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Optimization of Lubrication and Compression Process Parameters of Vitamin C Film-Coated Caplets

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ABSTRACT

Tablet production is a very intricate process influenced by numerous process variables or parameters. This study aimed to identify the critical processing variables that affect Critical Quality Attributes (CQAs) of vitamin C film-coated caplets utilizing a statistical experimental design. A two-level complete factorial design with two central points was used to examine the process parameters that posed the greatest risk to CQAs. The process variables investigated included mesh size and duration for the lubrication process, as well as speed and main thickness for compression. Statistical results showed that mesh number, lubrication time, and their interaction significantly affect flow rate, Hausner ratio, and compressibility index. Higher mesh number and longer duration improved flow properties; lower main thickness significantly increased core caplet hardness; and lower dissolution rates were observed at higher compression speeds. Based on this study, it can be concluded that mesh number and lubrication time only significantly affected the bulk quality attributes but did not have a significant impact on the quality attributes of vitamin C caplets. On the other hand, the parameters of the compression process, such as speed and main thickness, greatly impacted the quality attributes of vitamin C caplets. In this study, the use of mesh number 20 with 7 minutes of lubrication, and a speed of 17 rpm with a main thickness scale of 2.00 were determined as the optimal process parameters. The optimal process parameters for the lubrication and compression processes were obtained from statistical analysis of the response data.

Keywords: *Vitamin C film-coated caplets; lubrication; compression; parameter; optimization*

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INTRODUCTION

Ascorbic acid or vitamin C is an essential micronutrient because of its pleiotropic properties that relate to the ability to donate electrons (Carr & Maggini, 2017). This vitamin has been identified as one of the fastest-growing products in sales and shortage during the coronavirus disease (COVID-19) pandemic (Romano et al., 2021). This vitamin is essential for immune system functions, and adequate supplementation with ascorbic acid may positively affect different viral infections (Shahbaz et al., 2022; Hemilä & de Man, 2021).

During the COVID-19 pandemic in Indonesia, the Indonesian FDA (Food and Drug Administration) simplified and accelerated the registration of priority products, including health supplements, to maximize the product registration licensing process (BPOM RI, 2021; 2022). To ensure the effectiveness and safety of the product, health supplement products like vitamin C caplets must also comply with quality requirements. Quality by Design (QbD) approach can be used to produce good and consistent-quality medicines. QbD approach has been recognized as a scientific approach that describes the Quality Target Product Profile (QTPP), Critical Material Attributes (CMA), and Critical Process Parameters (CPP) that affect Critical Quality Attributes (CQAs) products. It is essential to understand the production process so that it can be designed with consistent parameters. Inconsistency of CPP in production might impact the CQAs of medicinal products, so it is necessary to control these process parameters (Grangeia et al., 2020; Peddapatla et al., 2021; Yu et al., 2014).

Caplets are preferred for administering vitamin C due to the high dosage of 500 mg per caplet. The caplet's design, resembling a capsule, makes it easier for patients to swallow, especially when dealing with larger doses. This study assessed CPPs for the quality characteristics of vitamin C film-coated caplets. The lubrication and compression stages were selected through a risk assessment process. A factorial design method was utilized to study the impact of lubrication and compression factors on the Critical Quality Attributes (CQAs) of vitamin C caplets that have been coated with film. This study aimed to investigate how Critical Process Parameters (CPPs) affect the quality of vitamin C film-coated caplets during lubrication and compression. The study also identifies the optimal CPPs for the product's quality attributes.

METHODS

Instruments and Materials

Various instruments and tools used in this study were analytical balance (Mettler Toledo XPR205, Swiss), Shaking Granulator 160 Roller Dia (Erweka, Germany), Polimon Sieve 1000, Mesh 30, Mesh 20, Mesh 14, Double Cone Mixer 10 L Machine (Toyo Teknik type DCM10L/201112, Japan), Tablet Compression Machine PTK PR-LM (PTK, Korea), Stirrer Mixer (Eurostar Ika Werke Type Euro STD, Jerman), Conventional Film Coating Machine, Hardness Tester (Erweka, Germany), Friability Tester (Vanguard type LIC-1, USA), Density Tester TDT (Wincom, China), Flowability Tester, Disintegration Tester (Vanguard type LIJ-2, USA), Dissolution Tester (Hanson Vision Elite 8, USA), and Laptop with licensed Minitab 21 program.

All ingredients used were USP Grade, including vitamin C or ascorbic acid (DSM Nutritional, UK), diluent (JRS Pharma, China), binder (BASF, Hongkong), disintegrant (Shandong Head, China), talc (Takehara, Japan) as glidant, and stearic acid (Croda, Singapore) as lubricant, coating agent (Colorcon, China), and coating solvent (Bratachem, Indonesia).

Factorial design of lubrication process parameters

A two-level factorial design experiment with two center points was conducted for lubrication parameters, as seen in Table 1. In this process, the mesh number for stearic acid and lubrication time (minutes) were observed on the response of the bulk and caplet quality attributes. The mesh numbers for stearic acid observed were 14, 20, and 30, while the lubrication time (duration) observed were 3, 5, and 7 minutes. The responses that were tested including bulk homogeneity, flow rate (FR), angle of repose (AR), Hausner Ratio (HR), compressibility index (CI), bulk assay (%), disintegration (minutes), core caplet weight variance (WV) (% acceptability), core caplet assay (%), core caplet dissolution (%), coated caplet WV (% acceptability), coated caplet assay (%), and coated caplet dissolution (%).

Table 1. Factorial design for lubrication process

Run	Mesh	Duration
1	-	-
2	+	-
3	-	+
4	+	+
5	0	0
6	0	0

Factorial design of compression process parameters

In a different batch, a two-level factorial design experiment with two central points for compression process parameters was also conducted according to Table 2. The compression speed in rpm and the main thickness scale were observed in response to the quality attributes of vitamin C caplets. Compression speeds of 15, 20, and 25 rpm and main thickness scales of 1.75, 2.00, and 2.25 were used. The observed responses were appearance, weight (mg), thickness (mm), hardness (kP), friability (%), disintegration (minutes), core caplet WV (% acceptability), core caplet assay (%), core caplet dissolution (%), coated caplet WV (% acceptability), coated caplet assay (%), coated caplet dissolution (%).

Table 2. Factorial design for compression process

Run	Speed	Main thickness
1	-	-
2	+	-
3	-	+
4	+	+
5	0	0
6	0	0

Statistical Analysis

All responses were tested using United States Pharmacopeia or Indonesian Pharmacopoeia standard methods and were statistically analyzed using the licensed Minitab 21 program. The effect of process parameter factors was analyzed to see which process parameters had a significant effect on quality attributes, using the Analysis of Variance (ANOVA) test with a 95% confidence level (significance level α=0.05)

Response Optimization

Response optimization was performed based on the obtained factorial design response. Optimization was carried out using licensed Minitab 21 to determine the process parameters that were estimated to be most optimal in the lubrication and compression process.

Production Process of Vitamin C Caplet

Figure 1 illustrates the production process, which involves the direct compression method for caplet manufacturing. vitamin C, disintegrant, and binders were sifted through a shaking granulator with Polimon 1000 to prepare the mixture. The resulting powder was then blended with a diluent in a double-cone mixer for 15 minutes at 30 Hz. The lubricant and glidant were sieved using mesh 14/20/30 (according to design) and mixed with Active Pharmaceutical Ingredient (API) and other excipients using a double cone mixer for

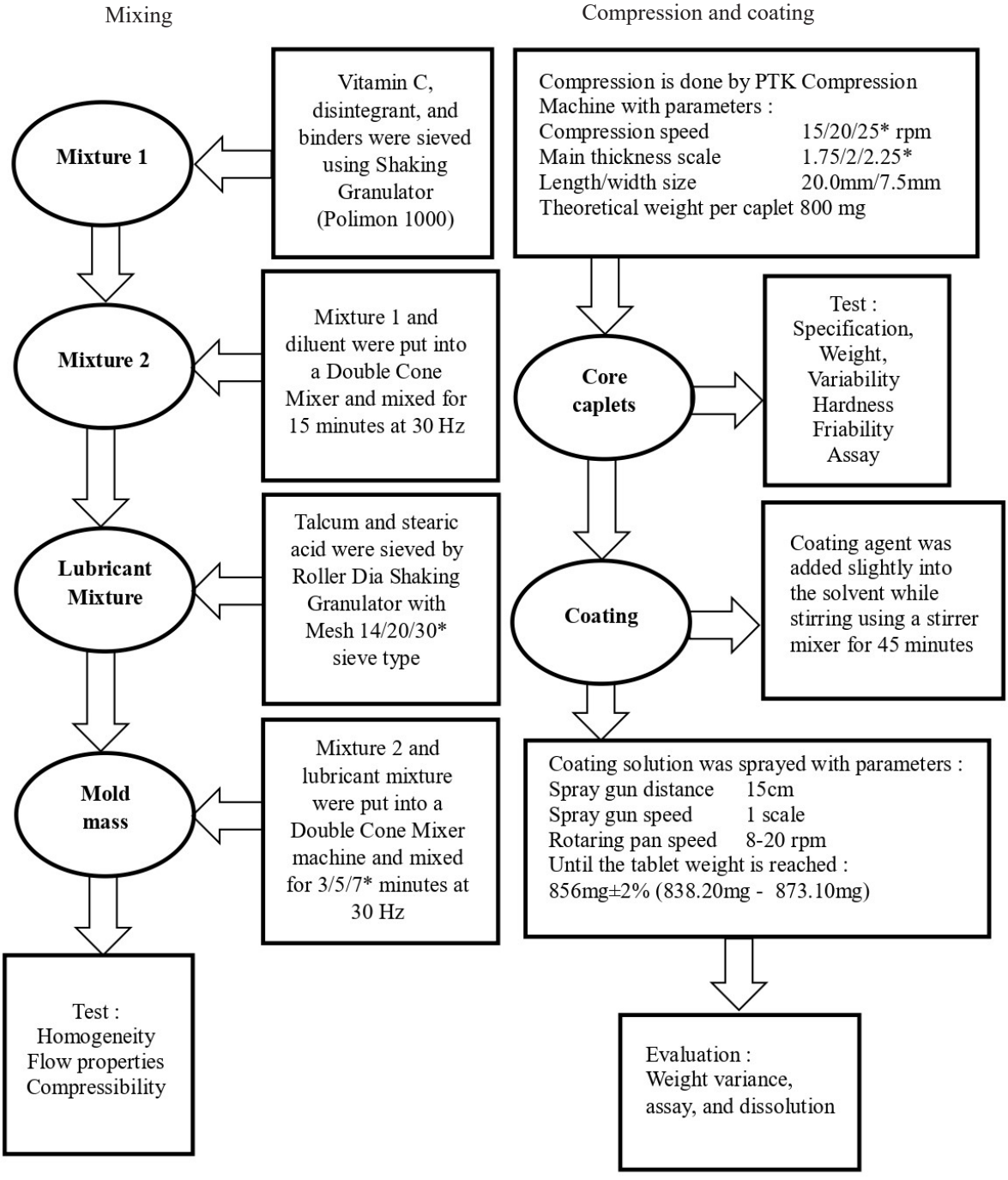

Figure 1. Production process flow chart of the vitamin C film-coated caplets

Table 3. Initial risk assessment of drug manufacturing process steps on CQAs

CQAs	Raw material sieving	Mixing	Lubricant and glidant sieving	Lubrication	Compression	Coating
Assay	Medium	Medium	Low	Medium	Medium	Low
Uniformity of preparation	Medium	Medium	Low	Low	High	Low
Dissolution	Low	Medium	High	High	High	Medium

3/5/7 minutes (according to design). The quality of bulk was evaluated. The compression was carried out using a PTK compression machine with a compression speed of 14/20/25 rpm (according to design) and a main thickness scale of 1.75/2.00/2.25 (according to design) to produce caplets with 20.0 mm theoretical length, 7.5 mm theoretical width, 800 mg theoretical weight. The quality of core caplets was evaluated. The coating agent was dissolved with the solvent and homogenized using a stirrer mixer for 45 minutes. The coating was performed using a conventional film-coating machine with a 15 cm spray gun distance and 8-20 rpm rotating pan speed until the caplet weight reached 856 mg±2% (838.80 mg-873.10 mg). The CQAs of coated caplets were also tested.

RESULTS AND DISCUSSION

Tablets are the most commonly used dosage form in the pharmaceutical industry because of their high physical and chemical stability, portability, dose clarity, and low cost. To produce tablets, external mechanical force is applied to the powder in a die using upper and lower punches. It is important to note that process parameters can affect the properties of the tablet (Ohsaki et al., 2020). A risk assessment was performed to analyze the effect of each stage in the vitamin C caplet production process on CQAs, and the results are shown in Table 3. The vitamin C film-coated caplets must be met with certain critical quality attributes (CQAs), including assay, uniformity of dosage units (weight variation), and dissolution. (Gray, 2018; Yu et al., 2014). Risk assessment indicated that lubrication and compression were high-risk steps, which may highly affect the CQAs of the product.

The sieving process of lubricants and glidants reduced its particle size. Due to the size reduction, an increase in the surface area of the lubricant led to the forming of a thin and evenly distributed layer of hydrophobic lubricant on the granules' surface during mixing. The hydrophobic coating interferes with wetting phenomena leading to a rise in the time required for tablets to disintegrate or dissolve (Hiremath et al., 2018; Li & Wu, 2014), resulting in a high risk of the tablet's dissolution. Not only particle size but over-lubrication due to the excessive number of revolutions may increase the disintegration time, which leads to problems such as poorer tablet dissolution (Morin & Briens, 2013; Nakamura et al., 2017).

In tablet compression, compaction force and dwell time are parameters that significantly affect the mechanical quality attributes of tablets (Anbalagan et al., 2017; Huang et al., 2020). Compression force is a complex parameter, and the thickness setting parameter of the tablet may influence its compression force. Meanwhile, the dwelling time depends on various factors such as the shape of the tablet tooling and the speed of the tablet press.

Production Process of Vitamin C Caplet

Tablets can be made by various methods, such as direct compression, wet granulation, dry granulation, fast melt granulation, and foam granulation (Nanda et al., 2020). Out of all the methods used to manufacture tablets, the direct compression method is the easiest and most preferred. This is because it offers advantages such as superior manufacturing efficiency and better physical and chemical stability. The use of direct compression method brings several benefits, including fewer manufacturing steps, shorter manufacturing time, reduced energy consumption, and lower production costs. Additionally, there is less production variability, improved stability of the active substance, easier validation of production, and a lower risk of microbial contamination. This method is particularly useful for active ingredients sensitive to moisture or heat (Chen et al., 2019; Franc et al., 2018).

The ascorbic acid caplets were manufactured using the direct compression method due to the API's instability and high reactivity to reversible oxidative reaction when exposed to light, heat, transition metals, or alkaline conditions. This reaction produces dehydroascorbic acid (DHA), which eventually transforms into 2,3-diketo-gulonic acid through hydrolysis. This transformation is irreversible, so choosing the direct compression method is essential to ensure the API remains stable and functions efficiently (Yin et al., 2022).

Table 4. The ANOVA results for bulk quality attributes after lubrication process

Factor	*p*-value					
	Y1	**Y2**	**Y3**	**Y4**	**Y5**	**Y6**
Mesh Number	0.539	0.011	0.900	0.028	0.026	0.982
Duration (minute)	0.634	0.005	0.706	0.008	0.009	0.765
Mesh Number*Duration	0.380	0.020	0.841	0.005	0.005	0.952

Y1: homogeneity (%CV), Y2: FR (grams/second), Y3: AR, Y4: HR, Y5: CI, Y6: core caplet assay

Table 5. The ANOVA results for the CQAs of vitamin C caplets under the influence of lubrication

Factor	*p*-value						
	Y7	**Y8**	**Y9**	**Y10**	**Y11**	**Y12**	**Y13**
Mesh Number	0.198	0.107	0.064	0.751	0.082	0.850	0.958
Duration (minute)	0.169	0.605	0.257	0.638	0.287	0.859	0.163
Mesh Number*Duration	0.077	0.282	0.399	0.995	0.251	0.721	0.964

Y7: disintegration (second), Y8: caplet WV (% acceptability), Y9: core caplet assay (%),
Y10: core caplet dissolution (%), Y11: coated caplet WV (% acceptability),
Y12: coated caplet assay (%), Y13: coated caplet dissolution (%)

Factorial design analysis of lubrication process

The ANOVA result of bulk quality based on the influence of mesh number and lubrication time (duration) can be seen in Table 4. From these results, it was found that the selection of mesh number, lubrication time, and their interaction had a significant effect on the FR (Y2), HR (Y4), and CI (Y5), as seen from the *p*-value smaller than the α value (*p*-value <0.05). The factorial plot showed that the flow rate was improved when the mesh number used was larger (smaller orifice diameter). In this study, sieves with mesh number 14 (⌀=1.410 mm), mesh no.20 (⌀=0.841 mm), and mesh no.30 (⌀=0.595 mm) were utilized. In general, the efficiency of boundary lubricants, like stearic acid, increased with the rise of the surface area due to particle size reduction. Increasing lubricant surface area can provide more surface coverage (Li & Wu, 2014; Morin & Briens, 2013). The use of a higher mesh can improve the flow properties, consistent with the low values of HR and CI observed in this study, which are the common values to assess flowability. The term HR refers to the ability of a powder to compress and the ways in which its particles interact with each other. In free-flowing powders, if there is not much interaction between particles, the bulk density and tapped density values will be very close. Overall, a low HR value indicates good flowability (Morin & Briens, 2013; Schlick-Hasper et al., 2022).

Regarding the response for CQAs, Table 5 shows the *p*-value of factorial design analysis based on ANOVA. This result showed that mesh number and lubrication time as well as their interaction had no significant effect on the CQAs of the caplets, including the disintegration time, weight variability, assay, and dissolution. This was proven by the *p*-values which were greater than the α value (*p*-value>0.05). ANOVA showed no significant difference between the influence of mesh number and lubrication time on the vitamin C caplet quality attributes and CQAs.

Lubricants are necessary for tablet manufacturing but may cause undesirable changes in tablet properties, such as tablet hardness, tensile strength, disintegration time, dissolution, tablet brittleness index, and variability of tablet mass. Tablet properties can be affected by the type and concentration of lubricants used, the lubrication method, and how they are combined in the mixture (Dun, 2020; Kuck & Breitkreutz, 2022; Morin & Briens, 2013; Paul & Sun, 2017). In this experiment, all tablet quality attributes were internally qualified and ANOVA results showed no significant changes in tablet CQAs due to differences in mesh number and lubrication time.

Factorial design analysis of compression process

The ANOVA results which describe the influence of compression process parameters on the caplet's quality attributes are presented in Table 6. Any range of compression parameter processes could produce caplets with an appearance that conforms to specifications: caplets, biconvex, white in color, and plain (no marks) on both sides. The results showed that compression speed and its interaction with the main thickness parameter

Table 6. The ANOVA results for the quality attributes of vitamin C film-coated capletsunder the influence of compression

Factor	*p*-value				
	Y1	**Y2**	**Y3**	**Y4**	**Y5**
Speed	0.063	0.865	0.314	0.652	0.709
Main Thickness	0.235	0.458	0.022	0.297	0.132
Speed*Main Thickness	0.921	0.833	0.616	1.000	0.651

Y1: weight (mg), Y2: thickness (mm), Y3: hardness (kP), Y4: friability (%friability), Y5: disintegration (sec)

Table 7. The ANOVA results for the CQAs of vitamin C film-coated caplets under the influence of compression

Factor	*p*-value					
	Y6	**Y7**	**Y8**	**Y9**	**Y10**	**Y11**
Speed	0.193	0.152	0.776	0.136	0.430	0.047
Main Thickness	0.948	0.834	0.759	0.388	0.051	0.540
Speed*Main Thickness	0.244	0.329	0.858	0.302	0.141	0.906

Y6: core caplet WV (% acceptability). Y7: core caplet assay (%). Y8: core caplet dissolution (%).
Y9: coated caplet WV (% acceptability). Y10: coated caplet assay (%). Y11: coated caplet dissolution (%)

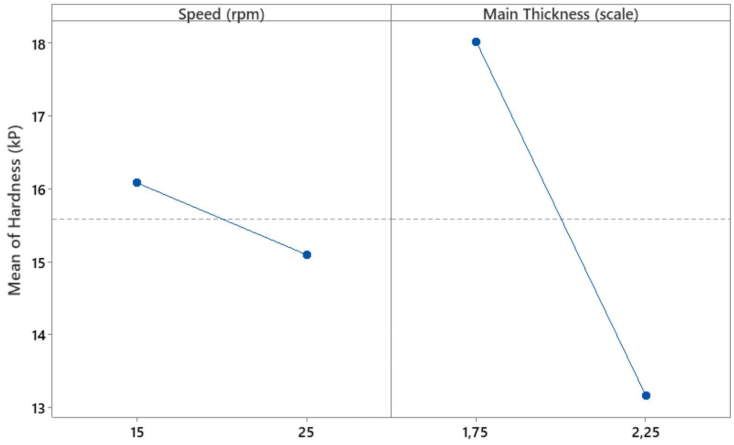

Figure 2. Plot of the effects of compression speed and main thickness on the core caplet hardness

had no significant effect on vitamin C core caplets' weight, thickness, hardness, friability, and disintegration time. This is proved by the *p*-values greater than the α value (*p*-value>0.05). Previous studies also found that the compression speed significantly influenced the mechanical strength of tablets and capsules through their experimental observations (Aoki et al., 2014; Roopwani & Buckner, 2021). Tablets will be mechanically weak at high compression speeds, leading to various defects and failure to comply with internal quality requirements (Roopwani & Buckner, 2021). This experiment showed no significant difference in the mechanical properties of vitamin C core caplets due to compression speed.

The hardness of caplets was significantly affected by the main thickness parameter. As presented in Figure 2, the caplets' hardness decreased as they were thicker. The tablet's dimensions, which are directly influenced by the reliability of the punch and dies used in manufacturing, are crucial in determining their weight and hardness (Natoli et al., 2017). A decrease in tablet thickness resulted in a rise of the tensile stress (Yohannes & Abebe, 2021). The pressure received by the bulk will be higher when the caplet is made in a lower thickness since the bulk is forced to become thinner while the dies volume of filling remains the same.

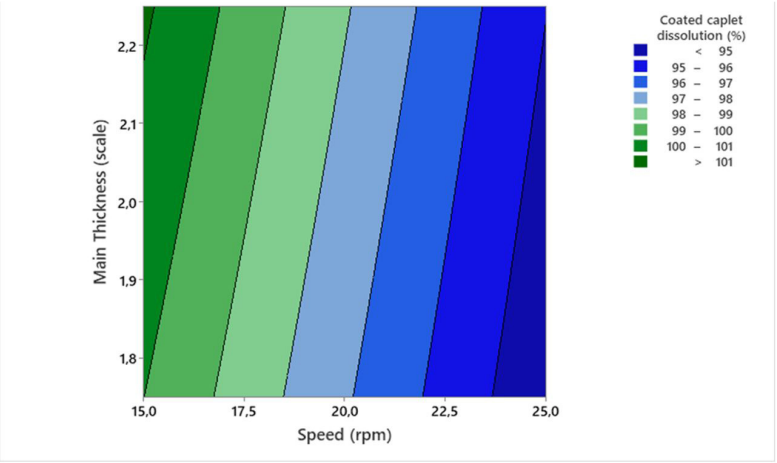

Figure 3. Contour plot of speed and main thickness parameter on the vitamin C film coated caplets dissolution

For the CQAs of vitamin C caplets, ANOVA results showed that compression speed significantly impacted the dissolution, as shown in Table 7. Dissolution is one of the CQAs showing the performance of vitamin C caplets and is also a prerequisite for the final product according to the 6th Indonesian Pharmacopoeia. Increasing compression speed will reduce the dissolution of coated caplets as seen in the contour plot depicted in Figure 3. This might occur because using a higher compression speed can lead to a rise in tablet porosity since the compression pressure obtained by bulk is lower (Xu et al., 2020).

The thickness of the coating agent and the core tablet's porosity are very important factors affecting the water penetration rates into the tablet core. An earlier study reported that a higher core porosity facilitates faster transport through the layer of protective film as a low porosity tablet core would cause an increased pressure on water intrusion with air replacing water and attempting to leave the system (Dong et al., 2023). However, a different phenomenon was observed in our study. When the tablet cores were exposed to the coating steps, some unacceptable changes in tablet dissolution behavior may occur after the film coating process. The penetration of moisture into the cores during application of an aqueous film coating can cause partial inactivation of disintegrant, and then impact dissolution (Ashland, 2019). In certain types of disintegrants, moisture absorption will potentially impair the tablet's disintegrant properties because the tablets were held in a gel matrix, thus preventing disintegration. Consequently, the tablet disintegration time is determined more by the extent of gel formation, rather than changes in tablet hardness. Therefore, increased water uptake to promote gelling is associated with longer tablet disintegration times (Uhumwangho & Okor, 2005).

Response optimization

The optimization was conducted using licensed Minitab 21 based on factorial design response. It is found that a mesh number of 19.65 (close to mesh number 20), with a duration of 7 minutes in the lubrication process; and a compression speed of 17 rpm with a main thickness scale of 2.00 in the compression process were expected to produce vitamin C caplets with optimal CQAs.

The tablets' dissolution rate can be affected by the surface area of the lubricant. The optimal lubricant's particle size and lubrication time affect the total surface area and coverage of the lubricant. Slower dissolution rates were associated with higher hydrophobic surface areas and longer lubrication time (Abe & Otsuka, 2012; Calahan et al., 2021; Morin & Briens, 2013). The speed at which the punch passes through the compression rollers during the compression process, as well as the thickness parameter's impact on the compression force, all of which impact the tablet's mechanical strength. (Adeleye, 2019). Optimal process parameters were expected to form tablets with the best and most consistent quality.

CONCLUSION

This study was a part of the screening process parameters with a systematic Quality by Design approach to analyze which process parameters have a significant effect on the quality attributes of vitamin C film-coated caplets produced by the direct compression method. Lubrication parameters had a significant impact on bulk quality attributes and compression parameters had a significant impact on the caplet quality attributes.

In the lubrication process, it was found that mesh number, lubrication time, and the interaction of both parameters significantly affected the powder's flow properties,

including flow rate, Hausner Ratio, and compressibility index. However, no significant effect was observed on the CQAs of core caplets and coated caplets. In the compression process, the main thickness parameter significantly impacted the caplet's hardness, while the compression speed parameter significantly affected the dissolution of vitamin C film-coated caplets.

Optimization of CQAs was successfully carried out based on the response data, and it was found that mesh number 20 with 7 minutes of lubrication, and compression speed of 17 rpm with 2.00 main thickness scale were determined as the optimal process parameters.

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