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# Effect of HPMC Concentration and Liquid Addition Method on Granules Properties using High-Shear Wet Granulator

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**Abstract**

*Enhancing the physical properties of medicinal powders is largely dependent on the granulation process. This study investigates the interaction between the concentration of hydroxypropyl methylcellulose (HPMC) and the liquid addition technique on the distribution of granule sizes and its porosity in a high-shear mixer setup. Both a 5% HPMC solution and distilled water (0% HPMC) were employed in the calcium carbonate powder granulation process. The results showed that while excessive liquid addition using the pouring method led to uneven growth and agglomeration, an increase in binder viscosity improved granule homogeneity. On the other hand, the syringe method provided more uniform granules, showing its effectiveness in achieving controlled nucleation and growth. The impact of these parameters on granule characteristics was further supported by the design of response surface plots and models made easier by statistical analysis using Design-Expert software. These findings provide important information for improving wet granulation methods in the manufacturing of pharmaceuticals, especially with regards to guaranteeing the stability and uniformity of the final product.*

**Keywords:** Granulation, HPMC, Liquid Addition, Granule Size, High-Shear Mixer, Design-Expert

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## INTRODUCTION

As one of the kye steps in the production of pharmaceuticals, granulation enhances the mechanical and physical properties of powdered materials. It improves characteristics like flowability and compressibility while reducing problems related to dust formation by clumping tiny particles into bigger, more cohesive granules. According to Suresh et al., (2017), these enhancements are essential for expediting subsequent procedures like tablet compression and capsule filling. High-shear wet granulation stands out among the other granulation techniques due to its capacity to generate uniformly thick granules quickly and effectively (Ennis, 2005).
An essential factor of wet granulation is the addition of binders, which improve particle adherence and cohesion and have a major impact on granule formation. The adaptability and effectiveness of hydroxypropyl methylcellulose (HPMC) in enhancing the mechanical strength of granules make it a popular

ingredient. Research has shown that the granule size distribution is significantly influenced by binder viscosity, which can be well represented by HPMC concentration. The work of Chitu et al., (2011), who emphasized the significance of balancing binder characteristics to maximize the nucleation and growth stages of granulation, is in line with this observation. The manner of liquid addition is an additional crucial factor in determining the properties of the granules. In contrast to less accurate methods like pouring, Melo et al. (2021) investigated the effects of controlled liquid addition techniques, especially the use of syringe. Their results show that controlled procedures result in granules with more uniform size distributions by lowering the chance of over wetting. According to Knight et al. (1998), granule strength and porosity are significantly influenced by the uniformity of liquid distribution, and syringe addition offers better control over liquid dispersion than the traditional pouring techniques.

It is essential for understanding how binder concentration and liquid addition technique interact in the context of pharmaceutical granulation. Significant relationships between these variables were found by Rahmanian et al. (2011), who pointed out that important granule characteristics like density, porosity, and strength are influenced by both liquid distribution and binder viscosity. The precise impacts of these interactions in high-shear wet granulation are still not well understood in the literature, despite these observations.

Using calcium carbonate as a model powder, this work aims to close this gap by examining the combined impacts of HPMC content and liquid addition method on granule size distribution. The study investigates how these parameters interact using Design-Expert software, offering a comprehensive statistical analysis and response surface modeling to identify the ideal granulation settings. By expanding the previous research, this work provides a more thorough understanding of process optimization in pharmaceutical wet granulation.

## MATERIALS AND METHOD

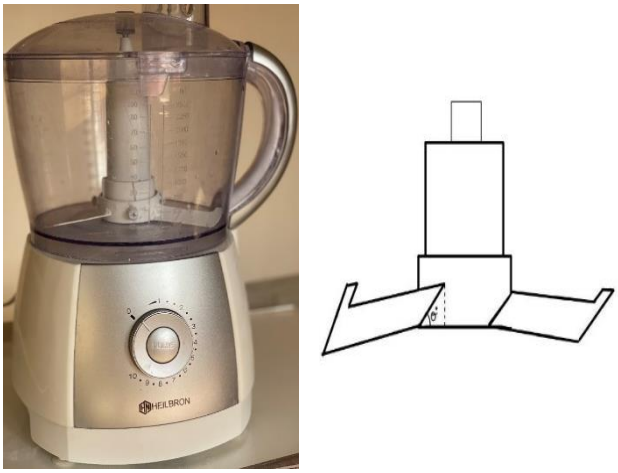
### Materials

Calcium carbonate powder ($CaCO_3$) was used as the primary solid component, while hydroxypropyl methylcellulose (HPMC) from Goomoo Chemical served as the binder was procured from Changsha Goomoo Chemical Technology Co., Ltd. (China). Two binder solutions were prepared: distilled water (0% HPMC) and a 5% HPMC solution.

### Method & Experimental Design

The granulation experiments were carried out using a modified domestic high-shear mixer equipped with aluminum blades, as shown in Figure 1 (a & b).

A factorial experimental design was employed to evaluate the effects of two independent variables: (1) HPMC Concentration: 0% and 5%; (2) Liquid Addition Method: syringe vs pouring



(a) (b)

Figure 1. Modified domestic high-shear mixer with aluminum blades used for granulation experiment

Each condition was tested at a fixed liquid-to-solid ratio (L/S = 1.8) and a mixing time of 6 minutes. The granules were subsequently characterized for size distribution. The results were analyzed using Design-Expert software, which facilitated the generation of response surface plots and statistical models. Table 1 presents an overview of the parameters studied and the corresponding experimental conditions.

Table 1. The Granulation Parameters

| No. Experiment | Liquid Addition Method | HPMC Concentration (%) |
|---|---|---|
| 1. | Syringe | 0 |
| 2. | Pouring | 0 |
| 3. | Syringe | 5 |
| 4. | Pouring | 5 |

### Granulation Procedure

A predetermined amount of calcium carbonate powder was weighed and placed into the high-shear mixer. Then, the liquid binder was introduced into the high-shear mixer using either using the syringe or pouring method while maintaining the mixing speed. Subsequently, calcium carbonate granules were formed and collected for further analysis.

### Characterization of Granules

Granule size distribution was determined using a Retsch sieve shaker, which employed mesh sizes of 1700, 850, 710, 600, and 425 μm. The cumulative percentage retained on each sieve was recorded, and the median particle size (*d50*) was subsequently calculated. Next, the particle size distribution was calculated using the following steps: Total mass calculation for each experiment by addition of the masses cumulatively from the largest to the smallest

sieve. Cumulative percentage was then calculated using Equation (1)

$$\%\ cumulative\ \left(\frac{cumulative\ mass}{Total\ mass}\right) \times 100 \qquad (1)$$

Finally, the Design-Expert software was used to develop regression models predicting the influence of experimental variables on D50.

## RESULTS AND DISCUSSION

The impact of different HPMC concentrations and liquid addition techniques on granule properties is illustrated by the findings of the four experimental settings, which are shown in Figure 2. Figure 2 clearly displays the effect of granulation parameters on the granule size distribution.

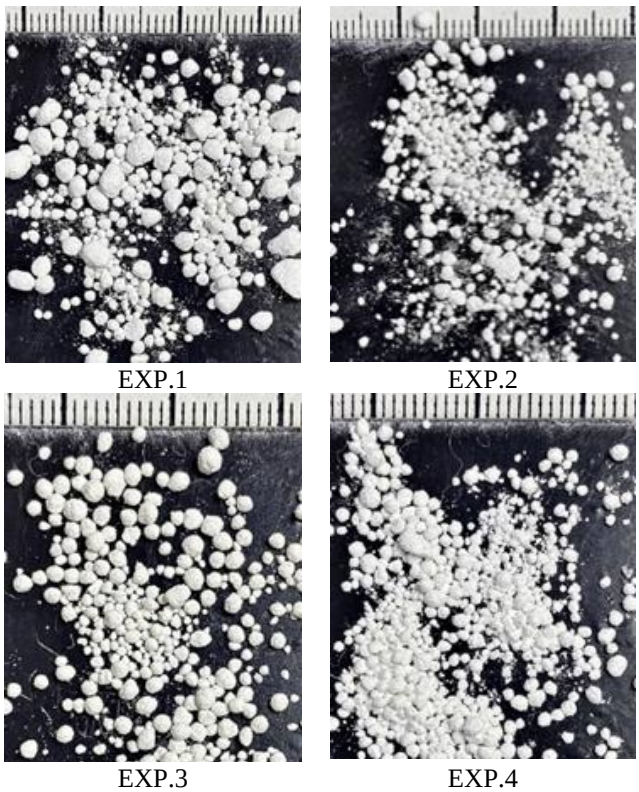



Figure 2. Calcium Carbonate Granules Obtained from Granulation Experiments

### Effect of HPMC Concentration

Larger and more homogeneous granules were formed when the concentration of HPMC rises, as demonstrated in Figure 2. Granule cohesiveness is greatly improved by the polymer's increased viscosity, which reduces fines and promotes particle coalescence.HPMC works well as a bridging agent, binding particles together to improve granule integrity and decrease dust generation. On the other hand, an overabundance of HPMC could prevent granule breakdown leading to the development of large masses.

### Effect of Liquid Addition Method

Compared to the pouring method, the syringe method produced granules that were more uniform and had a smaller size distribution. On the other hand, localized overwetting brought about by the pouring approach resulted in the production of massive agglomerates and an uneven size distribution. More consistent granule formation was ensured by the controlled dispersion made possible by syringe addition, which reduced the possibility of excessive binder accumulation in particular areas.

### Parameter Interaction Effect

The most consistent granules were obtained by combining 5% HPMC with syringe addition, while the highest variation in granule size was obtained when combining 0% HPMC with the pouring method. These results demonstrate the crucial significance that the interplay between the liquid addition technique and binder viscosity plays in maximizing granule qualities and attaining desired granule features.

### Particle Size Distribution Results

By presenting the distribution of calcium carbonate granule particles across different size ranges, the particle size distribution test provides important information about the granule production process. Granule homogeneity and the efficiency of the production parameters can be assessed due to this examination (Fan et al., 2023). Table 2 and 3 provide the summary of the calcium carbonate granule size distribution and its cumulative percentage.

After determining the cumulative percentage for each experiment, the data was plotted on an appropriate coordinate system to visualize the particle size distribution and compare the results across the different experiments, as shown in Figure.3.

Table 2. Calcium Carbonate Granule Size Distribution Results

| No. | 1700 µm< | 1700-850 µm | 850 -710 µm | 710-600 µm | 600-425 µm | 425µm > |
|---|---|---|---|---|---|---|
| 1 | 0.0811 | 0.0811 | 0.3533 | 0.4800 | 0.8668 | 15.9033 |
| 2 | 0.65 | 0.65 | 0.6373 | 0.8773 | 1.5652 | 10.2717 |
| 3 | 13.7176 | 13.7176 | 0.7869 | 0.9391 | 1.5742 | 3.256 |
| 4 | 0.1452 | 0.1452 | 0.7763 | 1.1871 | 1.5458 | 10.8229 |

Table 3. The Cumulative Percentage

| Sive Size (µm) | EXP.1 | EXP.2 | EXP.3 | EXP.4 |
|---|---|---|---|---|
| 425> | 0.41 | 3.13 | 33.23 | 18.91 |
| 425-600 | 11.37 | 35.71 | 84.12 | 77.39 |
| 600-710 | 13.15 | 38.86 | 86.02 | 81.06 |
| 710-850 | 15.56 | 43.08 | 88.21 | 88.44 |
| 850-1,700 | 19.93 | 50.61 | 92.11 | 99.95 |
| 1,700< | 100 | 100 | 100 | 100 |

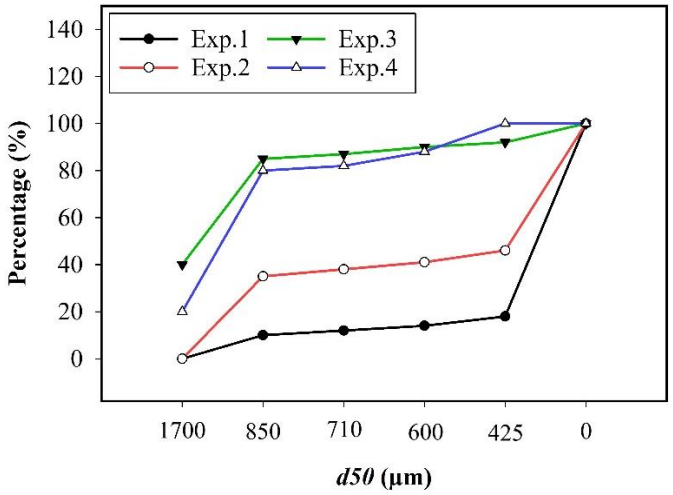



Figure 3. Median Particle Size (*d50*)

The (*d50*) value calculated from Figure 3 for Sample 1 is 159.62 µm. This value represents the median particle size of the sample, meaning that 50% of the particles are smaller than 159.62 µm and 50% are larger. The (*d50*) values for Sample 2, Sample 3, and Sample 4 are 585.90 µm, 1130.12 µm and 105.37 µm, respectively.

**Desiccation of Particle Size Distribution (*d50*) Results**

The cumulative particle size distribution depicted in Chart 1 highlights the effects of liquid addition methods and HPMC concentration on the granule size characteristics.

**Experiment 1 (Syringe, 0% HPMC)**

The granules produced with no HPMC and a syringe addition method exhibit the smallest *d50* value (159.62 µm). The controlled dispersion of liquid during syringe addition minimizes overwetting, leading to finer granules and a more uniform size distribution (Ulusoy, 2023).

**Experiment 2 (Pouring, 0% HPMC)**

In the absence of HPMC, the pouring method results in a significantly larger d50 (585.90 µm). This is attributed to localized overwetting caused by the less precise liquid addition, leading to the formation of larger agglomerates and a broader particle size distribution (Patel et al., 2023).

**Experiment 3 (Syringe, 5% HPMC)**

When 5% HPMC is added and the syringe method is used, the d50 increases to 1130.12 µm, indicating the formation of larger granules. The increase in viscosity due to HPMC enhances particle binding and coalescence, producing granules with greater size and reduced fines. The syringe method ensures uniform distribution of the viscous binder, contributing to this result (Yousif et al., 2022).

**Experiment 4 (Pouring, 5% HPMC)**

Using the pouring method with 5% HPMC yields a slightly lower d50 (105.37 µm) compared to Experiment 3. Despite the presence of a viscous binder, the irregular dispersion of liquid during pouring limits the formation of large granules. Localized over wetting likely led to the formation of agglomerates, but the overall granule size remained smaller compared to the syringe method with the same binder concentration.

**General Observations**

**(1) Impact of HPMC Concentration**: Increasing HPMC concentration consistently results in larger granules due to the polymer's ability to enhance cohesiveness and binding between particles. **(2) Effect of Liquid Addition Method**: The syringe method consistently produces more uniform granules with narrower size distributions compared to pouring, as shown by the smoother cumulative curves for Experiments 1 and 3.

**Data Analysis Using Design-Expert 13**

Design-Expert 13 was used for statistical analysis in order to better understand how the liquid addition method and HPMC concentration affect granule characteristics. Analysis of variance (ANOVA), response surface models, and graphical representations that highlight important patterns and interactions were made possible by the software.

**Interaction of Parameters Analysis**

The combined impact of the liquid addition method (D) and concentration (C) on the median particle size (*d50*) is shown in the interaction plot (Figure 4). An important relationship between these two parameters is indicated by the existence of intersecting lines. In particular, a rise in C resulted in an increase in *d50* when using the syringe method (D1). On the other hand, using the pour method (D2),

d50 decreased as C increased. This implies that the liquid addition technique has an impact on the granulation process, which is consistent with results from earlier research that emphasize the significance of wetting dynamics in particle development.

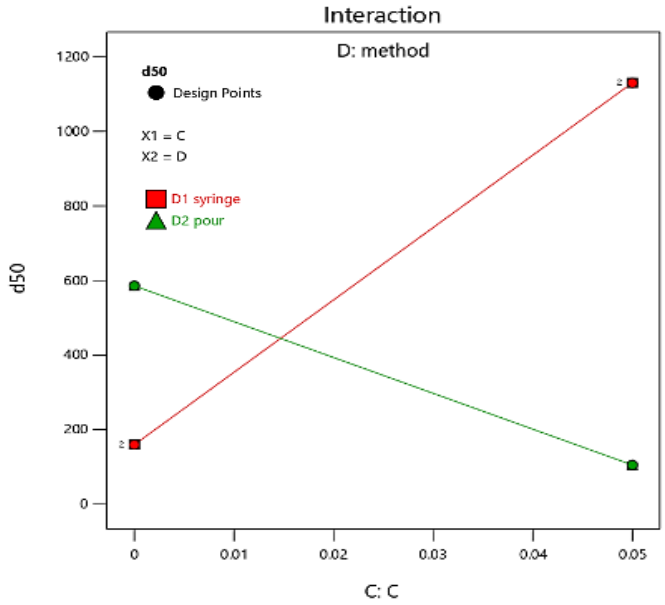



Figure 4. Interaction of the Parameters

Figure 4 provides more light on the interactions between these variables. The droplets are more localized when the liquid is supplied using a syringe, which results in more nucleation sites and a greater granule formation. By distributing the liquid more evenly, the pour approach, on the other hand, may encourage breakup or avoid excessive coalescence, leading to smaller grains at greater concentrations. For granule uniformity control and process parameter optimization, this effect is essential (Paschoal et al., 2024).

**Effect of Each Parameter analysis**

With the liquid addition method fixed (D = syringe), the impact of HPMC concentration (C) on the median particle size (*d50*) is shown in Figure 5. As the HPMC concentration increased to 0.05 when C = 0 (no HPMC), the *d50* increased noticeably. This suggests that the addition of HPMC causes a higher viscosity, which encourages granule coalescence and results in larger granules (Jin et al., 2023).

Additionally, the syringe and pour methods were used to compare the effects of the liquid addition method (D) on *d50*. The pour approach yielded a greater d50 than the syringe method when C = 0. This pattern changed, though, with the syringe approach yielding a higher *d50* at C = 0.05. This reversal implies a substantial interaction between the liquid addition method and HPMC concentration. As the red caution notice suggests, this interaction is probably caused by variations in liquid shipping and nucleation mechanisms between the two addition techniques (Butreddy, 2022).

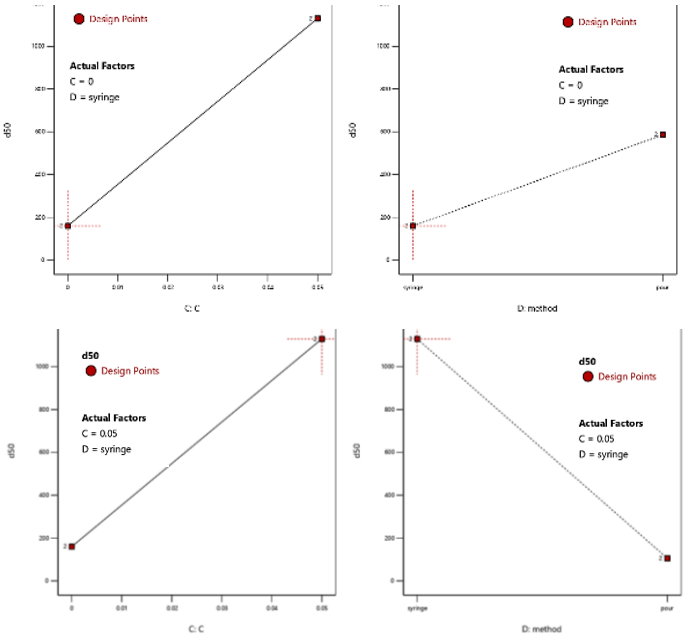



Figure 5. Effect of HMPM Concentration on *d50*

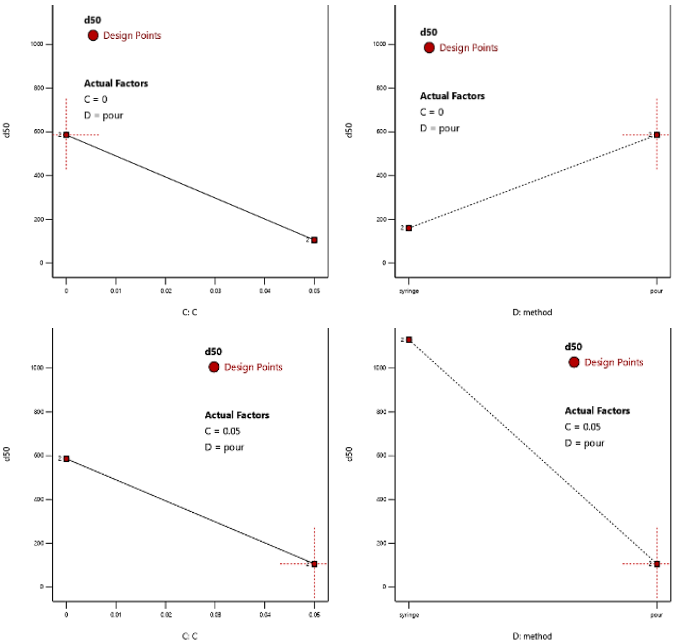



Figure 6. Effect of Addition Method on *d50*

The same parameters are utilized in Figure 6, but they are viewed differently (C = 0.05 with D = pour, and C = 0 with D = pour). When D = pour,raising C from 0 to 0.05 causes *d50* to fall rather than rise as would be predicted. This supports the substantial interaction between C and D and runs counter to the pattern seen for the syringe approach. The pour method's unexpected drop in *d50* at greater HPMC concentrations could be the result of excessive liquid bridging, which increases attrition or breaking during granule formation (Lee and Yoo, 2021).

**Analysis of 3D Surface Plots from Design-Expert 13**

The impact of the liquid addition method (D) and HPMC concentration (C) on the median granule size (*d50*) in a high-shear granulation process is shown in the 3D surface plots produced by Design-Expert 13 (Figure 7). Variations in *d50* are represented by the color gradient in the plots, where larger granules are represented by red and smaller ones by blue. The pouring method is depicted in the first plot, and the syringe approach is represented in the second.

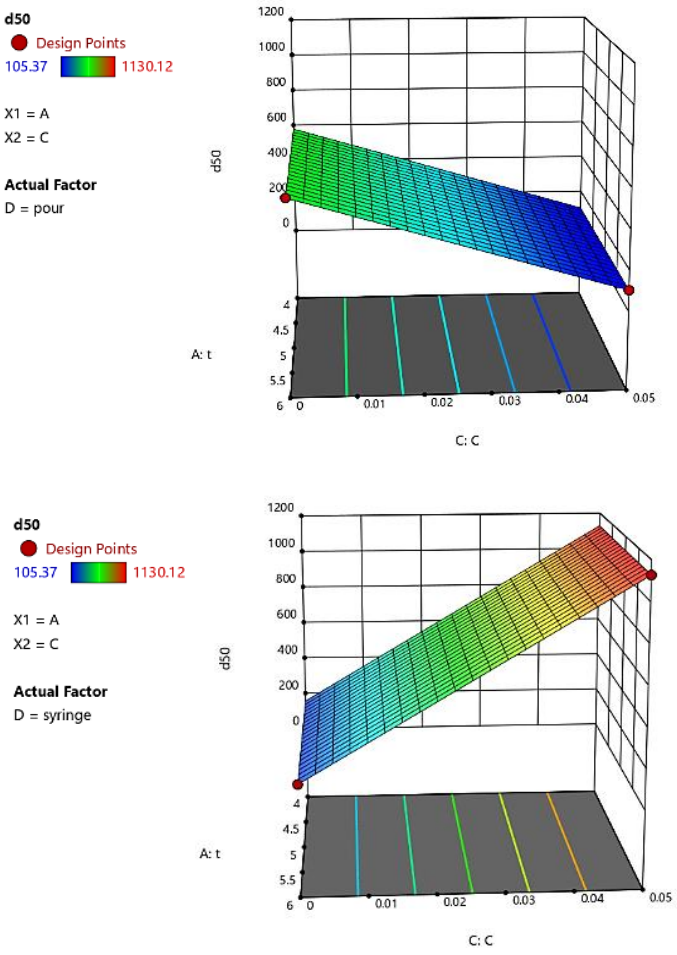



Figure 7. Analysis of 3D Surface Plots from Design-Expert 13

The HPMC content and *d50* are shown to be inversely related in the pouring method. D50 falls as C rises, suggesting that finer granules are produced by greater HPMC concentrations. This phenomenon is explained by the binding liquid's higher viscosity, which prevents it from penetrating the powder bed quickly. Liquid distribution consequently becomes less effective, resulting in smaller particle production and limited granule coalescence (Kromah et al., 2022). On the other hand, a clear correlation can be shown in the syringe approach, where *d50* rises as HPMC concentration does. This method's localized and regulated liquid injection improves liquid distribution, which makes it easier for bigger, more consistent granules to form. By enhancing interparticle adhesion and consolidation, HPMC's increased binding action at higher concentrations encourages granule development.

**Predicted vs Actual values**

The relationship between the actual experimental data and the values predicted by the statistical model is depicted in Figure 8. The data points should closely match the diagonal line (y = x) if the model is accurate, showing little difference between the expected and actual values. Significant departures from this line point to either unaccounted-for variability in the experimental settings or possible model limits. The graphic supports the statistical analysis carried out in Design-Expert 13 by confirming that the model offers a realistic prediction of granule size.

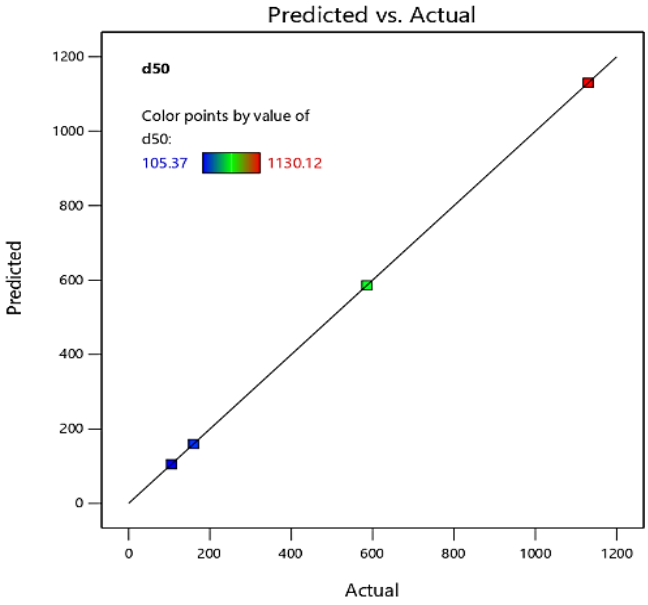



Figure 8. Predicted vs. Actual values

**CONCLUSION**

Granule size is primarily determined by the concentration of HPMC; larger and more cohesive granules are produced when granules coalesce more easily due to greater viscosity. Better control over liquid dispersion was shown by the syringe method, which reduced the production of large agglomerates and produced granules of a more uniform size. On the other hand, localized over wetting caused by the pouring process resulted in irregularities in granule size, especially when no binder was used.

According to optimization studies, the best granule characteristics for pharmaceutical applications are obtained while using a syringe containing 5% HPMC. By ensuring quality and uniformity in the finished granule product, these findings advance our knowledge of wet granulation process optimization

and provide insightful information for pharmaceutical manufacture.

The importance of controlling liquid input and binder viscosity in wet granulation is shown by this study. By improving nucleation control, the syringe approach successfully decreased the production of large agglomerates. Although HPMC increased granule cohesiveness, excessive agglomeration has to be controlled carefully. Syringe-based liquid addition improves granule size uniformity, and a high HPMC concentration does not always result in better granule characteristics, according to statistical analysis using Design-Expert analysis. These results imply that improving granulation efficiency in pharmaceutical processes through the optimization of liquid addition procedures can result in better processing outcomes and more consistent product quality.

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