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Effect of Mechanical and Formulation Variables on Granule Flowability in High-Shear Wet Granulation

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This study investigates the effects of crucial process factors in high-shear wet granulation (HSWG) on the flowability of riboflavin-based granules. Using a 2^4 complete factorial design, the effects of binder type, binder concentration, chopper speed, and impeller speed were thoroughly evaluated during sixteen experimental runs. The granule flowability was assessed using measurements of the angle of repose. The results showed that chopper speed, binder type, and binder concentration had a substantial effect on flowability, while impeller speed had a modest effect. Higher chopper speeds enhanced flow by reducing agglomeration size and increasing granule homogeneity, particularly in PVP-based formulations. HPMC-based formulations demonstrated higher sensitivity to processing parameters because of their inherent cohesiveness, thus requiring careful mechanical energy input adjustment. The three-way interaction between binder type, chopper speed, and impeller speed was particularly significant, emphasising the need to consider the combined effects of process variables. At 2.5% HPMC binder concentration, 2500 rpm chopper speed, and 60 rpm impeller speed, the best flowability of 27.08 was observed. These findings provide a solid basis for process optimisation in HSWG and help maintain regular granule flow parameters, which are essential for reliable tablet manufacturing.

Keywords: High-shear wet granulation, granule flowability, process parameter, riboflavin formulation, factorial design

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In various sectors, including food manufacturing, chemicals, pharmaceuticals, and agriculture, granulation is a crucial procedure that converts powders, molten liquids, or aqueous solution into granules with more uniform sizes and shapes. Granulation is of particular interest in the pharmaceutical sector as solid dosage forms such as tablets and capsules are the most commonly used methods for drug delivery due to their convenience for patients. Compared to untreated powders, granules minimise dust formation, enhance content uniformity, and reduce the risk of ingredient separation. These characteristics greatly affect the mechanical strength and dissolution characteristics of the final product, which subsequently impact the therapeutic efficacy, bioavailability, and suitability of the drug for large-scale production [1].

Based on the use of liquid binders, granulation technologies are generally divided into two categories: dry and wet. Because of its benefits in terms of mixing efficiency, processing time, high drug loading capability, and compatibility with enclosed or continuous processing, high-shear wet granulation (HSWG) is one of the most popular wet granulation techniques [2]. Despite its effectiveness, HSWG is a complicated multivariate process that is impacted by several interrelated variables, including binder properties, chopper speed, and impeller speed. Insensitive formulations may experience instability, fine generation, or clumping if these parameters are not properly controlled. Two of the most important factors influencing granule formation, flow characteristics, and the quality of the finished tablet are impeller and chopper speeds [3]. However, in many real-world pharmaceutical operations, granulation is still optimised through empirical methods rather than systematic scientific approaches, often resulting in inconsistent granule characteristics and difficulties in scale-up.

In light of these challenges, the process of optimisation and evaluation can be performed more cost-effectively and efficiently using tools like Design of Experiments (DoE) [4]. This study examines the impact of formulation and process parameters on granule flowability in high-shear wet granulation, utilising HPMC and PVP as model binders. The granule flowability was evaluated using the angle of repose response indicator. By improving formulation techniques and process control in HSWG, the study was undertaken with the aim of promoting consistent product quality and compliance with pharmacopeial standards.

Although various studies have examined the individual effects of process parameters or binder

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properties in high-shear wet granulation, only a small number of studies have focused on the combined interaction between mechanical forces and binder characteristics. Understanding these interactions is essential for optimising granule flowability and achieving consistent tablet performance [5].

EXPERIMENTAL

Chemicals and Materials

Hydroxypropyl Methylcellulose (HPMC K75) was purchased from Orioner Hightech Sdn. Bhd. (Kuala Lumpur, Malaysia). Polyvinylpyrrolidone (PVP K30), Talcum (Talc), Riboflavin (Calbiochem), Lactose monohydrate (EMPROVE) and Magnesium Stearate (Parteck) were supplied from Merck Sdn. Bhd. (Selangor, Malaysia).

Experimental Design

The experimental design was carried out using Design-Expert software (version 13; Stat-Ease, Inc., MN, USA). Following initial trials, four independent variables were selected, A (impeller speed), B (chopper speed), C (binder type), and D (binder concentration) [6]. These factors were evaluated at two levels to study their influence on the granules' physical properties. The full experimental matrix is illustrated in Figure 1. One response was chosen as the dependent variable, namely flowability [7]. To assess the significant factors and their interactions with these responses, analysis of variance (ANOVA) was performed. The most suitable mathematical model was selected by comparing several statistical metrics, such as the coefficient of determination (R^2) and adjusted R^2. Additionally, 3D response surface plots were created using the same software to visualise interactions among variables.

Empirical models were developed based on the statistical analysis of the experimental data. Using individual desire functions (di) that translate each response to a value between 0 and 1, the ideal formulation was found through simultaneous optimisation. The optimal combination of replies was then ensured by selecting the final set of design factors to optimise overall attractiveness.

Table 1. Design of Expert

Std	Run	Factor 1 A: Impeller Speed rpm	Factor 2 B: Chopper Speed rpm	Factor 3 C: Binder Type	Factor 4 D: Binder Concentration %	Response 1 Flowability %
16	1	60	500	HPMC	2.5	
13	2	150	2500	PVP	10	
11	3	150	2500	PVP	10	
7	4	60	2500	HPMC	10	
6	5	150	2500	HPMC	2.5	
15	6	150	500	HPMC	10	
10	7	60	500	PVP	2.5	
12	8	60	500	HPMC	10	
4	9	150	500	PVP	10	
2	10	150	2500	HPMC	2.5	
9	11	150	500	HPMC	10	
1	12	60	500	PVP	2.5	
3	13	150	500	PVP	10	
8	14	60	2500	PVP	2.5	
14	15	60	2500	PVP	2.5	
5	16	60	2500	HPMC	2.5	

Preparation of Granules

High-shear wet granulation was performed using a Shakti granulator from Ahmedabad, India, with a working capacity of 1.0 litre [8]. Before starting the granulation process, all the excipients were passed through a 30-mesh sieve, transferred into the granulation bowl, and pre-mixed for 3 minutes at an impeller speed of 100 rpm. Then, over ten minutes, distilled water was added at a rate of twenty millilitres per minute, keeping the liquid-to-solid ratio at 25% by weight. A measuring cylinder was used to deliver the water through the machine's nozzle. Lactose Monohydrate was either 94.5 per cent or 87 per cent weight by weight in the mixture, depending on the binder. Talc, magnesium stearate, and riboflavin were added at a weight percentage of 1% each. The Lactose Monohydrate content was modified using a binder, namely HPMC or PVP, at weight-by-weight concentrations of 2.5 per cent or 10 per cent. The weight of each batch made for the investigation was 800 grams. As shown in Figure 1, the granulation procedure was conducted using certain impeller speed, chopper speed, binder type, and binder concentration settings. Following granulation, the wet granules were dried for seven to eight hours at 60°C in a standard oven [9].

Evaluation of Granules Properties

The flowability of the granules was determined using the angle of repose Equation (1.0), looking into its flow behaviour, and reflecting the inter-particle friction. The funnel method is typically used to measure the angle of repose for granules. In this method, granules are poured into a funnel and allowed to flow freely onto a surface. The height of the granule pile and the horizontal distance from the centre of the pile to its edge is measured using a ruler. The lower the angle, the better the principal flow through the angle of repose [10]. For each experimental run, a 50g sample was measured using an analytical balancer and an angle of repose tester using Mettler Toledo. The surface flow behaviour through granules was determined in triplicates for each. The following was determined using the equation below [11].

RESULTS AND DISCUSSION

Evaluation of Granules Properties

Although individual standard deviation values and error bars are not included due to the unavailability of raw experimental data, the reliability of the results was confirmed through model adequacy testing. Statistical confidence was identified using ANOVA, indicating that the developed model was significant ($p < 0.05$) and exhibited no lack-of-fit ($p > 0.05$). The Shapiro–Wilk normality test ($W = 0.950$, $p = 0.735$) further verified that the residuals followed a normal distribution, supporting the consistency and robustness of the data. The close correspondence between predicted and actual flowability values provides additional evidence for the model's validity within the design space [12].

$$\tan\theta = hr$$

$\tan\theta$ = angle of repose

h = height of cone in cms

r = radius of powder cone in cms

Table 2. Angle of Repose

Flow property (º)	Powder flow characteristics
25-30	Excellent
31-35	Good
36-40	Fair aid not needed
41-45	Passable-may hang up
46-55	Poor-must agitate, vibrate
56-65	Very poor
>66	Very, very poor

The factor levels in this study were established based on prior research, preliminary trials, and machine capability constraints. The impeller speed range of 60 to 150 rpm was selected to ensure adequate mixing efficiency within the granulator's operational limits, despite higher speeds being reported in previous studies [13]. Chopper speed was varied from 500 to 2500 rpm to encompass low to high shear conditions typical of wet granulation [14]. The binder concentration was set between 2.5% and 10% (w/w), as preliminary trials indicated that concentrations below 2.5% produced weak granules, while the concentrations above 10% resulted in over wetting and agglomeration [15]. Two binder types, polyvinylpyrrolidone (PVP) and hydroxypropyl methylcellulose (HPMC), were chosen for their industrial relevance and contrasting properties: PVP is low-viscosity and fast-dispersing, whereas HPMC is highly viscous and adhesive [16,17].

The full factorial design matrix and corresponding experimental results for granule flowability are summarised in Table 3. The 16 runs generated from the 2^4 factorial design examined the effects of impeller speed (A), chopper speed (B), binder type (C), and binder concentration (D) on the measured angle of repose, the key indicator of granule flowability. These results formed the basis for statistical analyses, including ANOVA and regression modelling, which evaluated the significance and interactions among the four process variables.

The main variables that had a substantial impact on granule flowability are displayed in Figure 2 under normal probability plot of standardised effects. Impeller speed (A), binder concentration (D), binder type (C), the interaction between binder type and concentration (CD), and the interaction between impeller speed and binder concentration (AD) were the most significant factors. The orange highlights of these impacts show that raising their levels resulted in higher flowability values, which are correlated with worse flow. Conversely, the negative impacts are reflected by the blue display of chopper speed (B) and its interactions, including AB and AC [18]. This suggests that increasing chopper speed generally improves flowability. The results of the Shapiro-Wilk test, with a W value of 0.950 and a p-value of 0.735, confirm that the residuals are normally distributed, supporting the validity of the model.

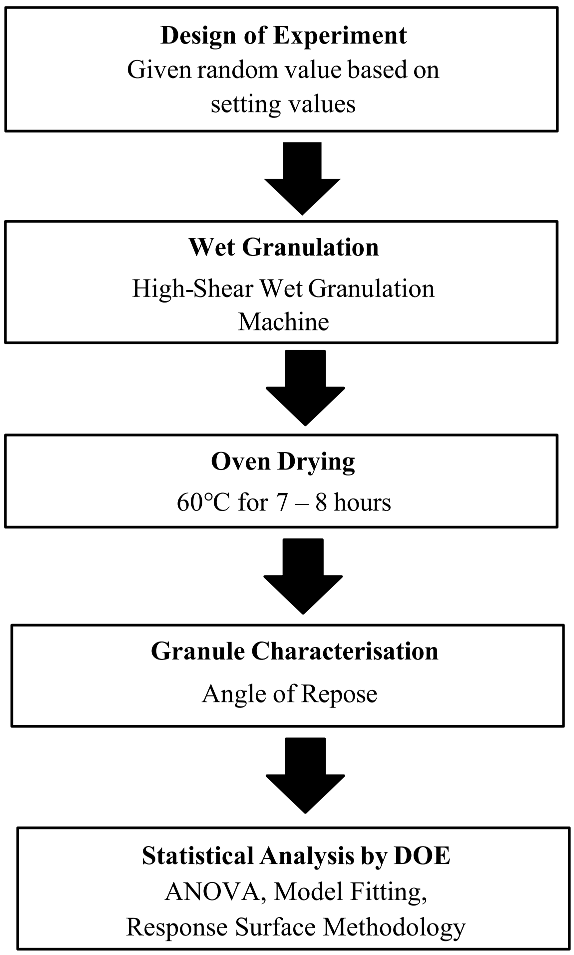


Figure 1. Simplified Flow Chart of the Project

Table 3. The 2-level factorial design suggestion and result of the experiment.

A	B	C	D	Flowability (º)
60	500	HPMC	10	30.7
150	2500	PVP	2.5	30.5
150	2500	PVP	10	31.47
60	2500	HPMC	10	28.86
150	2500	HPMC	2.5	25.4
150	500	HPMC	2.5	30.91
60	500	PVP	10	33.41
60	500	HPMC	2.5	26.19
150	500	PVP	2.5	28.37
150	2500	HPMC	10	28.25
150	500	HPMC	10	35.02
60	500	PVP	2.5	33.37
150	500	PVP	10	31.05
60	2500	PVP	10	29.62
60	2500	PVP	2.5	30.81
60	2500	HPMC	2.5	27.08

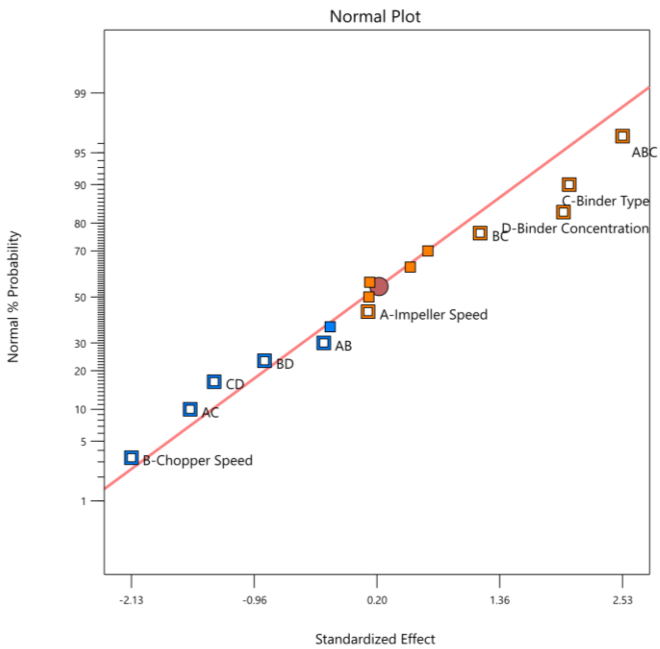


Figure 2. Normal probability plot of standardised effects

Figure 3 displays the Pareto chart of standardised effects, where the ABC interaction had the strongest influence, followed by B, C, D, and BC, all of which exceed the Bonferroni and 95% confidence limits. The t-value of each effect is plotted, allowing easy identification of statistically significant factors. Two reference lines indicate the Bonferroni limit (5.2472) for a highly significant effect and the t-value limit (2.57058) corresponding to the 95% confidence level [19]. Several chopper-related interactions (e.g., AC, CD, BD) showed negative effects, again suggesting enhanced flow. These findings are consistent with the normal probability plot, confirming that binder properties and chopper speed, along with their interactions with mechanical forces, are critical to flow performance [20].

Residual analysis showed that the residuals were randomly scattered and normally distributed, validating the regression model. Coefficients with positive values indicated synergistic effects (increase in response), while negative values suggested opposing trends. The magnitude of each coefficient reflected its influence on flowability.

Effect of Control on Flowability

A key goal of the granulation process is to improve the flow characteristics of powder materials [21]. The flowability of granules is closely linked to their angle of repose, as measured by their height and radius. This angle of repose is obtained by flowing the granule through the funnel. Then, prior to granulation, the powder blend in this investigation had an angle of repose of 48.36, indicating extremely poor flow. The angle of repose readings decreased to a range between 25.40 and 35.02 across several experimental settings following the granulation process, revealing a significant improvement in flowability. Granule flow performance is noticeably improved by this lowering. Based on regression analysis, the following empirical model was generated to describe the relationship between process variables and flowability:

$$\text{Flowability} = 30.06+0.0581A-1.06B+1.01C+0.9844D-0.1519AB-0.7856AC+0.589BC-0.4331BD-0.6719CD+1.26ABC$$

The intercept value of 30.06 represents the baseline flowability when all variables are at their centre levels. The model's coefficients provide useful data. Variable A indicates that flowability marginally improves as impeller speed increases, with a positive coefficient of (+0.0581). Variable B has the largest impact, with a negative coefficient of (-1.06), showing that flowability dramatically declines with increasing chopper speed. Increases in binder type and concentration are associated with higher flowability values, according to the positive coefficients for variables C and D, which are (+1.01) and (+0.9844), respectively. In this instance, higher numbers signify worse flow characteristics.

Table 4 presents the ANOVA results for flowability, indicating that a p-value below 0.05 denotes a statistically significant effect of a factor or interaction. Chopper speed (B) emerged as the most influential variable affecting flowability. Furthermore, Table 5 demonstrates that the statistical metrics p-value, W-value, adjusted R-squared, and PRESS (Predicted Residual Error Sum of Squares) of 33.83 remained consistent across all model types, including mean, linear, quadratic, and cubic. This finding indicates that increasing model complexity does not enhance predictive accuracy. Therefore, the linear model is deemed the most suitable due to its interpretability and reduced risk of overfitting [22,23].

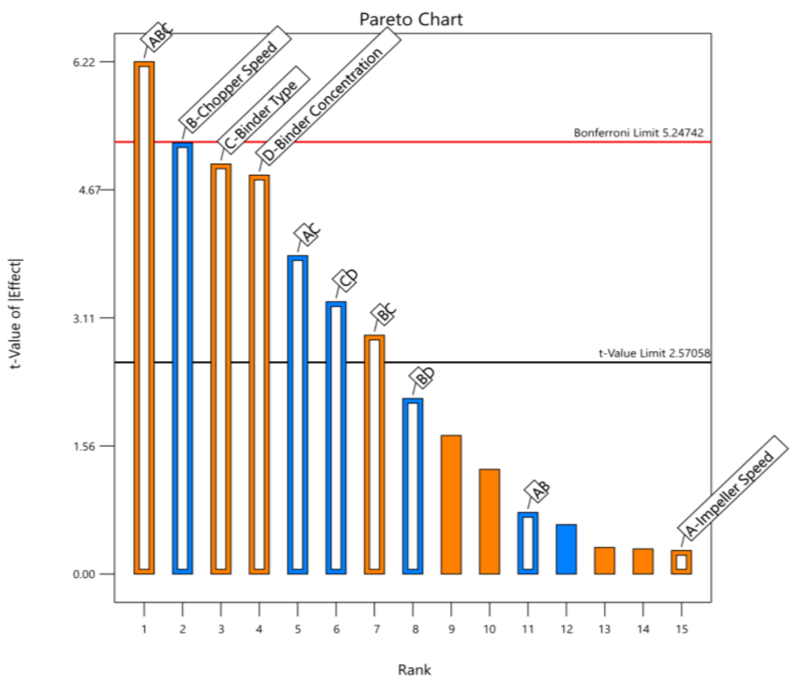


Figure 3. Pareto chart.

Model validation metrics further confirmed the model's adequacy. The lack-of-fit test was found to be insignificant ($p > 0.05$), demonstrating that the model fits the experimental data well without systematic error. The residuals followed a normal distribution, as confirmed by the Shapiro–Wilk test ($W = 0.950$, $p = 0.735$) and normal probability plot (Figure 4). The high coefficient of determination ($R^2 = 0.9056$) indicates that approximately 90.56% of the total variation in granule flowability is explained by the selected model, demonstrating strong agreement between the predicted and experimental results. This high R^2 value implies high prediction confidence, suggesting that the model can reliably estimate flowability within the studied design space.

The interaction terms provide a clearer understanding of how process parameters interact to influence granule behaviour [26]. One notable example is the three-way interaction ABC, which includes impeller speed, chopper speed, and binder type. This interaction showed a high positive coefficient of (+1.26), indicating a strong combined or synergistic effect. In addition, the two-way interactions BC and CD also showed significant influence, highlighting the important role that binder-related variables play in determining granule flow characteristics.

Table 4. Analysis of Variance (ANOVA) for Full Factorial of Flowability

Source	Sum of Squares	df	Mean Square	F-value	P-value	
Model	101.67	10	10.17	15.39	0.0038	significant
A-Impeller Speed	0.0541	1	0.0541	0.0818	0.7863	
C-Binder Type	16.38	1	16.38	24.79	0.0042	
D-Binder Concentration	15.50	1	15.50	23.46	0.0047	
AB	0.3691	1	0.3691	0.5585	0.4885	
AC	9.88	1	9.88	14.94	0.0118	
BC	5.56	1	5.56	8.41	0.0338	
BD	3.00	1	3.00	4.54	0.0863	
CD	7.22	1	7.22	10.93	0.0213	
ABC	25.58	1	25.58	38.71	0.0016	
Residual	3.30	5	0.6608			
Cor Total	104.98	15				

Table 5. Model comparison for the lack of fit for the design model

Type of model	w-value	p-value	Adjusted R2	PRESS
Mean	0.950	0.735	0.9056	33.83
Linear	0.950	0.735	0.9056	33.83
Quadratic	0.950	0.735	0.9056	33.83
cubic	0.950	0.735	0.9056	33.83

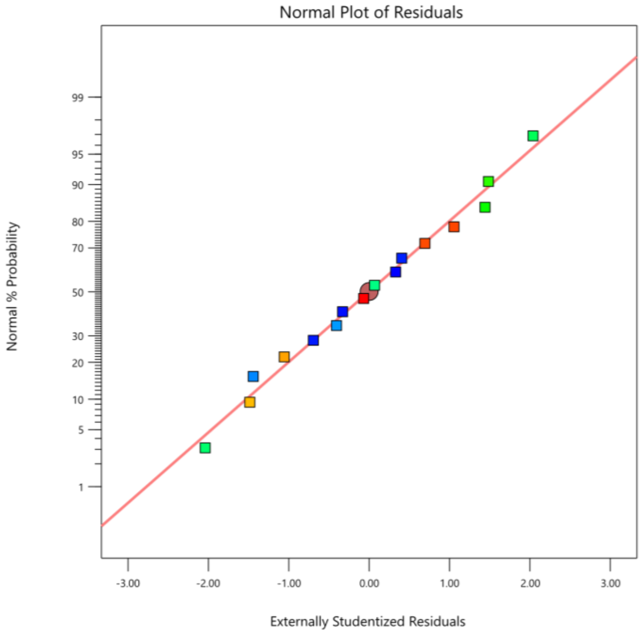


Figure 4. Normal Probability Plot of Residuals

Figure 4 provides essential insights into whether the residuals, which represent the differences between predicted and observed values, follow a normal distribution as a critical assumption for the validity of the regression model. Most of the points align closely with the red diagonal line, which represents the expected normal distribution. This alignment indicates that the residuals are approximately normally distributed, suggesting that the model fits the data well.

This suggests that the model is free from problems such as heteroscedasticity (unequal variance) and non-linearity [4]. Red denotes better flowability values and blue denotes lower ones. A few points at the extreme ends of the plot deviate slightly from the red line, but these deviations are minor and not large enough to be considered significant outliers. This suggests that the model is robust and not overly influenced by extreme values. The assumption of normalcy, which guarantees the reliability of hypothesis tests and confidence intervals obtained from the regression model, is supported by Figure 4. The model's ability to accurately forecast flowability within the specified date range is demonstrated by the lack of notable outliers or consistent deviations.

Figure 5 illustrates the randomness and independence of the residuals for the flowability data, which plays an important role in validating the experimental design and the reliability of the model. The red horizontal lines mark the critical thresholds at (±6.36429), where any residuals falling outside these limits may point to possible outliers. The plot also uses a colour gradient, with blue representing lower flowability values and red representing higher ones, offering a clear visual of the data distribution. Most of the residual points are scattered closely around the (0) line, indicating that the differences between the observed and predicted values are minimal in most experimental runs [27]. This consistent alignment suggests that the model closely reflects the actual results, confirming its accuracy in predicting flowability.

The points on the plot are randomly distributed with no visible pattern, evidencing the absence of systematic errors or biases tied to experimental runs. This implies that variables such as the sequence of experiments, environmental conditions, or equipment inconsistencies did not have a noticeable effect on the outcomes. The randomness in the distribution also confirms that each run was carried out independently, reinforcing the reliability of the study and supporting the conclusions drawn from the data.

This demonstrates both the reliability of the model used to analyse flowability and the resilience of the experimental design. Outliers are absent, the data are consistent, and neither systematic errors nor outside influences affect them. This guarantees that the findings about how the variables studied affect flowability are robust and reliable.

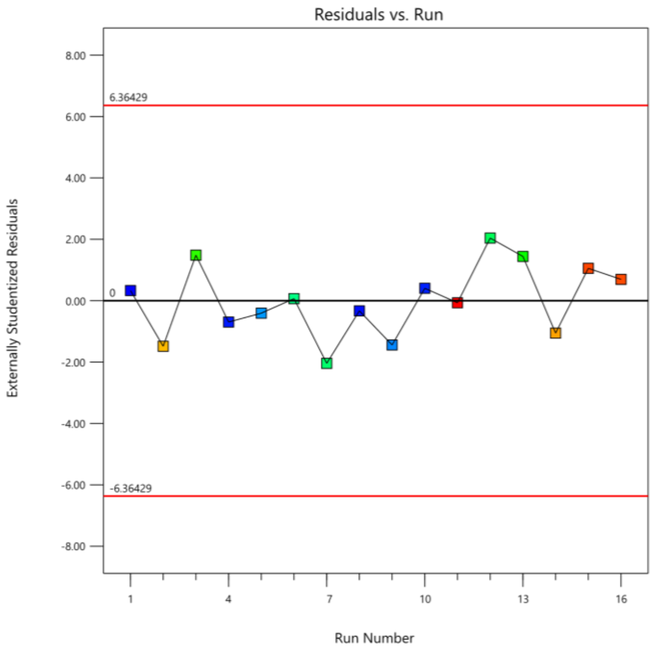


Figure 5. Residuals Versus Run

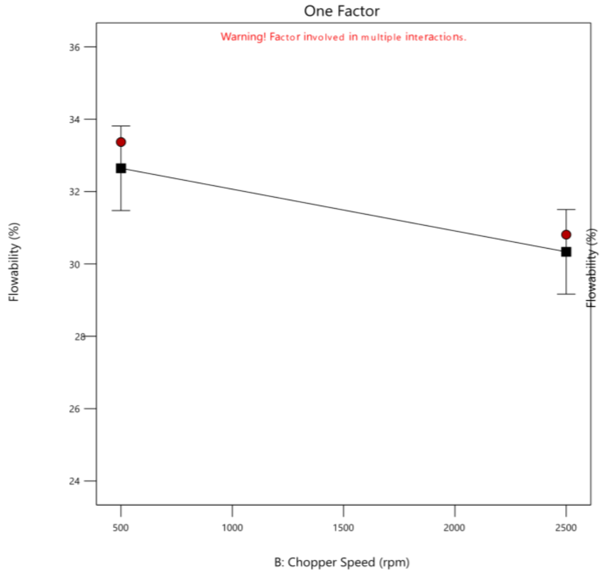
PVP-Based Formulations: Combined Effects of Impeller Speed, Chopper Speed, and Binder Concentration on Flowability

Figures 6 illustrate the combined effects of impeller speed, chopper speed, and binder concentration on the flowability of PVP-based granules. At a lower binder concentration (2.5%), flowability improved notably with increasing chopper speed (Figure 6a). This enhancement is attributed to stronger shear forces that promote better binder distribution and break down larger agglomerates, resulting in granules with more uniform size and smoother surfaces. This enhancement is attributed to stronger shear forces that promote better binder distribution and break down larger agglomerates, resulting in granules with more uniform size and smoother surfaces.

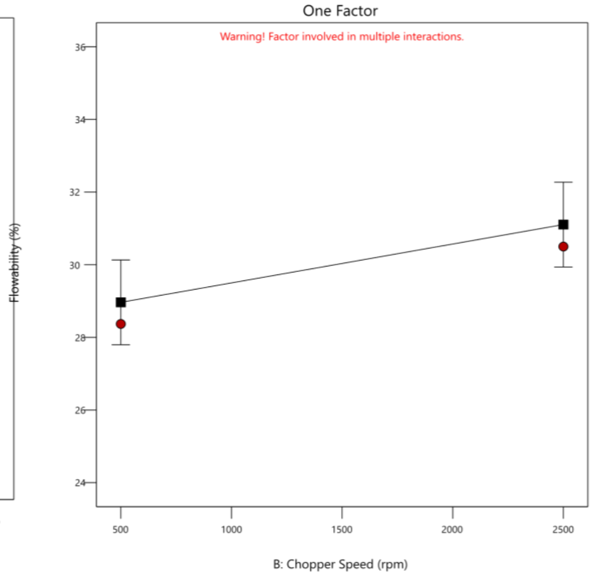
However (Figure 6b), as impeller speed increased, a slight decline in flowability was observed, likely caused by over-fragmentation and the formation of fine particles. These finer granules tend to increase interparticle friction, thereby reducing flowability. Interestingly, this reduction was often accompanied by improved granule densification and uniformity, which can enhance tablet compatibility even though flowability slightly decreased.

At a higher binder concentration (10%), as shown in Figures 6c and 6d, the influence of chopper speed became less pronounced, and flowability stabilised across impeller variations. This suggests that the binder content was sufficient to maintain granule cohesion, minimising the effect of additional shear. Nevertheless, when both impeller and chopper speeds were high, a mild decline in flowability was again observed, likely due to over-shearing and the generation of fines [28].

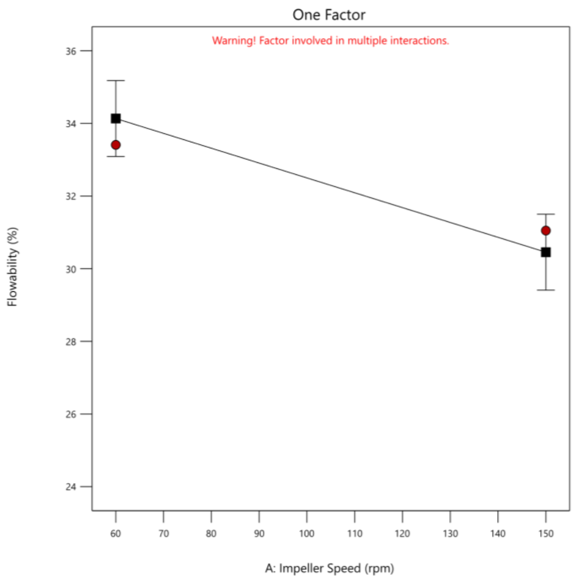
Overall, PVP systems display good process tolerance at moderate shear and binder levels, but excessive combined impeller and chopper speeds consistently reduce flow by promoting fines and surface roughness.



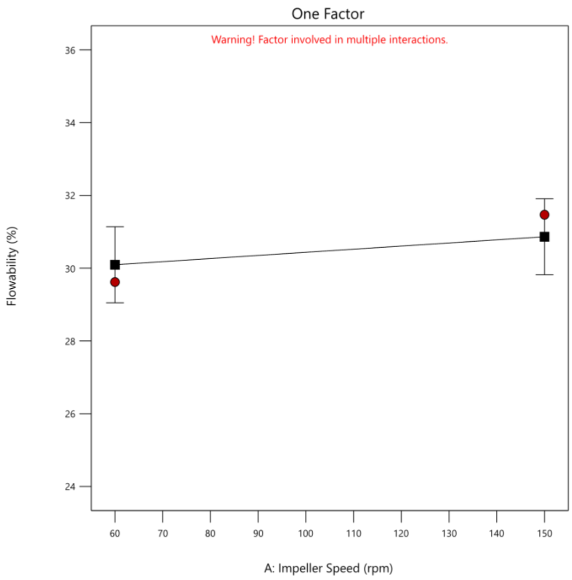
(a) At 2.5% binder concentration lowest impeller speed (60rpm)



(b) At 2.5% binder concentration highest impeller speed (150rpm)



(c) At 10% binder concentration lowest chopper speed (500rpm)



(d) At 10% binder concentration highest chopper speed (2500rpm)

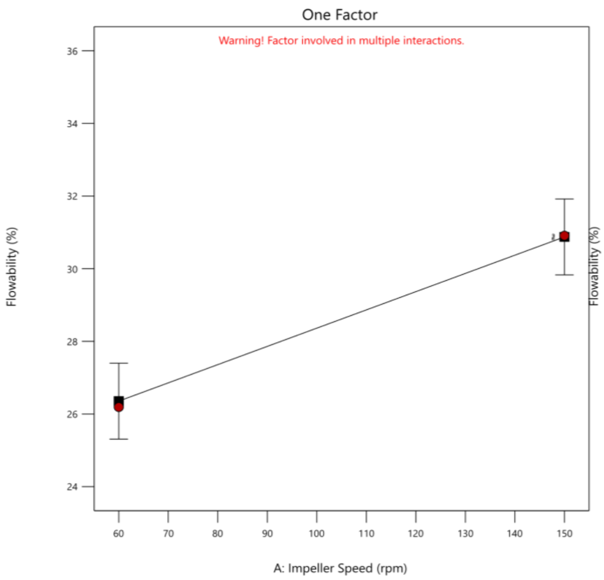
Figure 6. Effect of impeller speed and chopper speed on granule flowability at different binder concentrations using PVP as the binder

HPMC-Based Formulations: Combined Effects of Impeller Speed, Chopper Speed, and Binder Concentration on Flowability

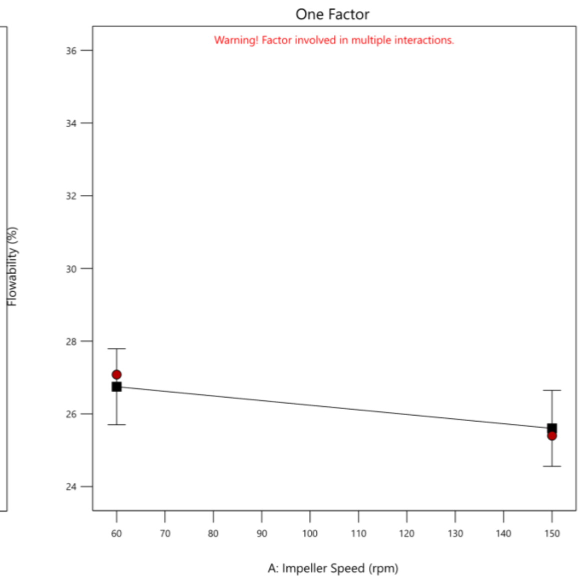
In contrast to PVP, HPMC-based formulations exhibited a more complex response to variations in mechanical and formulation parameters. At lower binder concentrations (2.5%), flowability improved significantly with increasing impeller and chopper speeds (Figure 7b). This enhancement can be attributed to efficient HPMC dispersion under high-shear, which promoted uniform binder distribution and reduced localised over-wetting. As a result, granules became more homogeneous and less cohesive, thereby improving flow behaviour [29]. However, at higher binder concentrations (10%), increasing mechanical energy produced a better effect (Figures 7c and 7d). Due to HPMC's high viscosity and strong adhesive nature, excessive shear at high impeller (150 rpm) and chopper speeds (2500 rpm) led to granule well cohesion and reduced clumping. These conditions formed thinner and stickier granules that exhibited reduced flowability.

Notably, optimal flow performance was achieved under high mechanical conditions, specifically at high impeller and chopper speeds, with both binder concentrations [30]. Under these conditions, the binder viscosity minimised cohesion while still providing sufficient granule integrity, resulting in smoother surfaces and improved flow.

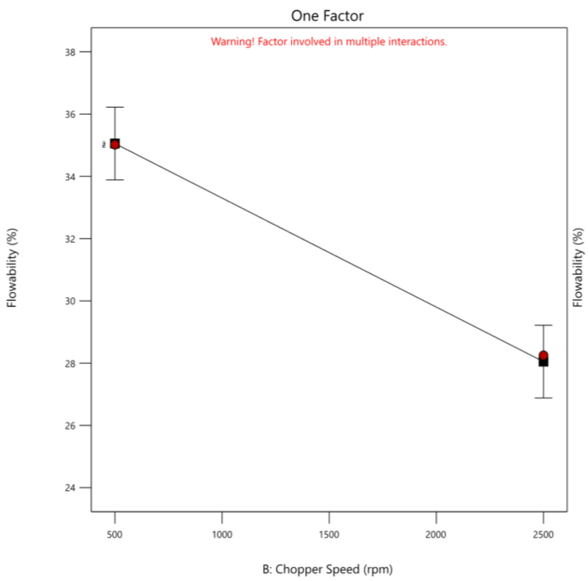
Overall, HPMC-based formulations demonstrated higher sensitivity to mechanical energy input compared to PVP. While moderate shear enhanced granule uniformity and flow, excessive energy or binder concentration negatively affected flowability by amplifying cohesion and frictional resistance between particles. This behaviour highlights the critical need for careful adjustment of both mechanical and formulation parameters when using viscous binders like HPMC to achieve consistent granule quality and optimal flow performance.



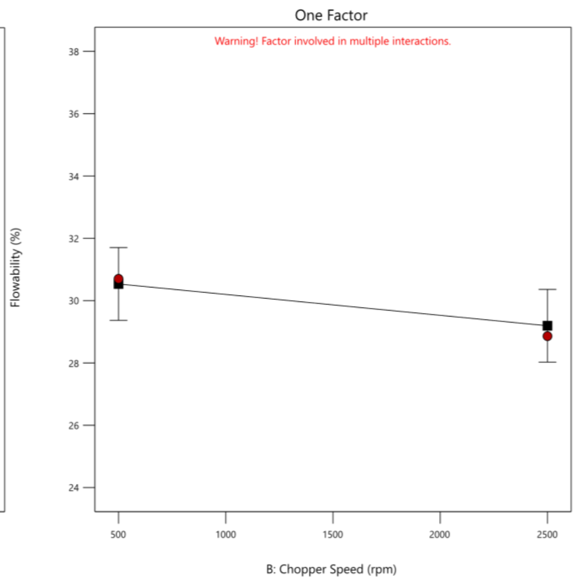
(a) At 2.5% binder concentration lowest impeller speed (60rpm)



(b) At 2.5% binder concentration highest chopper speed (2500rpm)



(c) At 10% binder concentration highest impeller speed (150rpm)



(d) At 10% binder concentration lowest impeller speed (60rpm)

Figure 7. Effect of impeller speed and chopper speed on granule flowability at different binder concentrations using HPMC as the binder

Overall Discussion of Mechanical and Binder Effects on Flowability

Across both PVP and HPMC-based formulations, it was clear that mechanical forces and binder concentration worked in tandem to influence granule flowability. Higher chopper speeds generally produced granules with more uniform particle sizes. This is because the stronger shear helped break down large agglomerates and distributed the binder more evenly throughout the mixture. This uniformity improved the extent to which particles aggregated and reduced friction between them, ultimately leading to better flowability.

However, these benefits were lost when the shear intensity or binder concentration became too high. Increasing binder concentration from 2.5% to 10% consistently reduced flowability, as reflected by higher angle of repose values. At these higher levels, the granules became over wet and overly cohesive, forming sticky clumps that resisted movement. In contrast, lower binder concentrations (2.5%) particularly in PVP formulations produced granules that were less cohesive and moved more freely, which enhanced flowability despite the granules being mechanically weaker.

Overall, these results highlight the need for balance. Achieving optimal flowability requires carefully adjusting both mechanical input and binder concentration. Moderate chopper speeds and lower binder levels promote uniform granules with minimal cohesion, while excessive binder or too much mechanical energy can lead to fines or clumping that disrupt consistent flow.

Interaction between Impeller Speed (A), Chopper Speed (B), and Binder Type (B), (ABC) on Flowability

From the Pareto chart, the interaction of ABC in Figures 8 and 9 was extremely significant because it crosses the Bonferroni limit, which indicates high confidence. Flowability (º) is significantly impacted by the interplay of binder type (C), chopper speed (B), and impeller speed (A). Since higher speeds (B) inject greater shear force, which results in uniform size and more cohesive granules, they also influence granule breakage, making chopper speed a crucial factor in determining granule size and strength [23]. Similarly, the formulation of granule distribution is influenced by impeller speed. Granules are probably more uniform at the higher chopper speed level (B), which enhances flowability. However, these effects are modulated by the binder type. For instance, PVP (C) appears to enhance flowability more effectively than HPMC (C), as evidenced by the predicted values shown in the cube plot.

The cube plot makes evident how changing one element while keeping the rest constant affects flowability. For instance, reducing the impeller speed (A) from 60 rpm enhances flowability when the chopper speed (B) rises from 500 rpm to 2500 rpm, particularly when PVP (C) is utilised as the binder in Figure 10. Conversely, for binder-type PVP at low binder concentration, Figure 9 shows the opposite. PVP behaves differently at low and high binder concentrations. This suggests that the concentration, granulation force (impeller speed), and fragmentation (chopper speed) have a major impact on its flowability-enhancing qualities [31]. With the help of these insights, producers can adjust process variables to provide their formulations with the best possible flowability.

The flowability patterns of PVP (polyvinylpyrrolidone) and HPMC (hydroxypropyl methylcellulose) show distinct differences when tested at a low chopper speed of 500 rpm and a binder concentration of 10%. For PVP, its relatively weaker binding ability promotes better binder distribution and more uniform granule formation under low shear conditions, allowing flowability to improve as impeller speed increases. In contrast, at higher impeller speeds, HPMC's stronger binding capacity results in overly cohesive and dense granules. This occurs due to the low chopper speed not providing enough shear force to counteract HPMC's strong adhesion, thus reducing flow performance.

The trends revert with the same concentration and high chopper speed (2500 rpm). PVP granules are unduly broken apart by the greater shear forces, resulting in smaller, more cohesive particles that impair flowability. However, HPMC gains from the higher mechanical energy, which improves flowability, encourages size homogeneity and lessens excessive cohesion. This indicates that HPMC needs greater mechanical pressures to overcome its cohesive tendencies, whereas PVP is better suited for low-shear circumstances [32].

The impact of binding characteristics on granule flowability is further demonstrated by the correlation between binder type and binder concentration. HPMC produced extremely cohesive and dense granules at a higher binder concentration (10%), which impairs flowability because of increased inter-particle friction and restricted granule separation [33]. Flowability was hampered by HPMC's intrinsic cohesive qualities, even at a reduced binder content (2.5%). On the other hand, PVP, a weaker binder, maintains decent flowability while forming granules with moderate cohesiveness at 10% concentration. When compared to HPMC, PVP exhibited substantially superior flowability at 2.5% concentration as it produced fewer cohesive, free-flowing granules.

Mechanical forces also played a critical role in amplifying these effects [34]. While higher shear forces at elevated impeller and chopper speeds improve PVP's flowability by enhancing granule uniformity, they fail to overcome HPMC's overly cohesive properties. At lower mechanical speeds, reduced shear forces further exacerbate HPMC's poor flowability, whereas PVP retains its superior flowability due to its weaker binding properties.

Under constant impeller speed (150 rpm) and binder concentration (2.5%), the interplay between chopper speed and binder type highlights the critical role of mechanical energy in controlling granule flowability. A high chopper speed (2500 rpm) for HPMC offers enough mechanical energy to break cohesive granules down, increase size homogeneity, and decrease clumping, all of which improve flowability. The lack of mechanical energy at low chopper speeds (500 rpm) causes granules to be poorly dispersed and too cohesive, which impairs flowability.

In contrast, PVP exhibits the best flowability at low chopper speeds, where moderate mechanical energy reduces inter-particle friction and preserves granule size. Excessive mechanical forces break apart PVP granules into smaller particles at high chopper speeds, increasing surface area and inter-particle interactions that impair flowability [35].

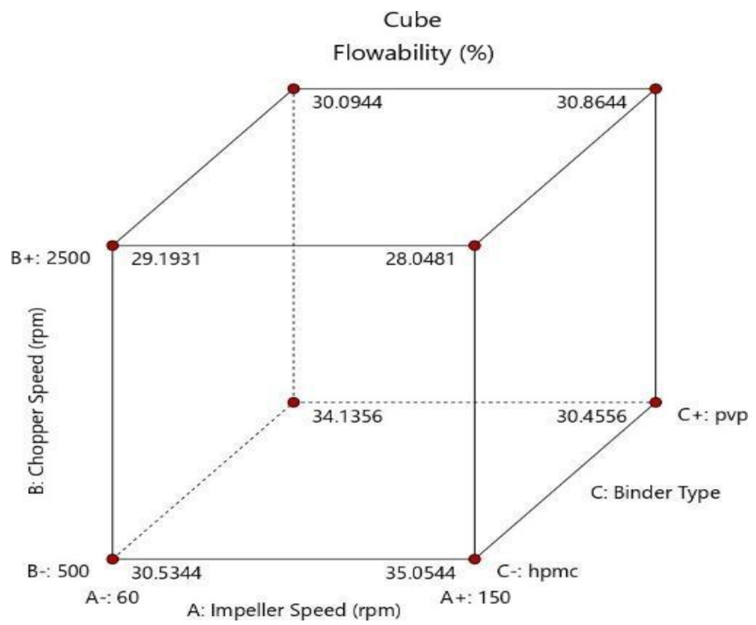


Figure 8. Cubic Effect of ABC with 10% binder concentration on flowability

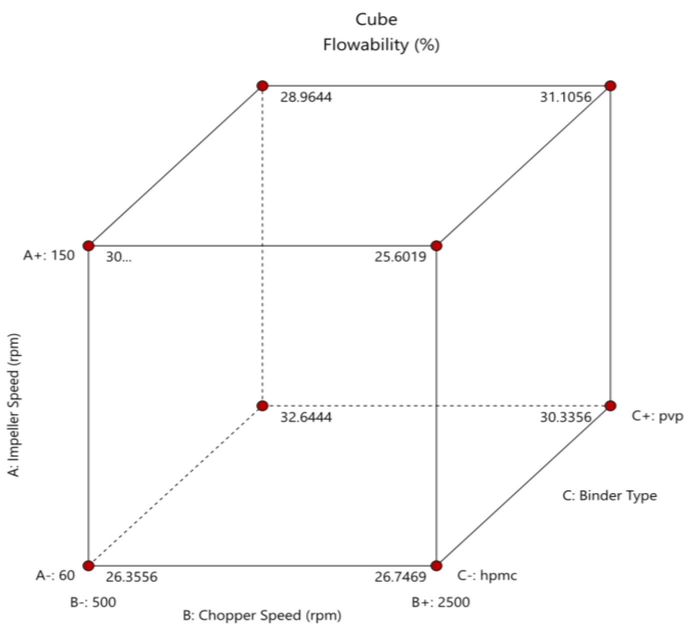


Figure 9. Cubic effect of ABC with 2.5% binder concentration on flowability

To achieve optimal flowability during granulation, it is crucial to carefully balance mechanical input and binder characteristics. This is highlighted by the combined influence of impeller speed, chopper speed, binder type, and binder concentration. While HPMC exhibits better flow behaviour when higher mechanical forces are applied to counteract its inherent cohesiveness, PVP performs better under conditions with lower mechanical stress because of its weaker binding capacity. These effects are further amplified by binder concentration, where higher concentrations favour HPMC in high-force situations and PVP in low-force situations. Understanding these interactions clearly provides a scientific basis for modifying processing parameters based on the formulation and binder used in pharmaceutical manufacturing.

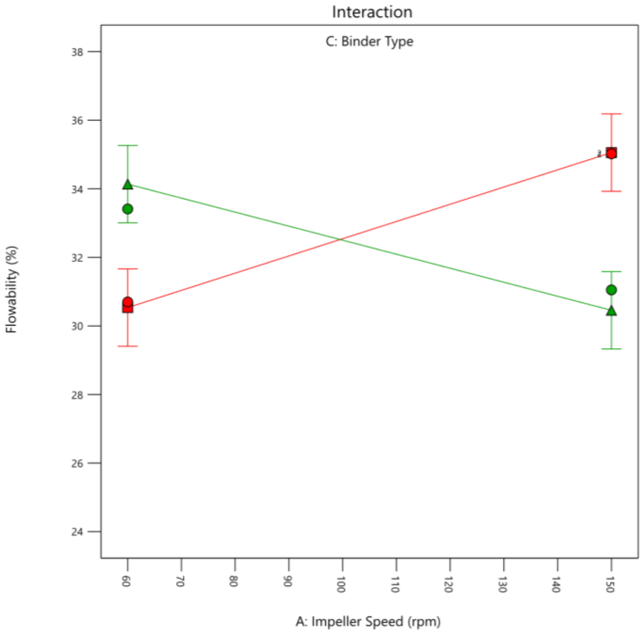


Figure 10. Two-Factor Interaction of Impeller Speed (A) against Binder Type (C) with Constant Chopper Speed 500rpm and Binder Concentration 10%

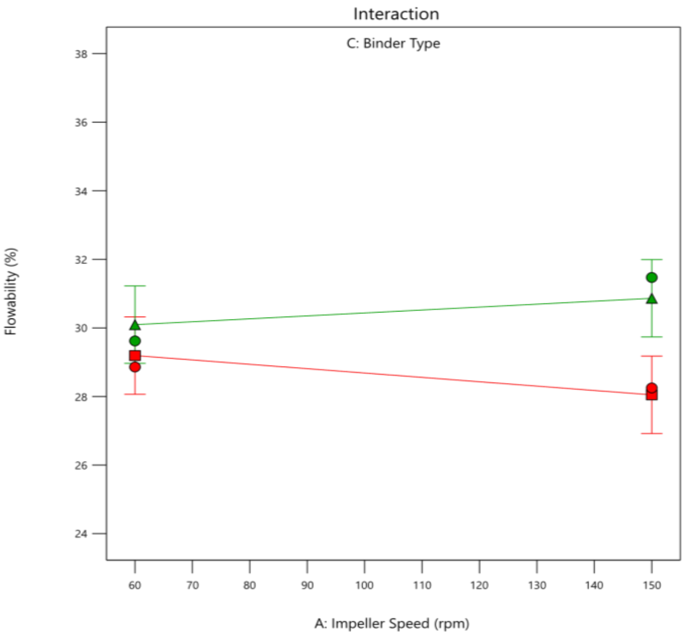


Figure 11. Two-Factor Interaction of Impeller Speed (A) Against Binder Type (C) with Constant Chopper Speed 2500rpm and Binder Concentration 10%

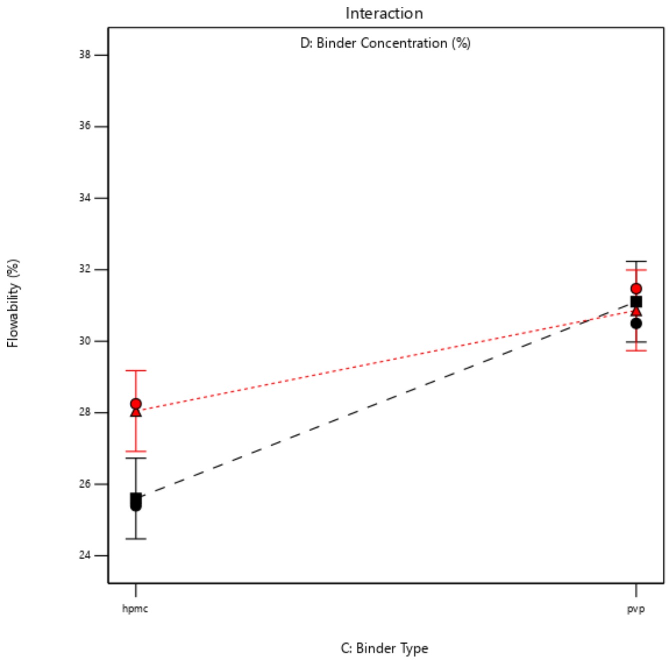


Figure 12. Two-Factor Interaction of Binder Type (C) Against Binder Concentration (D) with Constant Impeller Speed 150rpm and Chopper Speed 2500rpm

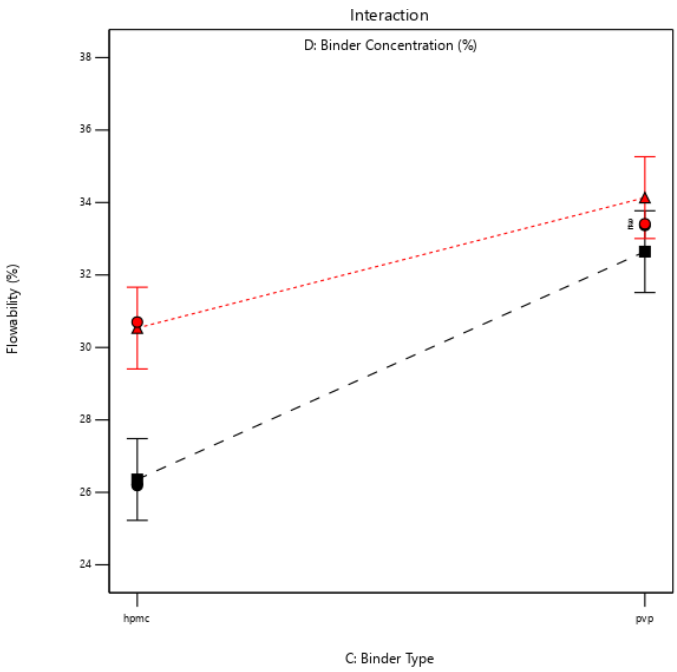


Figure 13. Two-Factor Interaction of Binder Type (C) Against Binder Concentration (D) with Constant Impeller Speed 60rpm and Chopper Speed 500rpm

Interaction between BD and AB on Flowability

As the balanced experimental settings and the moderate amounts of variables, the interactions between binder concentration and chopper speed, and between chopper speed ad impeller speed show little importance in their effects on flowability. The moderate binder concentration (10%) offers adequate binding for the interplay between chopper speed and binder concentration without adding too much cohesion for both HPMC and PVP. It was known that granule size and homogeneity were largely influenced by chopper speed (500–2500 rpm), but at low binder levels, granule cohesiveness was stable, reducing sensitivity to variations in mechanical energy. Flowability is further stabilised by the homogeneous mixing provided by the constant impeller speed of 105 rpm. Due to the complementing energy contributions of the chopper and impeller speeds, these interactions also exhibit a steady flowability trend [36,37].

Chopper speed is essential for reducing particle size, but a suitable impeller speed encourages uniform binder dispersion without resulting in segregation [38]. Using both HPMC and PVP as binder types helps balance out any significant variations in flowability, and maintaining a binder concentration of 6.25 per cent helps limit variability by providing a consistent level of granule cohesiveness. The absence of significant effects from certain interactions can be attributed to the steady experimental conditions, the balancing effects among variables, and the relatively low sensitivity of granule properties within the tested ranges, which kept the observed differences below statistical significance.

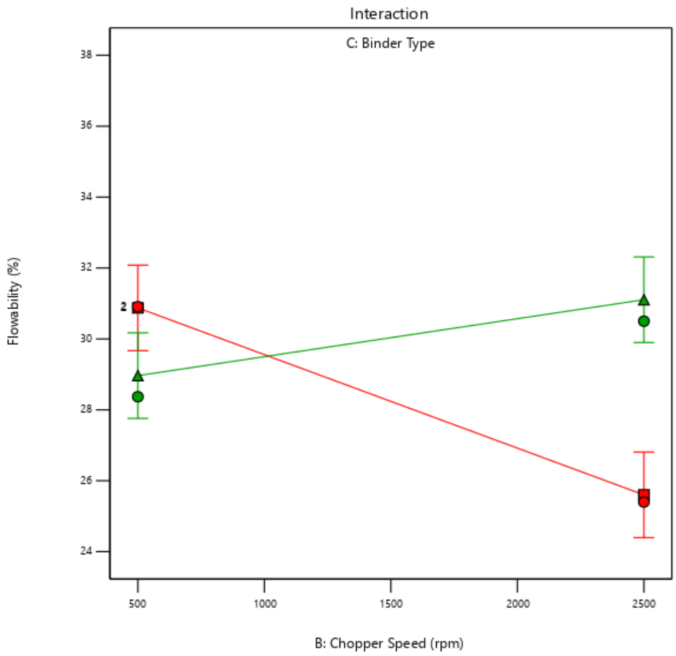


Figure 14. Factor Interaction of Chopper Speed (B) Against Binder Type (C) with Constant Impeller Speed 150rpm and Binder Concentration 2.5%

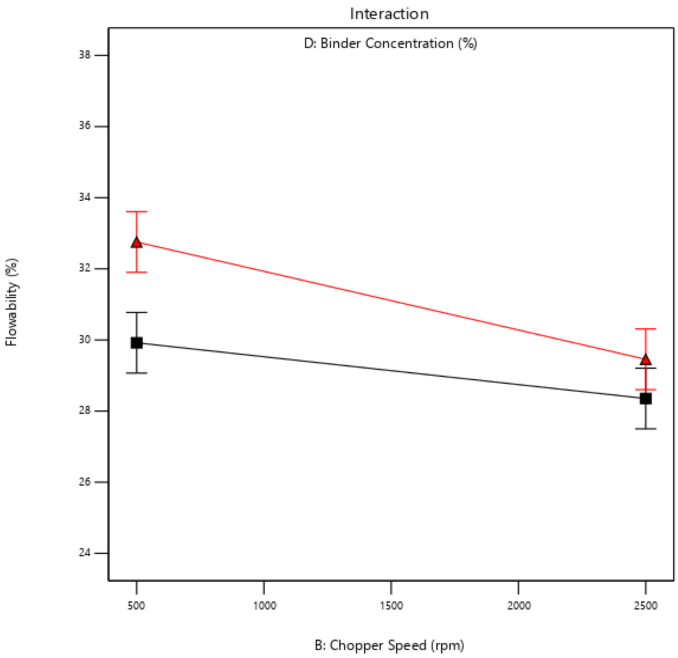


Figure 15. Two-Factor Interaction of Chopper Speed (B) Against Binder Concentration (D) with Constant Impeller Speed 105rpm and Binder Type (Average HPMC & PVP)

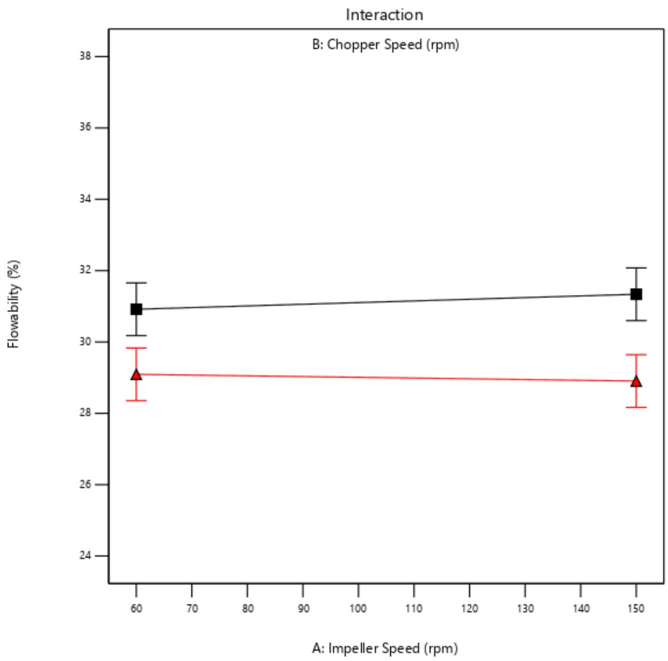


Figure 16. Two-Factor Interaction of Impeller Speed (A) Against Chopper Speed (B) with Constant Binder Type (Average HPMC & PVP) and Binder Concentration 6.25%

Optimisation Numerical Analysis and 3D Surface Plots

The combination of numerical optimisation and 3D surface plots provides a comprehensive framework for understanding and refining the wet granulation process. This approach enables the development of robust and scalable manufacturing processes.

The ideal parameters for granule flowability were determined by numerical optimisation HPMC as the binder type, 2.5% binder concentration, 60 rpm impeller speed, and 2500 rpm chopper speed. With flowability (27.08), which was probably caused by slight variations in binder dispersion or equipment calibration, experimentally confirmed these predictions. The model's resilience and usefulness are demonstrated by the agreement between the expected and experimental findings. This method ensures consistent granule performance while streamlining process development by reducing needless testing.

The Design of Expert (DOE) software's three-dimensional surface plots produced by Response Surface Methodology graphically illustrate how important processing parameters like chopper and impeller speeds interact to influence granule flowability [39]. These plots provide a better understanding of the granulation responses of formulations containing PVP and HPMC binders by highlighting different behavioural patterns. The surface plot for PVP-based formulations displays a comparatively flat profile, with flowability staying constant within a small range of roughly 29 to 30 (º). According to this stability, PVP offers a moderate binding strength, resulting in consistent flow characteristics that are not significantly impacted by changes in mechanical input.

On the other hand, formulations that contain HPMC exhibit steeper gradients in the 3D surface plots and a greater range of flowability values, usually between 26 and 29 (º). Since its stronger adhesive nature encourages granule densification and cohesion when ideal parameters are applied, this suggests that HPMC is more sensitive to changes in processing conditions. However, the surface plot's sharp slopes also indicate a higher chance of desirable results if processing conditions change, highlighting the necessity of exact control [39]. The minimum flowability is attained by PVP formulations at moderate impeller speeds of approximately 150 rpm with higher chopper speeds of around 500 rpm, while HPMC formulations reach their minimum flowability at moderate impeller speeds of about 150 rpm combined with higher chopper speeds near 2500 rpm. These differences can be attributed to the fundamental properties of each binder. PVP tends to generate granules with lower cohesiveness and relatively consistent flow due to its lower molecular weight and weaker binding ability. In contrast, HPMC's higher molecular weight and greater viscosity improve wetting and binding performance, producing denser granules that exhibit enhanced flowability when processed under ideal conditions.

Table 6. Best Suggested Conditions by Design of Expert

Formulation	Impeller Speed (rpm)	Chopper Speed (rpm)	Binder Type	Binder Concentration (%)	Flowability (º)	Desirability
1	113.234	1400.417	HPMC	4.153	27.447	1.000
2	150.000	2500.000	HPMC	10.000	28.048	1.000
3	60.000	500.000	HPMC	2.500	26.356	1.000

Table 7. Best Conditions by Experimental Run

Formulation	Impeller Speed (rpm)	Chopper Speed (rpm)	Binder Type	Binder Concentration (%)	Flowability (º)
16	60	2500	HPMC	2.5	27.08

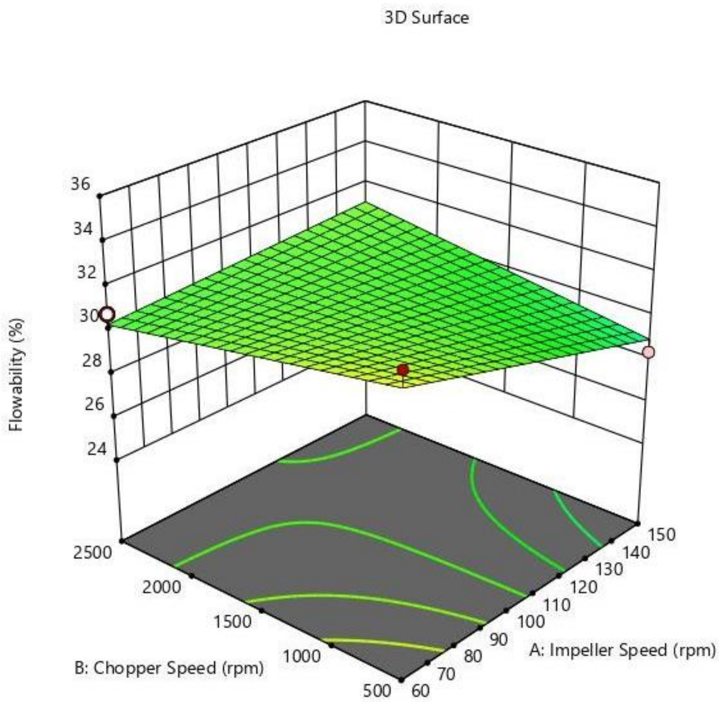


Figure 17. 3D Surface Influence of Chopper and Impeller Speed towards Flowability using 2.5% PVP as Binder Type

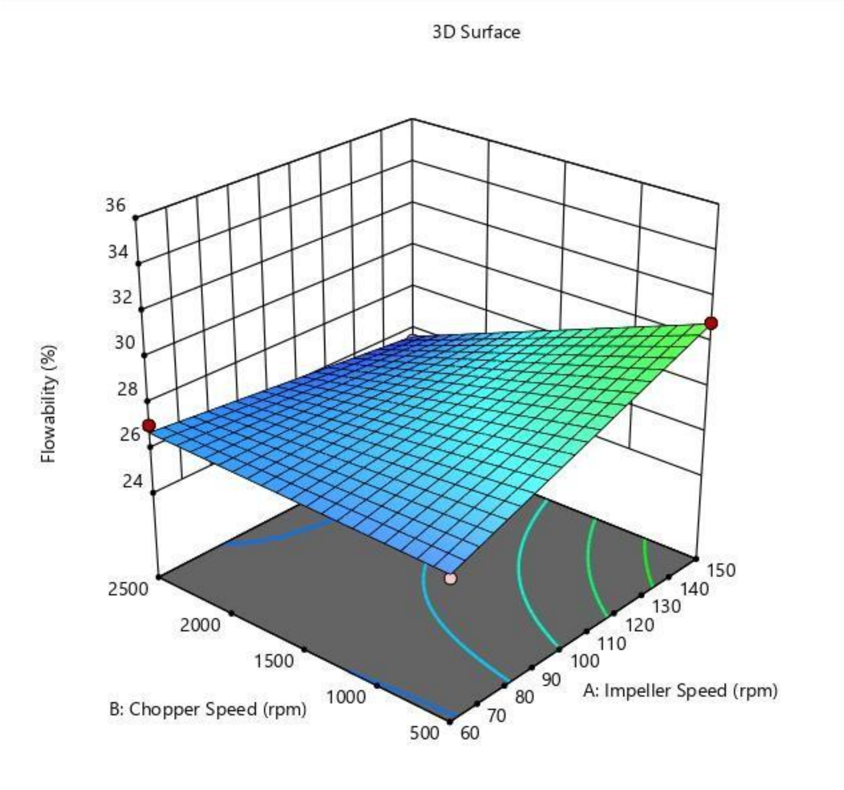


Figure 18. 3D Surface Influence of Chopper and Impeller Speed towards Flowability using 2.5% HPMC as Binder Type

CONCLUSION

Important granulation process parameters, such as binder type, binder concentration, chopper speed, and impeller speed, were found to have significant impacts on the flowability of riboflavin-based granules produced by high-shear wet granulation. It was found that chopper speed, binder type, and binder concentration had the most pronounced effects on granule flowability, while impeller speed had a secondary but contributing effect using a 2^4 complete factorial design. The interactions among variables, especially the three-way interaction between impeller speed, chopper speed, and binder type (ABC), revealed critical dependencies in achieving optimal flow characteristics. Empirical models generated from the experimental data were statistically significant and validated through ANOVA and residual analysis, supporting their predictive strength.

The formulations that employed HPMC at a 2.5% binder concentration, chopper speed of 2500 rpm, and impeller speed of 60 rpm showed the best flowability results. Also, HPMC compositions demonstrated heightened sensitivity to mechanical input, requiring cautious control of the chopper and impeller speeds to offset their cohesive properties. To guarantee repeatable production outcomes, enhance downstream tablet quality, and maximise granule flow, these findings offer a systematic foundation for HSWG parameter optimisation.

Compared to earlier HSWG optimisation studies, which often emphasised single-variable effects or individual formulation parameters, this work adopted a comprehensive factorial design integrating both mechanical (impeller and chopper speeds) and formulation (binder type and concentration) factors. This approach provided a more complete understanding of binder mechanical interactions, offering a data-driven pathway to improve flow performance and process robustness in pharmaceutical granulation. Future studies should explore how these optimised granules influence final tablet properties, such as hardness, friability, and dissolution, to further enhance formulation development and regulatory compliance.

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