RESEARCH ARTICLE

Exploring the impact of high shear mixing process parameters on the physical characteristics of excipient powder blend by design of experiments

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Objective: Dry-route manufacturing technology development poses challenges to pharmaceutical technology research specialists, relying on active substance characteristics, excipient selection, and parameter optimization. Amongst various technological possibilities high shear mixing generally ensures dosage uniformity and tablet dissolution through influential shear forces, potentially enhancing dry powder blend processability. This study explores the processability of a placebo formulation within the quality by design framework to address some of the aforementioned challenges.
Methods: A 2^4 full-factorial experimental design was used to assess the manufacturability of a placebo formulation via high shear mixing. The effect of impeller and chopper speed, high shear mixing time, and homogenization/lubrication times on powder blend rheology and compression properties was investigated.
Results: The findings of the present study showed that product critical quality attributes like resistance to crushing or disintegration time are mainly dependent on the mixing efficiency translated by the impeller speed and high shear mixing time. Software augmented process development enabled the attainment of the design space, ensuring the fulfilment of desired product performance criteria. Furthermore, the study has also shown that the careful selection of excipients is crucial in the case of dry-route manufacturing technologies, as sodium lauryl sulphate can noticeably influence the processability of powder blends due to its lubricant properties.
Conclusions: Considering the advantages and challenges raised by high-shear mixing, software aided data analysis can further augment the formulation, scale-up and lifecycle management of products developed using this technological process.

Keywords: placebo, design of experiments, full factorial, manufacturing technology optimization

Introduction

In the development of medicinal products choosing the appropriate manufacturing technology is crucial for the processability and optimal bioavailability of moisture-sensitive and poorly soluble active ingredients. Generic formulations employing dry route manufacturing processes are advantageous in several aspects. First, various excipients are available for these technologies having superior flowability and tableting properties. Second, dry route manufacturing techniques are time and cost effective compared to wet granulation. Lastly, dry route manufacturing is deemed appropriate when unstable, moisture sensitive active pharmaceutical ingredients need to be formulated. Despite its advantages and apparent simplicity, thorough optimization is required to ensure the appropriateness of the critical quality attributes throughout the entire lifecycle of the product.

In modern pharmaceutical research and development, the adoption of computer-controlled experimental designs, such as Design of Experiments (DoE), represents a progressive shift in quality assurance practices. DoE offers numerous advantages over conventional research and development approaches. Whereas traditional experimental designs relied on the "change one factor at time" (OFAT) technique, DoE allows for systematic and multivariate experimentation, leading to a more comprehensive understanding of the manufacturing processes and products. Moreover, it enables the identification of parameter settings and limits that ensure product quality [1, 2].

One key aspect of manufacturing technologies for moisture-sensitive and poorly soluble APIs is the selection of suitable processing methods and excipients to protect the API from moisture-induced degradation and enhance its solubility [3]. Dry granulation techniques, such as roller compaction [4, 5], and direct compression [6] are commonly used to minimize moisture exposure during processing. These methods involve compressing the API and excipients into granules or tablets without the need for wet granulation, reducing the risk of moisture uptake and degradation. Furthermore, advanced manufacturing technologies, such as hot melt extrusion and spray drying, offer alternative approaches for formulating poorly soluble APIs [7–9].

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The utilization of high shear mixing in the processing of moisture-sensitive active pharmaceutical ingredients represents a strategic approach to overcome formulation challenges while maintaining product stability and efficacy. This versatile technique is advantageous as it facilitates rapid and efficient blending of the ingredients promoting a better dispersion of not only the API but also functional excipients, thus ensuring consistency in product quality and performance by minimizing variations in material properties. Moreover, the intense shear forces generated during mixing can aid in particle size reduction and deagglomeration, improving powder flow properties and dissolution rates, enhancing not only the manufacturability of the product but also contributing to its bioavailability and efficacy [10–12].

The primary objective of this study was to examine the impact of formulation variables during high-shear mixing on the production feasibility of a placebo formulation designed to incorporate water-sensitive active pharmaceutical ingredients. Moreover, our objective was to perform experiments following the quality by design approach, aiming to comprehensively examine the impacts and interplays of impeller and chopper speed, high shear mixing time, and homogenization/lubrication time on the rheological and compression properties of the powder blend.

Methods
Materials
Laboratory scale batches incorporated Lactose, anhydrous, Supertab 22AN® (DFE Pharma, Goch, Germany) as filler; Hydroxypropyl cellulose, L-HPC, LH-11® (Shin-Etsu Chemical Co. Ltd, Tokyo, Japan) as binder; Croscarmellose Sodium, Disolcel® (Mingtai Chemical Co. Ltd, BahDer City, Taiwan) as disintegrant; Sodium lauryl sulphate (Kao Corporation S.A, Barbera Del Valles, Spain) as wetting agent; and Glyceryl dibehenate, Compritol 888 ATO® (Gattefossé, Lyon, France) as lubricant. All materials were of Ph. Eur. grade, compliant with their compendial monographs in the 11th Edition of Ph. Eur.

Pharmaceutical formulation and manufacturing technology
Table I presents the qualitative and quantitative composition of the investigated pharmaceutical formulation. Half of the quantity of Lactose, anhydrous (Supertab 22AN®) and Sodium lauryl sulphate were manually sieved through

Table I. Qualitative and quantitative composition of the placebo powder blend

Components	Quantity (g / batch)	Quantity (% / batch)
Lactose, anhydrous (Supertab 22AN®)	513.0	85.5
Hydroxypropylcellulose (L-HPC, LH-11®)	36.0	6.0
Croscarmellose sodium (Disolcel®)	30.0	5.0
Glyceryl behenate (Compritol 888 ATO®)	18.0	3.0
Sodium lauryl sulphate	3.0	0.5
Total	600.0	100.0

a 1.0 mm mesh size. The resulting mixture was loaded manually into the Glatt TMG 1/6 high-shear mixer-granulator (Glatt GmbH, Binzen, Germany) and mixed according to the predetermined duration and rotation speed specified by the experimental design (High shear mixing phase I). In the subsequent step, the remaining quantity of Lactose, anhydrous (Supertab 22AN®), and Hydroxypropyl cellulose (L-HPC, LH-11®) were added to the mixture and similarly mixed according to the predetermined duration and rotation speed (High shear mixing phase II). The resulting powder blend was homogenized with Croscarmellose sodium (Disolcel®) in the Erweka AR402 double cone mixer (Erweka GmbH, Heusenstamm, Germany) and subsequently lubricated with Glyceryl dibehenate in the same system. Finally, the resulting powder blend was compressed into round, biconvex tablets with a diameter of 10 mm using the RIVA Piccola D8 rotary tablet press (Riva Ltd. Hampshire, United Kingdom).

In-process control
The flow-out time and bulk density of powder mixtures were measured using a Pharmatest PTG S4 powder testing system (Pharma Test Apparatebau AG, Hainburg, Germany). Tablet disintegration time was recorded using a Pharmatest PTZ AUTO 1EZ Single Position Semi-Automated Disintegration Testing Instrument (Pharma Test Apparatebau AG, Hainburg, Germany). Tablet physical properties, i.e. resistance to crushing was determined using a Pharmatest PTB-411 E tablet testing system (Pharma Test Apparatebau AG, Hainburg, Germany).

Risk assessment
A comprehensive risk analysis was undertaken prior to conducting the experimental trials at laboratory scale to ground the chosen parameters for testing based on previous knowledge and literature data. Ishikawa diagram and Failure Mode and Effects Critical Analysis were employed as risk assessment methods.

Design of Experiments
A full factorial design of experiments was built using MODDE 13.0 software (Sartorius Stedim Data Analytics AB, Göttingen, Germany), with three replicated centre points. Within the design of experiments, the influence of impeller (X1) and chopper (X2) rotation speeds and time of high shear mixing phases (X3 – High shear mixing phase I + II) were included to characterize the mixing phase. Furthermore, the impact of Homogenization + Lubrication times (X4) were assessed in the experimental design. The obtained lubricated mixtures were compressed to tablets at 10 kN, using round, Ø = 10.0 mm, biconcave punches. Powder and tablet physical characteristics were analysed for rheological properties in terms of flow-out time (Y1) and bulk density (Y2). The obtained tablets were characterized based on resistance to crushing values (Y3) and tablet disintegration time properties (Y4). Model factor settings

and responses are included in Table II. The experiments were conducted based on a random list recommended by the computational software (Supplementary Table I).

Data Analysis
The experimental model was evaluated from the perspective of the model performance indicators by calculating the goodness of fit (R^2), goodness of predictability (Q^2) of the fitted model and model validity and reproducibility. The impact of input factors was assessed through the creation of coefficient plots, which unveiled the significance, magnitude, and direction of the exerted effects. Model performance was assessed by ANOVA F-tests for model significance and lack-of-fit. The computation of the design space, or the range of factor combinations that yield the desired quality profile aimed to pinpoint a robust formulation. Through the utilization of fitted polynomial models and Monte Carlo simulations, the experimental region was charted in relation to the probability of failure, quantified as a percentage (%). An acceptance threshold for the probability of failure was established at 1%.

Technological Process Optimization
Following the evaluation of the results, two laboratory scale batches were manufactured with specific process parameter settings taking into consideration the robust setpoint given by the software. Model performance was evaluated by the predicted vs. observed results obtained.

Results
Risk assessment
The performed risk assessment revealed that process parameters such as impeller and chopper rotation speed, homogenization/lubrication times and tablet compression might be considered as critical process parameters for the assessment of the performance of the manufacturing technology. The created Ishikawa diagram is presented in Supplementary Figure 1.

Data analysis
The results for selected responses from the manufactured batches are detailed in Supplementary Table I. The constructed design demonstrated suitability with a condition

number of 1.06 and the model was fitted with the partial least squares (PLS) regression method. Performance indicators of the model, including goodness of fit (R^2) values ≥ 0.50, indicated a strong fit, while goodness of predictability (Q^2) values surpassed 0.80 apart from Y1. Flow-out time (Y1) presented a relatively non-significant model indicating that this response is unaffected by different input variations ($p = 0.075$). The reproducibility of the model was notably high, exceeding the required limit of 0.5 and reaching values > 0.99 for parameters such as bulk density (Y2) and resistance to crushing (Y3). Driven by this high reproducibility (low pure error inside the model), model lack-of-fit was detected for these responses, $p = 0.022$ and $p = 0.018$ for bulk density and resistance to crushing, respectively. Model validity indicators were acceptable for flow-out time and disintegration time, although they fell below the required threshold of 0.25 for resistance to crushing and bulk density. The statistical descriptors of the model performance indicators are presented in Figure 1.

Flow-out time
None of the individual factors assessed had a significant effect on the flow-out time (Figure 2a) of the powder blend ($p > 0.05$). Among the interactions, the impeller rotation speed and the high shear mixing time (X1*X3) presented a slight positive correlation with the flow-out time ($p = 0.074$).

Bulk density
Contrary to the flow-out time, the bulk density of the powder blends was significantly influenced by most of the factors assessed ($p < 0.05$) and a positive correlation was observed in all cases (Figure 2b). Chopper speed did not exhibit a noteworthy impact on bulk density.

Resistance to crushing
The tablet hardness values showed a strong inverse proportional relationship with the rotation speed of the impeller as well as high shear mixing time ($p < 0.001$). Homogenization and lubrication times also influenced in a noteworthy manner ($p = 0.024$) the resistance to crushing of tablets (Figure 2c).

Table II. List of examined process parameters and selected responses

FACTORS					
Factor name	Abbreviation	Unit		Settings	
Impeller rotation speed	X1	rpm		50 - 550	
Chopper rotation speed	X2	rpm		300 - 2100	
High shear mixing time	X3	sec		(36+24) - (324+216) [a]	
Homogenization and lubrication time	X4	sec		(72+36) - (648+324) [b]	
RESPONSES					
In-process control	Abbreviation	Unit	Min	Target	Max
Flow-out time	Y1	sec	-	25	60
Bulk density	Y2	g mL^{-1}	40	60	70
Resistance to crushing	Y3	N	60	80	120
Disintegration time	Y4	sec	-	180	900

a Indicates the high shear mixing time of the two phases (High shear mixing I + II), b indicates the time of subsequent blending steps (Homogenization + Lubrication time)
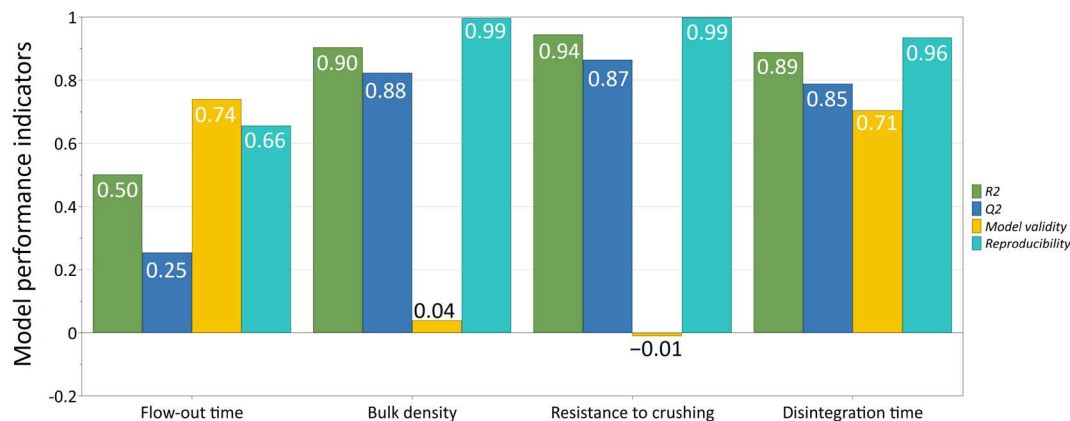
Fig. 1. Illustration of model performance indicators for the selected responses of the experimental design

Disintegration time

Likewise resistance to crushing, the disintegration time exhibited a significant and negative correlation with the individual factors (Figure 2d), particularly with the Impeller rotation speed (X1) and the High shear mixing time ($p <$ 0.001). The interaction (X1*X3) of these factors were also considered to significantly impact the disintegration time of the resulted tablets. Besides high shear mixing, homogenization and lubrication times had a relevant impact on disintegration time ($p = 0.028$). For this response chopper rotation speed showed a tendency towards significance ($p = 0.085$).

MODDE based optimization

4D design space was obtained for the selected responses where the parameter settings ensured the optimal critical quality attributes of the tested product (Figure 3a).

Assessment of the generated design space was conducted by manufacturing two validation batches at laboratory scale. In the first experiment, the impeller speed was set

to 200 rpm and the centre points for high shear mixing time (300 sec) and homogenization/lubrication time (540 sec) were chosen (Validation batch 1). In the second experiment, the high shear mixing, and homogenization/lubrication times were doubled to 600 sec and 1080 sec, respectively (Validation batch 2). The main scope to conduct an experiment outside the experimental domain was to further elucidate the magnitude of impact of impeller speed in contrast to high shear mixing time and homogenization/lubrication time on product critical quality attributes. Since preliminary experiments revealed that the chopper has no impact on the powder blend and tablet properties, the setting of 1200 rpm was maintained for this process parameter. The predicted response profile for Validation batch 1 (Figure 3b) indicated that the selected process parameters would resolve in a probability of failure of 0.38% and 0% for resistance to crushing and disintegration time, respectively. In contrast, doubling of the high shear mixing and homogenization/lubrication times (Validation batch 2, Figure 3c) would remarkably increase the
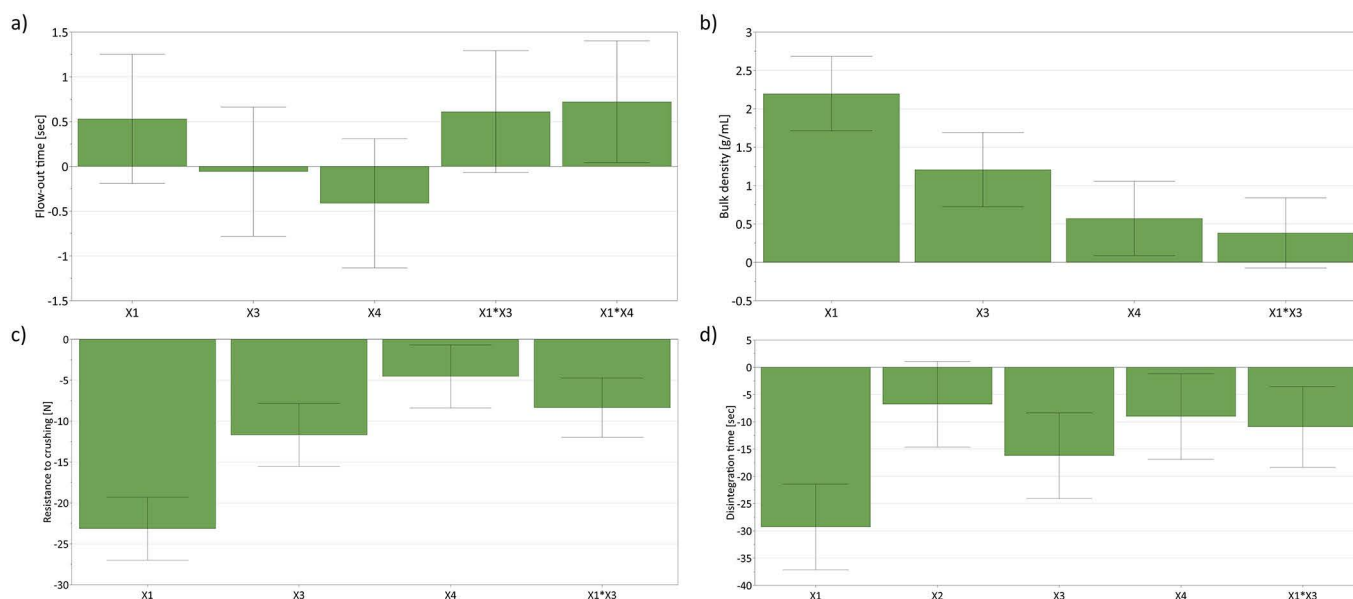

Fig. 2. a) Factors influencing the flow-out time of the powder mixture. b) Factors influencing the bulk density of the powder mixture. c) Factors influencing the resistance to crushing of tablets. d) Factors influencing the disintegration time of tablets. X1 – Impeller rotation speed, X2 – Chopper rotation speed, X3 – High shear mixing time, X4 – Homogenization and lubrication time

probability of failure of resistance to crushing from 0.38% to 20%, which inherently will impact disintegration time as well. The predicted vs. observed results for the optimized setpoints are summarized in Table III.

Discussions

The experimental design conducted to evaluate the physical properties of the tested pharmaceutical formulation yielded favourable model performance indicators. The R^2 values were acceptable, showing a good fit of the model. However, relying solely on R^2 is inadequate. Q^2, a better measure of predictability, should not differ by more than 0.25 from R^2. The model performed well for bulk density, resistance to crushing, and disintegration time but less so for flow-out time. The flow-out time (Y2) exhibited a narrow range of 20 to 25 seconds across experiments and appeared unaffected by the tested factors. This suggested that regardless of parameter adjustments, significant variability in powder flow-out time was not captured by the model.

Additionally, the ample quantity of filler, particularly Supertab 22AN®, in the formulation might have played an important role. The particle size distribution of this excipient, provided by the manufacturer, indicates large particle sizes (X10 = 70 μm, X50 = 220 μm, X90 = 380 μm) [13]. This, coupled with its high proportion in the pharmaceutical composition (85%), has contributed to the excellent flowability of the powder blend, irrespective of process parameter variations. Such pharmaceutical behaviour is desirable for high-yield manufacturing, as optimal powder flowability is crucial for consistent die filling and uniform tablet compression processes. The crucial impact of flowability on further product processing was also elucidated by Tang et al. Their findings evidenced that material properties, particularly powder flowability, influence filling performance and fill weight consistency [14].

The finding that the bulk density of the powder mixtures was predominantly affected by the impeller speed (X1), high shear mixing time (X3), and homogenization/
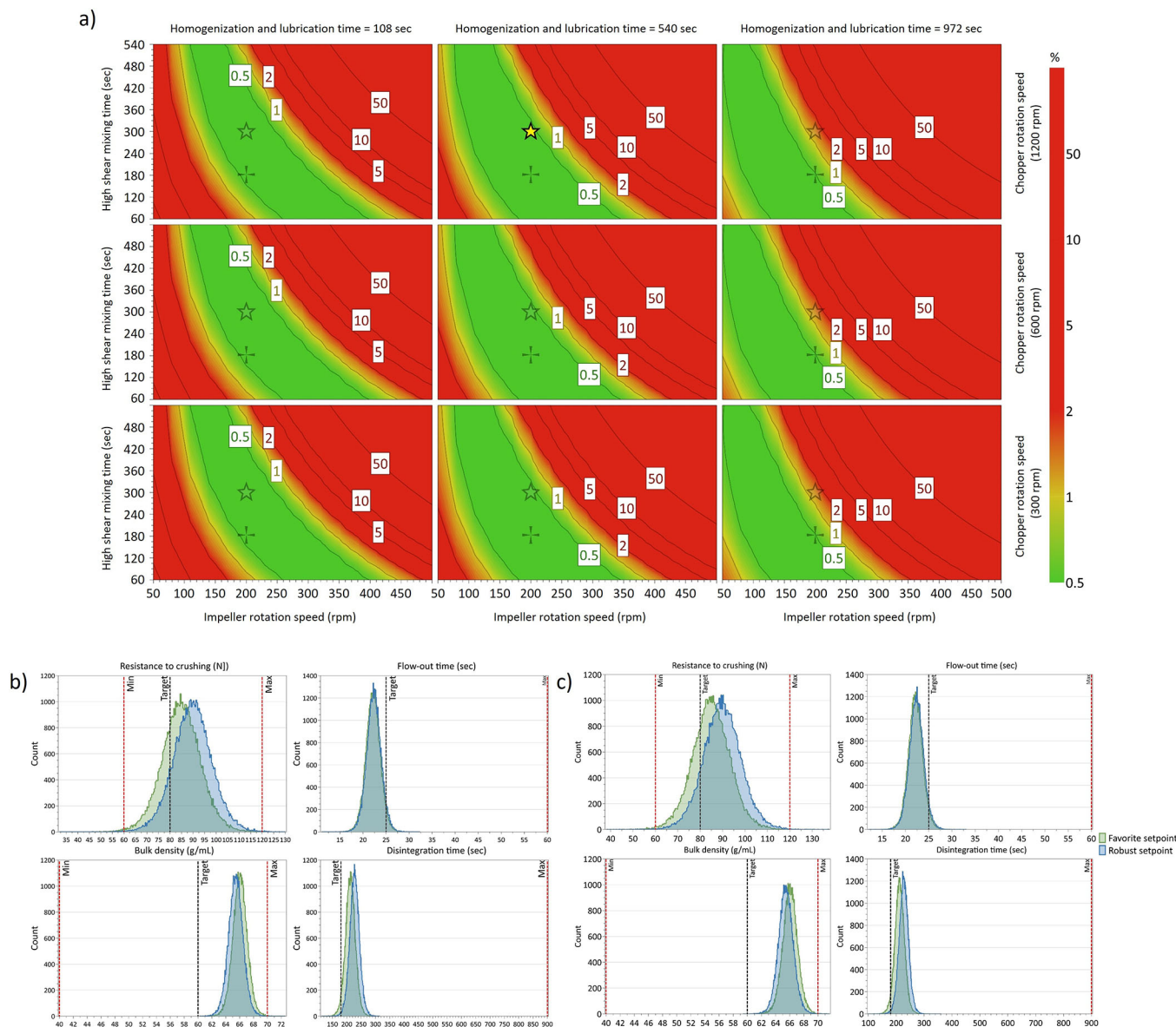

Fig. 3. a) Design space plot. + - robust setpoint ★ - validation batch 1. b) Setpoint comparison of robust setpoint and validation batch 1 setpoints. c) Setpoint comparison of robust setpoint and validation batch 2 setpoints

Table III. Summarizing table of predicted vs. observed results of validation batches

Model factors and responses		Validation batch 1	Validation batch 2
Factors	X1	200	200
	X2	1200	1200
	X3	300	600
	X4	540	1080
Responses	Y1-P	22.7 (21.3-22.8)	20.7 (19.3-22.3)
	Y1-O	21.0	22.0
	Y2-P	65.9 (65.5-66.5)	68.1 (67.0-69.0)
	Y2-O	66.6	68.4
	Y3-P	86.5 (82.4-90.6)	69.7 (61.2-78.2)
	Y3-O	84.1 (75.6-92.1)	72.2 (65.6-80.2)
	Y4-P	218 (206-231)	183 (163-205)
	Y4-O	221 (211-245)	207 (183-239)

X1 – Impeller rotation speed, X2 – Chopper rotation speed, X3 – High shear mixing time, X4 – Homogenization and lubrication time, Y1 – Flow-out time,
Y2 – Bulk density, Y3 – Resistance to crushing, Y4 – Disintegration time, P – predicted, O – observed.

lubrication times (X4) underscores the significance of process parameters in shaping the physical attributes of pharmaceutical formulations. Elevating the impeller rotation speed was likely to help blending efficiency by fostering a higher particle attrition, thereby resulting in increased bulk density. Likewise, prolonging the duration of high shear mixing and homogenization/lubrication stages facilitated more thorough dispersion and uniform distribution of excipients and active compounds, leading to denser powder mixtures. This positive relationship between process variables and bulk density underscored the critical role of process optimization in attaining desired product qualities and ensuring manufacturing consistency. Furthermore, these findings pinned out the importance of precise adjustment and control of processing conditions to attain optimal powder characteristics, which ultimately would contribute to the quality and effectiveness of the final pharmaceutical formulations.

The model performance indicators for resistance to crushing (Y3) were similar to those observed in the case of bulk density. This observation indicated that tablet resistance to crushing is highly dependent on the bulk density of the compressed powder blend and having in focus the tested factors an inverse proportionality was obtained for Y3 and Y2. While bulk density showed a direct proportionality with X1, X3 and X4 in the case of resistance to crushing these factors negatively influenced this response. This phenomenon was attributed to several underlying mechanisms. Generally, the mechanical resistance of a material is affected by particle size as smaller particles provide a larger contact surface area available for bonding during compression, enhancing strength [15, 16]. Furthermore, extended lubrication times might lead to excessive coating of excipient particles with lubricant, which can interfere with interparticle adhesion and decreased tablet compaction [17].

Theoretical explanations were sought to understand the rationale lying behind the observed phenomenon that higher impeller speeds yield in lower resistance to crushing values and implicitly lower disintegration times. One interesting aspect was associated with the addition of sodium lauryl sulphate in the high shear mixing phase. Besides its role as wetting agent, sodium lauryl sulphate also possesses lubricant properties [18]. This effect is acknowledged from 0.5% [19] in tablet formulation and was assessed up to 5% according to literature data [20]. Furthermore, it is also known that functionality related characteristics of lubricants [21] as well as process times (e.g. lubrication time) [22] can impact the critical quality attributes of tablets. Therefore, it is considered that over-lubrication of the powder mixture with sodium lauryl sulphate might contribute to the impact of impeller rotation speed on product performance indicators. Moreover, this pharma-technological impact of sodium lauryl sulphate is also noticeable in the case of bulk density. As shown in Figure 2b. higher impeller speed yields higher bulk density. In the light of the lubricant properties of sodium lauryl sulphate in the case of higher impeller speeds an improved distribution of this excipient is achieved, leading to a more reduced friction between particles resulting in higher bulk density. This observation also highlights the importance of choosing the proper manufacturing technology, process steps and excipients in pharmaceutical formulations.

Finally, disintegration time (Y4) was the response that resulted in the best model performance indicator values. Not only that R^2 and Q^2 value were appropriate but both model reproducibility and validity were well above the thresholds for these indicators. These results were particularly important as model fitting and prediction are crucial for achieving a disintegration time which ensures proper release of the incorporated active pharmaceutical ingredients. Similarly to resistance to crushing the disintegration time was also negatively influenced by the speed of the impeller and mixing times (high shear mixing or homogenization / lubrication phase), which also impacted in a significant manner this response (Figure 2c, 2d).

The 4D design space (Figure 3a) revealed the optimal settings for the investigated factors. Optimal setpoints for the impeller rotation speed is encompassed between 200 and 400 rpm as high shear mixing time should be carefully selected for impeller speed settings. In the lower region of these parameters the probability of failure exceeds the threshold of 1% as it is expected that tablets with relatively high resistance to crushing are obtained, which would re-

sult in prolonged disintegration time and putatively altered API dissolution. On the other end, high impeller speeds combined with lengthened mixing times would result in improper resistance to crushing that would hinder the further processing of the pharmaceutical product whether it be film-coating or primary packaging. Moreover, at both extremes of the design space, the significant influence of sodium lauryl sulphate is reflected in the crucial quality attributes of the final product. At lower impeller rotation speeds the lubricant effect is less pronounced as such higher tablet resistance to crushing was achieved and on the contrary at high impeller rotation speed as well as prolonged blending times the over-lubrication of particles would have resulted in reduced tabletability and lower tablet resistance to crushing.

The optimization of the manufacturing technology has underlined the predictive capacity of the developed models. Parameter setting showing differences only in mixing and homogenization / lubrication times had similar predictions and the final, observed results were closely obtained to those predicted. This observation has further indicated that the impeller speed was the most important variable that influenced the manufacturing technology and pharmaceutical product performance and that by extending the mixing times lower resistance to crushing values are obtained.

Conclusion

High shear mixing plays a pivotal role in addressing the formulation challenges associated with downstream processability of different powder blends. Our findings have shown that process parameters such as impeller speed or different mixing times can critically influence the physical properties of powder blends. The experimental design built for this purpose was able to find factor to response impacts and to elucidate the direction and magnitude of these relationships. Besides the advantages related to these aspects, the development of a design space and the investigation of model predictive performance has shown the importance of software aided solutions in modern pharmaceutical research and development. Another aspect of the present study elucidates the importance of careful selection of excipients and manufacturing process steps and order for material addition. The inclusion of sodium lauryl sulphate from the early phases of the manufacturing process, i.e. high shear mixing has highlighted the lubricant properties of this excipient. As such the dual effect of excipient properties and process parameter settings, i.e. impeller speed and high shear mixing time, impacted in a critical manner tablet properties such as resistance to crushing and disintegration time both confining the fate of pharmaceutical products.

The 4D design space identified optimal settings for impeller rotation speed and mixing time, crucial for achieving desired tablet properties. At lower impeller speeds, tablets exhibited higher resistance to crushing, potentially prolonging disintegration time, while at higher speeds, improper resistance to crushing could hinder further processing. Additionally, sodium lauryl sulphate's significant influence on product quality attributes was evident across the design space, impacting tablet lubrication and resistance to crushing.

Although the present study has its limitations regarding the testing of the pharmaceutical formulation with an active pharmaceutical ingredient, it managed to elucidate some noteworthy aspects regarding the importance of addressing the compositional and technological challenges of high shear mixing and the utility of the design of experiments framework in the augmentation of these decisions.

Authors' contribution

BK (Conceptualization, Investigation, Methodology, Writing – original draft), EOT (Data curation; Formal analysis, Writing – original draft), ÉKK (Project administration; Resources, Supervision, Writing – review & editing), KZ (Project administration; Resources, Supervision, Writing – review & editing), ES (Investigation, Data curation; Formal analysis), BKD (Data curation; Formal analysis, Writing – original draft), ISzSz (Conceptualization, Investigation, Writing – original draft), FB (Data curation; Formal analysis, Writing – review & editing), TC (Methodology, Formal analysis, Writing – review & editing).

Acknowledgments

Conflict of interest

None to declare.

Funding

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