RESEARCH ARTICLE

Optimization of Slugging and Compression Process for Bicalutamide Tablets

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ABSTRACT

The critical nature of pharmaceutical dosage forms necessitates the optimization of manufacturing process variables to achieve the desired product quality. In this study, slugging (Dry granulation) was selected as an appropriate granulation method to mitigate poor flow properties in the final bicalutamide blend. The chosen process variables include slug hardness, mill screen size, and mill speed. A 2^3-factorial design was employed to investigate these variables. Process parameters were reproducible, with minimal impact on tablet properties, even when roller speeds varied. Response surface models effectively examine the relationship between response variables and quantitative parameters. The input and process variables for the compression process were predetermined based on the desired quality attributes of bicalutamide tablets. Notably, the *p-value* for the slugging process was not more than 0.05, indicating their insignificance in tablet content uniformity. Product quality attributes affected by the compression process step include content uniformity, disintegration time, and dissolution. The optimal hardness range was found to be 2.0 to 7.0 kp.

Keywords: Bicalutamide tablets, Factorial design, Slugging process, Dissolution, Content uniformity.

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INTRODUCTION

Drug delivery system optimization using factorial design[1-6] is a systematic approach for assessing the impact on the response variable in product and process development. While the slugging (dry granulation) process is well-established in pharmaceutical manufacturing,[7] its independent variable parameters have undergone optimization. Among these parameters, the roller speed of the mill plays a critical role in dry granulation. Identifying critical process parameters (CPP) during dry granulation (milling)[8,9] is essential. In the pharmaceutical industry, the initial objective is to establish baseline operating parameters that ensure compatibility and reproducibility. Additionally, there is a need for rapid parameter optimization in custom application environments, which may change over time. Our work explores the optimization of parameters for dry granulation in pharmaceutical manufacturing, considering factors such as compatibility, reproducibility, and supportive data. This aligns with the industry's current emphasis on the factorial design approach as part of quality by design (QbD).[10,11]

MATERIALS AND METHOD

Materials

Bicalutamide was obtained as a gift sample from AARTI Pharma Labs. Anhydrous lactose (Super Tab 21 AN) (DMV International), maize starch (C☆PharmGel) (Univar Solution), sodium starch glycolate (Primojel/Type A) (JRS Pharma), colloidal silicone dioxide (Aerosil 200) (Cabot Sanmar) Talc (Luzenac), magnesium stearate (Ferro/Peter Grevens) were used as received.

Dissolution Method

Bicalutamide tablets 50 mg dissolution was determined as per the USFDA, dissolution database. Dissolution testing apparatus II fitted with paddles. The dissolution test was carried out with 1000 mL of 1% sodium lauryl sulfate (SLS) in water kept at 30 ± 0.5°C and 50 rpm.

Content Uniformity

Content uniformity was assessed through the uniformity of dosage test using analytical grade reagents. High-performance liquid chromatography with a C18 column, a flow rate of 2 minutes, and a gradient method at 275 nm with a UV detector was employed.

Experiment

Sifting and blending

- Bicalutamide, lactose anhydrous (Super Tab 21 AN), Maize Starch (C☆PharmGel), and sodium starch glycolate (Primojel/Type A) were sifted through a 40 mesh.

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- Blend these sifted ingredients in an octagonal blender for 30 minutes.
- Colloid talc was sifted through a 100 mesh, and colloidal silicon dioxide (Aerosil 200) was sifted through a 40 mesh.
- Add these sifted excipients to the above blend and blend for 15 minutes in an octagonal blender.

Compression

- Magnesium stearate sifted through a 60 mesh was transferred to a blender.
- Lubricate the blend for 5 minutes.
- Compress the lubricated blend using 9.0 mm punches at a target weight of 135 mg, achieving a hardness range of 6.5 to 8.5 kp.

Milling and sifting

- Mill the slugs through a 10.0 mm S.S. screen, slow speed, knives forward, using a comminuting mill.
- Sift the milled material through a #20 mesh, collecting oversize granules.
- Repeat the same process using 8.0 mm, followed by 2.5 mm, and then 1.5 mm S.S. screens.

Final steps

- Sift talc through a 60 mesh.
- Mix the sifted talc with the above blend in an octagonal blender for 10 minutes.
- Sift magnesium stearate through a 60 mesh and lubricate an octagonal blender for 5 minutes.
- Compress the final lubricated blend with 9.0 mm punches at an average weight of 128.0 mg.

Experimental Design

Design Expert 8 software is used for the present study. A simple formulation is taken and used on the different screen sizes of the mill speed of the mill and optimization of the process. Factorial design is done to find out significant factors speed of the mill. Dry granulation process optimization was done through design space and, based on that, optimized the slugging & milling process. There are two main experimental objectives for which DoE can be used; those are screening and optimization.

RESULT

A 2^3-factorial study was conducted, and the results are summarized in Table 1. In this study, three independent variables were considered: slug hardness, screen size, and roller speed. These variables were tested at two levels (high and low). The study involved two replications of eight experiments each. The optimization process prioritized significant factors and leveraged the experience gained from other dry granulation processes for product development. The generated models exhibit a linear response, and the design also accounts for the three-factor interaction effects observed during individual tests.

During the screening phase, the experimental plan and the run matrix are provided by the factorial design strategy. Additionally, Table 2 provides details about the characteristics and retention of bicalutamide granules across different sieve sizes.

Table 1: Summary of optimization study of slugging and milling process

Batch No.	*Hardness of the slug*	*The screen size of the mill (mm)*	*Speed of mill*	*Content uniformity (%)*
BCT-001MOS-22	8	5	High (1500 RPM)	100.03 (AV:4.45)
BCT-002MOS-22	9	8	Slow (850 RPM)	95.15 (AV: 6.20)
BCT-003MOS-22	9	5	High (1500 RPM)	100.45 (AV: 5.25)
BCT-004MOS-22	8	8	Slow (850 RPM)	98.75 (AV: 8.23)
BCT-005MOS-22	7	5	High (1500 RPM)	99.03 (AV:4.80)
BCT-006MOS-22	9	8	Slow (850 RPM)	101.25 (AV: 3.65)
BCT-007MOS-22	8	5	Slow (850 RPM)	100.25(AV: 2.05)
BCT-008MOS-22	2	8	High (1500 RPM)	95.75 (AV: 6.75)

Table 2: Granules characteristics

Batch No.	*Bulk density (g/cc)*	*Tap density (g/cc)*	*Response studies*					
			Retention on on # 20(%)	*Retention on # 40 (%)*	*Retention on # 60(%)*	*Retention on # 80% (%)*	*Retention on # 100 (%)*	*Pass through # 100 (%)*
BCT-001MOS-22	0.613	0.935	0.000	15.365	12.800	11.840	6.340	43.350
BCT-002MOS-22	0.612	0.907	0.000	6.660	14.150	12.176	9.260	47.350
BCT-003MOS-22	0.645	0.967	0.000	15.250	15.990	6.980	7.850	47.380
BCT-004MOS-22	0.625	0.967	0.000	8.660	17.120	10.990	9.260	43.670
BCT-005MOS-22	0.652	0.962	0.000	9.270	15.200	8.500	8.670	44.850
BCT-006MOS-22	0.652	0.935	0.000	18.248	11.500	21.500	7.500	53.500
BCT-007MOS-22	0.625	0.965	0.000	1.800	11.800	20.500	8.500	51.500
BCT-008MOS-22	0.610	0.981	0.000	12.200	11.750	12.500	8.000	51.335

Table 3: Effects of process variables

Variables	*Effects*
	Tablets CU (%)
Main effects	
Hardness of the slug (kp)	-0.325
Screen size (mm)	2.045
Mill speed (rpm)	0.160
Hardness of the slug (kp)* Screen size (mm)	1.500
Hardness of the slug (kp)* Mill Speed (rpm)	-0.495
Screen size (mm)* Mill Speed (rpm	-2.435

Note: Negative or positive information about whether the impact of the variable on response is positive or negative.

Statistical Analysis

The Pareto chart demonstrates the impression of bicalutamide tablet formulation process variables on tablet content uniformity (%). The assessed effects for each term are summarized in Table 3.

Additionally, the main effect plot showcases how formulation variables influence tablet content uniformity within the study.

Furthermore, the tablet content uniformity (Acceptance Value) remains below 9.0 for the studied range of variables. Consequently, we can conclude that the selected variables within this range have no significant impact on tablet content uniformity (Acceptance Value).

Although the interaction plot expresses second-order interactions among all the variables, none of these interactions exhibit a significant impact on the response (Tablet Content Uniformity). However, it's worth noting that if the range of studied variables were increased, there might be a significant impact of interactive variables on tablet content uniformity.

Model Evaluation

A mathematical model was assessed using statistical terminology, as outlined in Table 4. Here are the key findings:

- The *p-value* for the slugging process is less than 0.05, indicating that these factors are insignificant for tablet content uniformity (Acceptance Value).
- The range of slug hardness studies was 2 to 9 kp. Within this range, the tablet content uniformity acceptance value remains below 9.0 for the studied variables.
- Consequently, we can conclude that the selected range will not significantly impact the critical quality attributes (CQA) of the bicalutamide tablet.

Design Space

The data from the factorial design indicates that experimental runs conducted within a selected range did not exhibit any impact on CQA. Consequently, this chosen range is a design space in which any alterations do not affect the critical quality attributes of drug products.

Tablet Compression Process Optimization

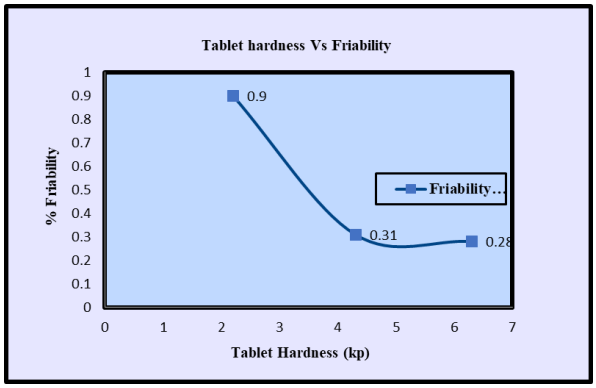
The input and process variables for the compression process were predefined based on the desired quality attributes of the bicalutamide tablet. Compression stage and in-process checks were closely monitored, including the uniformity of weight, hardness, thickness, and friability.

The product quality attributes that would be affected by the compression process step include assay, content uniformity, disintegration time, and dissolution.

Tablet hardness

The tablet hardness is considered potentially critical because it directly affects several key parameters, including friability, disintegration time, and, subsequently, dissolution of the drug. To explore this impact, three experiments were conducted at a laboratory scale, varying the tablet hardness.

For further details, you can refer to Table 5 for information on the three batches, as well as Figures 1-3.



Source: The tablet hardness directly affects the friability of the bicalutamide tablets

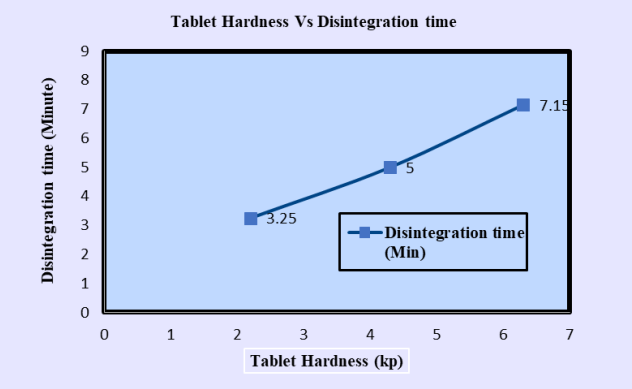
Figure 1: Tablets hardness *vs* friability

Table 4: Model evaluation

Response	*Terms included in a reduced model*	*Co-efficient*	*p-value*	*Justification for inclusion*
Tablet Content Uniformity (Acceptance Value)	Constant	-14.697200		The *P-value* for all the terms is greater than 0.05 indicating insignificant impact on content uniformity.
	Hardness of the Slug (kp)	-0.722195	0.424	
	Screen Size (mm)	2.840440	0.085	
	Mill Speed (rpm)	0.017677	0.670	
	Hardness of the Slug (kp)* Screen Size (mm)	0.142856	0.117	
	Hardness of the Slug (kp)* Mill Speed (rpm)	-2.18E-04	0.328	
	Screen Size (mm)*Mill Speed (rpm)	-0.002497	0.073	

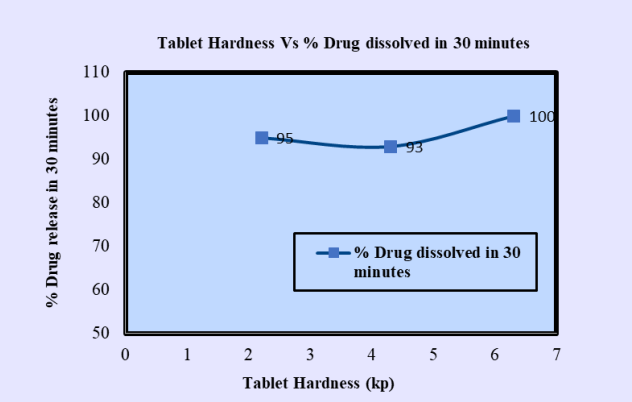
Table 5: Tablet hardness, friability, disintegration time, and dissolution results

Parameters	*Batch No. BCT-001MOCH-22 Batch size: 1000 Tablets*	*Batch No. BCT-002MOCH-22 Batch size: 1000 Tablets*	*Batch No. BCT-003MOCH-22 Batch size: 1000 Tablets*
Tablet hardness (Mean, kilopascals)	2.2	4.3	6.3
Friability (%)	0.9	0.31	0.28
Disintegration time (min)	3 min 25 sec	5 min	7 min 15sec
%Dissolution in 30 minutes	95	93	100



Source: The tablet hardness directly affects the disintegration time of the bicalutamide tablets

Figure 2: Tablets hardness *vs* disintegration time



Source: The tablet hardness directly affects the dissolution of the bicalutamide tablets

Figure 3: Tablets hardness *vs* drug dissolved in 30 minutes

No significant change was observed when tablets were compressed at low, optimum, and higher compression pressure. However, to ensure the production of tablets without any manufacturing defects and to withstand mechanical stress during handling, the optimum hardness range was determined to be 2.0 to 7.0 kp.

CONCLUSION

The results from the factorial design studies indicated that experimental runs conducted within a specific range of independent variables showed no significant impact on CQA, including CU and dissolution, as well as other in-process test results. As a result, this defined range can be considered a design space where modifications will not affect the critical quality attributes of drug products.

Furthermore, it was concluded that appropriate statistical design and optimization techniques can successfully be used to optimize process parameters in dry granulation.

In relation to the slugging process variables and their influence on tablet content uniformity, the *p-value* exceeds 0.05, signifying a lack of substantial impact on CU. The slug hardness studies encompassed a range of 2 to 7 kp, and within this interval, the tablet CU acceptance value (AV) remains below 9.0. Furthermore, other factors like screen size and mill speed do not significantly affect CU.

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