Dijlah Journal of Engineering Science (DJES) Vol. 3, No. 2, June, 2026, pp.378-390
ISSN: Printed: **3078-9656, Online: 3078-9664**, paper ID: 172

Impact of Granulation Parameters on the Porosity and Disintegration Time of HPMC Granules Prepared by Fluidized Bed Technique

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Article Info

Article history:

Received Mar., 15, 2026
Revised Apr.,18, 2026
Accepted May.,10, 2026

Keywords:

Fluidized bed granulation
HPMC
Porosity
disintegration
Design-Expert 13

ABSTRACT

Fluidized bed granulation is widely applied in several industrial sectors. The present study examines how key process parameters (air flow rate, liquid-to-solid (L/S) ratio, granulation time, and feed mass) affect the porosity and disintegration time of (HPMC) granules. Experiments were carried out using A lab-scale, top-spray fluidized bed granulator and a full factorial experimental design was employed and analyzed both the individual and interactive effects of the selected variables. The findings show that an increase in feed mass resulted in higher bed porosity, while higher airflow rates tended to decrease porosity. The increased in feed mass likely promoted the formation of larger, less densely packed agglomeration. The L/S ratio and granulation time showed a major interactive effect, with higher levels promoting structural consolidation and reduced porosity. Disintegration time was primarily prolonged by higher L/S ratios, whereas increased granule porosity facilitated faster liquid penetration and shorter disintegration time.

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1. INTRODUCTION

Granulation is one of the most essential unit operations in particulate processing industries, enabling the transformation of fine powders into larger, more uniform granules.[1],[2],[3]. Fluidized bed granulation (FBG) represents one of the most versatile and efficient granulation techniques. It allows simultaneous spraying, wetting, drying, and cooling in a single system, making it suitable for precise control of granule properties through adjustment of operational parameters [4],[5].Small particle agglomeration enhances the powder's handling qualities, such as its ability-flow, and lessens the production of dust, Additional enhancements to the agglomerated powder include a faster rate of dissolution through decreased lump formation or powder flotation [6],[7]. Granule porosity which governs the density, mechanical strength, and dissolution behavior of solid dosage forms, is one of the key characteristics directly influenced by the granulation process. Agglomeration produces a larger bulk density, which lowers transportation costs and improves compatibility for a subsequent tabletting operation [8],[9]. Previous studies have showed that the physical structure of granules produced by fluidized bed granulation plays a fundamental influence in dictating key performance parameters such as porosity and disintegration behavior.In particular, granule porosity, controls liquid penetration, internal capillary action, and mechanical integrity, which directly influence downstream processing performance and disintegration time [10]. Hemati et al., (2003) reported that binding quantity and exposure to air time obviously influence pore formation inside granules produced in fluidized bed systems. Larsson et al., (2008) examined the granulation behavior of hydrophilic polymers and proved that partial dissolution and polymer swelling during wetting contributes to pore development in granules, these porous enhance water penetration during contact to dissolution media, speeding disintegration. Anywise, the long time for the granulation process increase particle consolidation, decreasing porosity and slowing disintegration. De Simone et al., (2019) studied the influence of airflow on granule structure and showed that the increase dryness is attributed to the high air content, which leads to reduced porosity and stronger particles with a long disintegration time. On the other hand, modest airflow conditions contribute to balanced drying and pore conservation, which resulting in granules with improved disintegration performance. In this work, Hydroxypropyl methyl-cellulose (HPMC) is used as the main feed solid instead of than merely as a binder. Upon wetting, HPMC particles subject to partial dissolution and surface softening, this lead to the formation of dense bridges that help consistency, mechanically stable granules. This characteristic allows uniform moisture distribution and reduce over-wetting or particle breakage during granulation [13],[11].Despite these findings, most previous studies focused on mechanical strength, particle size, or dissolution behavior, with limited emphasis on the combined evaluation of porosity and disintegration time for HPMC granules produced by FBG. Thus, the present study aims to bond this gap by systematically investigating how process parameters influence granule porosity and, subsequently, disintegration performance.

2. METHOD

In this study the feed matrial was Hydroxypropyl Methylcellulose (HPMC), provided as a fine powder with a median size of (79.796)µm was determined by using Shimadzu SALD-2300(wing II: Version 3.4.6)size analyzer. See (fig.1). Distilled water was used as a binder for the granulation process. The distilled water was introduced into the granulation chamber through a pneumatic spray nozzle to achieve a homogeneous distribution and controlled wetting.

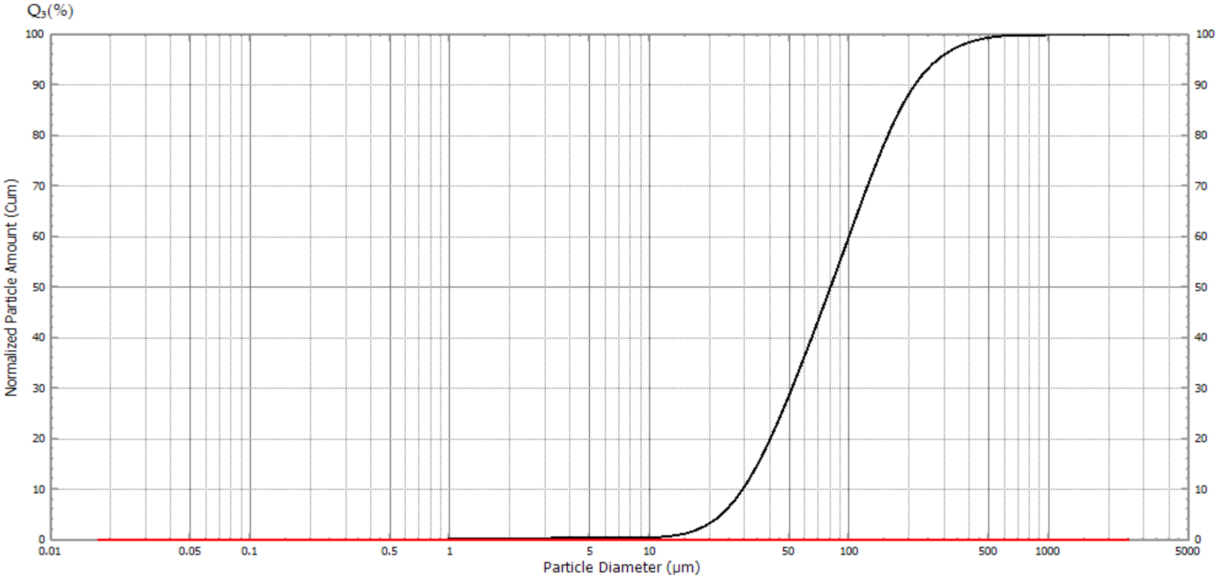


Figure 1. size distribution of HPMC powder

2.2. Apparatus and Experimental Setup

The experimental setup as shown in figure (2a). The experiments were achieved in a batch, small-scale, top-spray fluidized bed granulator, fig. (2b), locally planned and invented using transparent Perspex material. Compressed air from an air compressor passed through a Rota-meter for flow measurement and was preheated by an electric heater before entering the granulation chamber. A therm o-couple constantly monitored the inlet air temperature to keep stable operating conditions. A stainless steel distributor plate (2 mm perforation) covered with a fine wire mesh to prevent particle back flow. The chamber was armed with temperature and humidity sensors, allowing real-time monitoring and control of process stability. A two-fluid pneumatic spray nozzle, positioned Inside the chamber atomized the binder solution provided from A container. An air compressor supplies compressed air to the nozzle for controlling the spray rate and to distribute the droplets on the powder bed. At the top section of the chamber, a cylindrical air filter prevented particle loss, while excess air and moisture were discharged through an air outlet harbor, maintaining constant internal pressure.

Figure 2a.Experimental setup of Bach fludized bed granulater

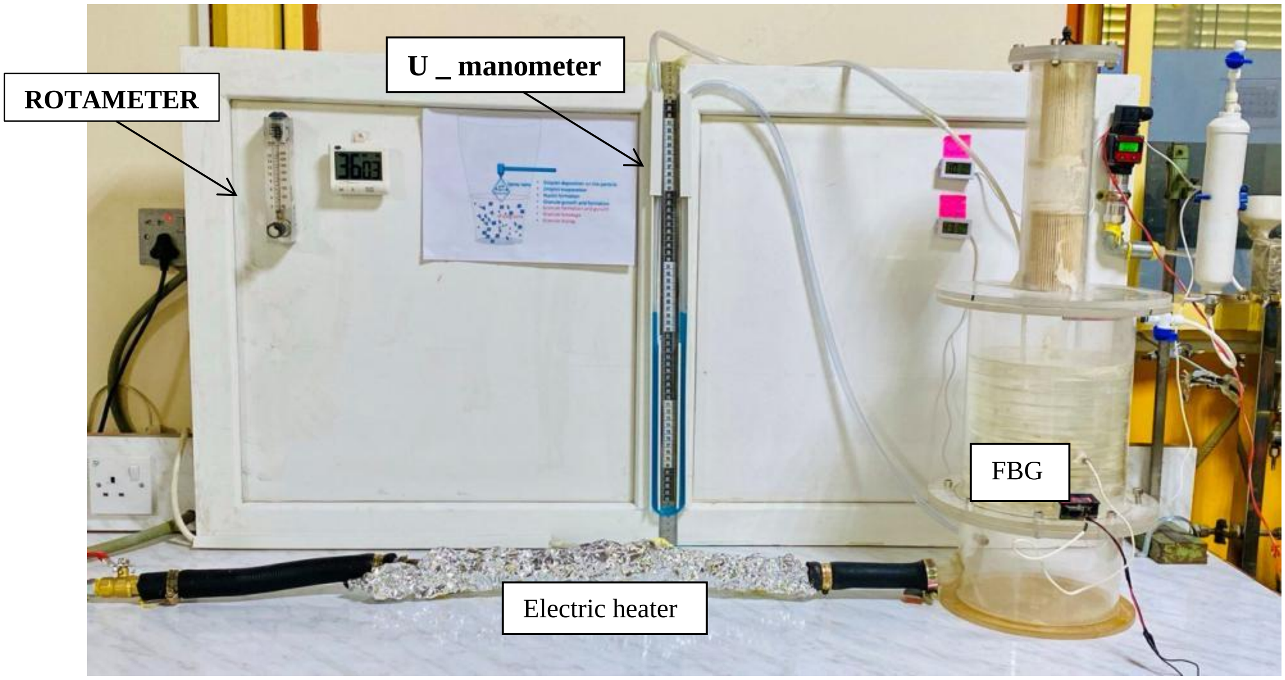


Figure 2b: Batch fluidized bed granulator

2.3. Granule characteristic.

2.3.1. porosity

Porosity of the granulated HPMC samples was determined using a liquid displacement method, in this method a liquid doesn't penetrate the pores of the granules is used to determine the external volume of the granules[14][15].

.A fixed mass of granules (2 g) was used. This approach , based on volume displacement and density comparison between the apparent density and the true density of the granules, is a particle method to quantify porosity in particulate systems[16]. Bulk density can be determined accurately by measuring the mass of the container when empty and when filled, along with knowing its volume. The apparent density of the granules was determined using kerosene displacement in a 10-ml volumetric pycno-metry. The porosity (ε) was calculated using the following equation:

$$\varepsilon = 1 - \frac{\rho \quad apparent}{\rho \quad true} \tag{1}$$

The apparent density was calculated as :

$$\rho\ apparent = \frac{M\,g}{V} \tag{2}$$

Where : Mg mass of the granules, (g).
V is the displaced liquid volume,(ml).

2.3.2 Disintegration time

The disintegration time of HPMC based granules was evaluated to characterize their breakdown behavior. Hydroxypropyl methyl cellulose (HPMC) is a hydrophilic polymer that tends to form a viscous gel layer upon hydration; this typically slows down the disintegration process compared to rapidly dissolving formulations. In this study, disintegration time is defined as the interval required for the granules to break down into smaller particles that can pass through a (10- mesh) screen. To determine this, approximately 1 g of HPMC granules was placed in 1000 ml of distilled water at room temperature using(Pharma Test, granule Disintegration Tester, Germany).

2.3.3 Statistical analysis

Statistical analysis was carried out using Design Expert 13 (A randomized full factorial design which consist of 20 run, see table 1), to evaluate the individual and interaction effects of the selected parameters. Experimental designs are widely used in pharmaceutical science.

Table 1 Parameters of the Granulation Experiments.

Factor 1		Factor 2	Factor 3	Factor 4
Run	A: feed	B: air inlet rate	C: L/s	Granulation time
1	150	180	0.25	5
2	50	120	0.25	10
3	100	150	0.35	7.5
4	150	180	0.25	10
5	150	120	0.25	10
6	50	180	0.25	10
7	100	150	0.35	7.5
8	150	120	0.45	10
9	150	120	0.25	5
10	100	150	0.35	7.5
11	150	120	0.45	5
12	150	180	0.45	10
13	50	120	0.25	5
14	50	120	0.45	10

15	50	180	0.25	5
16	50	120	0.45	5
17	50	180	0.45	10
18	100	150	0.35	7.5
19	150	180	0.45	5
20	50	180	0.45	5

The DOE analysis shows that the porosity model is highly reliable, explaining about 91% of the data variation with excellent agreement between predicted and actual values as shown in table (2) below.

Table 2: A nova and R-squared results for the porosity prediction model.

Std. Dev.	0.9736	**R^2**	0.9157
Mean	45.63	**Adjusted R^2**	0.8314
C.V. %	2.13	**Predicted R^2**	0.6347
		Adequate Precision	12.6306

3. RESULTS AND DISCUSSION

A 32 randomized full factorial design was used and the effect of independent variables (loading feed , l/s ratio, air flow rate and granulation time) was studied on the response variables (porosity and disintegration time) using Design Expert® software trial version 13 (Stat- ease Inc., Minneapolis, MN, USA).

3.1. Effect of Process Parameters on porosity.

Table (2) presents the experimental porosity values obtained from the different runs. The results show noticeable variations in porosity depending on the operating conditions.

Table (2): values of porosity

Exp.no.	Porosity (ε)	Exp.no.	Porosity (ε)
1	0.4144	11	0.4686
2	0.4958	12	0.40.16
3	0.4628	13	0.4587
4	0.4415	14	0.4588
5	0.4663	15	0.4643
6	0.4937	16	0.4575
7	0.4518	17	0.4644
8	0.4337	18	0.4715
9	0.4388	19	0.4793
10	0.4438	20	0.4597

In general, Feed amount (A) is the strongest positive factor, meaning that increasing the feed leads to higher porosity. In contrast, the air flow rate (B) shows a negative effect, where higher airflow reduces porosity while the interaction between L/S ratio (C) and granulation time (D) also plays a major role (positive interaction)suggests that changing these two factors together enhances porosity. Meanwhile, the negative (ACD) interaction indicates that combining high levels of feed, L/S ratio, and granulation time tends to decrease overall porosity. Based on the cube plot, the maximum porosity occurs at the high levels of the key factors (A = 150, C = 0.45, D = 10). This results should be carefully studied to realize accuracy control over the final product properties. The curvature test refers to a nonlinear relationship, meaning the optimal porosity resides in the design space.

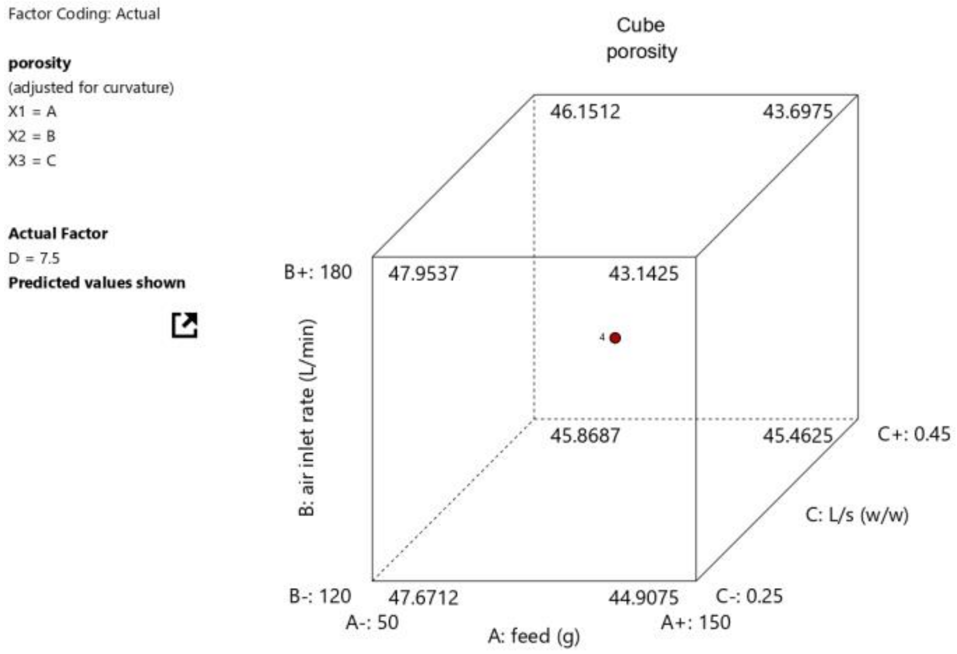
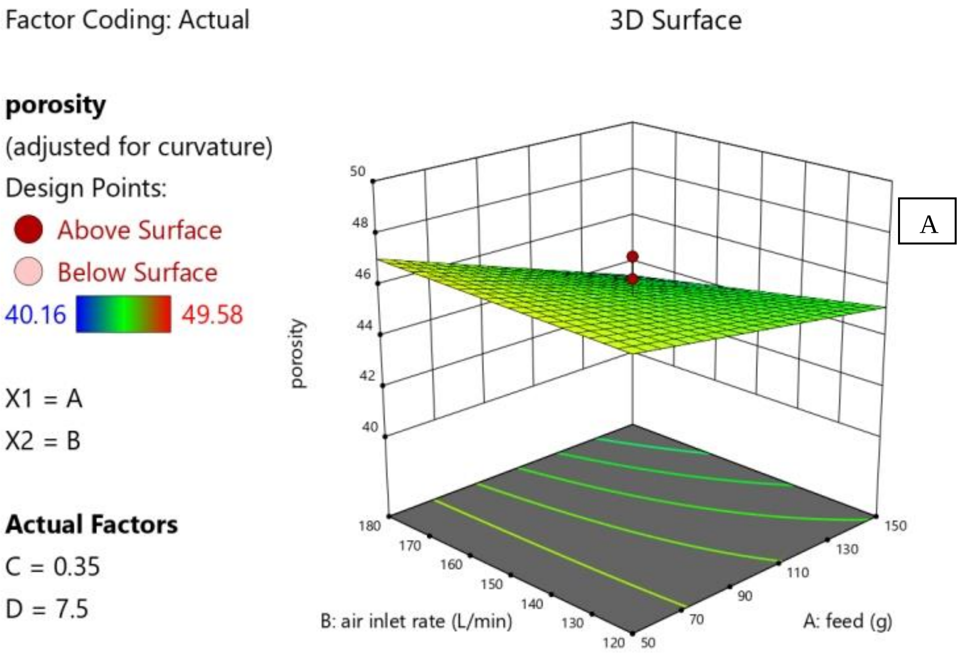


Figure 3: analysis of variables on porosity

3.1.1 The 3D surface analysis

Figure (4) shows the effect of process variables on granule porosity during fluidized bed granulation. it can be detected that porosity decreases with increasing (L/S) ratio and granulation time due to improved binder bridging and stronger solid ponding that lead to more dens granules, similar results that noted by Faraj shamam [17].In contrast ,feed mass and air inlet rate show relatively minor effects on porosity. Sorokina & Goryanin,[18], they indicated that operational parameters mainly affect granule growth behavior more than internal structure. Experimental work by Rao et al., [19] showed that higher binder levels lowers granule porosity by filling interstitial voids and improving particle solidity. Collectively, these studies corroborate the interpretation that binder ratio and processing duration are the dominant contributors to porosity reduction in the 3D models, while other variables exert more moderate influence.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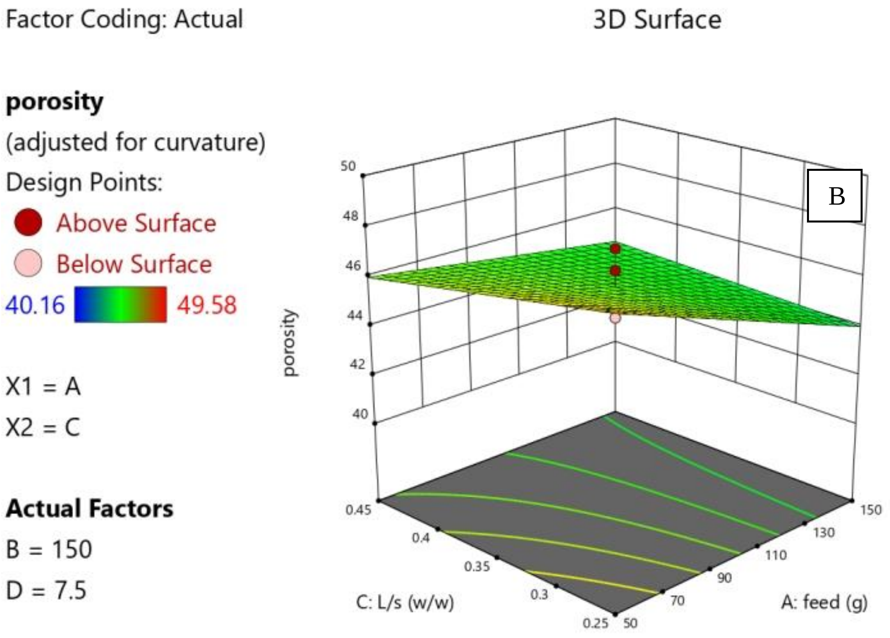
3D Surface
porosity
(adjusted for curvature)
Design Points:
● Above Surface
○ Below Surface
40.16
49.58
X1 = A
X2 = B
Actual Factors
C = 0.35
D = 7.5
A
porosity
50
48
46
44
42
40
B: air inlet rate (L/min)
180
170
160
150
140
130
120
A: feed (g)
50
70
90
110
130
150


Factor Coding: Actual
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(adjusted for curvature)
Design Points:
● Above Surface
○ Below Surface
40.16
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X1 = A
X2 = C
Actual Factors
B = 150
D = 7.5
B
porosity
50
48
46
44
42
40
C: L/s (w/w)
0.45
0.4
0.35
0.3
0.25
A: feed (g)
50
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90
110
130
150

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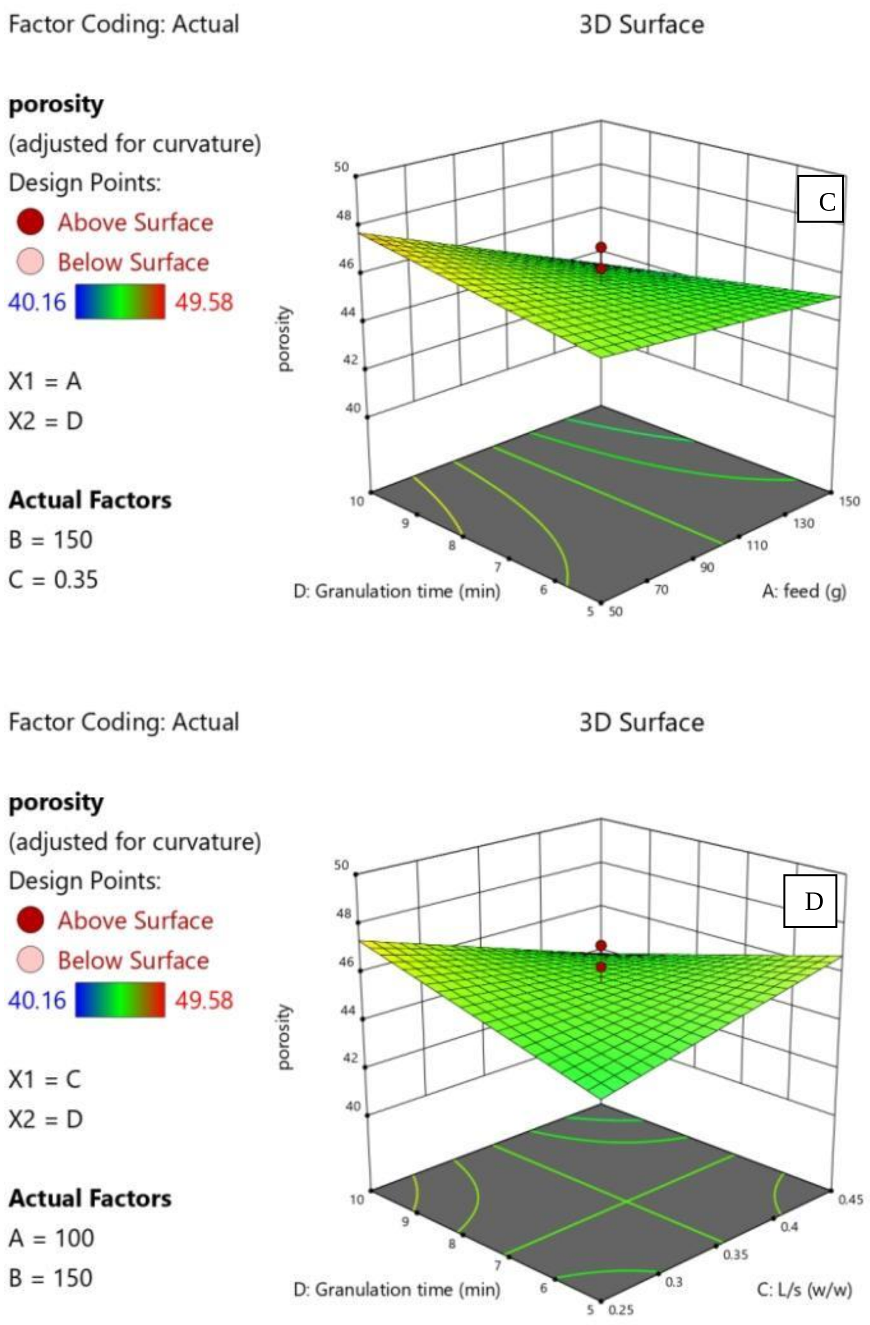


Figure 4: 3D plots for porosity using 13 design experts.A:Interaction between air inlet rate and feed, B: Interaction between feed and l/s ratio.C :Interaction between feed and granulation time. D : Interaction between l/s ratio and granulation time.

3.2.1 Predicted vs. Actual Plot Analysis for porosity

As shown in figure (5) illustrates the a high level of model accuracy, between the experimentally measured porosity values (Actual) and those estimated by the developed model (Predicted). Most of the data points lie very close to the45-degree diagonal reference line.This strong correlation indicates that the developed describing the response behavior with minimal error. Additionally, the color-coded represents the disintegration visually confirms the physical relationship between the two responses:

-lower porosity (high density) :corresponds to longer disintegration times(red points),indicating a more consolidated internal structure.
-Higher porosity : corresponds to faster disintegration time(blue points), as the increased void space facilities liquid penetration.
This integration of porosity data and disintegration results validates the models reliability in describing the physical characteristics of the granules.

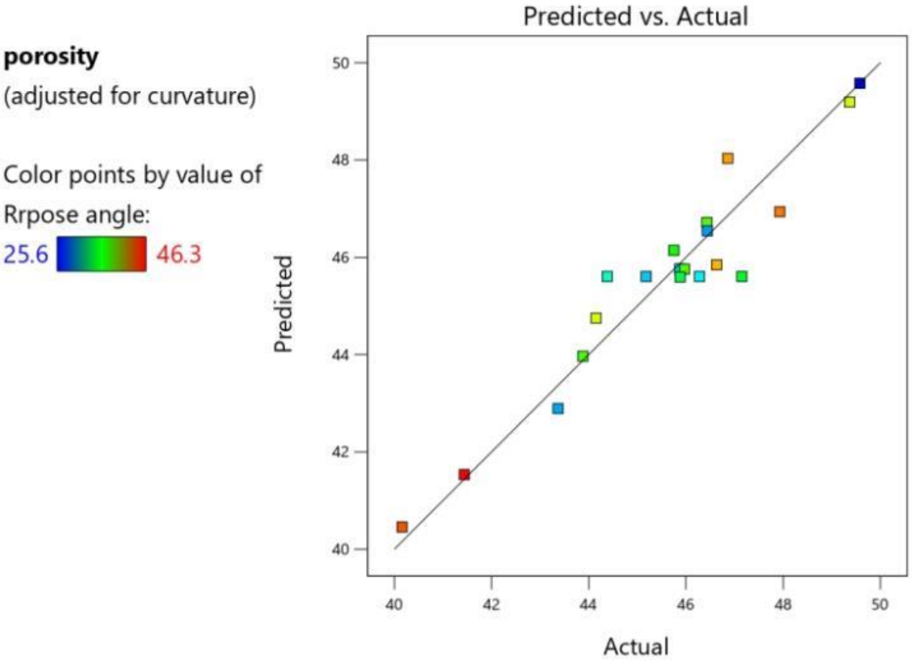


Figure 5.predicted vs actual plot for analysis porosity

3.2. Effect of Process Parameters on Disintegration Time.

As shown in table (3), the result of disintegration illustrate a significant impact of factors (feed A, airflow rate B, L/S ratio C, and granulation time D). This variation is attributed to differences in process variables applied within the designed experiments (DOE), that the slow disintegration of HPMC granules is mainly due to gel layer formation upon hydration, which limits water penetration into the granule core[14],[20],[21]. Consistent with the statistical significance observed in the results (p = 0.0001) and with R^2= 0.9648 as shown in A nova fit statistics table (4).

Table (3): values of Disintegration time

Exp.no.	Disintegration	Exp.no.	Disintegration
1	1330	10	4130
2	1860	11	3456
3	3190	12	3467
4	2820	13	2400
5	3000	14	3580
6	1860	15	3900
7	3780	16	4550
8	2340	17	3600
9	1550	18	5509
10	3360	19	4920

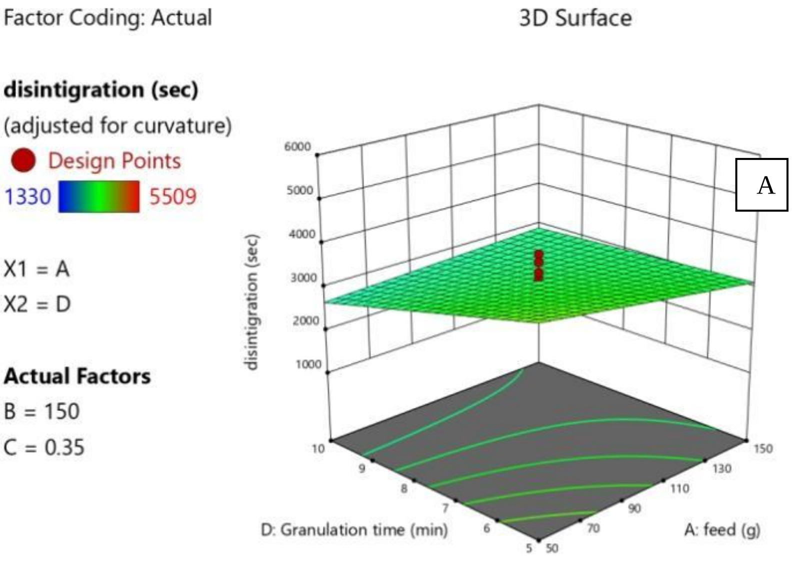
8	1330	20	4130
9	1860	10	3456
10	3190	11	3467

Table 4: Anova and R-squared results for the disintegration prediction model.

Std. Dev.	286.41	**R²**	0.9648
Mean	3230.10	**Adjusted R²**	0.9367
C.V. %	8.87	**Predicted R²**	0.8461
		Adeq Precision	19.2915

3.2.1 The 3D surface analysis

A three-dimensional response surface plots as in Figure(6).The graphical analysis indicates that the liquid-to-solid ratio (C) has a pronounced effect on the response. As the liquid addition increases, the disintegration time increase noticeably across the response surfaces. In contrast, granulation time (D) shows a moderate inverse tendency, where longer granulation periods slightly reduce the disintegration time. The surfaces also reveal interactions between the operating variables, although the curvature appears relatively mild within the investigated design space, moreover the visual displacement of the center points from the expected plane Prove existence of localized curvature. Which indicates the process sensitivity changes as it become near the central operating region. Generally' these surfaces show map of the design space, that while liquid to solid ratio acts as primary influencing factor , while parameters such as granulation time and air inlet rate acts as secondary variables affecting the final granule behavior.



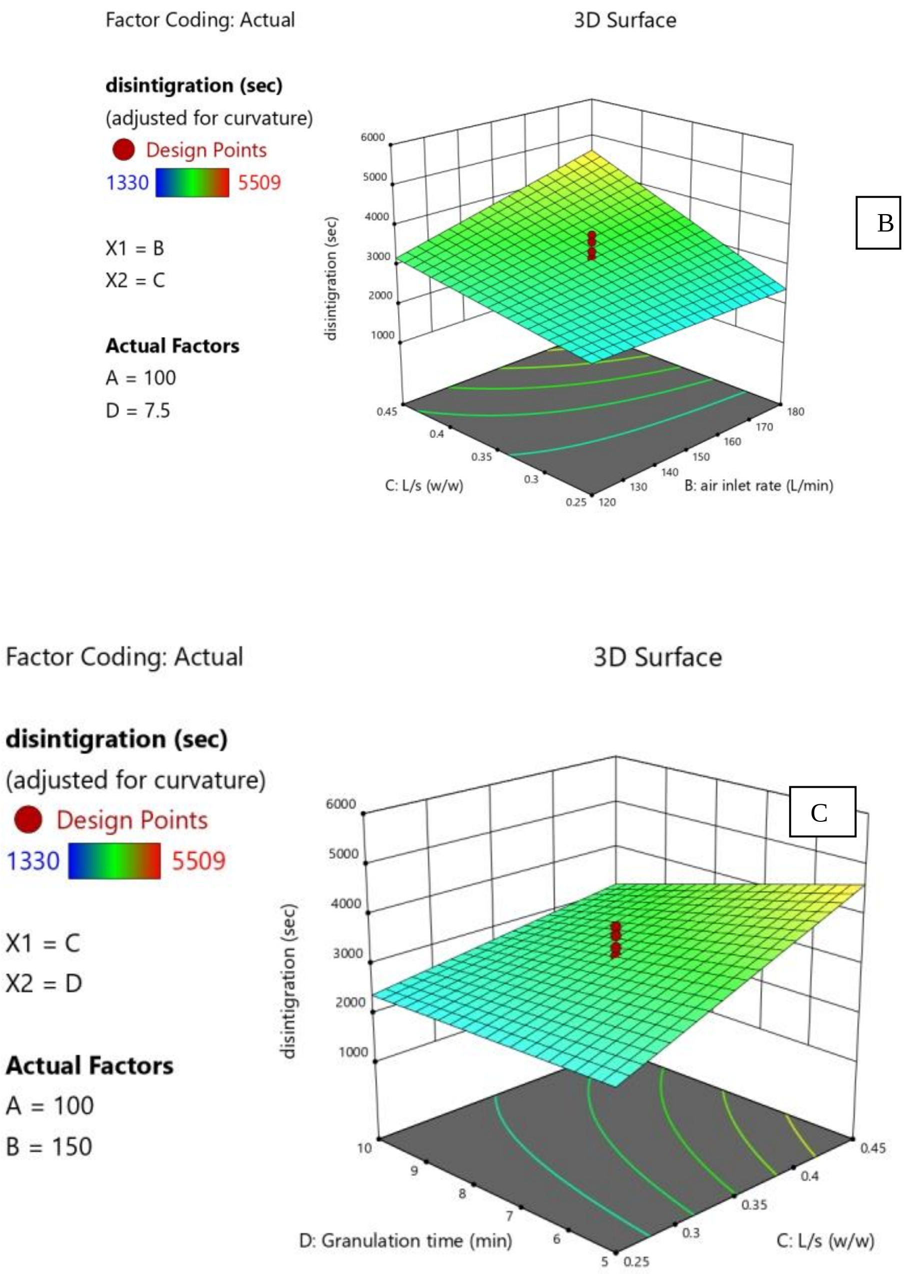


Figure 6 :3D plots for disintegration time using 13 design experts.
A :Interaction between granulation time and feed. B: Interaction between L/S ratio and air inlet rate.
C:Inetraction between granulation time and L/S ratio.

3.2.2 The Predicted vs. Actual plot

Offers a comprehensive evaluation of the model’s ability to represent and predict the measured response (disintegration). Figure(7), the experimentally observed values are plotted against the corresponding values generated by the fitted regression model.The close alignment of the data points along the ideal 45-degree line, indicating that the selected factors and their interactions contribute meaningfully to the response.

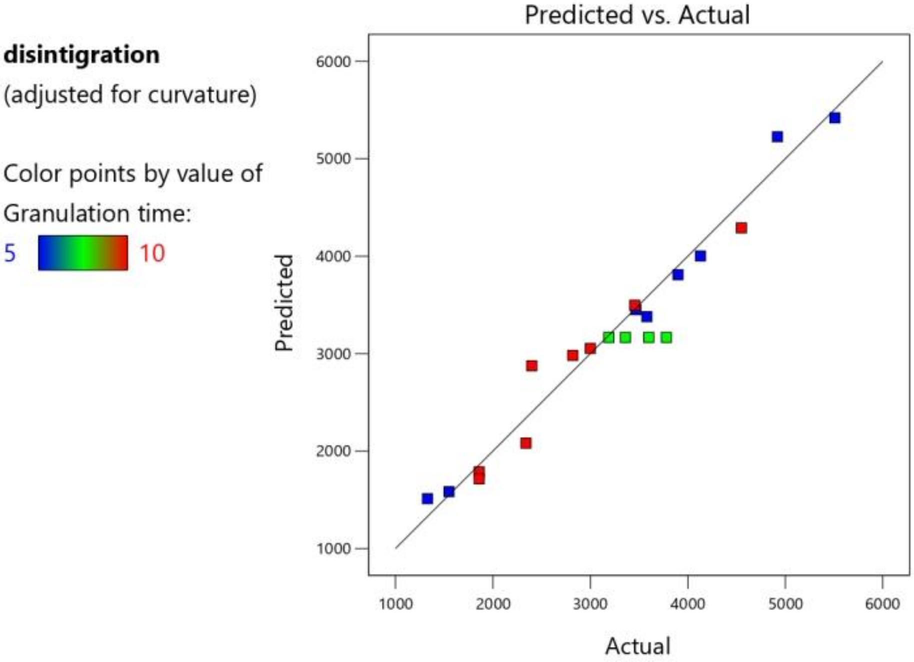


Figure 7:predicted vs actual plot for porosity

4. CONCLUSION

This study systematically investigated the impact of critical fluidized bed granulation parameters namely (feed mass, airflow rate, L/S ratio, and granulation time) on the porosity and disintegration behavior of HPMC granules. The results show that:

1. Porosity is mostly increase by higher feed and is decrease by increased airflow rates due to quick drying and consolidation. The L/S ratio and granulation time reacts strongly, by improved particle bonding and basic consolidation with the higher levels that supporting denser, less porous solids.
2. The time to disintegration is largely determined by the porosity of the granules and the L/S ratio. Higher porosity simplifies more fast liquid penetration and minimize disintegration period, while increased L/S ratios lead to formation gelatinous layer and denser matrices, this lengthening disintegration.

ACKNOWLEDGEMENTS

The Authors gratefully acknowledge the technical support and laboratory facilities provided by the chemical engineering department at university of Diyala. One of the authors (Hiba .H) would like to thank her father for his constant support in completing this work.

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