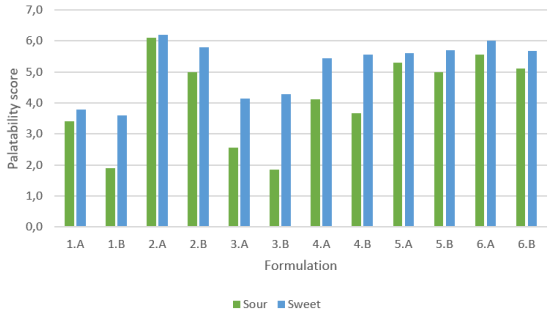

Figure 7: Bar chart of the palatability score of each oral solution formulation.

for the mentioned period of time and conditions. However, this results are very limited given that no significant information regarding stability can be taken from here, therefore further stability tests should be performed in the future.

4. Conclusions

The development of magnesium dosage forms carried during this research work complied with the main objectives initially proposed. The development process was carried through a combination of literature review and research work based on the several QbD concepts suggested in the ICH guidelines Q8 and Q9.

In this project, immediate release tablets, containing a considerable bioavailable magnesium source, were satisfactorily manufactured through direct compression method and taking in consideration the QbD approach.

The formulation design studies allowed the selection of a suitable magnesium source and the establishment of a combination of excipients with an output performance in accordance with the QTPP. In particular, magnesium citrate was selected as the nutritional substance, Aerosil 200 as glidant, SSF as lubricant and croscarmellose sodium as superdisintegrant. During the magnesium salt selection, it was found that the presence of glidant and lubricant in the formulation was crucial for the accomplishment of the QTPP appearance criteria.

The impact of superdisintegrants on the formulation performance was study through two different DoE. The first, considered SSG level and hardness as factors, while the second considered croscarmellose level and hardness. Disintegration time and friability were taken as responses for both experiments. Four mathematical models were established to evaluate the variability of the responses as function of the factors. These models satisfactorily fitted the data and had an adequate predictive ability. From this study it was possible to conclude that variation in SSG level, croscarmellose level and hardness have a significant impact on disintegration time and friability. In particular, it was found that the disintegration time of tablets containing SSG was more sensitive to tablet hardness variation than to SSG level variation. Whereas, the disintegration time of tablets containing croscarmellose was substantially impacted by its concentration, being less sensitive to hardness variation. It was also found that croscarmellose sodium had a greater impact on the tablets disintegration time. Specifically, croscarmellose was more effective at lower formulation amounts when compared to SSG, suggesting a higher disintegration capacity. Increasing levels of both superdisintegrants appeared to cause increasing tablet friability. However, from both superdisintegrants, croscarmellose had the less negative impact on this attribute. Furthermore, it was found that tablet hardness increment, had a negative impact on disintegration time but a positive impact on tablet friability. Thus, it seams crucial to control this attribute in order to jointly satisfy disintegration and friability requirements. Finally, the models analysis resulted in the identification of two nearly optimal formulations (one containing SSG and another containing croscarmellose). As result of the predicted and observed responses, the optimal formulation containing croscarmellose sodium ($5\,\%w/w$) was chosen as the final formulation.

In conclusion, this research allowed the optimization of formulation settings, thereby resulting in a final formulation that complies with the QTPP criteria for appearance, friability and disintegration time. Furthermore, it may be concluded that mathematical models represent a useful tool to predict and understand the relationship between the formulation attributes and the input variables, supporting a more efficient product development.

Some of the limitations encountered during tablet development form the basis for future work. In particular, it was not possible to perform studies of process understanding. Thus, it seems relevant to study the impact of process parameters variation on the formulation performance (specially of those assessed as high risk factors). Only through these studies it would be possible to develop a manufacturing process that consistently gives an output product with the desired quality attributes. Moreover, time and resource constraints prevented the complete study of the tablets performance. Therefore, the impact of formulation variables on the tablets dissolution and uniformity of content shall be further studied. Additionally, the extent of the experimental data was also found as a project limitation. If more variation levels were considered during experimentation, the models would have a better predictive ability and the risk of false predictions would be lower. The poor model experimental validation is another important limitation to

considered. Such experimental validation shall be performed to increase the confidence level on the optimal formulation settings identified. Finally, a particular limitation of this research is the investigation of hardness as an independent variable (i.e. model input). Hardness is impacted by formulation and process variables, being dependent on the experimental design. However, compression force could not be precisely adjusted and controlled due to limitations within the compression machine system. Therefore, in a scenario where this parameter can be adjusted and controlled, hardness shall be studied as a response of compression force variation. Additionally, it also seems relevant to study the efficiency of different types and levels of superdisintegrants when incorporated in tablets containing highly soluble components.

Regarding the oral solution development, it is possible to conclude that the designated QTPP was properly established based on literature review and prior knowledge. Thereby, allowing the identification of possible product CQAs. In addition, this quality profile served as basis for the formulation design studies. The design studies enable the selection of magnesium L-pidolate as the oral solution nutritional substance (along with vitamin B6). Moreover, it was possible to select combinations of excipients that comply with the desired palatability, thus, reducing the risk associated with the accomplishment of this product CQAs. The real time and accelerated stability studies showed that the solutions 2.A and 5.A were stable through 30 days, in what concerns palatability, appearance and pH. Summarizing, the oral solution development fulfilled the overall aim initial proposed. However, time and resource constrains prevented the study of several product CQAs.

The limitations found during the oral solution development lay the foundation for future work concerning the impact of process parameters and formulation variation on the product CQAs. In particular, it was not possible to study the impact of process variables (e.g. solvent preparation or mixing time and seep) in the identified product CQAs. Thus, it is important to further study the effect of process parameters variation on the product CQAs and, thereby, define a robust manufacturing process that consistently gives a quality product. Furthermore, it should be interesting to study the impact of formulation variability in the following product CQAs: assay, impurities, microbial growth and uniformity of content. These studies would jointly contribute for the understanding of how the formulation attributes and process parameters impact the out-put product CQAs. This knowledge is crucial for the establishment of meaningful specifications. Notwithstanding the above, the present research may serve as groundwork for the accomplishment of such knowledge.

Overall, it may be conclude that the QbD tools applied throughout this work contributed for an efficient development process of magnesium dosage forms. The systematic approach to food supplements development enabled the overcoming of many formulation design challenges. Furthermore, as result of this project, immediate release tablets of magnesium and vitamin B6 were develop complying with the appearance, disintegration and friability targets. Similarly, two magnesium oral solutions complying with dosage strength, appearance, palatability and pH targets were formulated.

References

[1] International Council for Harmonisation. PHARMACEUTICAL DEVELOPMENT Q8(R2). 8(August):1–28, 2009.

[2] Edina Pallagi, Rita Ambrus, Piroska Szabó-Révész, and Ildikó Csóka. Adaptation of the quality by design concept in early pharmaceutical development of an intranasal nanosized formulation. *International Journal of Pharmaceutics*, 491(1-2):384–392, 2015.

[3] Lan Zhang and Shirui Mao. Application of quality by design in the current drug development. *Asian Journal of Pharmaceutical Sciences*, (July), 2016.

[4] Burcu Mesut, Yıldız Özsoy, and Buket Aksu. Review article The Place of Drug Product Critical Quality Parameters in Quality by Design (QBD). *Turk J Pharm Sci*, 12(1):75–92, 2015.

[5] FDA. Pharmaceutical CGMPs for the 21s Century - A risk-based approach. *Fda*, (September):32, 2004.

[6] Lawrence X. Yu, Gregory Amidon, Mansoor A. Khan, Stephen W. Hoag, James Polli, G. K. Raju, and Janet Woodcock. Understanding Pharmaceutical Quality by Design. *The AAPS Journal*, 16(4):771–783, 7 2014.

[7] Simone R.B.M. Eussen, Hans Verhagen, Olaf H. Klungel, Johan Garssen, Henk Van Loveren, Henk J. Van Kranen, and Cathy J.M. Rompelberg. Functional foods and dietary supplements: Products at the interface between pharma and nutrition. *European Journal of Pharmacology*, 668(SUPPL. 1):S2–S9, 2011.

[8] Betsy Davis. The Link Between Big Pharma and the Supplement Industry, 2017.

[9] José Augusto Felício. Estudo de Mercado - Consumo de Suplementos Alimentares em Portugal. *Centro de Estudos de Gestão - Instituto Superior de Economia e Gestão*, page 180, 2006.

[10] EFSA. Scientific Opinion on Dietary Reference Values for magnesium. 13(7):1–63, 2015.

[11] Jennifer Grebow. How a Quality by Design model can benefit the dietary supplements industry — Nutritional Outlook, 2018.

[12] Larry L. Augsburger and Stephen W. Hoag. *Pharmaceutical Dosage Forms: Tablets. Volume 2*, volume 2. Informa Healthcare, third edition, 2008.

[13] Parind Mahendrakumar Desai, Celine Valeria Liew, and Paul Wan Sia Heng. Review of Disintegrants and the Disintegration Phenomena. *Journal of pharmaceutical sciences*, 105(9):2545–2555, 9 2016.

[14] Janet Roche Johnson, Li-Hua -H Wang, Marc S. Gordon, and Zak T. Chowhan. Effect of formulation solubility and hygroscopicity on disintegrant efficiency in tablets prepared by wet granulation, in terms of dissolution. *Journal of Pharmaceutical Sciences*, 80(5):469–471, 1991.

[15] Marc S Gordon. Process considerations in reducing tablet friability and their effect on in vitro dissolution. *Drug Development and Industrial Pharmacy*, 20(1):11–29, 1994.

[16] Z. T. Chowhan, I. C. Yang, A. A. Amaro, and Li-Hua -H Chi. Effect of moisture and crushing strength on tablet friability and in vitro dissolution. *Journal of Pharmaceutical Sciences*, 71(12):1371–1375, 1982.

[17] Sarfaraz Niazi K. *Handbook of Pharmaceutical Manufacturing Formulations: Liquid products*, volume 6. CRC Press, Florida, 2009.

[18] M.E. Aulton. *Pharmaceutics: The science of dosage form design*. Churchill Livingstone, 2 edition, 2001.

[19] Shivang Chaudhary. Quality by design model for "Liquid oral solution". *Drug Development and Industrial Pharmacy*, (July), 2016.