การออกแบบการทดลองเพื่อลดแกรนูลไม่พึงประสงค์ในกระบวนการทำแกรนูลเปียกของยาเม็ดเมตฟอร์มิน
Experimental Design to Minimize Rejected Granules in Wet Granulation Process of Metformin Tablets

นิพนธ์ต้นฉบับ

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Original Article

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บทคัดย่อ

วัตถุประสงค์: เพื่อศึกษาพารามิเตอร์ของกระบวนการทำแกรนูลเปียกที่ทำให้เกิดแกรนูลไม่พึงประสงค์ในเครื่องบดแห้ง และหาค่าพารามิเตอร์ที่เหมาะสมในการผลิตระดับอุตสาหกรรม **วิธีการศึกษา:** การวิเคราะห์พารามิเตอร์ของกระบวนการอาศัยแผนภูมิก้างปลาเพื่อระบุสาเหตุการเกิดแกรนูลไม่พึงประสงค์ จากนั้นออกแบบการทดลองแบบแฟกทอเรียลเต็มรูปเพื่อหาระดับที่เหมาะสมของปัจจัยต่าง ๆ โดยศึกษาปัจจัยของกระบวนการทำแกรนูลเปียก 5 ตัวแปร ตัวแปรละ 2 ระดับ แบบ 2 ซ้ำ ได้แก่ เวลาในการลดขนาดก้อนวัตถุดิบเมตฟอร์มิน (15 และ 20 นาที) อัตราการไหลของลมทางเข้าของเครื่องทำแห้งแบบฟลูอิดเบด (1,700 และ 1,900 ลูกบาศก์เมตรต่อชั่วโมง) อุณหภูมิในการถ่ายแกรนูลจากเครื่องทำแห้งแบบฟลูอิดเบดไปยังเครื่องบดแห้ง (25 และ 30 องศาเซลเซียส) ความกว้างในการเปิดแฟลบขณะถ่ายแกรนูล (80% และ 90%) และความสูงของตำแหน่งใบพัดแร่งในเครื่องบดแห้ง (3 และ 7 มิลลิเมตร) จากนั้นหาระดับดีที่สุดของตัวแปรและยืนยันผลการทดสอบตัวแปรใหม่ **ผลการศึกษา:** การวิเคราะห์ข้อมูลแสดงปัจจัยหลักที่มีผลต่อการเกิดแกรนูลไม่พึงประสงค์ ได้แก่ เวลาที่ใช้ในการลดขนาดก้อนวัตถุดิบเมตฟอร์มิน ความกว้างในการเปิดแฟลบขณะถ่ายแกรนูล และความสูงของตำแหน่งใบพัดแร่งในเครื่องบดแห้ง เมื่อทำการทดสอบเพื่อยืนยันผลในกระบวนการทำแกรนูลเปียกของยาเมตฟอร์มิน จำนวน 50 รุ่นการผลิต พบว่าปริมาณแกรนูลไม่พึงประสงค์ลดลง มีปริมาณเฉลี่ยลดลงจาก 13 กิโลกรัมถึงปริมาณที่น้อยกว่า 1 กิโลกรัม **สรุป:** มีพารามิเตอร์กระบวนการทำแกรนูลเปียก 3 ตัวที่ไม่ระบุไว้ในเอกสารการขึ้นทะเบียนยา มีผลต่อปริมาณแกรนูลไม่พึงประสงค์ โดยมีระดับที่ดีที่สุดของตัวแปร คือเวลาในการลดขนาดก้อนวัตถุดิบเมตฟอร์มิน 20 นาที ความกว้างในการเปิดแฟลบขณะถ่ายแกรนูล 80% และความสูงของตำแหน่งใบพัดแร่งในเครื่องบดแห้ง 7 มิลลิเมตร และสามารถนำไปใช้ในกระบวนการทำแกรนูลเปียกของเมตฟอร์มินที่มีขนาดการผลิต 600 กิโลกรัมได้

คำสำคัญ: ยาเม็ดเมตฟอร์มิน; การออกแบบการทดลอง; กระบวนการทำแกรนูลเปียก; แกรนูลไม่พึงประสงค์

Abstract

Objectives: To study the wet granulation process parameters which caused rejected granules in dry mill and optimize such process parameters in large-scale industrial production. **Methods:** Process parameters were examined using fish bone diagram to identify root cause of rejected granules. Full factorial design was performed to find optimal factor levels. Specifically, 5 factors and 2 levels including delumping time (15 and 20 minutes), inlet air flow of fluid bed dryer (1700 and 1900 m^3/h), transfer temperature between fluid bed dryer to dry mill (25 and 30 ºC), transfer flap opening between fluid bed dryer to dry mill (80% and 90%) and dry mill blade position (3 and 7 millimeters) were studied in duplicate. Response optimizer and validation of optimized parameters were analyzed. **Results:** It was found that delumping time, transfer flap opening between fluid bed dryer to dry mill and dry mill blade position were the main factors affecting rejected granules. Optimized parameters were applied and validated among 50 batches. The quantity of rejected granules was reduced from 13 kilograms to less than 1 kilogram on average. **Conclusion:** Three process parameters which were not stated in the drug registration dossier were found to have an impact on reject granules quantities. Delumping time at 20 minutes, transfer flap opening between fluid bed dryer 80% and dry mill blade position up to 7 millimeters were optimized and successfully applied in 600-kilogram batch size of metformin granulation. This work could be a good platform for other formulations and pharmaceutical process development.

Keywords: metformin tablets; design of experiment; wet granulation process; rejected granules

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Introduction

Wet granulation process, a particle size enlargement process, is widely used in pharmaceutical industry especially in the production of tablets and capsules. Advantages of wet granulation process are to reduce dust powder, improve content uniformity, dissolution rate, flowability and tabletability in order to get density and strength granules by means of binder addition to bring particles agglomeration composed of capillary pressure, surface tension and viscous forces.[1,2] Furthermore, wet granulation can prevent segregation of critical components by reducing the

difference in particle size and density.[3] Particles possess 3 stages; nucleation, agglomeration and breakage phenomena. Nucleation occurs during binder addition into dry powders. Then, small granules are formed and collided causing compaction and increase in granule size during agglomeration stage. Breakage stage lastly happens when shear forces deform weak granules to small particles. Changing formulation and process parameters can influence the transform stage.[4]

In general, wet granulation starts with binder preparation in the vessel before loading raw materials to high shear granulator. The high shear granulator has 2 types of blades, agitator and chopper. At first, dry mixing with agitator appears to decrease powder agglomeration and then homogeneously mix with internal excipients and binder while chopper is used depending on product requirement. After complete binder addition, both agitator and chopper usually run together to produce powder agglomerates which are called wet mass or damp mass. Wet granules are transferred to fluid bed dryer for drying. The last stage is dry granules transfer to dry mill to reduce granules size and increase uniformity of granules using sieve.[3]

In wet granulation, process parameters could have a direct effect on granules properties. Simone et al studied impeller rotation speed and binder flow rate using full factorial design and reported that both factors affected particle size distribution and granulation yield.[4] While Badawy et al studied four parameters; water level, impeller tip speed, wet massing time and water addition time for brivanib, razaxaban and pexacerfont formulations to characterize particle size distribution, density, flow, compaction and dissolution rate. Increasing water amount, higher impeller speed and wet massing time affected to flow rate significantly.[5] Furthermore, drying parameters such as filling time, drying time, air flow and drying air temperature were examined against size distribution and moisture content of granules by Leersnyder et al. Increasing drying time, airflow and drying temperature was reported to affect moisture content of granules.[6]

Metformin hydrochloride tablets are manufactured by wet granulation process before compression to tablets. Industry database has shown that one of the wastes from this product mainly came from remaining granules in dry mill which were called as rejected granules (Figure 1a and 1b). Rejected granules were found up to 22 kilograms per batch while tablet department was responsible for producing this product more than 720 batches per year. This loss could have significant impact on company resources including materials, machines, man and methods and thus, could reduce the productivity.

Metformin hydrochloride, an oral antidiabetic drug for patients with type 2 diabetics, is categorized in Biopharmaceutics Classification System (BCS) Class III drug which means the drugs with high solubility but low permeability to cell membrane. The melting point of metformin is 222 - 226 ºC.[7] This drug commonly becomes agglomerated during storage since its chemical structure is connected by hydrogen bonding with water molecules in the air. This fact causes metformin sensitive to moisture with high agglomeration.[8-11] Due to its poor flowability and tabletability, metformin is usually manufactured by wet granulation to make ingredients uniform and suitable for tableting.[12]

The objectives of this work were to study process parameters affecting rejected granules and optimize wet granulation process parameters in industrial scale production to reduce metformin rejected granules.

Methods

Materials and machines

Metformin hydrochloride (Abhilash Chemicals and Pharmaceuticals, India), an active pharmaceutical ingredient (API), was used as a model drug. Excipients include Povidone K-30 (JH Nanhang Life Sciences, China), corn starch (Friendship Corn Starch, Thailand) and colloidal silicon dioxide (Wacker Chemic AG Nunchritz, Germany). The granulation process was designed as a closed transfer system. Binder preparation vessel (Glatt GmbH, India), drum squeezer, lump breaker suction lance (Dec Group, Switzerland), vibrosifter (Russell Finex, United Kingdom), high shear granulator (Glatt GmbH, India), fluid bed dryer (Glatt GmbH, India), dry mill (Glatt GmbH, India) and transfer system (Glatt GmbH, India) were used to produce metformin granules as in Figure 1c.

Design of experiment (DoE)

Full factorial design is one of the analysis and statistical tools in DoE used for studying two or more factors. Each factor may have many levels. The full factorial design was

chosen for optimizing process parameters to reduce rejected granules in wet granulation process. Five process parameters; namely, metformin delumping time (X_1), inlet air flow of fluid bed dryer (X_2), transfer temperature between fluid bed dryer to dry mill (X_3), transfer flap opening between fluid bed dryer to dry mill (X_4) and dry mill blade position (X_5) with two levels as Table 1 were studied. The quantity of rejected granules (Y) was the main response. All randomized 32 runs of full factorial design (Table 2) were performed in duplicate. Minitab software was used for managing run order and data analyzing.

Process optimization

Validation of optimized process parameters was performed with 50 batches of metformin wet granulation process to ensure the feasibility of the optimal factors. Minitab software was used for predicting multiple response process parameters. Rejected granules of each batch were weighed in kg.

Wet granulation process

Wet granulation process of metformin was performed in a production batch size of 600 kilograms (kg). Wet granulation with water as a binder was used in this study. Povidone K-30 was soaked in 22.25 liters of purified water, mixed by paste preparation vessel with speed 25 rpm and heated at temperature not less than 75 ºC. Corn starch was dissolved in 1.75 liters of purified water, poured into Povidone K-30 solution, mixed and decreased temperature to 45 to 50 ºC before use. Metformin lumps were squeezed in drum squeezer to reduce the size of the lumps and suctioned by lump breaker suction lance to transfer powder to high shear granulator. Then, API was delumped in high shear granulator by using agitator speed 100 rpm and chopper speed 1500 rpm for 10 minutes. Internal excipients were then sifted with vibrosifter (sieve size 30 mesh), added to high shear granulator to mix with API by using agitator speed 75 rpm for 4 minutes and agitator speed 75 rpm and chopper speed 1500 rpm for 1 minute, respectively. Binder paste was added in high shear granulator by using agitator speed 100 rpm and chopper speed 1500 rpm in 2 minutes and then, mixed with repeated speed for 2 minutes. Wet mass was transferred to fluid bed dryer for drying. Finally, dry granules were passed through a dry mill with a 2 millimeters (mm) round hole sieve for speed 250 rpm and stored in an intermediate bulk container for further process (Figure 1d).

Rejected granules

Rejected granules were defined as undesirable granules with a particle size more than 2 mm. They were obtained at the last step of wet granulation as these granules cannot pass through the 2-mm sieve in dry mill. Rejected granules were collected in plastic bag, weighed by balance Mettler-Toledo, and recorded in Electronic Batch Record (EBR).

Results and Discussions

Design of experiment (DoE) of rejected granules

The amount of metformin rejected granules, collected from 100 batches, was found in the range of 8.28 to 21.54 kg or 13.09 kg as average. Fishbone diagram was used to investigate all process-related causes of undesirable granules in wet granulation (Figure 2). Process parameters including binder addition time, agitator speed, chopper speed, sieve size, were fixed in the drug registration dossier while the following parameters namely delumping time, inlet air flow of fluid bed dryer, transfer temperature between fluid bed dryer to dry mill, transfer flap opening between fluid bed dryer to dry mill and dry mill blade position were not specified in the dossier. In previous studies, it has been revealed that increasing mixing time in the high-speed granulator resulted in smaller granule size.[5] Moreover, Vengateson et al. studied higher inlet air velocity of fluid bed dryer which led to smaller granule.[13] While temperature between fluid bed dryer to dry mill and transfer flap opening between fluid bed dryer to dry mill has not been specified in granulation process, it could affect granule properties. Additionally, the clearance between blade and sieve of dry mill, varied by changing dry mill blade position, could influence on velocity of granules.[14]

The full factorial design (2^5) demonstrated the process parameters affecting rejected granules quantity as seen in Table 2. Regarding the main effect plot (Figure 3), increasing delumping time and dry mill blade position resulted in decreasing rejected granule quantities. Figure 4 shows interaction plot which reflects no interaction between delumpimg time and inlet air flow of fluid bed dryer, transfer temperature between fluid bed dryer to dry mill, transfer flap opening between fluid bed dryer to dry mill. Meanwhile, inlet

air flow of fluid bed dryer, transfer temperature between fluid bed dryer to dry mill, transfer flap opening between fluid bed dryer to dry mill and dry mill blade position were found to interact among each other including delumpimg time and dry mill blade position. In addition, it is apparent that rejected granule quantities decreased when increasing dry mill blade position. In Figure 5, the Pareto chart highlighted the process parameters that significantly affected reject granules quantities included delumping time, transfer flap opening between fluid bed dryer and dry mill blade position. Similarly, Figure 6 shows that these 3 process parameters had P-value less than 0.05, meaning that these parameters influenced on waste granules.

Delumping time is the duration for breaking dry metformin lumps in high shear granulator before adding binder paste. This factor was specified to 15 and 20 minutes because of increasing this period led to longer contact time between the surface of lumps and the blades, agitator and chopper. This factor has not been revealed before while dry mixing time was generally studied in granulation process. Dry mixing time takes a short period typically 5 to 15 minutes based on powder properties.[3] Mahours et al studied dry mixing time of 5, 10 and 15 minutes and reported that increasing dry mixing time could decrease granulation flowability but slightly increase hardness and disintegration time.[15] Metformin lumps became smaller than its raw material before mixing homogeneously with internal excipients and binder paste. After wet massing time, the granules became stronger and denser.[16] Eventually, wet granules were dried in a fluid bed dryer but were not stiff.

Transfer flap opening between fluid bed dryer to dry mill is air-controlled temperature channel used for transferring dry granules from fluid bed dryer to dry mill. Large openings with high temperature may cause hot air contact to granules. They could probably be too dry, large, and stiff which cannot pass through 2-mm sieve of dry mill. Therefore, optimal transfer flap opening size (80% and 90%) was set under consideration of inlet air temperature and manufacturing process.

Dry mill is used for screening the particle size of dry granules transferred from fluid bed dryer through 2-mm round hole. The key components for dry mill are sieve and blade. Common factors of dry mill are speed, screen size and space between blade and sieve. Previously, the clearance between blade and sieve was set at 1.4 mm which potentially caused many rejected granules. This limited room was possibly not enough for collision and milling.[17] Hu et al studied blade clearance variation between blade and inner wall of vessel and concluded that small clearance brought about higher particle velocity than large clearance.[14] In addition, Daraio et al reported similar findings in a vertical-stirred mill.[18] This work varied the clearance between blade and sieve by increasing a height of blade for 3, 4, 5, 6 and 7 mm, stainless steel ring was used for these adjustments (Figure 7a and 7b). Thus, the clearance became 2.5, 2.6, 2.7, 3.4 and 3.5 mm respectively. In other words, changing dry mill blade position could affect the clearance between blade and sieve. The more increasing position, the more clearance between blade and sieve. Thus, the granules are milled in a larger area which could lead to the small granules size and less rejected granules quantities. Table 2 emphasizes that all experiments using 7-mm stainless steel ring had much less rejected granules quantities than those using 3-mm stainless steel ring.

Regarding inlet air flow of fluid bed dryer, it was set up based on the upper and lower limit of actual value obtained from previous batches. Gao, et al. concluded that inlet air velocity maintained proper fluidization while excessive inlet air velocity caused poor fluidization which can be seen from loss on drying data.[19] Furthermore, Hemati, et al. reported that high inlet air flow affected slower granule formation than low inlet air flow.[20] While transfer temperature between fluid bed dryer to dry mill was studied in the of 25 and 30 ºC close to ambient conditions.

Process optimization

Response optimizer was done to find the most appropriate process parameters that caused minimal rejected granules. Composite desirability was 0.9794 which close to 1 indicating the settings tend to achieve favorable results for the response. The optimized process parameters were presented in Figure 8, delumping time 20 minutes, inlet air flow of fluid bed dryer 1900 m^3/h, transfer temperature between fluid bed dryer to dry mill 30 ºC, transfer flap opening between fluid bed dryer to dry mill 80% and dry mill blade position 7 millimeters, respectively resulting the reduction of rejected granules from 13.09 kg per batch in average before the experiment were applied to 0.6 kg. The possibility of response was in the range of -1.46 to 2.67 at 95% confidence interval. Validation of optimized parameters

Table 1 Process parameters (factors) and factor level.

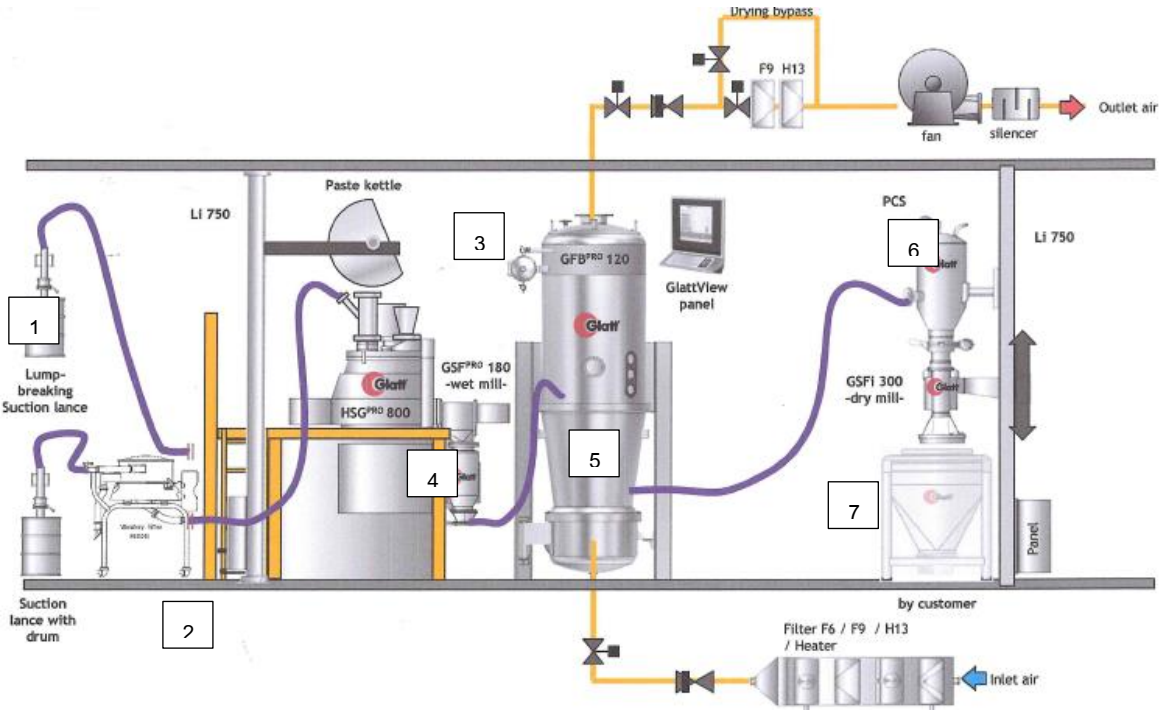
Symbol	Factors	Low level	High level	Unit
X_1	Delumping time	15	20	minutes
X_2	Inlet air flow of fluid bed dryer	1,700	1,900	m^3/h
X_3	Transfer temperature between fluid bed dryer to dry mill	25	30	ºC
X_4	Transfer flap opening between fluid bed dryer to dry mill	80	90	%
X_5	Dry mill blade position	3	7	mm

Table 2 Design of experiment and results.

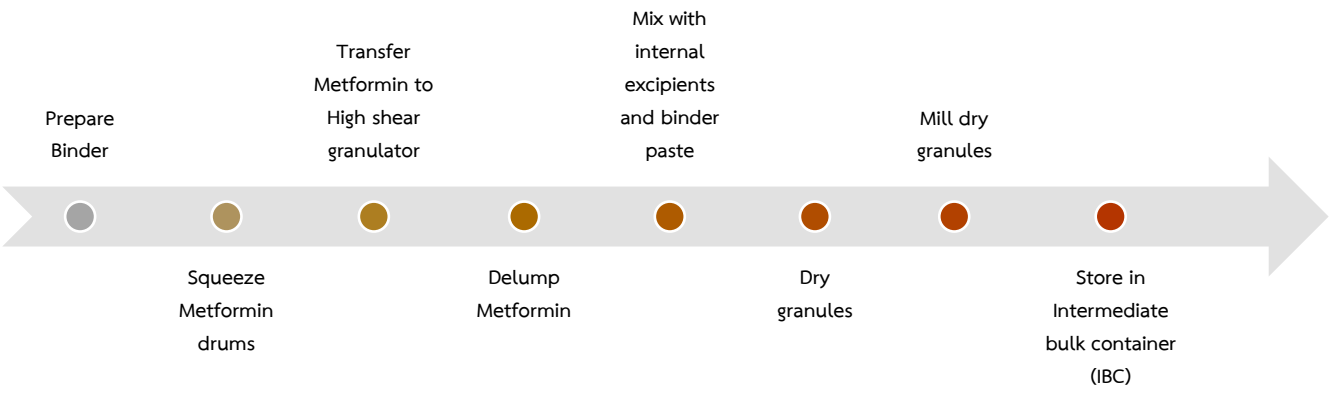
Experiments	Delumping time (minutes)	Inlet air flow of fluid bed dryer (m^3/h)	Transfer temperature between fluid bed dryer to dry mill (ºC)	Transfer flap opening between fluid bed dryer to dry mill (%)	Dry mill blade position (mm)	Rejected granules run 1 (kg)	Rejected granules run 2 (kg)
a	15	1900	25	80	3	7.8	9.4
b	15	1700	25	90	3	7.6	8.8
c	15	1900	25	90	3	7.8	8.2
d	15	1700	25	80	3	7.6	8.2
e	20	1700	25	90	3	5.2	6.4
f	20	1900	25	80	3	5	6.4
g	20	1900	25	90	3	5.4	6.2
h	20	1700	25	80	3	5.4	5.2
i	15	1700	25	90	7	3.2	3.4
j	15	1700	25	80	7	3.6	3.0
k	15	1900	25	90	7	3.4	2.0
l	20	1700	25	90	7	1	1.8
m	20	1700	25	80	7	3.6	1.6
n	20	1900	25	90	7	2.2	1.6
o	20	1900	25	80	7	1	1.6
p	15	1900	25	80	7	3.6	0.9
q	15	1700	30	90	3	9.2	10.1
r	15	1900	30	90	3	8	9.6
s	15	1700	30	80	3	7.6	9.4
t	15	1900	30	80	3	8	9.0
u	20	1700	30	90	3	5.2	7.8
v	20	1900	30	90	3	5.8	7.4
w	20	1900	30	80	3	5.2	7.0
x	20	1700	30	80	3	5.8	5.6
y	15	1900	30	90	7	3.4	3.8
z	15	1900	30	80	7	2.8	3.0
aa	15	1700	30	80	7	3.2	2.6
bb	20	1700	30	90	7	2	2.6
cc	15	1700	30	90	7	3.4	2.2
dd	20	1700	30	80	7	2	1.2
ee	20	1900	30	90	7	2	1.2
ff	20	1900	30	80	7	0.4	0.8

(a)

(b)



(c)



(d)

Figure 1 Rejected granules (a); rejected granules that cannot pass through the sieve with 2-mm diameter in dry mill (b); wet granulation machines as closed transfer system composed of 1.lump breaker suction lance, 2.vibrosifter, 3.binder preparation vessel, 4.high shear granulator, 5.fluid bed dryer, 6.dry mill and 7.transfer system (c); flow chart of metformin wet granulation process (d).

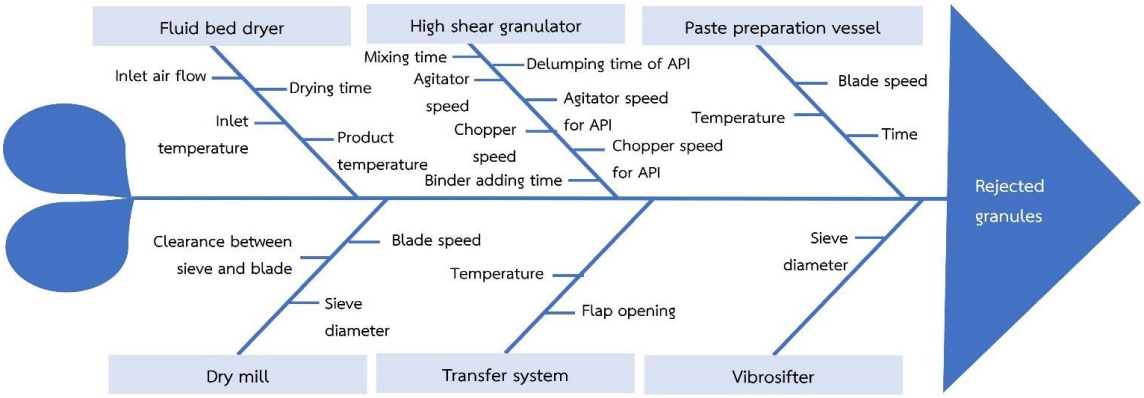


Figure 2 Process-related cause of rejected granules.

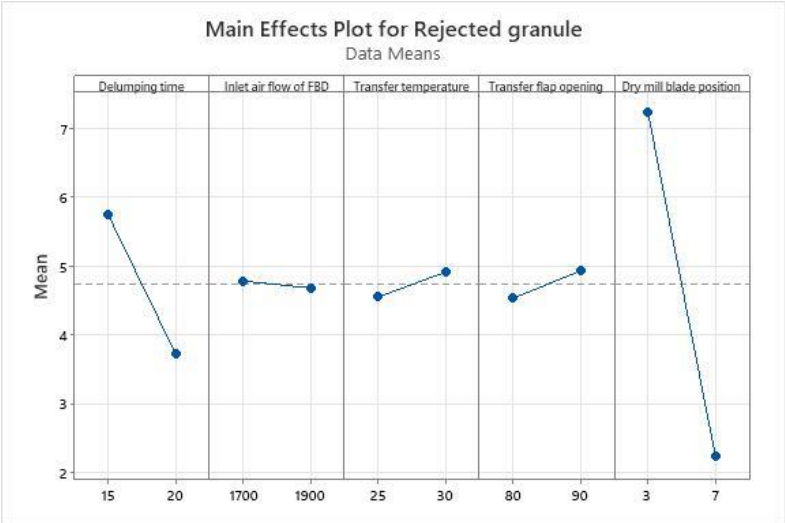


Figure 3 Main effects plot of wet granulation process parameters.

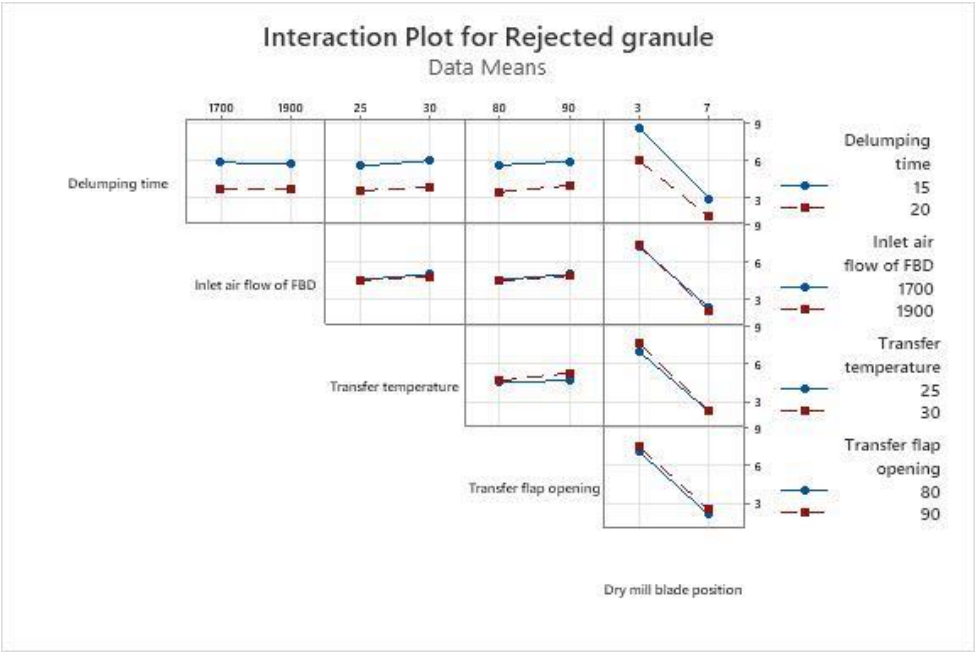


Figure 4 Interaction plot of wet granulation process parameters.

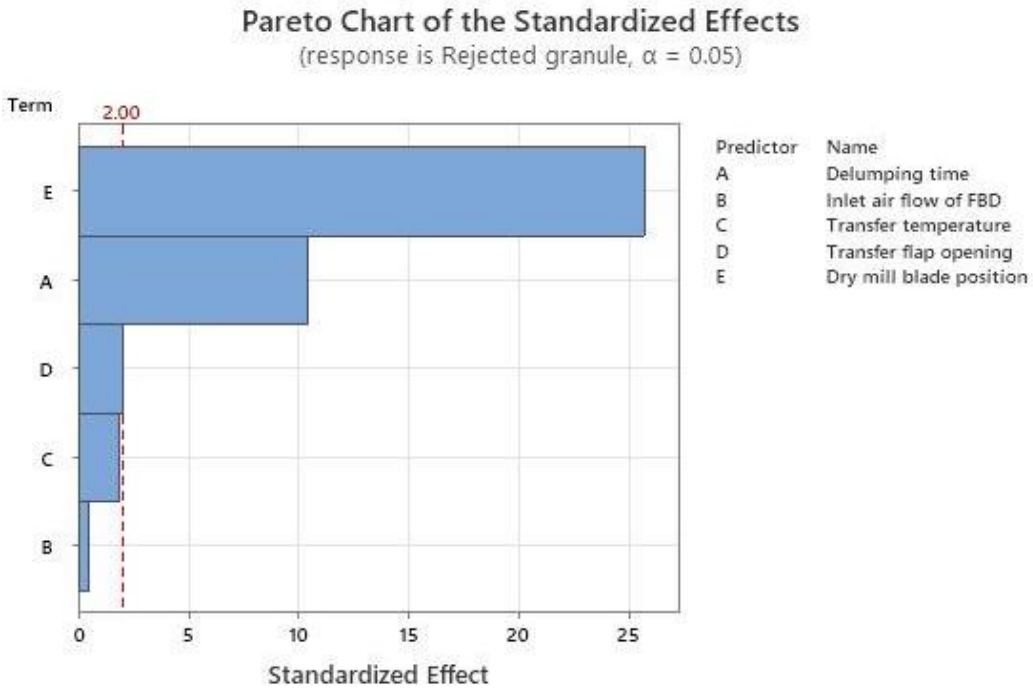
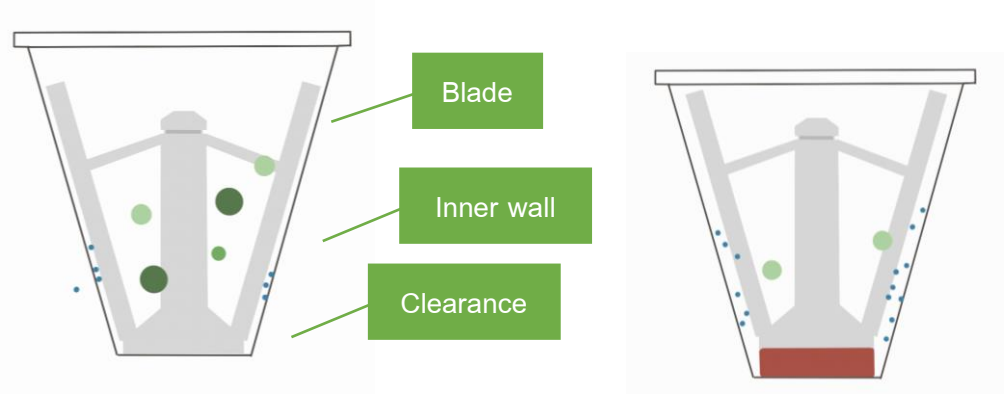


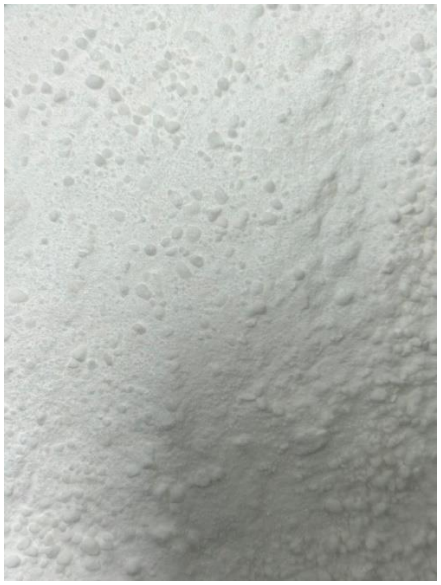
Figure 5 Regression analysis result.

Source	DF	Adj SS	Adj MS	F-Value	P-Value
Regression	5	468.031	93.606	155.50	0.000
Delumping time	1	65.206	65.206	108.32	0.000
Inlet air flow of FBD	1	0.160	0.160	0.27	0.608
Transfer temperature	1	2.102	2.102	3.49	0.067
Transfer flap opening	1	2.560	2.560	4.25	0.044
Dry mill blade position	1	398.003	398.003	661.18	0.000
Error	58	34.914	0.602		
Lack-of-Fit	26	13.024	0.501	0.73	0.791
Pure Error	32	21.890	0.684		
Total	63	502.944			

Figure 6 Analysis of variance.



(a) (b)



(c)

Figure 7 (a) Before changing dry mill position (b) After changing dry mill position with stainless steel ring (c) Optimized prepared granule characteristic.

Variable	Setting
Delumping time	20
Inlet air flow of FBD	1900
Transfer temperature	30
Transfer flap opening	80
Dry mill blade position	7

Response	Fit	SE Fit	95% CI	95% PI
Rejected granule	0.600	0.585	(-0.591, 1.791)	(-1.463, 2.663)

Figure 8 Response optimizer for set up metformin wet granulation process parameters.

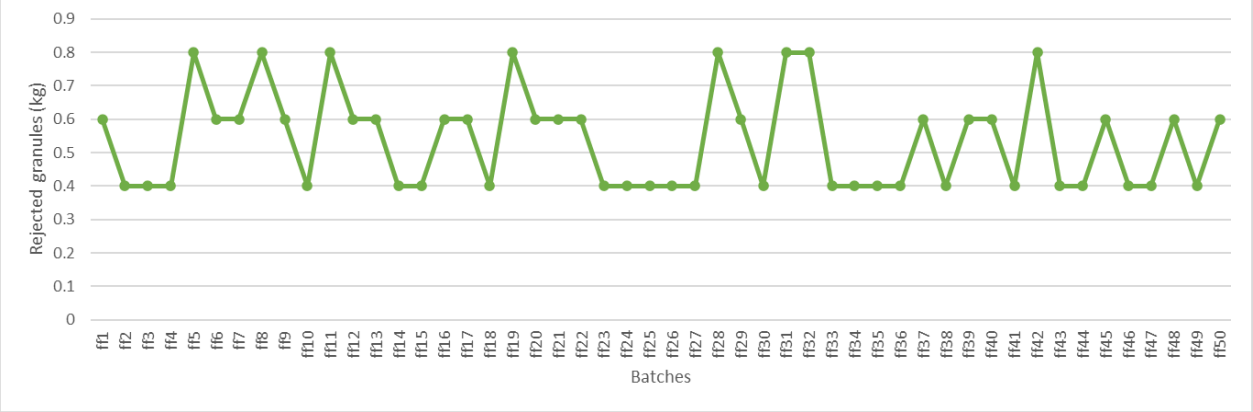


Figure 9 Amount of rejected granules in 50 batches of wet granulation after response optimizer.

was performed with 50 batches to evaluate the feasibility of the new settings. Rejected granules ranged from 0.4 to 0.8 kg with the average of 0.5 kg as in Figure 9. The small fluctuation of this result was relating to the readability of balance at 0.2 kg as the balance was also used to weigh the yield of 600 kg granules in the production site. The result showed that delumping time, transfer flap opening between fluid bed dryer and dry mill blade position significantly affected reject granules quantities which led to decreasing rejected granules by 96.18%. These data agreed well with the data analysis and can be applied to practical use. Moreover, the new process variables with minimized rejected granules could have a direct relationship with the cost control of materials.

However, there could be other aspects that may influence granules' properties. Kim, et al. studied metformin formulation by 2-level full factorial design and response surface methodology for optimizing tablet components.[21] Aodah et al used full factorial design and quality by design to develop metformin orally disintegrating tablet with moisture activated dry granulation.[22] Meanwhile, partial least squares multilinear regression was applied for formulation development of metformin immediate release tablet with comparable dissolution profiles to the innovator.[23]

Conclusion

In summary, this work demonstrated three process parameters in wet granulation that have an impact on reject granules quantities by using 2^5 full factorial design. Delumping time of 20 minutes, transfer flap opening between fluid bed dryer to dry mill of 80% and dry mill blade position of 7 mm were optimized. Validation of optimized process parameters was performed to ensure the feasibility of new setups. The average amount of reject granules was successfully reduced from 13.09 to 0.5 kg which is beneficial to the cost control of materials. On the other hand, adjusting these selected process parameters is probably not the best solution for solving the problem of waste granules. Other process parameters and formulation aspects could be taken into consideration if a new drug registration dossier is planned to be submitted in the future. For example, speed of blades, screen size, or time of binder addition could be further studied. Finally, the optimized process parameters in this work can be applied to other formulations using wet granulation in large scale production.

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