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Quality by design strategies in fluidized bed granulation: A focus on granules for tablet manufacturing

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ABSTRACT

The study aimed to apply the quality by design (QbD) methodology to optimize the fluidized-bed granulation process to produce high-quality pharmaceutical granules intended for tablet manufacturing. Research focused on defining the quality target product profile (QTPP) and identifying critical quality attributes (CQAs), critical material attributes (CMAs), and critical process parameters (CPPs) crucial to ensuring product quality. The experimental design employed a three-level fractional factorial design to investigate the effects of key process parameters, including the mass flow rate of the binder, the temperature of the inlet air, and the drying time, on the granulation results. Measurements such as particle size distribution, moisture content, and flowability were used to assess the granules. The results indicated that parameters such as the inlet air temperature and drying time significantly impact the quality of the granules, confirming their status as CPPs. Further analysis of tablet mass and hardness revealed that these granule properties directly influenced tablet uniformity and mechanical strength.The application of the failure mode and effect analysis (FMEA) matrix helped to identify and prioritize these critical parameters based on their risk priority number (RPN). The study concluded that a systematic QbD approach, combined with a robust experimental design and risk management, is crucial for optimizing the fluidized-bed granulation process. This ensures consistent production of granules with the desired quality attributes and enhances the safety and efficacy of the final pharmaceutical product.

Keywords: flowability, quality by design, process optimization, fluidized bed granulation, granule properties, tablet manufacturing

INTRODUCTION

Fluidized bed granulation is a key process in the pharmaceutical industry, used primarily to produce essential granules for tablet formulations and other dosage forms [1, 2]. This process involves selecting appropriate powders and excipients, which are fluidized by an upward stream of air or gas, allowing a binder solution to be sprayed onto the particles, causing them to adhere and form granules. After granulation, the granules undergo a drying phase to remove moisture, preventing excessive stickiness, followed by cooling, sieving, and mixing with additional excipients or active pharmaceutical ingredients to finalize the formulation [3]. The key parameters influencing the granulation process include inlet air temperature, airflow rate, and spray rate, which affect granule size, fluidization quality, and drying efficiency [4, 5]. Precise control of these parameters is critical to achieve uniformity and high-quality granules. Fluidized bed granulation offers advantages such as the production of uniform granules with enhanced flow properties, the benefit of tablet manufacturing, and the improvement of the dissolution rate of poorly soluble drugs [6]. However, it also presents challenges related to process complexity and stringent moisture control.

Additionally, the properties of granules obtained during the fluidized bed granulation process significantly influence the quality of tablets produced in subsequent steps. Key attributes such

as granule size distribution, flowability, and compressibility directly impact tablet characteristics, including weight uniformity, hardness, and friability. Understanding and optimizing these relationships is essential to ensure high-quality final dosage forms.

The research presented in this article addresses a critical gap in the optimization of fluidized bed granulation using the QbD approach. While this method is widely applied in the pharmaceutical industry, limited research details the specific impact of process parameters on the CQA of granules essential for subsequent tablet production. The application of QbD enables a deeper understanding of these parameters and their influence on granule quality, ensuring better control and consistency in tablet formulation manufacturing [7].

Furthermore, the use of calcium carbonate, known for its high compressibility [8], combined with sodium naproxen, which exhibits poor flowability [9, 10], complicates the direct compression process (tablet formation from powder). Therefore, indirect tableting, which involves first granulating the materials, is advantageous, as it enhances the flowability and compressibility.

Details about the QbD framework and its components will be discussed in more detail in Chapter 2, where we will define the QTPP, identify CQAs and outline the risk assessment and control strategies necessary for optimizing the granulation process.

MATERIALS AND METHODS

Quality by design for design of fluidized-bed granulation

QbD integrates predefined quality into products through a systematic approach, incorporating risk management to enhance both product and process understanding [11]. The key pillars of QbD include [12, 13]:

- Quality target product profile (QTPP).
- Comprehensive understanding and design of the product, with an emphasis on identifying critical material attributes (CMAs).
- Detailed design and understanding of the drug product manufacturing and scaling process, including the identification of CPP.
- Establishment of a design space that correlates CPPs and CMAs with CQAs.
- Development of a control strategy.
- Commitment to continual improvement.

A quality target product profile

The QTPP outlines the drug product's properties, including dosage form, strength, stability, purity, sterility, and pharmacokinetics (LADME: liberation, absorption, distribution, metabolism, excretion). CQAs, derived from the QTPP, must be maintained within specific limits to ensure desired product quality [14, 15].

Understanding and design of the product with identification of CMAs

To ensure consistent quality, a drug product must align with the QTPP and clinical outcomes. Key evaluations include physical (particle size, polymorphism, solubility), chemical (pKa, stability), and biological properties (bioavailability, permeability) [11, 13, 16]. These attributes guide solid form selection and biopharmaceutical classification system (BCS) categorization [17]. Mechanical properties, critical for efficient manufacturing, enable excipient selection to address poor API flow [18]. CMAs must meet defined limits to ensure quality and facilitate processing [19]. Compatibility studies, using techniques like differential scanning calorimetry (DSC), are vital for maintaining formulation stability [20].

Design and understanding of drug product manufacturing and scaling, including identification of critical process parameters (CPPs)

The drug product's form is influenced by unit operations including milling, mixing, granulation, drying, and compression [21]. Process design involves selecting the appropriate processes, determining scale, and understanding variability to control CPPs that impact CQAs. This requires verifying parameter criticality, establishing limits, and using design of experiments (DOE) for further optimization [22].

Creating a design space linking CPPs and CMAs to CQAs

The design space integrates CMAs and CPPs to ensure drug quality as defined by the QTPP [12]. QbD evaluates interactions between variables and their impact on CQAs, with deviations from the design space requiring regulatory approval. Scale and equipment limitations often necessitate empirical approaches to process scale-up [13]. DOE uses models like Plackett-Burman

and Box-Behnken to optimize processes and focus on proactive quality control [23].

Control strategy

The final phase of QbD involves developing a control strategy to ensure consistent process performance and product quality. This strategy includes monitoring process parameters, material attributes, and facility conditions [24]. Control strategies operate at three levels [25]. Level 1 uses automation and process analytical technology (PAT) for real-time adjustments, ensuring consistent quality but requiring deep process understanding. Level 2 combines end-product testing with flexible parameters, reducing testing needs. Level 3, applied when process knowledge is limited, relies on extensive testing to mitigate quality risks.

Continual improvement

Continuous improvement of product quality is required throughout the product lifecycle. This is achieved by gathering and analyzing data during routine manufacturing to ensure process stability and control Process stability can be assessed using performance (Pp) and capability (Cp) indices [26].

The QTPP and risk analysis

Sodium naproxen, the active pharmaceutical ingredient (API) in tablet production, is a non-steroidal anti-inflammatory drug (NSAID) that inhibits its COX-1 and COX-2 enzymes, reducing pro-inflammatory prostaglandins [27]. The foundation of the QbD approach involves developing the QTPP, which incorporates patient requirements. The QTPP was specifically developed for the final dosage form, which in this case is tablets, and is detailed in Table 1. Based on the QTPP, the second phase of the QbD methodology involved the selection of CQA. These CQAs for the tablets were derived from the study conducted by Djuris [28], encompassing particle size, the water content, and the flowability (measured by the angle of repose).

Risk analysis

Risk analysis is a crucial element within the QbD methodology. For risk identification, the Ishikawa diagram, also known as the fishbone diagram, is utilized. On the basis of initial experimental data and the risk identification process, a failure mode and effect analysis (FMEA) matrix is constructed to analyze the process parameters of fluid bed granulation. Each parameter is evaluated according to severity (S), probability (P), and detectability (D).

The RPN is calculated by multiplying S, P, and D together. Severity (S), probability (P) and detectability (D) are rated on a scale from 1 to 5, with 5 representing the worst-case scenario, 1 the best-case scenario, and 3 a moderate case. The evaluation of the RPN indicator is based on the criteria outlined in Table 2.

The fluid bed granulation process is inherently complex and depends on a multitude of process parameters, certain parameters deemed critical [29]. These critical process parameters exert considerable influence over the quality attributes of the final product, thereby affecting its safety and efficacy. In the FMEA matrix presented below (Table 3), we systematically assess the criticality of these process parameters based on empirical knowledge and practical experience.

Based on the FMEA matrix, it is evident that process parameters such as inlet air temperature, binder mass flow rate, drying time, and drying temperature are critical due to their high risk priority

Table 2. Scale of RPN

RPN	Risk
RPN < 20	Low
20 ≤ RPN < 40	Medium
40 ≤ RPN < 80	High
RPN ≥ 80	Very high

Table 1. Profile of the quality target product

QTPP elements	Target	Criteria
Drug form	Tablets	Patient requirements and pharmacokinetics
Characteristics of drug forms	Non-coated tablets	Patient requirements and pharmacokinetics
Route of administration	Oral	Patient requirements and pharmacokinetics
Dose	200 mg	Pharmacodynamics of naproxen
Physical properties of product	Free-flowing, white tablets	Patient and marketing requirements

Table 3. FMEA matrix for fluid-bed granulation

Process parameters	Impact on CQAs	S	P	D	RPN
Time of fluid bed heating	Mass homogeneity	4	1	2	8
Inlet air temperature	Mass uniformity, PSD od granules hardness	5	4	4	80
Atomization pressure	Mass uniformity	3	4	3	36
Binders mass flow rate	Mass uniformity, PSD of granules, hardness	5	5	4	100
Inlet air flow rate	Moisture content, hardness mass uniformity	3	4	3	36
Drying time	Moisture content, hardness, friability, flowability	5	4	4	80
Drying temperature	Moisture content, hardness, flowability, stability	5	5	4	100

number (RPN), indicating a significant risk. These parameters are categorized as CPPs. Consequently, stringent control measures must be implemented for these CPPs, as they exert a substantial influence on product safety, efficacy, and quality.

Design of the experiment

A preliminary study was conducted to establish a stable process framework, optimizing key parameters such as batch size, fluidization velocity, atomization pressure, and heating duration. To develop the experimental design, we employed Statistica software. A three-level fractional factorial design (33-1) was applied to test critical process parameters like binder mass flow rate, inlet air temperature, and drying time (Table 4).

Table 4. Experimental plan for the fluid-bed granulation process

Batch	Process parameters		
	Binder mass flow rate [g/min]	Inlet air temperature [°C]	Drying time [min]
1	13.3	45	4
2	31	35	1
3	20.45	40	2
4	13.3	35	1
5	20.45	40	1
6	13.3	35	2
7	31	40	4
8	20.45	45	2
9	31	45	4

Formulation for the granulation

The materials selected for the study were the following: sodium naproxen (d90 = 258 μm) from Divi,s Laboratories, India; calcium carbonate (d90 = 5 μm) from Chempur, Poland; microcrystalline cellulose (d90 = 178 μm) from FMC BioPolymer, US; polyvinylpyrrolidone (d90 = 50 μm) from Sigma-Aldrich, US. These selected materials were used to prepare the mass of the formulation in the following percentage proportions of mass: 20% sodium naproxen, 68% calcium carbonate, 7% microcrystalline cellulose, 5% polyvinylpyrrolidone. The functions of each material in the formulation are summarized in Table 5. The DSC studies showed an interaction between sodium naproxen and calcium carbonate. The use of calcium carbonate in the formulation also improves the bioavailability of naproxen [30].

Laboratory-scale granulation system

Fluid bed granulation and drying processes were carried out using a Star O fluidization multiprocessor from I.C.F. & Welko, Italy (Figure 1) Each 300 g batch was loaded onto the multiprocessor, fluidized and preheated for approximately 3 minutes under predefined conditions to enhance fluidization. The air flow rate was maintained at a constant of 15 m/s. The granulation and drying temperatures were consistent between individual batches, but varied between experimental series according to the experimental design. Upon establishing optimal fluidization conditions, the binder solution, containing 20% PVP, was sprayed onto the fluidized bed. Atomizing pressure was kept constant at approximately 2 atm in all experiments. The spray rate varied per batch and was regulated

Table 5. Function of the individual material in the formulation

Material	Function
Sodium naproxen	Active ingredient
Calcium carbonate	Filler
Microcrystalline cellulose	Improvement of tabletability
Polyvinylpyrrolidone	Binder

Figure 1. Fluidized bed granulator

by adjusting the calibrated rotation speed of a peristaltic pump. The duration of the spraying phase depended on the spray rate since the volume of the binder solution remained constant for each batch. Following completion of the spraying phase, the drying phase began. Drying time, identified as a CPP, was varied between three levels according to the experimental plan.

Tablet press

The tablets were prepared using a manual tablet press, model TDP 0, supplied by LFA Machines Oxford LTD (United Kingdom). The compression process was carried out with a pressing force of 3 kN to ensure proper compaction. The die used in the tablet press had a diameter of 6 mm.

Characterization of materials and granules

Characterization of raw materials and the final product included the following measurements: particle size and granule size, water content in the finished product, and angle of repose.

Particle and granule size

For particle and granule size characterization, we used two different methods: sieve analysis for granules and laser diffraction for particles.

Sieve analysis – sieve analysis was performed using a laboratory shaker with a set of sieves of nominal mesh sizes: 36, 75, 150, 250, 500, 1000, and 2000 µm, all manufactured by EKO-LAB-11-200 (Jasie, Poland). In the study, a sample of 100 g of granulated mass was used. Before starting the shaking process, the sieves were weighed. The analysis was carried out on dry sieves at an amplitude of 1.5 mm for 10 minutes using a vibratory shaker. After being sieved, each sieve was weighed together with the retained material. The difference in sieve weight before and after the analysis allowed for the determination of the mass of each fraction. The results are presented as mass percentages for each fraction.

Laser diffraction – measurements were performed using a Mastersizer 2000 Hydro MU (Malvern Instruments, Malvern, Worcestershire, UK), which enables particle size measurements within the range of 0.01 to 2000 µm through dynamic light scattering. Measurements were made in accordance with ISO 13320-1:1999. The analyzer provides output data in the form of particle size distributions (PSDs), which are normalized based on the mass of the particles for each sample.

Moisture content measurement

Humidity was determined using a RADWAG MA.R laboratory moisture analyzer (Radom, Poland) at 110 °C. Humidity measurements were conducted until a constant mass of the sample was achieved at the specified temperature. The measurement error was approximately 0.25%.

Angle of repose measurement

The angle of repose indices were measured using a powder characteristic tester PT-S (Hosokawa Micron, Japan). The measurement error for the angle of repose was 2%.

Characterization of tablets

The tablets were subjected to quality assessment through the evaluation of critical quality attributes (CQAs), including hardness and mass uniformity. Tablet hardness was measured using

a static method with a hardness tester manufactured by CDK Gliwice (Poland). Tablet mass was determined using an Ohaus Pioneer PX224 analytical balance (Switzerland). Measurements were performed on 20 tablets from each batch.

RESULTS AND DISCUSSION

The fluidized bed granulation process resulted in the production of white spherical granules. The particles were characterized by the size distribution of the granules, angle of repose, and moisture content.

Granule size distribution

The mechanical, rheological and pharmacokinetic properties of granules are significantly influenced by the size distribution of the granule, which plays a pivotal role in the consistency and efficiency of pharmaceutical production processes, particularly in tablet manufacturing [31, 32]. Figure 2 illustrates the distribution of the granule size in multiple batches. The variation in granule sizes observed between batches is largely attributable to changes in process parameters, which directly impact granulation outcomes. These parameters include factors such as binder flow rate, temperature, and drying time, all of which influence granule formation and breakdown.

In Batch 1, the size of the modal granule was within the range of 250–150 µm. The process parameters of this batch, specifically the combination of high temperature and low binder flow rate, suggested a low rate of agglomeration. This lower rate of agglomeration can be explained by the rapid evaporation of water from binder droplets, induced by elevated temperature. The extended drying time further contributed to the attrition and breakdown of the granules. The resulting smaller size of the granule is often favorable for ensuring homogeneity in the formulation, but excessive breakdown could compromise the structural integrity required for tablet formation.

On the other hand, batch 2 showed a modal granule size greater than 2 mm, with a wider granule size distribution, a direct result of an increased binder flow rate, lower temperature and reduced drying time. The higher binder flow rate facilitated the formation of larger droplets, which did not evaporate as rapidly under the lower temperature conditions. These larger droplets coalesced to form larger granules. Although the granules in Batch 2 were more robust, the wide size range posed challenges for subsequent tablet production, as uniform granule size is crucial for tablet hardness and dissolution rates.

Batches 3, 4, 5, and 6 demonstrated similar granule size distributions, with modal values between 500–1000 µm. Despite the variations in binder flow rates across these batches, the

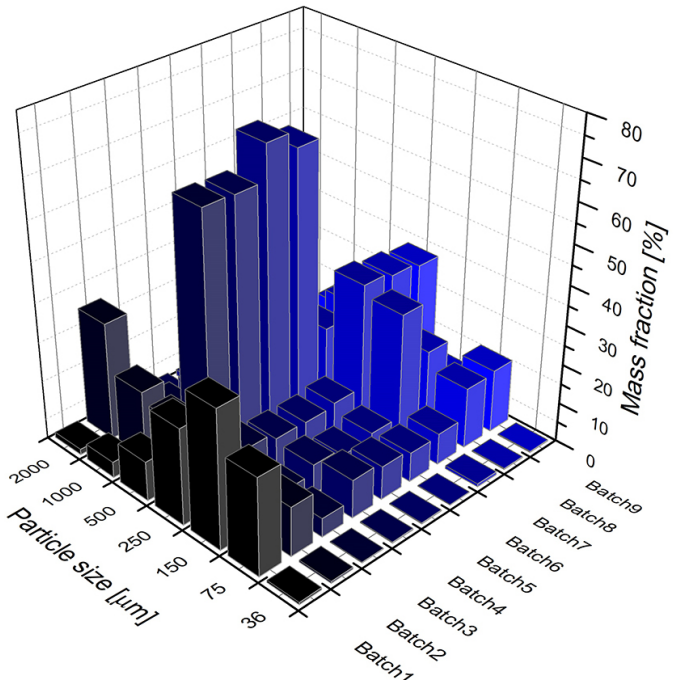

Figure 2. Granule size distribution of the finished product

temperature played a dominant role in regulating the droplet size of the binder. The consistency of the drying times also ensured that the granule sizes remained within a similar range. This suggests that, while the binder flow rate is an important factor, maintaining appropriate temperature and drying conditions is key to achieving consistent granule size distributions.

In Batches 7, 8, and 9, increases in binder flow rate, temperature, and drying time shifted the modal granule size to the 250–500 µm range. This size range is particularly advantageous for tableting processes, as it enhances both the flowability of the granules and their compressibility, critical parameters for high-quality tablet production [33]. The combination of moderate binder flow, sufficient temperature, and extended drying allowed granules that maintained structural integrity while remaining within the ideal size range.

The size distribution of the granules is crucial in tablet manufacturing, as it affects several critical parameters, including compressibility, flowability, and dissolution rates [34]. The ideal granule size for tablet production typically lies between 250–500 µm. Granules that are too small may cause problems such as powdery formulations, resulting in poor flowability and uneven tablet hardness. On the contrary, larger granules (as seen in Batch 2) may cause challenges in achieving uniform tablet weight and dissolution rates, which are key quality attributes in pharmaceutical products.

Granules in the 250–500 µm range, as seen in Batches 7, 8, and 9, are optimal for direct compression into tablets. These granules exhibit not only good flow properties, but also compress easily into tablets without excessive force, ensuring that the active pharmaceutical ingredient (API) is evenly distributed. Moreover, the uniformity in the size of the granules leads to consistent tablet hardness, an important factor for mechanical stability during packaging and transport.

From a QbD perspective, achieving the desired granule size distribution is a critical quality attribute that must be carefully controlled through the process parameters. Granulation process parameters, such as binder flow rate, temperature, and drying time, are identified as critical process parameters that need to be optimized to maintain the size of the granule within the desired range. By controlling these CPPs, manufacturers can ensure that the granules meet the quality specifications necessary for efficient tablet production.

When transitioning from lab-scale to industrial-scale granulation, maintaining control over the granule size distribution becomes even more challenging. Factors such as equipment size, fluidization dynamics, and heat transfer rates can alter the granulation process, potentially leading to larger or more variable granule sizes. To address these challenges, the use of process analysis technology (PAT) and real-time monitoring systems can offer more precise control over CPPs during scale-up. These technologies allow continuous adjustments to process parameters, ensuring that the distribution of granule size remains within acceptable limits, even under large-scale production conditions.

Moisture content of granules

The moisture content in the granules plays a crucial role in determining their mechanical and rheological properties, which are directly related to the performance of the final pharmaceutical product [35]. Moisture content affects the cohesion, flowability, and compressibility of the granules, all of which are vital for the tableting process [36]. The presence of moisture influences the hardness of the tablet by modifying the adhesive forces between the powder particles, thereby affecting the behavior of the granules during compaction and formation of the tablets. Therefore, understanding the moisture content of granules is essential to ensure that the granulation process produces material suitable for subsequent tablet production.

The moisture content of the granules is primarily influenced by process parameters such as temperature, binder flow rate, and drying time. Each of these factors plays a distinct role in determining how much moisture remains in the granules after the drying phase of the granulation process.

Table 6. Moisture content and angle of repose of granules in each batch

Batch	Moisture content [%]	Angle of repose [deg]
1	3.55	43.2
2	10.98	38.5
3	6.42	41.1
4	5.52	42.4
5	5.28	45.6
6	6.72	44.6
7	4.82	45.8
8	8.1	46.1
9	4.6	38.4

In Batch 1, the lowest moisture content was observed, which can be attributed to the high granulation temperature, combined with a low binder flow rate and extended drying time (Table 6). These conditions promoted rapid water vaporization of the granules. The increased evaporation rate resulted in a lower residual moisture content, improving the flowability and compressibility of the powder, which are critical for the subsequent tablet production process. The extended drying time further ensured that moisture was effectively removed from the granules, resulting in a product that was particularly dry and well suited for tableting.

In contrast, Batch 2 exhibited a higher moisture content due to the inverse combination of process parameters: specifically, a high binder flow rate, a lower temperature and a shorter drying time. The higher binder flow rate led to larger binder droplets, which did not evaporate as efficiently at the lower temperature. This hindered the vaporization of the solvent, resulting in higher residual moisture levels. Furthermore, the shorter drying time did not allow enough time for complete removal of water from the granules, leaving them with a higher moisture content. This moisture retention could negatively affect tablet formation, potentially leading to issues such as poor compressibility or increased tablet friability.

Moisture content significantly affects the overall quality of granules and their suitability for tablet production. If the moisture content is too high, the granules may become sticky, leading to poor flowability and challenges to achieve consistent tablet weight during compression. On the other hand, too dry granules may lack sufficient cohesion, resulting in weak tablets that are prone to break or crumbling during handling and packaging.

For optimal tablet production, it is essential to maintain a controlled and balanced moisture content in the granules. Excess moisture can cause variations in tablet hardness, dissolution rates, and bioavailability. However, too little moisture can reduce the binding capacity of the granules, negatively affecting the integrity of the tablet. Therefore, the process parameters must be carefully calibrated to strike the right balance between moisture removal and granule stability.

The moisture content for batches 3, 4, 5, and 6 was similar due to the consistent drying times and moderate binder flow rates between these batches. While some variations in temperature were observed, relatively controlled conditions resulted in moderate moisture content levels that fell within acceptable ranges for tablet production. This demonstrates that process consistency is key to ensuring uniform moisture content and, by extension, consistent granule quality for subsequent tableting operations.

The interaction between the process parameters that control moisture content, namely temperature, binder flow rate, and drying time, is complex, as highlighted in Figure 3. The relationship between these variables is not linear, meaning that changes in one parameter can have varying impacts on the moisture content depending on the values of the other parameters.

For example, an increase in the binder flow rate can lead to higher moisture retention if not balanced with a sufficient increase in temperature or drying time. On the contrary, higher drying temperatures may lead to excessive drying if the binder flow is too low, resulting in granules that are too dry and brittle. These nonlinear interactions emphasize the importance of optimizing all process parameters simultaneously to achieve the desired moisture content in granules.

The multifactorial regression analysis performed on the data provided a deeper understanding of how these parameters interact. The empirical equation developed from this analysis is expressed as follows:

$$\textit{Moisture content} = -1.179 \times A - 0.029 \times \\ \times B + 0.136 \times C + 7.191 \quad (1)$$

where: A is the temperature [°C], B is the binder flow rate [g/min] and C is the drying time [min].

This model quantifies the relationship between process parameters and moisture content, enabling a more precise prediction of moisture levels based on the selected values of temperature, binder flow rate, and drying time. The negative coefficient for temperature (-1.179) indicates that an increase in temperature leads to a significant reduction in moisture content, which aligns with the observation that higher temperatures promote water vaporization. The coefficients for the binder flow rate and drying time (0.029 and 0.136, respectively) suggest that these parameters have a more moderate influence on moisture content, but their impact is crucial to achieve the desired moisture balance in the final product.

When scaling from laboratory-scale production to industrial-scale granulation,

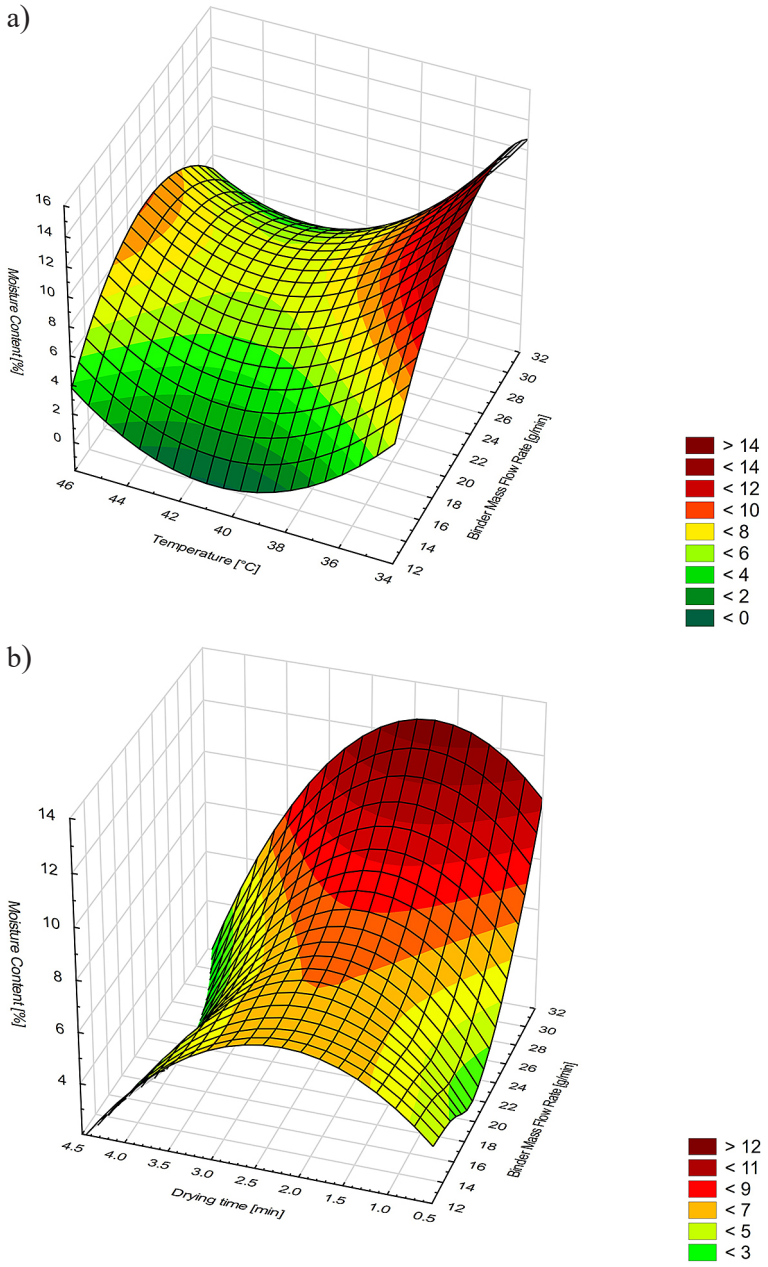

Figure 3. Influence of process parameters on the moisture content of the granules: (a) Effect of the temperature and the mass flow rate of the binder on the moisture content of the granules. (b) Effect of drying time and binder mass flow rate on granule moisture content

maintaining control over moisture content becomes even more critical. The larger equipment and the larger batch sizes involved in industrial production can introduce additional challenges to achieving uniform drying across all granules. Inconsistent drying can result in high-moisture granule pockets, leading to variability in tablet quality. To address this issue, it is essential to implement robust control strategies, such as PAT, which allows real-time monitoring and adjustment of process parameters. By continuously monitoring moisture levels during the granulation process, manufacturers can make immediate corrections to temperature, binder flow rate, or drying time, ensuring consistent moisture content in all granules.

Moreover, the use of design space principles within the QbD framework allows for better prediction and control of moisture content during scale-up. By defining acceptable ranges for process parameters and understanding their interactions, manufacturers can ensure that the granules meet the desired quality attributes, even at larger production scales.

Angle of the repose as an indicator of flowability

The angle of repose is a widely used parameter for evaluating powder flowability [37], which is essential for various pharmaceutical processes, including granulation and tableting. It is defined as the steepest angle at which a pile of granules or powder remains stable without collapsing [38]. A smaller repose angle indicates better flowability, which is crucial for ensuring uniform dosing, consistent tablet weight, and efficient manufacturing operations. In the context of pharmaceutical granulation, improving powder flowability is a primary goal, as enhanced flow properties allow better handling, compression, and overall processing efficiency [39].

The primary objective of the granulation process is to improve the flowability of powders, which is especially important for active pharmaceutical ingredients (APIs) or excipients with poor flow properties. Granulation transforms fine powders into larger, more consistent granules, which exhibit superior flow characteristics as a result of their increased size and reduced surface area interactions. The angle of repose, therefore, serves as a valuable indicator of whether the granulation process has successfully enhanced the material's flowability.

In this study, the static angle of repose was used as a quantitative measure of flowability. The results, presented in Table 6, demonstrate significant variations in flowability between different batches, which can be attributed to differences in process parameters such as binder flow rate, temperature, and drying time. The reference angle of repose for the ungranulated material was 48.7°, indicating poor flowability. This is expected for fine powders, which typically exhibit higher repose angles due to their tendency to form clumps and resist free flow.

Among the batches studied, Batch 9 exhibited the lowest repose angle, which signifies the best flowability. This improved flowability is likely due to the medium granule size (250–500 μm) and the low moisture content. Granules in this size range offer a balance between sufficient cohesiveness and free-flowing properties. The low moisture content further contributed to reduced interparticle cohesion, which allowed the granules to flow more freely and settle at a lower angle when heaped. This combination of optimal granule size and low moisture makes Batch 9 particularly suitable for tablet production, where consistent and smooth powder flow is critical to maintaining uniform tablet weight and quality.

In contrast, Batch 8 showed the highest repose angle, indicating poor flowability. This can be mainly attributed to the high moisture content in this batch. Excess moisture increases the adhesive forces between particles, causing granules to stick together and resist flow. As a result, the granules form steeper heaps, reflected in the higher angle of repose. This highlights the importance of moisture control in the granulation process: Although some moisture is necessary to facilitate granule formation, excess moisture can hinder flowability and compromise the efficiency of downstream processing steps such as tablet compression.

Interestingly, Batch 2 exhibited a relatively high moisture content, but also had the largest granule size, which paradoxically suggested better flowability. Larger granules generally flow more easily than smaller ones, because their size reduces the surface area for cohesive interactions. However, the high moisture content in Batch 2 counteracted some of the benefits of the larger granule size, leading to a moderate angle of repose. This indicates that while the size of the granules is a key determinant of flowability, it must be balanced with other factors, such as moisture content, to achieve optimal results.

The relationship between process parameters and the angle of repose is complex and nonlinear, as illustrated in Figure 4. Several key factors, including temperature, binder flow rate, and drying time, interact to influence the flowability of granules. Higher temperatures tend to promote better flowability by reducing the moisture content and improving the drying of the granules. Similarly, an increase in drying time allows for more thorough moisture removal, resulting in less cohesive granules with improved flow properties.

However, as seen in this study, the binder flow rate also plays a critical role. A higher binder flow rate can lead to the formation of larger, more cohesive granules, which may improve or impair flowability, depending on the balance between granule size and moisture content. Too much binder can result in over agglomeration and higher moisture retention, leading to poor flowability, while too little binder can lead to insufficient granule formation and excessive fines, also compromising flow properties.

The empirical equation developed from multifactorial regression analysis captures these intricate relationships between process parameters and the angle of repose. The model is represented by the following equation:

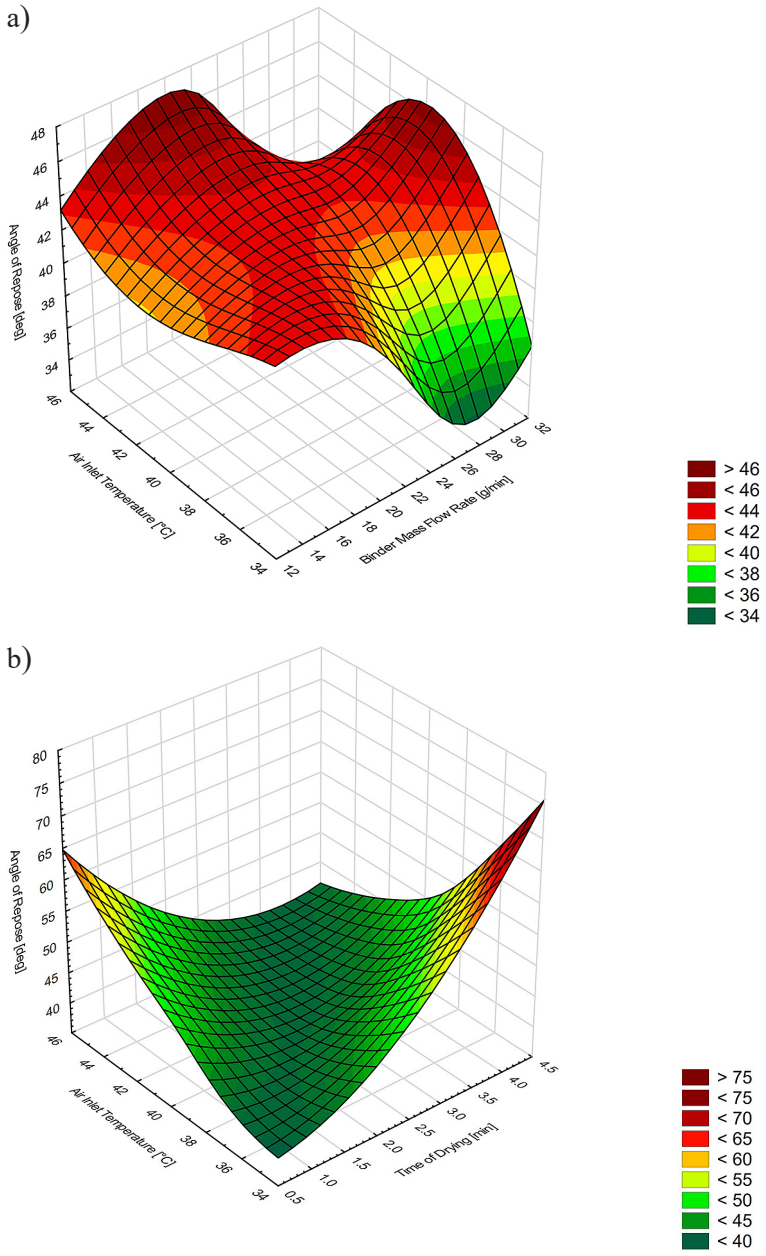

Figure 4. Influence of process parameters on the angle of repose of the product: (a) Effect of the temperature and binder mass flow rate on the angle of repose of the granules. (b) Effect of drying time and temperature on the angle of repose of the granules

$$Angle\ of\ repose = -0.137 \times A + 0.063 \times \times B - 0.183 \times C + 44.452 \quad (2)$$

where: A is the temperature [°C], B is the binder flow rate [g/min] and C is the drying time [min].

In this model, the negative coefficient for temperature (-0.137) suggests that increasing the temperature generally leads to a reduction in the angle of repose, which aligns with the observation that higher temperatures enhance moisture evaporation, resulting in drier and more free-flowing granules. The positive coefficient for the binder flow rate (0.063) indicates that increasing the binder flow rate can increase the angle of repose, likely due to the formation of larger, more cohesive granules that resist flow. The negative coefficient for drying time (-0.183) shows that extended drying times improve flowability by further reducing moisture content, leading to a lower angle of repose.

The control of the angle of repose becomes even more important during the scale-up of granulation processes from laboratory to industrial scale. In larger production settings, maintaining consistent flowability is critical to ensure that granules

are fed smoothly into tablet presses without clogging or jamming. Variability in granule flowability can pose significant challenges in maintaining uniform tablet weight and dosage accuracy.

To ensure consistent flowability during scale-up, manufacturers must carefully monitor and adjust process parameters using advanced PAT. Real-time monitoring of moisture content, granule size, and flowability can help identify and correct deviations from the target angle of repose. By maintaining control over these critical parameters, manufacturers can minimize the risk of flow-related issues during industrial-scale production, ensuring a smooth transition from granulation to tableting.

In addition, the QbD framework plays a key role in optimizing the process parameters that affect the angle of repose. By establishing a design space that correlates temperature, binder flow rate, and drying time with flowability metrics, manufacturers can ensure that the granulation process consistently produces granules with optimal flow properties. This proactive approach to process control improves product quality and reduces the likelihood of variability in the final product.

Influence of granule properties on tablet quality

The granules with a modal size range of 250–500 µm, observed in Batches 3–6 and 8, demonstrated optimal flowability, compressibility, and die-filling properties, leading to consistent tablet mass and stable mechanical strength. Figure 5 illustrates the average tablet mass and standard deviation for all batches. Batches 3–6 exhibited the least variability in tablet mass, while Batch 2, which had a significant proportion of granules > 1 mm, showed the highest mass variability, exceeding the pharmacopoeial limit of 5%. This variability was primarily due to uneven die filling caused by the broad particle size distribution in Batch 2, where larger particles likely hindered uniform compression, affecting tablet mass consistency. Flowability issues were notably observed in Batches 1 and 2. Batch 1, consisting of directly tableted powders, suffered from channeling in the feeder, leading to inconsistent die filling and high weight variability [40]. Similarly, Batch 2, with oversized granules, required sieving to remove particles >2 mm before further processing. This adjustment helped mitigate the mass variability observed in subsequent batches. The regression equation for the average tablet mass, derived from the granulation process parameters, is:

$$\textit{Average tablet mass} = -4.3087 \times A + \\ + 2.0924 + B\ 428.2092 \quad (3)$$

where: A represents the inlet air temperature [°C], and B is the binder mass flow rate [g/min].

The negative relationship between Inlet Air Temperature and tablet mass suggests that higher temperatures may lead to less uniform granule formation, which could negatively impact the weight consistency of the tablets. On the other hand, the positive influence of binder mass flow rate indicates that higher binder rates facilitate the formation of more consistent granules, resulting in a more uniform tablet mass.

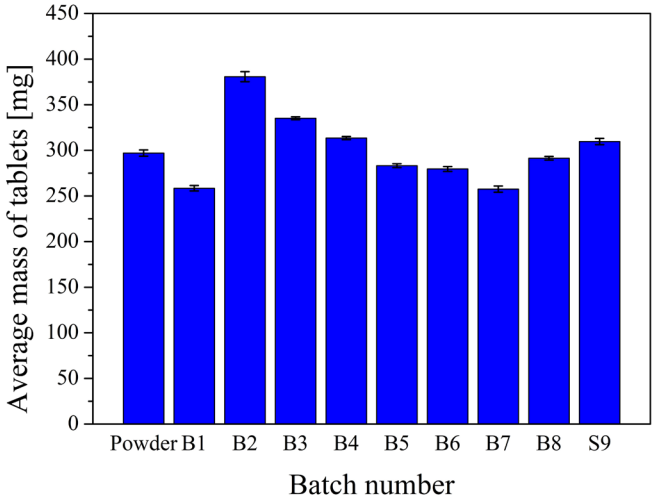

Figure 5. Average mass of tablets

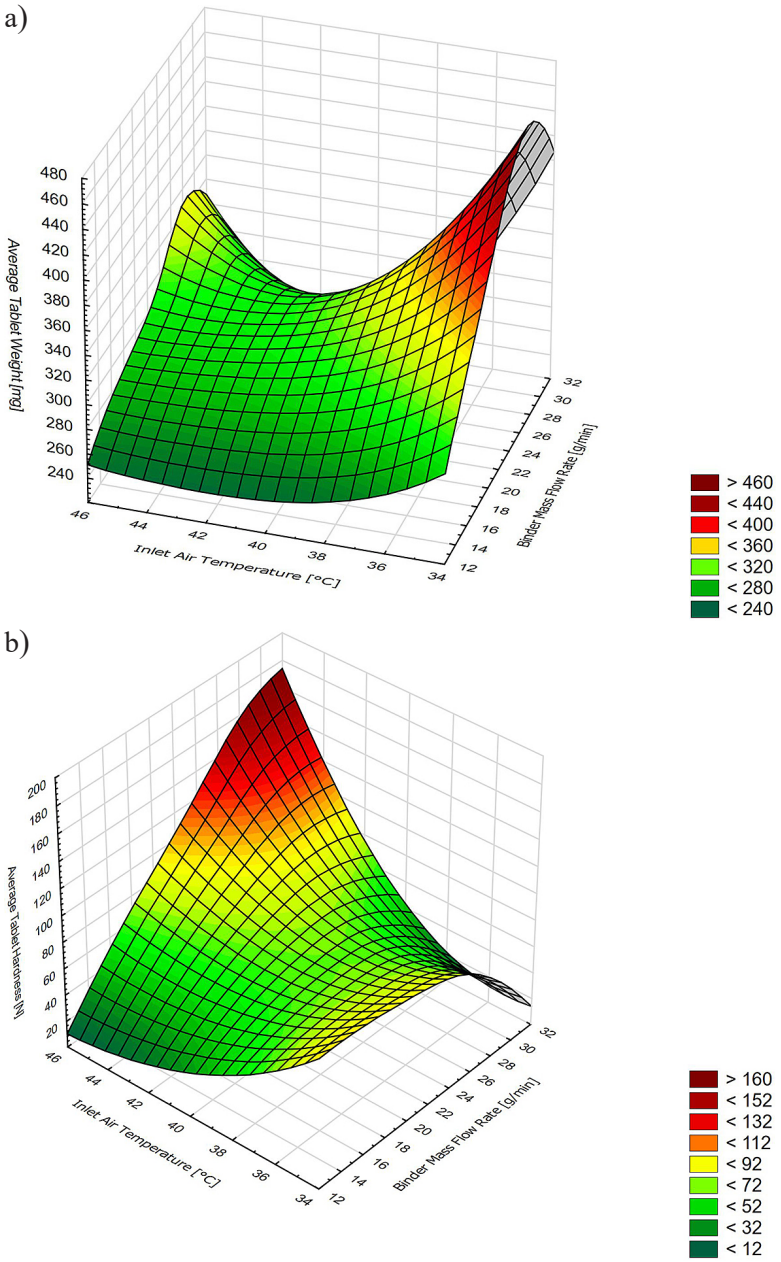

Figure 6. Influence of process parameters on the properties of tablets: (a) Effect of the inlet air temperature, and the binder mass flow rate on the average tablet mass. (b) Effect of the inlet air temperature, and the binder mass flow rate on the average tablet hardness

The response surface analysis in Figure 6a further supports these findings, demonstrating that lower binder flow rates and drying temperatures result in increased variability in tablet mass. This is likely due to the insufficient control over granule growth and moisture content. On the contrary, higher binder flow rates and drying temperatures result in more uniform granules and less variation in tablet mass, highlighting the importance of carefully controlling these parameters during granulation. Tablet hardness, a critical mechanical property, was also strongly influenced by granule characteristics and the applied compression force [41, 42]. Figure 7 presents the average hardness of tablets across all batches. Batch 9 exhibited the highest hardness (145.34 N), which can be attributed to increased compression force and a higher proportion of small granules that enhanced particle bonding and compactness. However, Batch 9 also exhibited significant variability in hardness, likely caused by uneven drying of the granules, which resulted in inconsistencies in the moisture content and the overall uniformity of tablet formation. The response surface analysis in Figure 6b illustrates

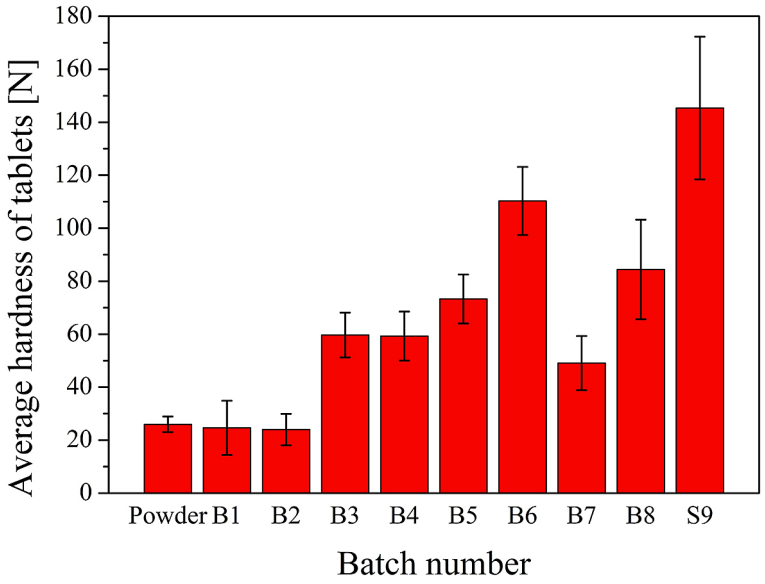

Figure 7. Average hardness of tablets

the impact of granulation and drying parameters on tablet hardness. The analysis indicates that higher binder flow rates and drying temperatures lead to improved hardness by increasing granule cohesion and compactability. These factors likely reduce porosity in the final tablets, resulting in stronger mechanical properties. However, excessive binder flow rates also led to moisture retention within the granules, which in turn negatively affected the uniformity of hardness, likely due to the formation of uneven granules with different moisture contents. The regression equation for the average tablet hardness is:

$$\textit{Average tablet hardness} = 1.9635 \times \\ \times A + 0.2770\, B - 14.5182 \qquad (4)$$

where: A is the Inlet air temperature [°C], and B is the binder mass flow rate [g/min].

The equation suggests that both higher temperatures and binder flow rates generally improve tablet hardness, reinforcing the idea that increasing compression forces and optimizing granule cohesion lead to stronger tablets. However, high binder flow rates could also introduce excessive moisture, which may reduce the uniformity of tablet hardness due to inconsistent granule drying.

The data also indicate a strong relationship between binder flow rates and tablet hardness. As binder flow increases, it likely leads to more uniform granules, improving hardness. This is particularly evident in Batches 5 and 6, where increased binder flow rates resulted in improved tablet hardness, as seen in Figure 5. In contrast, lower binder flow rates and longer drying times, especially for larger granules, negatively impacted tablet hardness by delaying moisture evaporation, which in turn caused inconsistencies in the compression process.

CONCLUSIONS

This study demonstrates the effectiveness of the QbD approach in optimizing fluidized-bed granulation to produce an intermediate product with ideal properties for tableting, thereby ensuring the attainment of optimal tablet quality. Key process parameters (CPPs), such as inlet air temperature, drying time, and binder mass flow rate, significantly influenced granule properties, including particle size distribution, moisture content, and flowability. Granules in the ideal size range of 250–500 µm showed optimal flowability and compressibility, leading to consistent tablet weight and mechanical strength, while larger or more inconsistent granules caused variability in tablet quality. Moisture content was closely linked to process parameters, with higher temperatures and longer drying times resulting in lower moisture levels. Batches with consistent granule size and moisture content exhibited improved flow properties, indicated by lower repose angles, enhancing tableting performance. The use of DOE and FMEA provided a solid framework for controlling these factors, ensuring consistent quality and compliance. Although the study was conducted at the laboratory scale, which may present challenges for industrial-scale applications, the findings underline the importance of process

control. Future research should focus on scaling up the process, integrating real-time PAT, and exploring the interaction of excipients and active ingredients to refine formulation strategies. These steps will further strengthen QbD applications and enhance pharmaceutical manufacturing processes.

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