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IMPROVE OF DISSOLUTION SHIFT OF BCS CLASS II DRUG PRODUCT (BICALUTAMIDE TABLETS)

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ABSTRACT
Poor bioavailability is a major impediment in the development of an effective dosage form of poorly soluble BCS class II drugs. The present study aimed to improve the dissolution rate of a poorly soluble BCS class II drug product (Bicalutamide Tablets). The absorption rate of a poorly water-soluble drug, from the orally administered solid dosage form is controlled by its dissolution rate and it's often the rate-determining step in drug absorption. In the present work, the BCS class II drug substances were formulated into granules by slugging and compaction techniques. The process variables selected are the hardness of the slug, the Screen size of the mill, and the Speed of the mill. 2^3 factorial designs were applied in this study. Process parameters were reproducible having minimal impact on tablet properties in the case of different roller speeds of mill. The relationship between one or more response variables and set quantitative parameters can be examined well by using response surface models. The study concludes that Dry granulation was chosen as an appropriate granulation technique to enhance the dissolution shift of poorly water-soluble BCS class II drugs.

KEYWORDS: Bicalutamide Aqueous Solubility, Bicalutamide Tablets, Factorial Design, Critical Slugging Process, Quality Attributes (CQA), Dissolution.

INTRODUCTION
Factorial Design[1-6] is a structured method used to evaluate how different variables affect a response in product and process development. Although the slugging technique in pharmaceutical production[7] is well-established, its variables, such as mill roller speed, are crucial to dry granulation (slugging)[8-9] and require optimization. Identifying these critical process parameters is vital. The pharmaceutical sector initially aims to define baseline operational parameters that guarantee consistency and reproducibility. There's also a pressing need to swiftly optimize these parameters for specific applications that may evolve. Our research focuses on fine-tuning dry granulation parameters in pharmaceutical production, taking into account factors like compatibility and consistency, backed by data. This research supports the industry's growing focus on implementing Factorial Design within the framework of Quality by Design.[10-11]

Bicalutamide solubility as function of pH
Bicalutamide exhibits varying aqueous solubility across the physiological pH range. Specifically, its solubility is less than 250 ml at pH 1.2 to 4.5 and greater than 250 ml at pH 6.0 to 7.8. According to the Biopharmaceutics Classification System (BCS), Bicalutamide falls into Class II (Low Solubility) and details of Bicalutamide Solubility at different pH are provided in Table 1.

The dose solubility volume for Bicalutamide at pH 1.2-7.8 demonstrated that Bicalutamide is soluble at low pH and solubility decreased significantly between pH 2.8-4.5. The solubility remained relatively constant between pH 6.0-7.8 (Poorly Soluble). The absolute aqueous solubility for the Bicalutamide in water is approximately 0.030 mg/ml. The aqueous solubility of the drug substance (Bicalutamide) seems to be low and can have an impact on the in-vitro dissolution.

Reference tablets dissolution data (Slow down upon stability/Dissolution shift)
The dissolution evaluation of Bicalutamide Tablets 50mg (Calutide-50) was comprehensive. The dissolution method involved using 1000 ml of water with a 1% SLS solution in apparatus II - paddle at 50 rpm and a temperature of 37±0.5ºC. NLT 80% (Q) within 30 minutes. The details of 24 months long long-term stability data are provided in Table 2 and the graphical representation of dissolution shift upon stability is presented in Figure 1.

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

The release rate of Bicalutamide Tablets 50mg was determined according to the USFDA website, dissolution database using the Dissolution testing Apparatus II (model TDT-60T, Electro lab, India) fitted with paddles. The dissolution test was executed by using 1000 ml of 1% Sodium lauryl sulfate in water kept at 30±0.5℃ and 50 rpm.

Experiment

Dry granulation (Slugging) and Milling process optimization

Bicalutamide, Lactose anhydrous, Maize Starch, and Sodium Starch Glycolate were sifted through # 40. Blend these sifted ingredients in an Octagonal blender for 30 minutes. Colloid Talc was sifted through # 100 and colloidal silicon dioxide was sifted through #40. These sifted excipients were added to the above blend and blended for 15 minutes in an octagonal blender. Magnesium stearate was sifted through #60 transferred to a blender and Lubricated for 5 minutes.

The lubricated blend was compressed using 9.0 mm Punches at an average weight of 128mg at a hardness range of 6.5-8.5 kp. Milled the slugs through 10.0mm S.S Screen, slow speed, knives forward using a comminuting mill. Milled material was sifted through #20 and oversize granules were collected. The same process was repeated by using 8.0mm followed by 2.5 mm followed by 1.5 mm S.S.Screen, slow speed, knives forward using a comminuting mill.

Talc was sifted through #60 and mixed with the above blend in an octagonal blender for 10 minutes. Magnesium stearate was sifted through #60 and lubricated in an octagonal blender for 5 minutes. Finally, the Lubricated blend was compressed with 9.0 mm punches at an average weight of 128.0 mg. Dry granulation (slugging) was selected as the appropriate granulation method to mitigate poor flow properties in the final blend. The process map below illustrates the finalized formulation for Bicalutamide Tablets 50mg.

Dissolution method

The release rate of Bicalutamide Tablets 50mg was determined according to the USFDA website, dissolution database using the Dissolution testing Apparatus II (model TDT-60T, Electro lab, India) fitted with paddles. The dissolution test was executed by using 1000 ml of 1% Sodium lauryl sulfate in water kept at 30±0.5℃ and 50 rpm.

Content uniformity

Content Uniformity by Uniformity of Dosage test was carried out using analytical grade reagents, HPLC (Water make), C18 column, flow rate 2.0min, and gradient method at 275nm using UV detector.

RESULT AND DISCUSSION

A factorial study using a 2^3 design was carried out, with the findings detailed in Table 3. The investigation evaluated three variables: the hardness of the slug, the mesh size, and the speed of the roller compactor, each at two levels—high and low. The experimental setup included two sets of eight trials. During optimization, significant factors were identified and insights from previous dry granulation processes were applied to enhance product development. The resulting models showed a linear relationship, taking into account the interaction effects of all three factors as observed in individual experiments.

Statistical analysis

The Pareto chart demonstrates the impression of Bicalutamide tablet formulation process variables on Tablet Content Uniformity (%) in Figure 2**.** Additionally, the main effect plot showcases how formulation variables influence Tablet Content Uniformity within the study in Figure 3. Furthermore, the Tablet Content Uniformity (Acceptance Value) remains below 9.0 for the studied range of variables. Consequently, we can conclude that there is no significant impact of the selected variables within this range on Tablet Content Uniformity (Acceptance Value). Although the interaction plot expresses second-order interactions (in Figure 3) 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 % Dissolution at 30 minutes.

Design space

The results from the factorial design suggest that variations within a predefined range had no significant effect on the Critical Quality Attributes (CQA). Therefore, this range can be considered a design space where changes do not influence the drug product's critical quality characteristics.

Tablet compression process optimization

The variables for the compression stage in the Bicalutamide tablet manufacturing were predetermined to align with the targeted quality attributes. Throughout this stage, in-process controls were rigorously observed, focusing on the consistency of tablet weight, hardness, thickness, and friability.

Press Speed (Compression machine speed)

Three experiments were conducted to evaluate the impact of press speed on tablet quality. Specifically, tablet weight uniformity was assessed at three different press speeds and details are provided in Table 5. For more details, press speed and tablet in-process results are provided in Table 6 for information on the three batches, as well as Figures 5, 6, and 7**.**

No significant difference was observed in uniformity of weight and hardness for change in compression machine speed from 2400 Tablets/hrs to 3600 Tablets/hrs but content uniformity (Acceptance value) was increased as machine speed increased but still, it was within the limit of Pharmacopeial limit (Acceptance Value Less than 15) and the optimum range of machine speed was found 2400 Tablets/hours to 3600 2400 Tablets/ hours.

Tables

Table 1: Bicalutamide solubility.

Media		Bicalutamide (Batch No: BI-22-48876)	
		Quantitative solubility (mg/ml)	Dose Solubility Volume* (Calculated at 37ºC)
			Maximum Dose (50mg)
pH 1.2	0.1 N HCL	29.61	0.84
pH 2.1	0.01N HCL	3.4	7.35
pH 2.8	Acetate buffer	44.73	0.56
pH 4.5	Acetate buffer	0.59	42.73
pH 6.0	Phosphate buffer	0.05	500
pH 6.8		0.03	833.33
pH 7.2		0.03	833.33
pH 7.8		0.03	833.33
Purified Water		0.03	833.33

**Dose Solubility Volume: Dose solubility volume is calculated as the highest dose divided by solubility in mg/ml.*

Table 2: Long-term (25°C/65%RH) stability of Bicalutamide Tablets 50mg at controlled room temperature.

Batch # ⇩ / Frequency	Dissolution Release Data (%)						
	Initial	3 months	6 months	9 months	12 months	18 months	24 months
GJ90940	91%	88%	86%	83%	82%	78%	73%
GJ90954	96%	90%	88%	84%	80%	77%	70%
GJ90961	94%	90%	86%	79%	76%	72%	71%
GJ90973	91%	88%	87%	81%	73%	70%	73%
GJ90978	89%	90%	88%	85%	79%	74%	71%
GJ90981	90%	88%	85%	81%	80%	74%	71%
GJ90986	92%	88%	84%	82%	80%	74%	73%
GJ90991	90%	88%	85%	80%	78%	76%	69%
GJ90999	92%	88%	86%	81%	79%	77%	71%
GJ10005	90%	86%	82%	80%	75%	69%	64%

Table 3: Summary of optimization study of Slugging and Milling process.

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

Table 4: Model evaluation.

Response	Terms included in the reduced model	Coefficient	P-Value	Justification for inclusion
% Dissolution at 30 minutes	Constant	97.6430	0.00000	The P-value is greater than 0.05
	SSG	0.49000	0.29250	
	Conc of Lubricant	-1.00000	0.55200	
	Ratio of Pregelatinised starch to Lactose Anhydrous	0.24900	0.10500	
	PSD of Lactose Anhydrous	-5.44850	0.07180	
	Conc of SSG *Ratio of starch to Lactose Anhydrous	3.00000	0.16800	

Table 4: Press speed.

Parameters	Batch No. BCT-001MOCP-22 Batch size: 1000 Tablets	Batch No. BCT-002MOCP-22 Batch size: 1000 Tablets	Batch No. BCT-003MOCP-22 Batch size: 1000 Tablets
Press speed (Tablets/hr)	2400	3000	3600
Tablet weight range (mg)	124.8-128.1	123.6-127.0	121.9-124.8
Weight difference (mg)	3.2	3.3	2.9

Table 5: Press Speed and Tablet in process result.

Batch #	Press speed (Tablets/hr)	Tablet Hardness (Mean, kp)	Friability (%)	Disintegration time (min)	Content Uniformity (AV: NMT 15.0)
BCT-001MOCP-22	2400	4.7	0.2	5 min 35 sec	3.55
BCT-002MOCP-22	3000	4.3	0.31	5 min	5.95
BCT-003MOCP-22	3600	3.8	0.31	5 min 5 sec	8.53

Figures

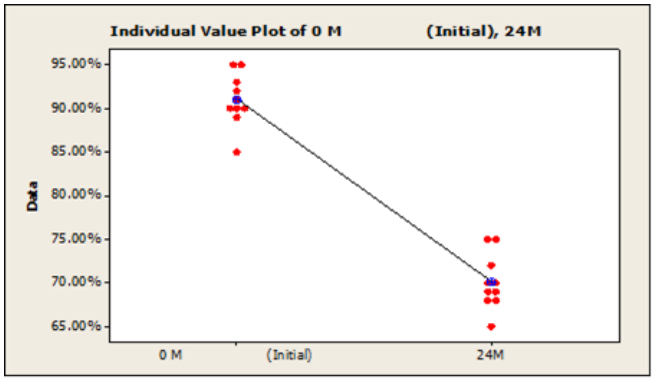

Figure 1: Graphical representation of dissolution shift upon stability.

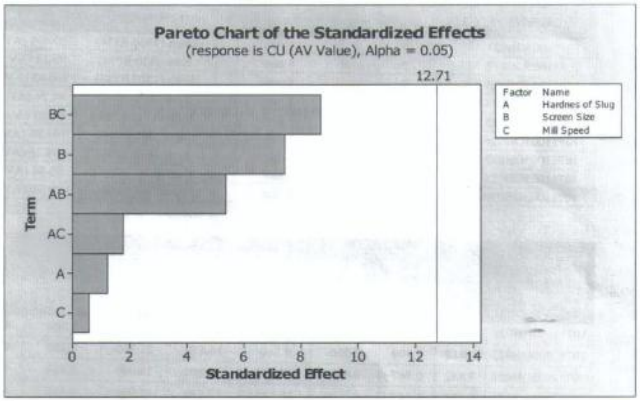

Figure 2: Pareto Chart of slugging process variables on Tablets CU (%).

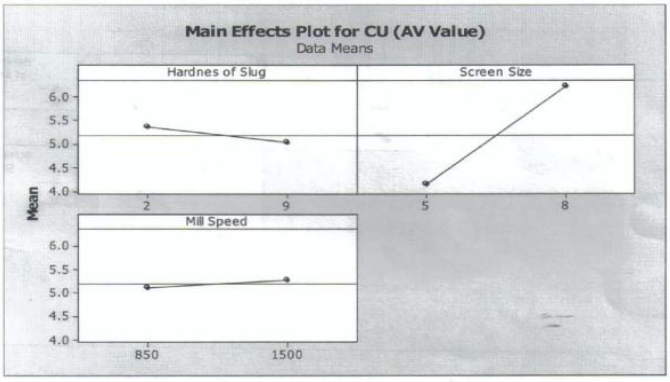

Figure 3: The main effect Plot and Range impact Tablet Content Uniformity (%).

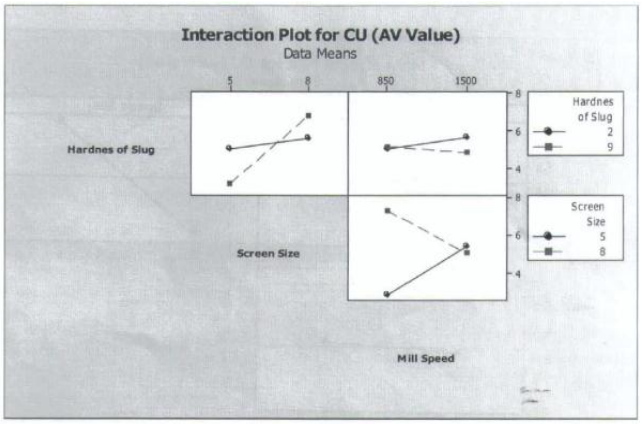

Figure 4: Interaction Plot of Slugging Process Variables on Tablet Content Uniformity.

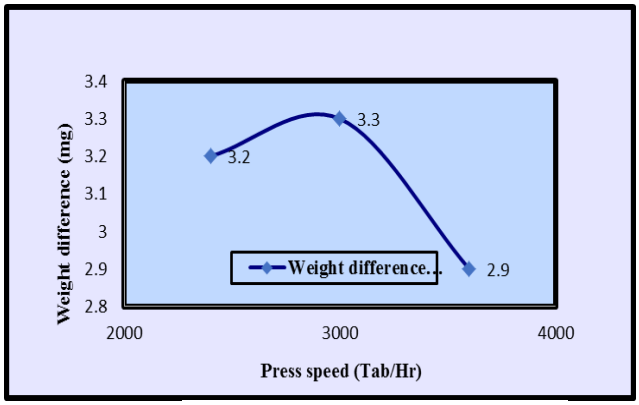

Figure 5: Press Speed Vs Weight difference.

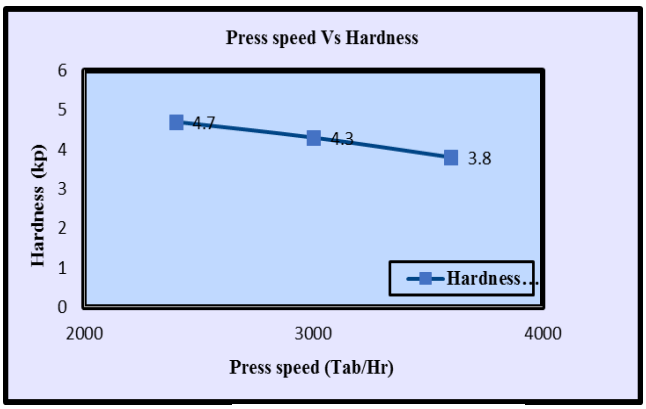

Figure 6: Press Speed Vs Hardness.

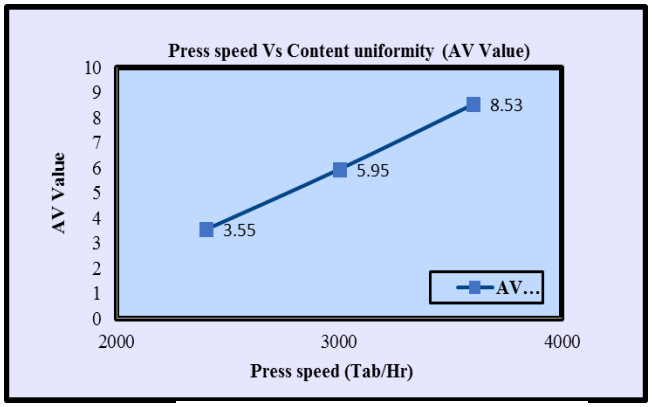

Figure 7: Press Speed Vs Content Uniformity.

CONCLUSION

The results from Factorial Design studies indicated that experimental runs conducted within a specific range of independent variables did not significantly impact Critical Quality Attributes (CQA) or other in-process test results. Consequently, this selected range can be considered a design space where changes are unlikely to affect critical quality attributes of drug products. The study concluded that Factorial Design and optimization techniques can effectively optimize process parameters in dry granulation. Notably, the hardness range observed in slug studies (2-9 kp) ensured that tablet content uniformity (CU) Acceptance value (AV) remained below 9.0. Additionally, the dry granulation process, involving eight experiments, assessed the effects of two-level four factors and their interactions. Factorial design approaches were employed to optimize the formulation and address dissolution shift.

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