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Effect of HPMC Concentration and Liquid Addition Method on the Porosity of Granules produced by High-Shear Mixer - Wet Granulation

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Abstract

In the chemical and pharmaceutical industries, granulation is a crucial procedure that enhances the flowability, compressibility, and homogeneity of powders. The mechanical strength, dissolving characteristics, and general stability of pharmaceutical formulations are all significantly influenced by the porosity of the granules. This work examines the effects of liquid addition method and hydroxypropyl methylcellulose (HPMC) concentration on granule porosity in wet granulation using a high-shear mixer, with a focus on instances with L/S = 1.8 and a 6-minute mixing period. The solid phase was calcium carbonate, and the binders were distilled water and 5% HPMC solution. Pouring and syringe adding were the two liquid addition methods used in the studies. The results show that a more denser structure results from increased cohesion and film formation caused by an increase in HPMC concentration, which decreases granule porosity. However, over-wetting brought on by excessive binder saturation at high L/S ratios further reduced porosity. While the pouring method produced non-uniform

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granule morphologies and increased local voids because of uneven binder dispersion, the syringe method produced more uniform granules with decreased porosity. Additionally, granule fragmentation caused by extended mixing (6 minutes) in the pouring method increased porosity as fine particles were produced.
The results obtained the need of controlling binder concentration and liquid addition methods in wet granulation to ensure acceptable granule characteristics. In pharmaceutical manufacturing, where granule porosity control is essential for enhancing tablet quality, drug release, and mechanical strength, the study offers insightful information.
Keywords: Wet granulation, HPMC, porosity, high-shear mixer, binder addition method, pharmaceutical processing.

الملخص

في الصناعات الكيميائية والصيدلانية، تعد عملية التحبيب إجراءً أساسيًا يعزز من قابلية تدفق المساحيق وقابليتها للانضغاط وتجانسها. تؤثر مسامية الحبيبات بشكل كبير على القوة الميكانيكية وخصائص الذوبان والاستقرار العام للمستحضرات الصيدلانية. تبحث هذه الدراسة في تأثير طريقة إضافة السائل وتركيز هيدروكسي بروبيل ميثيل سيليلوز (HPMC) على مسامية الحبيبات في التحبيب الرطب باستخدام الخلاط عالي القص، مع التركيز على الحالات التي يكون فيها نسبة السائل إلى الصلب (L/S) تساوي 1.8 وزمن الخلط 6 دقائق.المادة الصلبه المستعمله هي كربونات الكالسيوم، بينما كانت المواد الرابطة المستخدمة هي الماء المقطر ومحلول HPMCبتركيز 5%. تم استخدام طريقتين لإضافة السائل في التجارب، وهما الصب والحقن بالسرنجة.
أظهرت النتائج أن زيادة تركيز HPMC تؤدي إلى زيادة التماسك وتكوين الأغشية، مما ينتج عنه بنية أكثر كثافة ويقلل من مسامية الحبيبات. ومع ذلك، فإن التشبع الزائد بالمادة الرابطة عند نسب L/S العالية أدى إلى تقليل إضافي في المسامية بسبب الإفراط في الترطيب. لوحظ أيضًا أن طريقة الصب أدت إلى تشكيل حبيبات غير متجانسة وزيادة الفجوات المحلية نتيجة التوزيع غير المتساوي للمادة الرابطة، في حين أن طريقة الحقن بالسرنجة أدت إلى إنتاج حبيبات أكثر تجانسًا مع انخفاض في المسامية. علاوة على ذلك، تسبب التكسير الميكانيكي للحبيبات نتيجة الخلط المطول (6 دقائق) في طريقة الصب في زيادة المسامية بسبب تكوّن الجسيمات الدقيقة.
تشير النتائج إلى أهمية التحكم في تركيز المادة الرابطة وطريقة إضافة السائل في التحبيب الرطب لضمان خصائص مقبولة للحبيبات. تقدم هذه الدراسة رؤى قيمة في تصنيع المستحضرات الصيدلانية، حيث يُعد التحكم في مسامية الحبيبات أمرًا أساسيًا لتحسين جودة الأقراص وإطلاق الدواء وقوتها الميكانيكية.
الكلمات المفتاحية :التحبيب الرطب ، المسامية ، HPMC، خلاط عالي القص،صناعات صيدلانيه

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Introduction:

In industries like food, chemicals, and pharmaceuticals where powder qualities need to be changed to improve processability and end product performance, granulation is a commonly used technique (Kristensen and Schaefer 1987). Because it can increase powder flowability, content uniformity, and compressibility, wet granulation is especially preferred in the pharmaceutical sector (Salmon, Hounslow, and Seville 2007). Granule porosity, which controls the density, mechanical strength, and dissolving behavior of solid dosage forms, is one of the primary characteristics impacted by granulation.

A key factor in granule design, porosity influences the mechanical stability, dissolution rates, and compressibility of tablets (Iveson et al. 2001). While very low porosity might result in hard granules that may impair medication breakdown, high porosity can produce weak granules that are more likely to break (Litster and Ennis 2004). Porosity must be optimized to ensure pharmaceutical formulations of good quality, necessitating research into the effects of formulation and process parameters on this feature.

A common binder in wet granulation, hydroxypropyl methylcellulose (HPMC) is well-known for its capacity to enhance granule cohesiveness and create films (Schæfer and Mathiesen 1996). By encouraging better interparticle interaction and resulting in decreased porosity, increasing HPMC concentration improves granule strength (Scott, Hounslow, and Instone 2000). On the other hand, high binder concentrations may cause

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overwetting, which would fill in the spaces between particles and further reduce porosity (Ennis, Tardos, and Pfeffer 1991). Optimizing pharmaceutical formulations requires a thorough understanding of the relationship between granule porosity and binder concentration.

Granule structure and homogeneity are strongly influenced by the liquid addition method (Knight et al. 1998). According to(Scott et al. 2000), the pouring method frequently produces an uneven distribution of liquid, which results in non-uniform granule sizes and increased porosity because of localized saturation. The syringe method, on the other hand, promotes more homogeneous and compact granules with lower porosity by enabling regulated liquid distribution.

At a fixed L/S ratio of 1.8 and a mixing period of six minutes, the effects of HPMC concentration and the liquid addition method on granule porosity are the main focus of this investigation. The goal of the study is to give optimal granulation parameters for pharmaceutical applications by assessing granule structure, porosity, and uniformity.

Research Problem:

To ensure the appropriate dissolution rate, mechanical strength, and tablet integrity in medical products, granules must have an appropriate porosity. Nevertheless, managing porosity in wet granulation is still very difficult, particularly when using different binder concentrations and liquid addition techniques. This work is significant as it offers a methodical analysis of the effects of HPMC concentration and liquid addition method

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on granule formation. Formulation scientists might use the results to inform their decision-making when developing new processes.

Research Questions:

The following research questions were developed in order to further define the study's parameters:

1. How is the porosity of granules generated through high-shear wet granulation affected by the content of Hydroxypropyl Methylcellulose (HPMC)?

2. How does granule porosity change depending on whether liquid is added by pouring or using a syringe?

3. How do these two factors work together to impact the granules' internal structure and quality?

Research Significance:

This work provides important new information about how formulation parameters affect granule microstructure. This study helps pharmaceutical producers improve granule consistency, reduce process variability, and refine granulation protocols by clarifying the effects of HPMC concentration and binder addition techniques. In the end, the study provides greater control over the characteristics of the final dosage form, including stability, mechanical strength, and dissolution rate.

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Research Objectives:

Since porosity is a crucial physical characteristic that indicates the caliber of the finished granules, this study aims to assess the impact of different HPMC concentrations on the porosity of granules generated by high-shear granulation. In order to determine whether the method results in a more uniform liquid distribution inside the powder bed, it also examines the effects of the binder delivery method—whether by syringe or pouring—on the porosity. Additionally, the study investigates if binder concentration and addition technique might work in concert and how this might affect porosity results. This helps the optimization of processing parameters and advances our understanding of the granulation mechanism.

Research Methodology:

The effects of two independent variables—HPMC concentration and liquid addition method—on granule porosity were examined using a quantitative experimental approach. A high-shear mixer was used to create granules under strictly regulated circumstances. Porosity, which was measured with modern equipment, was the main response. Data analysis and experiment structuring were done using Design-Expert 13 software.

Research Procedures:

Four experiments in total, all methodically planned using a full factorial approach, were included in the study. Pharmaceutical-grade chalk was used for the powder base, distilled water served as the granulation fluid,

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and hydroxypropyl methylcellulose (HPMC) was added as a binder in two different concentrations: 0% and 0.5%. The two binder methods of syringe addition and pouring were examined. In a high-shear mixer fitted with specially made aluminum blades as seen in (figure 1), granules were created. Every experiment was carried out with a fixed mixing period of six minutes and a consistent liquid-to-solid ratio (L/S = 1.8). Following granulation, the Autotap (for Apparent Density measurement) and Ultrapyc (for True Density measurement) were used to determine the porosity, which calculated using Equation (1) ,of the four granule samples that were chosen based on their physical attributes. An overview of the factors under investigation and the associated experimental settings is given in Table 1.

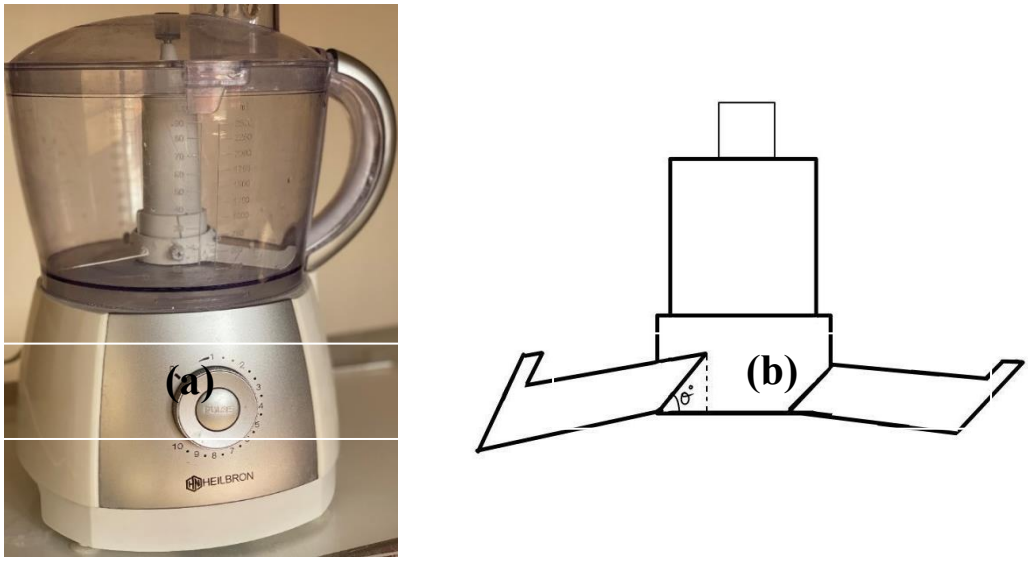

Figure.1 Modified household high-shear mixer with aluminum blades was used for granulation

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Table 1. Granulation process factors

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

$$porosity = 1 - \frac{Apparent\ Density}{True\ Density} \quad \text{.....(1)}$$

Results and Discussion:

The results of the four experimental settings are displayed in Figures (2) to demonstrate the effects of various HPMC concentrations and liquid addition methods on granule porosity. It is obvious from these figures how the different combinations impact the porosity.

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C= 0

C= 0.05

SYRINGE

POURING

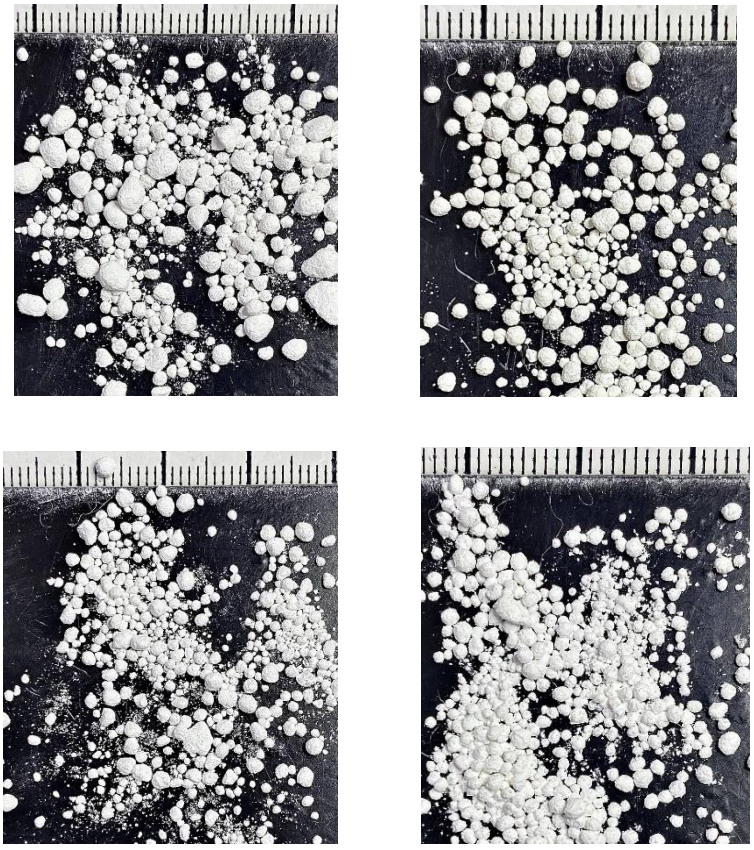

Figure 2: granulation results measurement in mm

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porosity Results

Table 1 presents the apparent density, true density, and porosity for all experiments:

No.	apparent density	true density	Porosity
1	1.0654	2.7210	0.608453
2	1.2195	2.6500	0.539811
3	1.2806	2.2545	0.43198
4	0.9478	2.6442	0.641555

Table 2: porosity results

Effect of HPMC Concentration on Porosity

Granule porosity was greatly affected by HPMC addition. Porosity at 5% HPMC was heavily reliant on the liquid addition technique. The findings show that, when dispersed correctly, HPMC encourages granule densification, as shown in Sample 3, where the syringe method generated a compact structure with few voids. However, Sample 4 (pouring method) showed poor granule consolidation and increased porosity due to inappropriate viscous binder dispersion.

Effect of Liquid Addition Method on Porosity

Granule porosity was largely determined by the liquid addition method, especially when considering binder concentration:

The pouring method produced lower porosity (0.5398) than the syringe method (0.6085) at 0% HPMC (Samples 1 and 2). This implies that

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pouring improved granule packing and decreased voids by allowing the liquid to spread more evenly in the absence of HPMC.

The syringe approach produced a much lower porosity (0.4320) at 5% HPMC (Samples 3 and 4) than pouring (0.6416). This suggests that greater wetting and granule consolidation were achieved at higher viscosity levels by syringe-controlled liquid distribution, which also prevented the creation of extra voids.

Combined Effect of HPMC Concentration and Liquid Addition Method on Porosity

Important patterns in granule formation are highlighted by the combined effects of HPMC concentration and the liquid addition method: At 0% HPMC, the pouring method beat the syringe method in terms of porosity reduction. This results in improved granule packing since the low-viscosity liquid spreads evenly when poured.

At 5% HPMC, the syringe method yielded denser granules with reduced porosity, indicating that controlled addition improves liquid distribution and avoids overwetting for very viscous binders.

The 5% HPMC pouring condition had the highest porosity (0.6416), showing that pouring a highly viscous binder causes uneven wetting, which produces weak and porous granules

Data Analysis Using Design-Expert 13:

To assess the effects of the liquid addition method and HPMC concentration on granule porosity, statistical analysis was conducted

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using Design-Expert 13. The program made it easier to use response surface models, analysis of variance (ANOVA), and graphical representations, which allowed for the discovery of important trends and interactions affecting porosity.

Effect of each factor analysis

The graphical results, which are displayed in Figures 3 and 4, clearly illustrate the main effects of the concentration of Hydroxypropyl Methylcellulose (HPMC) (C) and the liquid addition method (D) on porosity. These figures show how granule structure and porosity are affected by these parameters. Porosity and HPMC concentration have a complex relationship that varies based on the experimental setup. In certain situations, porosity rises with increasing HPMC content, while in others, it falls. This variability highlights the intricacy of the interactions involved and implies that porosity is impacted by factors other than HPMC concentration alone.

Additionally, the liquid addition method (pour vs. syringe) has a substantial impact on porosity. The distinct trends under various experimental settings show how complexly HPMC concentration and the liquid addition method interact. This interaction is particularly evident in Figure 4, which demonstrates how the liquid addition technique significantly influences the way HPMC concentration influences porosity. When using the syringe approach, porosity decreases with increasing HPMC concentration, suggesting that targeted binder administration improves granule densification. On the other hand, a higher HPMC content results in enhanced porosity when the pour method is used,

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indicating that uniform binder dispersion encourages the creation of a more porous structure.

These results highlight how crucial it is to take into account how the liquid addition method and HPMC concentration interact when designing experiments to maximize porosity. According to the research, reaching the appropriate porosity levels necessitates an advanced knowledge of the ways in which these variables interact under specific conditions. This complexity highlights the necessity of thorough statistical analysis and careful experimental design in order to clarify the underlying mechanisms and extract useful findings.

In summary, the analysis shows that a complex interaction of factors affects porosity, with the liquid addition method and HPMC content having a particularly important impact. The findings highlight how crucial it is to design experiments completely, taking into account the impacts of each individual element as well as how they combine, in order to attain the best possible granule structure and porosity results. One important factor influencing porosity is the interplay between HPMC concentration and the liquid addition method; understanding this relationship is essential for maximizing granule properties in a variety of applications.

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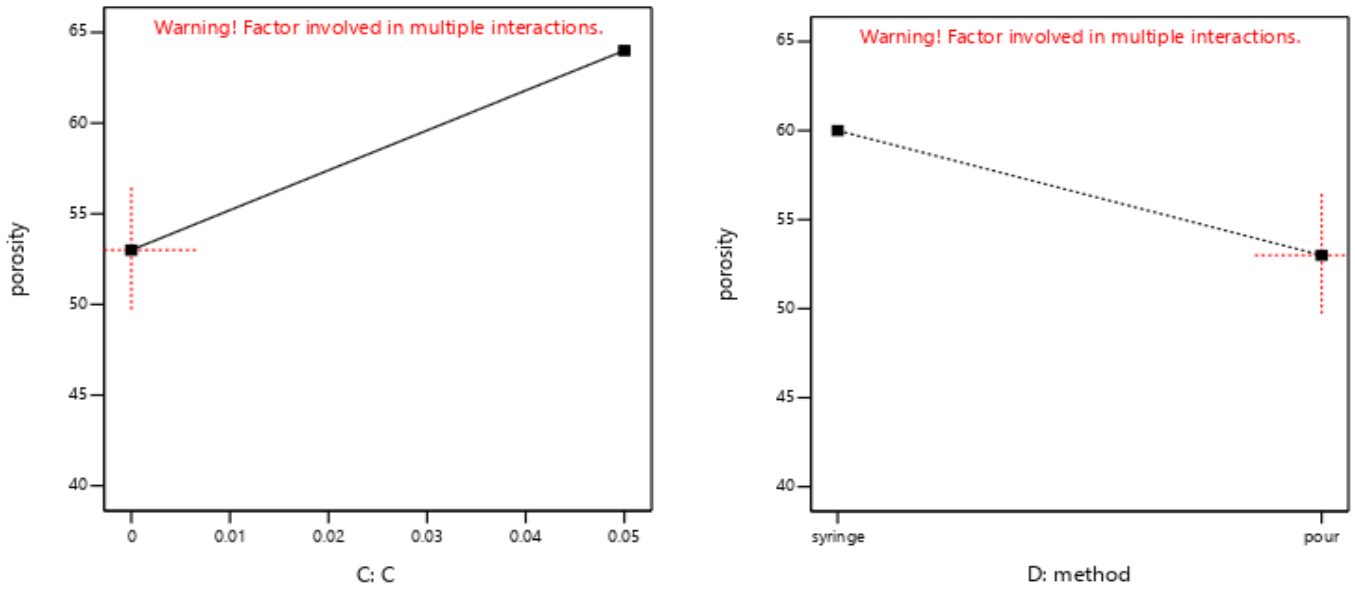
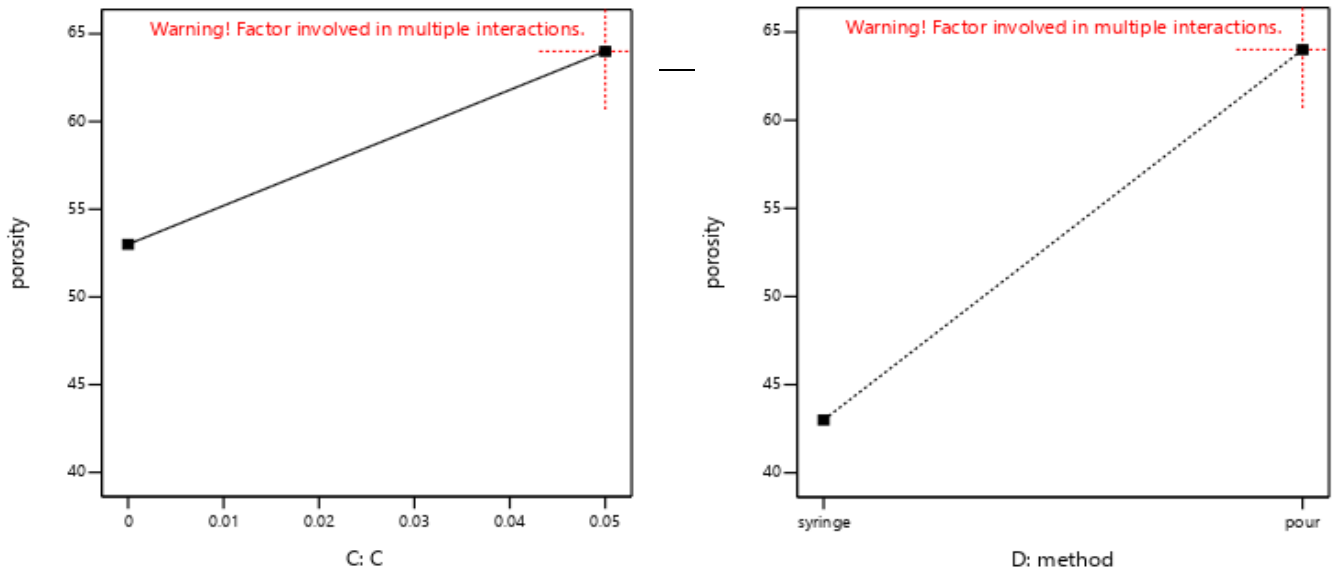


Factor Coding: Actual

porosity
Design Points

Actual Factors
A = 5
B = 0.18
C = 0
D = pour



Factor Coding: Actual

porosity
Design Points

Actual Factors
A = 5
B = 0.18
C = 0.05
D = pour

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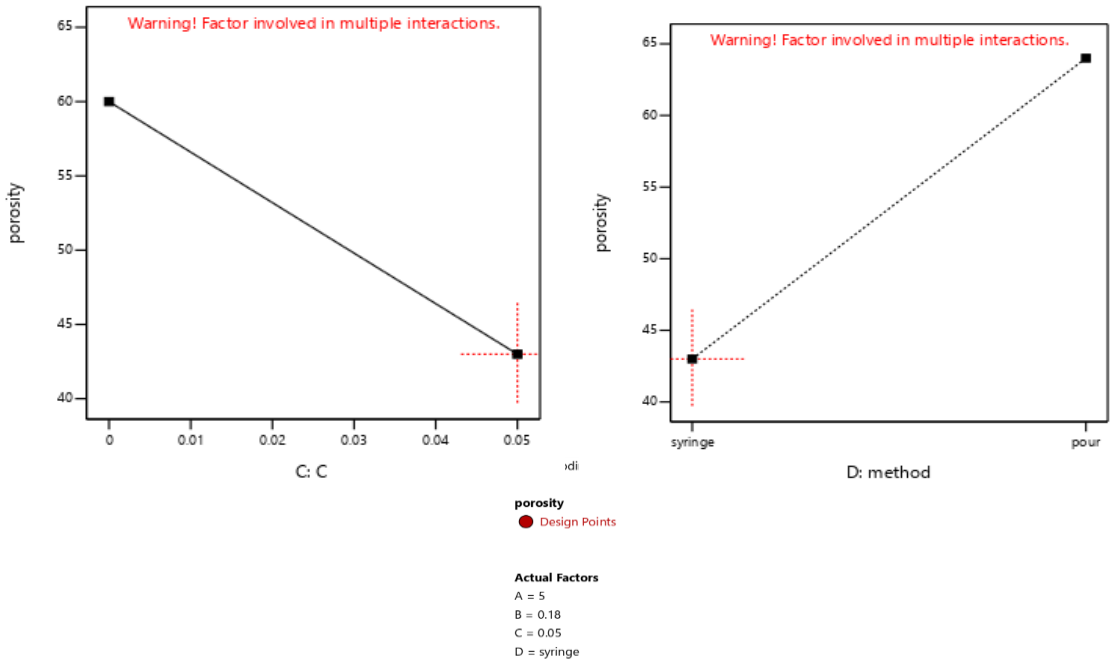
Figure 3. Effect of concentration factor and pour method on porosity



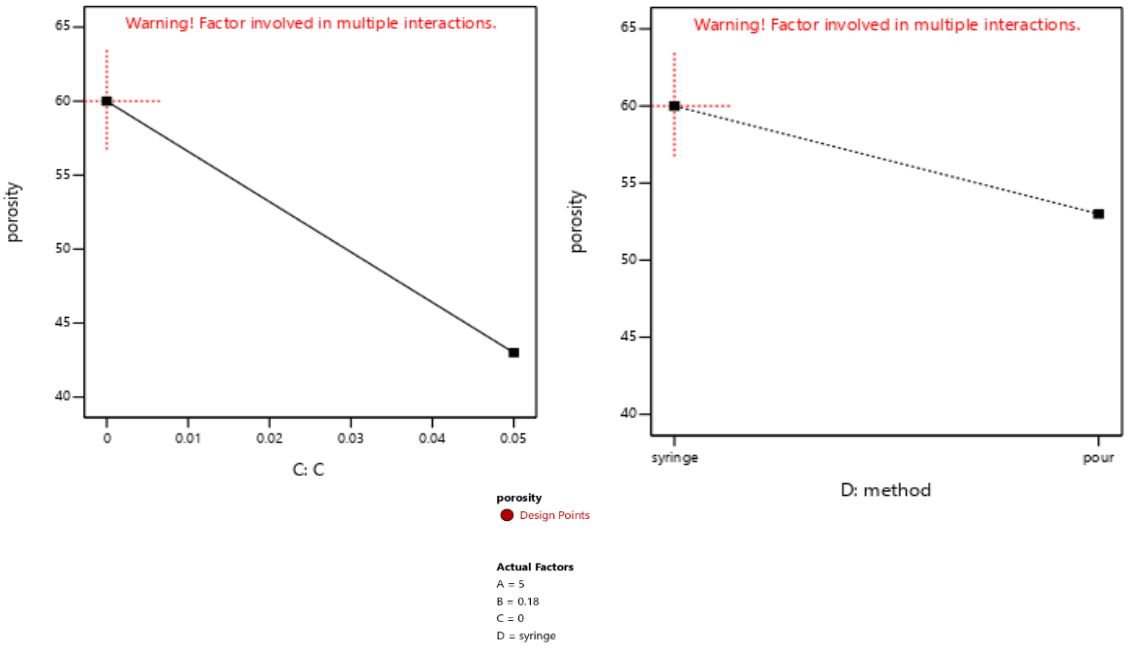


Figure 4. Effect of concentration factor and syringe method on porosity

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Interaction of factors Analysis

A combination of the liquid addition method (D) and HPMC concentration (C) and their combined impact on porosity are shown in figure 5. Porosity reduces with increasing HPMC concentration when using the syringe method. This implies that granule densification is improved by localized binder delivery, which is accomplished via the syringe method. Stronger interparticle bonds are probably encouraged by the binder's targeted control, which results in a more compact and less porous structure. The idea that localized wetness enhances granule densification is supported by this data. On the other hand, porosity rises with increasing HPMC concentrations when the pour method is used. This suggests that the pour method's consistent binder dispersion promotes the formation of a more porous granule structure. A higher absence fraction within the granules may be supported by the connection formed by the binder's even distribution.

The dependency of porosity on both parameters is further supported by the significant interaction between HPMC concentration and the liquid addition method. This interaction shows how crucial it is to take into account both the liquid addition technique and the HPMC concentration when creating procedures or experiments meant to regulate porosity. The results indicate that the effect of HPMC concentration on granule properties can be considerably changed by the method of liquid addition selected.

In summary, the data shown in Figure 5 indicates that the interaction between HPMC concentration and the liquid addition method has a complex impact on porosity. At greater HPMC concentrations, the syringe method's targeted binder control results in decreased porosity and improved

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densification. On the other hand, the pour method produces more porosity due to its consistent binder dispersion. These revelations highlight the necessity of a complex experimental design strategy that takes into consideration the intricate relationships between these crucial elements in order to get the required porosity levels.

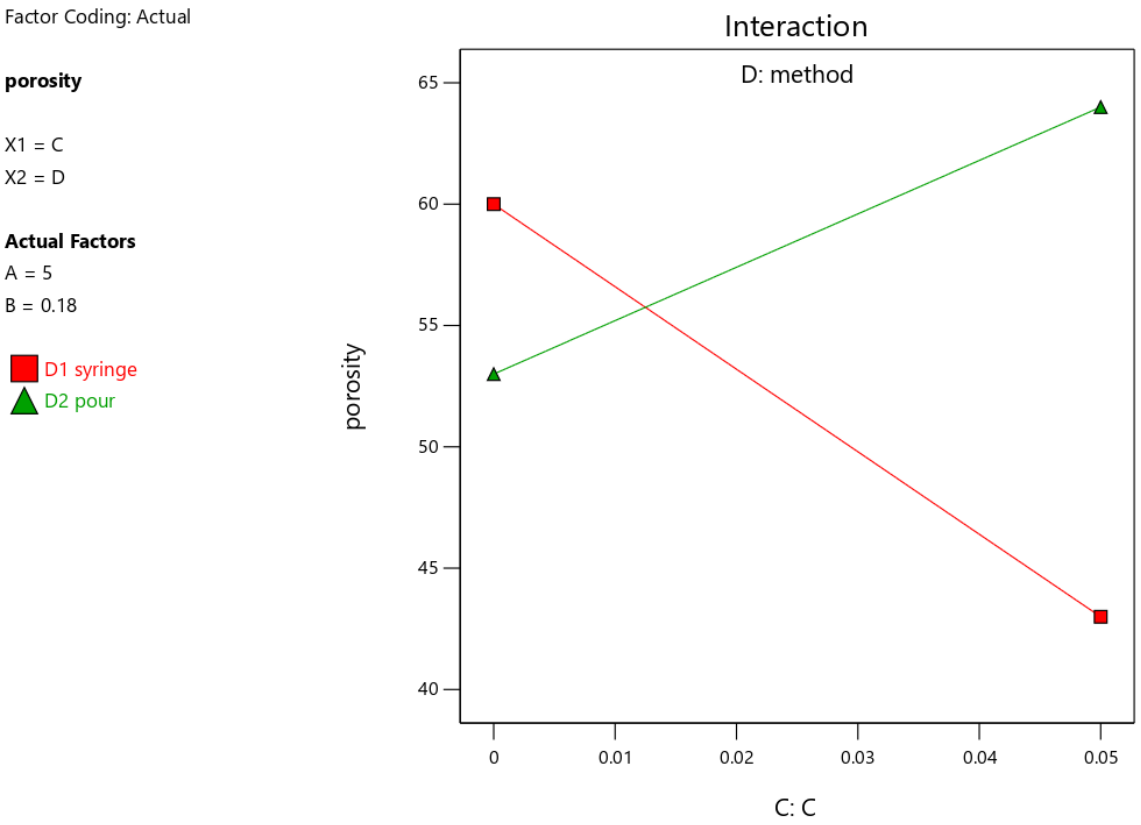

Figure 5. The interaction of the factors

Analysis of 3D Surface Plots from Design-Expert 13

The relationship between the liquid addition method (D) and HPMC concentration (C) and how they both affect porosity is shown in Figure 6. Depending on the liquid addition method, different trends can be seen in the response surface plots.

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The response surface plots in Figure 6 show how porosity varies with the liquid addition method and different HPMC concentration levels. The curvature and interactions between these variables are shown in the 3D surface plots, which show how the granules' surface morphology is affected. Because of the syringe method's confined and possibly uneven binder dispersion, the surface plot likely displays an upward trend in porosity as HPMC concentration rises. A decreasing trend in porosity with increasing HPMC content would be seen in the surface plot for the pour method, suggesting denser granule formation and more uniform binder dispersion.

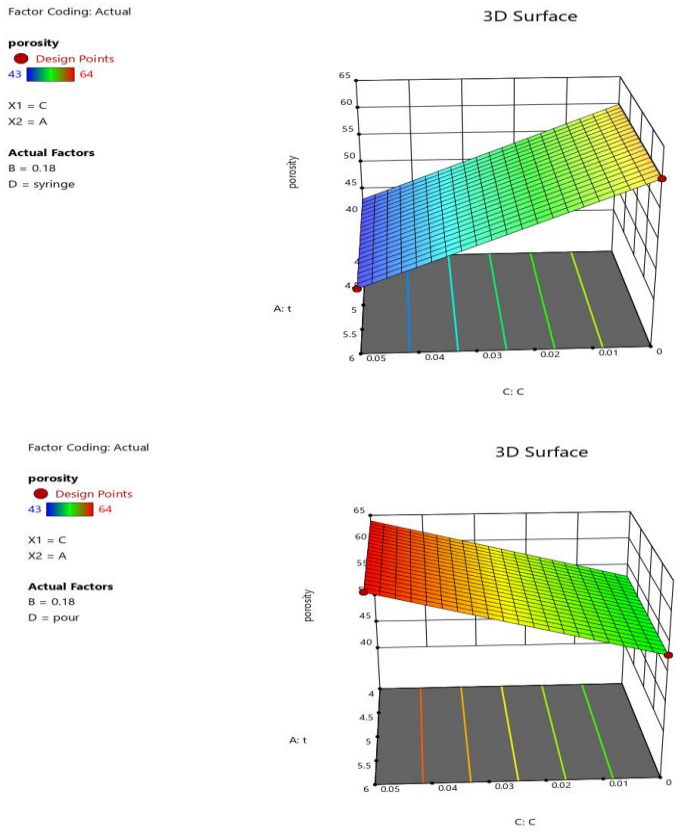

Figure.6: Analysis of 3D Surface Plots from Design-Expert 13

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Predicted vs. Actual values

A comprehensive evaluation of the predictive model's accuracy in determining porosity can be seen in Figure 7Predicted vs. Actual plot. This graphic shows how well the model fits the observed data by contrasting expected porosity values with the experimentally measured (actual) values. Analyzing this figure is essential for determining how well and consistently the model captures the underlying causes of porosity. The porosity values, which vary from 43 to 64, are used to color-code the sites in Figure 7. The expected values and actual observations across various porosity levels can be clearly seen due to this color gradient.

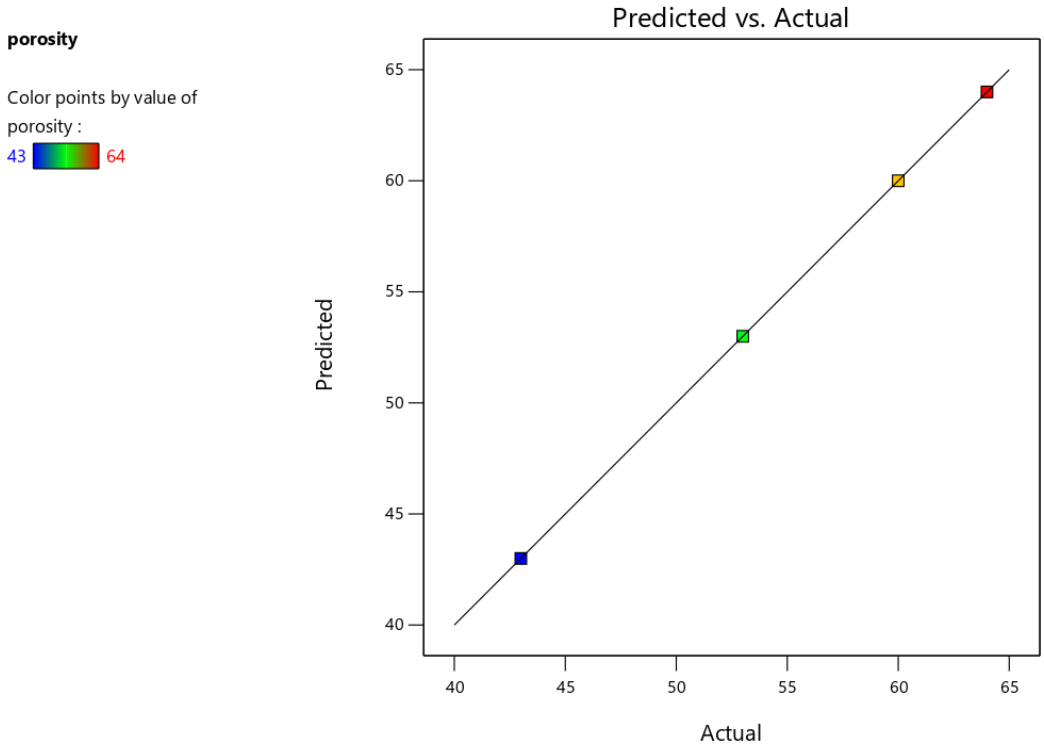

Figure 7. Predicted vs. Actual values

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The points would gather closely around the diagonal line (where anticipated values equal actual values) if there was a high association. Deviations from this line indicate locations where the model may over- or under-predict porosity, indicating differences in the predictive power of the model.

With intermediate values of 45, 50, and 55, the anticipated porosity values range from 40 to 60. This range shows that the model can predict porosity under a variety of conditions.

The experimental data shows good agreement with the model's predictions, as evidenced by the fact that the actual porosity values, which range from 40 to 65, nearly match the expected range. Though some variations at particular values would necessitate more research, this shows that the model is catching the overall increases in porosity.

In conclusion, Figure 7 offers an easily understood and clear explanation of the model's porosity prediction performance. Although the observed variances highlight the need for additional improvement, the alignment between projected and actual values indicates that the model is usually accurate. The accuracy and resilience of the model depend on this research, especially in applications where exact porosity control is crucial. Future iterations of the model can be enhanced to better represent the complex interactions between the elements determining porosity by correcting the differences that have been found. This will ultimately increase the model's predictive capacity.

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Conclusion:

With calcium carbonate as the solid phase and either distilled water or a 5% HPMC solution as the binder, the experiments were carried out under controlled conditions, maintaining a fixed liquid-to-solid ratio (L/S = 1.8) and a mixing time of six minutes. The results highlight the significant impact of the interaction between HPMC concentration and liquid addition method in determining granule porosity and structural stability. This study examines the effect of Hydroxypropyl Methylcellulose (HPMC) concentration and liquid addition techniques (syringe vs. pouring) on granule porosity within wet granulation processes using a high-shear mixer.

Main Findings:

1. Granule porosity is often decreased by increasing HPMC concentration because of improved cohesion and film formation, which results in denser granule structures. Nevertheless, excessive binder saturation may happen at higher HPMC concentrations, further decreasing porosity and perhaps changing the characteristics of the granules. These results are consistent with earlier research by Schaefer and Mathiesen (1996) and Scott et al. (2000), which found that HPMC strengthens interparticle interaction to increase granule cohesiveness and reduce porosity.
2. Granule porosity was discovered to be significantly influenced by the liquid addition technique. Granules with reduced porosity and enhanced homogeneity were generated by the syringe approach, which permits regulated and localized binder distribution, especially

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at higher HPMC concentrations. On the other hand, because of uneven wetting and localized saturation, the pouring method—which is characterized by less regulated binder dispersion—produced increased porosity. These findings confirm those of Knight et al. (1998) and Scott et al. (2000), who showed that granule homogeneity and porosity are greatly influenced by liquid addition strategies.

3. This study also shows that the combination of liquid addition techniques and HPMC concentration has an important effect on granule porosity. By avoiding overwetting and encouraging stronger interparticle interaction, the syringe method was especially successful in lowering porosity and enhancing granule growth when paired with higher HPMC concentrations. On the other hand, because it allowed for a more even dispersion of the binder, the pouring method worked better with lower HPMC concentrations. These results highlight the need to optimize granule properties by considering both parameters into account at the same time.

Recommendations for Future Research:

To further improve granule quality and process efficiency, future study should concentrate:

1. Investigation of Other factors:

   Future research should look into how other factors, like granulation time, mixing speed, and binder types, affect granule porosity. This would assist uncover more variables that affect porosity and offer a more thorough understanding of the granulation process.

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2. Advanced Optimization and Modeling:

   Predictive models for porosity could be further improved by utilizing machine learning algorithms and sophisticated statistical techniques. Granulation procedures would become more effective and efficient as a result of these models' improved capacity to optimize granule properties under varied settings.

3. Expansion Research:

   The results of this study would be more validated and its application in industrial settings would be guaranteed with larger-scale experimentation. This is especially crucial for the production of pharmaceuticals, where scalability and consistency are essential.

4. Comprehensive Mechanistic Research:

   Deeper understanding of how HPMC concentration and liquid addition techniques affect porosity may be possible with additional investigation into the mechanisms of interparticle bonding and binder dispersion. Better control over granule characteristics and the creation of more efficient granulation procedures could result from this.

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