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Application Of Factorial Design To Optimize Lubricant Concentration And Granule Mixing Time In The Formulation Of Sour Star Fruit (*Averrhoa bilimbi* L) Ethanolic Extract Tablet

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Abstract

The use of lubricant in tablet compaction can reduce both intergranular and granule to die-wall friction that in turen improve granule flow properties and reduce adhesion of granule mass to the die wall. However, the concentration and method of adding lubricants into granule mass has also been known to influence the physical properties of tablets, such as hardness, friability, disintegration time and dissolution. This study aimed to apply 2-factor-2-level-factorial (22) design to determine the effect of lubricant concentration in granule mass (factor A) and the granule mixing time (factor B) on the physical properties of granules and tablets of starfruit leaves (Averrhoa bilimbi L.) ethanolic extract and to obtain the optimum setting of both factors that results in responses that satisfy most of the predefined criteria. The factorial design was set as follows: (l) = 2.5%, 5 minutes, a = 5%, 5 minutes, b = 2.5%, 15 minutes, and ab = 5%, 15 minutes. The lubricant used was a mixture of magnesium stearate and talc in a ratio of 1:9. Experimental design and optimization were carried out using Design Expert 13.0 software with granule flowability, angle of repose, and compressibility, as well as tablet weight uniformity (%RSD), hardness, friability, and disintegration time as responses. Optimum results were obtained with 2.5% lubricant and 5 minutes factor combination. The verification test to the optimum parameters showed that the granule flowability, angle of repose, tablet hardness and tablet friability are within the prediction interval range (PI 95%).

Keywords: tablet, Averrhoa bilimbi L, lubricant, concentration, granule mixing time, factorial design

INTRODUCTION

Belimbing wuluh (*Averrhoa bilimbi* L.; *pickle tree* (English); *pias* (Philippines); *ta ling pling* (Thai); *huang gua shu* (Chinese); *limao de caiena* (Brazil); *vilimbipuli* (India); *khe tay* (Vietnamese); *taling pling* (Thailand); and belimbing buluh and blimbing asam (Malaysia) (Alhassan & Ahmed, 2016)) is one of the Indonesian plants that is used as an antihypertensive by boiling the leaves and drinking the boiled water (Desmariyenti, 2021). The ethanol extract of starfruit leaves has been reported to be effective as an antihypertensive in cats with a diuretic mechanism by administering the extract at a dose of 25 mg/kgBW (Hernani et al., 2009).

Lubricant is needed in the process of granules compaction into tablets, especially to reduce both intergranular and granule to die-wall friction, hence, improve flow properties (as glidant) and reduce adhesion of granule mass to the die wall facilitating the tablet ejection (Puspadina et al., 2021). However, the concentration and method of adding lubricants into granule mass has also been known to influence the physical properties of tablets,

such as hardness, friability, disintegration time and dissolution. This is attributed to the formation of film of lubricant particles on the surface of granul particles that disrupt the bonding between granule particles during compaction (Apeji et al., 2022), and hinder the penetration of water during disintegration and dissolution due to hydrophobic nature of the film (Wang et al., 2010).

Magnesium stearate (Mg stearate) is a lubricant used in tablet formulations because of its excellent properties and is usually used at a concentration of 0.25-5% (w/w)(Zarmpi et al., 2020). It belongs to metallic salt of fatty acid type of lubricants that is hydrophobic in nature and can form films on other tablet excipient particles surface. The hydrophobic film coating reduces the mechanical strength of the tablet(Paul & Sun, 2018). High concentration of Mg stearate and long granule mixing times have negative effects, i.e. reducing tablet hardness, prolonging disintegration and dissolution processes (de Backere et al., 2020).

The use of Mg steartate is often combined with talc to reduce the detrimental effects of Mg stearate (Ajala et al., 2012). Talc is used in tablet formulations as a lubricant and glidant at concentrations of 0.5-3% and up to 5% (w/w) (Wang et al., 2010).

In general, the lubricant is added to the dry mixture after the other components have been homogenized and only mixed within a few minutes (Syukri, 2018). The effectiveness of adding lubricant into tablet formulation depends on its concentration and its mixing time of the granule mass (Uchimoto et al., 2013). The difference in lubricant concentration and mixing time will cause variations in the distribution and attachment of the lubricant to the granule surface. Small changes in mixing time and concentration of lubricant can significantly affect the flow properties of the granules and can affect the weight uniformity, friability, hardness and disintegration time of the tablets produced. In order to obtain tablets with good physical properties, it is necessary to optimize both the lubricant concentration in the tablet formula and its mixing time with the granule mass (process variable).

In this study the effect of lubricant concentration and its mixing time with the granule mass of belimbing wuluh (*Averrhoa bilimbi* L) ethanolic extract tablet formulation was investigated and the optimum setting of both factors was determined in terms of desired responses, including the granule and tablet physical properties. The study was conducted using 22 factorial design method.

RESEARCH METHODOLOGY

Materials

Belimbing wuluh leaves were obtained from the trees located in Pabelan Village of Kartasura District in Sukoharjo region Central Java Indonesia. All ingredients, including 70% ethanol, distilled water, magnesium stearate, talc, lactose, Eksplotab®, and starch were of pharmaceutical grade and purchased from local vendor CV Mitra Medika.

Preparation of ethanolic extract of starfruit leaves (Averrhoa bilimbi L)

Belimbing wuluh leaves were dried under the sun, covered with black cloth. Subsequently, the dried leaves were ground intou powder. One kilogram of dried leaves powder was soaked in 5 L of 70% ethanol in a vessel and left for 5 days with regular stirring. After 5 days it was filtered and concentrated using a rotary evaporator at 50ºC. The concentrated liquid extract obtained is reheated in a water bath until a thick extract is formed. The thick extract is then dried by adding aerosil with an extract:aerosil ratio of 2:1.

Formulation and production of belimbing wuluh (*Averrhoa bilimbi*. L) leaves ethanolic extract tablets

This research uses a two factor factorial design with each factor consisting of 2 levels. The factors in this research are the level of lubricant in the formula and the mixing time of the granules. The lubricant used was

Table 1. Two-factor, two-level factorial design for lubricant concentration and granule mixing time of belimbing wuluh (*Averrhoa bilimbi* L.) leaves extract tablet formulation

Treatment	Lubricant concentration (A)	Granule mixing time (min.) (B)
(l)	2,5%	5
a	5%	5
b	2,5%	15
Ab	5%	15

Note: (l): low level factor A and low level factor B; a: high level factor A and low level factor B; b: low level factor A and high level factor B; ab: high level factor A and high level factor

magnesium stearate and talc (1: 9) with low level concentration of 2.5% and high level of 5%. The granule mixing times were 5 minutes for the low level and 15 minutes for the high level of the mixing time factors (**Table 1**).

The complete formulations of the belimbing wuluh (*Averrhoa bilimbi* L.) ethanol extract tablet is listed in Table 2, showing the weights of each ingredient of a single 500 mg tablet. Formula A and B designate the formula for low and high levels of lubricant, respectively. The lactose was considered inert to the responses, i.e. its variation range used in the present study was assumed to have no influence to the physical properties of the tablets.

Table 2. Formulations of the belimbing wuluh *(Averrhoa bilimbi* L.) ethanol extract tablet of a single 500 mg tablet

Material	Formula	
	Formula A (mg)	Formula B (mg)
Dry extract of belimbing wuluh	325	325
Magnesium stearate	1.25	2.50
Talk	11.25	22.50
Starch	50.00	50.00
Lactose	92.50	80.00
Explotab®	20.00	20.00
Total	500	500

Dry extract of blimbing wuluh consisted of 216.67 mg belimbing wuluh thick extract and 108.67 mg Aerosil®. Formula A and B designate the formula for low and high levels of lubricant, respectively.

All the ingredients were weighed according to the formula (**Table 2**). Starch powder was converted into mucilage by suspending it in water with continuous stirring and heating until clear glue mass was formed. The dry ethanolic extract of belimbing wuluh leaves, lactose and explotab were mixed manually. Starch mucilage was then added to the mixed powder and gently mixed and kneaded to form damp granule mass. The wet granule was passed through 12 mesh sieve and dried in the oven at 60ºC for 24 h, after which it was passed through 14 mesh sieve. Lubricant (Mg stearate and talc) was added into the dry granule mass and mixed subsequently according to the treatment recipe (**Table 1**). The mass was then tested for its physical properties and compacted thereafter.

Evaluation of granule physical properties

Granule mass flow time and angle of repose test

The granules were weighed as much as 100 g, then put into a funnel through the funnel wall. The lid of the funnel was opened and the granules were allowed to flow out and the time required for all the granules to come out was recorded and the base diameter and the height of the cone-shaped granule bed were measured. The test was done in triplicates.

Granule compressibility indeks

The granules were put into the graduated cylinder of volumenometer (Vanguard Pharmaceutical Machinery, Inc.) to a volume of 100 ml. The cylinder was then installed on the volumenometer then turned on to tap several times, each for 100 taps, until it reached constant volume. The initial volumes were recorded as V0 and the constant tapped volume as VF. The compressibility index was calculated as follows (Kementerian Kesehatan Republik Indonesia, 2020):

$$Compressibility\ Index = 100 \times \left(\frac{V_o - V_F}{V_o}\right) \quad (1)$$

Evaluation of tablet physical properties

Tablet weight uniformity

The tablet weight uniformity was expressed as the coefficient of variation (CV) or relative standard deviation (RSD) of the weight of 20 tablets. The tablets were weighed one by one using an analytical balance (Ohouse). Subsequently, their average (X) and coefficient of variation (CV) were calculated.

Tablet hardness

The tablet hardness test was carried out using a hardness tester (Vanguard YD-1, Vanguard Pharmaceutical Machinery, Inc.). One tablet was placed at the end of the tool in a horizontal position, and the initial scale was 0. The knob was rotated until the tablet was depressed and broke, then the scale printed on the tool was read when the tablet broke. The scale obtained states the hardness of the tablet. The experiment was carried out three times, and the average was calculated.

Tablet friability

A total of 20 tablets were dedusted and then weighed. The tablet is inserted into the friabilator (Vanguard Pharmaceutical Machinery, Inc.) and turned on for 4 minutes or 100 rotations. The tablet was removed from the friabilator, dedusted and then weighed. The difference in tablet weight before and after testing divided by the initial weight and multiplied by 100% indicates the friability of the tablet. The experiment was carried out three times, and the average was calculated.

Tablet disintegration time

The tablet disintegration time test was carried out by placing one tablet each in 6 basket tubes in a disintegration time tester containing 1 L of water at a temperature of 37º±2ºC. The time required for all tablets to completely disintegrate was recorded. The disintegration time requirement for extract tablets is less than 30 minutes (Badan Pengawas Obat dan Makanan Republik Indonesia, 2014).

RESULT AND DISCUSSION

Determination of the plant species

Plant determination was carried out at the Sebelas Maret University Biology Laboratory by providing samples of wuluh starfruit leaves, samples of small starfruit plants and photos of wuluh starfruit fruit. From the results of plant termination carried out with letter number 020/UN27.9.6.4, it was found that the key to determining the starfruit plant (*Averrhoa bilimbi* L.) was 1b-2b-3b-4b-12b-13b-14b-17b-18b-19b-20b-21b-22b-23b-24b-25b-26b-27a-28b-29b-30b-31a-32a-33a-34a-35a-36d-37b-38b-39b-41b-42b-44b-45b-46e-50b-51b-53b-54b-56b-57b-58b-59d-72b73b-74a-75b-76a-77a-78b-103c-104b-106b-107a-108b-109a-110a-111b-112a-113a Family: Oxalidaceae. The determination results show that the starfruit plant used can be confirmed to come from the *Averrhoa bilimbi* L type.

Physical properties of the ground leaves and its thick ethanolic extract

Examinations were carried out on dry leaf powder and ethanol extract of starfruit leaves including form, odor, color, taste and moisture content (**Table 3)**.

Table 3. Physical properties test results of ground dry belimbing wuluh (*Averrhoa bilimbi* L.) leaves and its ethanolic extract

Test	Ground dry leaves	Ethanolic extract of ground dry belimbing wuluh leaves
Form	Powder	Thick extract
Odor	Specific of belimbing wuluh leaf	Specific belimbing wuluh extract
Color	Light green	Brownish green
Taste	Bitter	Bitter
Loss on drying	-	7.48%

Test Results for Physical Properties of Granules and Tablets

Examination of the physical properties of granules and tablets was carried out to determine whether they meet the specified requirements. Examination of the physical properties of the granules included flowability, angle of repose, compressibility and evaluation of the physical properties of the

Table 4. Results of examination of the physical properties of granules and tablets of ethanolic extract of belimbing wuluh leaves (*Averrhoa bilimbi* L.)

Examination	Treatment			
	(l)	a	b	ab
Granule flowability (g/dt)	17.32 ± 0.50	14.41 ± 1.09	12.14 ± 2.35	16.35 ± 2.90
Granule angle of repose (°)	31.50 ± 0.75	35.48 ± 1.36	32.40 ± 0.79	33.51 ± 0.25
Granule compressibility index (%)	6.67 ± 1.53	8.75 ± 1.65	8.75 ± 1.64	4.17 ± 1.44
Tablet weight uniformity (%)	1.54 ± 0.45	1.55 ± 0.92	1.56 ± 0.55	1.90 ± 0.60
Tablet hardness (kg)	7.80 ± 0.19	7.71 ± 1.06	6.91 ± 0.35	5.45 ± 0.38
Tablet friability (%)	0.34 ± 0.055	1.80 ± 0.60	0.50 ± 0.07	0.85 ± 0.82
Tablet disintegration time (min)	13.90 ± 0.43	18.55 ± 1.33	12.32 ± 1.14	18.20 ± 1.16

tablets including weight uniformity, hardness, friability and disintegration time, the results of which can be seen in **Table 4.**

Granule flowability

The results in Table 4 show that the highest flowability occurred in treatment (l), i.e. the treatment with a lubricant concentration of 2.5% with a mixing time of 5 minutes, while the lowest value occurred in treatment b, i.e. the treatment with a lubricant concentration of 2.5% with a mixing time of 15 minutes. The factorial model equation (Tabel 5) showed that lubricant concentration had positive effect to the granule flowability with slope value of +0.332 and the granule mixing time had larger negative effect with slope value of -0.818. It can be hypotetized at certain point, the length of mixing time causes segregation of lubricant particle in the granul mixture. The equation showed a large value of interaction term, which was supported by the plot in Figure 1. The plot showed that when the mixing time factor was at the high level, the rise in the lubricant concentration increased the granule flowability, while when the mixing time was at the low level the rise in the lubricant concentration decreased the granule flowability.

Granule angle of repose

The angle of repose for all treatments ranged from 31.50° ± 0.75° to 35.48° ± 1.36°. This means that the flowability of the granules in all treatments is within a good flowability range, namely 25°-40° (Rori et al., 2020). Contrary to the fowability response, the angle of repose factorial equation model revealed that the lubricant concentration gave positive effect to the response, which meant negative effect to the flow property of the granule. Meanwhile, the mixing time factor also in contrast with the phenomenon of the flowability response, i.e. it had negative effect to the angle of repose response, meaning negative effect to the flow property of the granule mass. The interaction term was not quite profound, which was also seen in the response plot (Figure 1B) where slightly non-paralel lines were noticed rising with the rise of lubricant concentration, both when the mixing time factor was at low and high levels.

Granule compressibility indeks

A smaller compressibility index (T%) indicates better granule flow properties. The ab treatment (lubricant with a concentration of 5% and mixing time of 15 minutes) has the smallest T% value among the other formulas. Apart from that, the T value in all tablet formulas complies with the standard, i.e. less than 20% (Cahyani et al., 2023). An index value of more than 20% causes the particles in the hopper to form bridges due to the low bulk density so that the granules have poor flow properties. All coefficients of the terms in the model equation revealed negative effects of lubricant concentration, granule mixing time, and the interaction of both factors. The interaction term coefficient indicated quite profound influence, which was also evident in the interaction plots (**Figure 1C**) where the two lines crossed each other, indicating

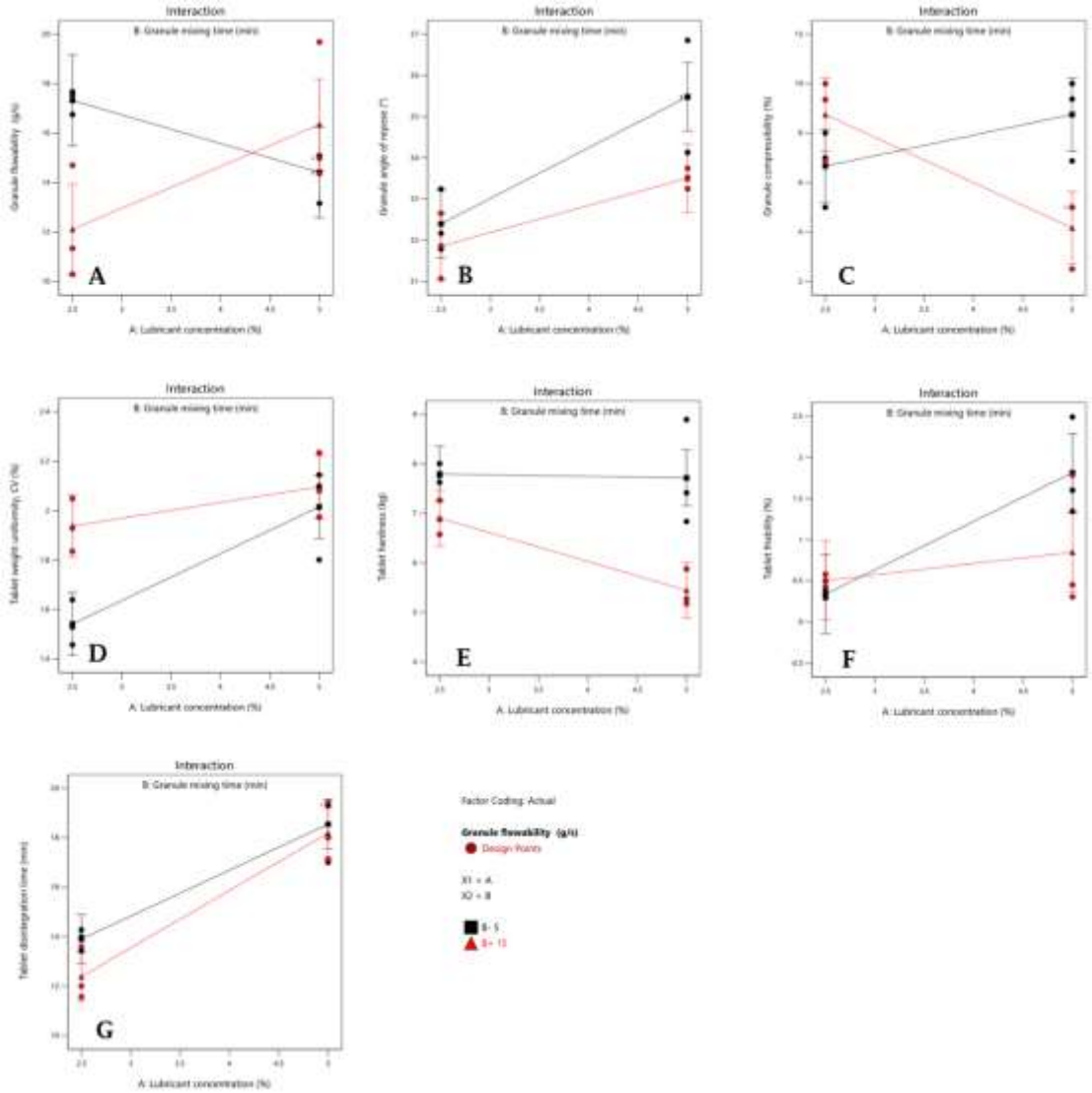

Figure 1. Interaction plot of responses, granule flowability (A), granule angle of repose (B), granule compressibility (C), tablet uniformity (D), tablet hardness (E), tablet friability (F) and tablet disintegrating time (G), showing the effect of the factors setting to each response

profound interaction. The plot showed that the rise of the lubricant concentration decreased the granule compressibility, meaning increase its flowability, when the mixing time is at high level. Meanwhile, when the granule mixing time factor was at low level the rise in lubricant concentration increased the granule compres-sibility response or decrease its flowability.

Tablet weight uniformity

Tablet weight uniformity was determined by calculating the CV value (%) of the weight of 20 tablets, which is a general parameter of uniformity in statistics (Usuda et al., 2021). The CV value (%) of the preparations from all treatments showed good weight uniformity, namely less than 2% (**Table 4**). The evaluation of the effect of the factors on the CV value revealed a slight positive effect for both factors, as indicated by the small positive coefficient of both terms in the model equation (**Tabel 5**). The interaction term showed a smaller negative effect in the equation, as was also inferred from the non-parallel nature of

Table 5. The factorial model equation for each response to the physical properties of the tablet is the concentration factor of the lubricant (A) and the granule mixing time (B).

Response	Model equation	Sig.
Granule flowability (g/dt)	Y = 15.05 + 0.3322A – 0.8184B + 1.79AB	0.0466
Granule angle of repose (°)	Y = 33.31 + 1.18A – 0.6292B – 0.3587AB	0.0045
Granule compressibility index (%)	Y = 7.08 – 0.625A – 0.625B – 1.67AB	0.0210
Tablet weight uniformity (%)	Y =1.90 + 0.1579A + 0.1192B- 0.0788AB	0.0043
Tablet hardness (kg)	Y = 6.97 – 0.3858A – 0.7908B – 0.3458AB	0.0044
Tablet friability (%)	Y = 0.8769 + 0.4538A - 0.1992B - 0.2821AB	0.0301
Tablet disintegration time (min)	Y = 15.76 + 2.61A – 0.4675B + 0.2892AB	0.0002

both rising lines, representing the rise of the tablet weight uniformity with the increase of the lubricant concentration factor (**Figure 1D**).

Tablet hardness

The hardness value indicates the tablet's ability to withstand pressure or shock during the packaging or transportation process. The test results showed that the tablet hardness values (Table 4) in all treatments met good hardness standards, i.e., in the range of 4–10 kg (Fadhilah & Saryanti, 2019). The model equation of the tablet hardness response revealed the small negative effects of both factors on the tablet hardness response, with slight interaction indicated by a small negative coefficient for the interaction term. It was also seen in the slightly non-parallel pattern of both response lines that rose with the increasing concentration of the lubricant in the formulation (Figure 1E). Based on the interaction graph (**Figure 1**), it shows that treatment with low level mixing time (5 minutes) and increasing the concentration of lubricant did not have any effect on tablet hardness. Meanwhile, in the treatment with a high level of granule mixing time (15 minutes), with increasing concentration of lubricant, tablet hardness decreased. This is because in formulas with high levels of mixing time, increasing the concentration of lubricant will reduce the bond between particles after compression due to the increase in the amount of lubricant on the granule surface (Nakamura et al., 2017). In addition, increasing the concentration of lubricant and mixing time allows overmixing to occur which causes the expansion of the lubricant covering the granules so that tablet hardness decreases (Nakamura et al., 2017).

Tablet friability

Good tablet friability values were found in treatments (l), b, and ab because they had friability values of less than 1%, namely 0.34 ± 0.05%, 0.50 ± 0.07%, and 0.85 ± 0.815% (**Table** 4).

The friability value in treatment a, which is more than 1%, indicates that a high concentration of lubricant with a mixing time of 5 minutes will produce bonds between particles that are less strong, so the friability value is higher. The model equation of the friability response showed that the lubricant concentration factor had a positive effect on

Table 6. Criteria for desired physical properties of granules and tablets of ethanol extract of starfruit leaves (*Averrhoa bilimbi* L) for factor optimization

Test	Criteria	Target
Granule flowability (g/dt)	10-20	Maximize
Granule angle of repose (°)	25-40	Minimize
Granule compressibility index (%)	2-9	Minimize
Tablet weight uniformity (%)	0-3	Minimize
Tablet hardness (kg)	4-10	Maximize
Tablet friability (%)	0-0,5	Minimize
Tablet disintegration time (min)	0-30	Minimize

Table 7. Verification results of the optimum formula evaluating the physical properties of belimbing wuluh leaf extract granules and tablets (*Averrhoa bilimbi* L.)

Response	Predicted Mean	95% PI low	Data Mean	95% PI high
Granule flowability (g/dt)	17.3	13.7	14.1	21.0
Granule angle of repose (°)	32.4	30.7	32.3	34.1
Granule compressibility index (%)	6.67	3.72	1.67	9.62
Tablet hardness (kg)	7.80	6.67	7.78	8.93
Tablet friability (%)	0.34	-0.61	0.30	1.3
Tablet weight uniformity (%)	1.54	1.29	0.46	1.79
Tablet disintegration time (min)	13.9033	11.9165	17.6100	15.8902

the response while the granule mixing time factor had a slight negative effects as shown by their term coefficients (**Table 5**). A negative interaction was observed, indicated by the negative coefficient in the interaction term of the equation. The tablet friability plot also showed the interaction phenomenon represented by the crossing lines of effect lines of both factors. Although the increase of lubricant concentration seemed to rise the effect line when the granule mixing time was at high level, its slope was smaller than the same increasing effect when the mixing time was at low level, meaning the effect of increasing friability by the increase of the lubricant concentration was more profound when the mixing time was in low level. This may be due to the fact that the bond between the particles on the edge of the tablet is not strong enough, so that when friction occurs on that part, the particles come off easily (Puspadina et al., 2021).

Tablet disintegration time

The disintegration time test revealed that the disintegration time of tablets of all treatments meet the kriteria for extract tablets, i.e. less than 30 min (Badan Pengawas Obat dan Makanan Republik Indonesia, 2014). Tablets with high levels of lubricant concentrations (treatments a and ab) showed longer disintegration time values compared to tablets with low levels of lubricant ((l) and b), with tablets in treatment a having the longest disintegration time, namely 18.55 ± 1.33 minutes, and treatment b with the fastest disintegration time (12.32 ± 1.14 minutes). The properties of Mg stearate and talc lubricants which have high water repellency form a hydrophobic layer on the surface of particles and tablets, thereby inhibiting water penetration into the tablet and causing the tablet to disintegrate for a long time (Uchimoto et al., 2010). Apart from that, the mixing time in the formulation will also affect the disintegration time and dissolution process of the tablet (Abe & Otsuka, 2012). However, this is not revealed in the present study as the disintegration time are not profoundly different between treatment a and ab, as well as between (l) and b. Further analysis of the effect of both factors on the tablet disintegration time response showed that the lubricant concentration factor had a positive effect on the response while the granule mixing time had a negative effect, as can be seen in the coefficients of both factor terms in the model equation (Table 5). A small positive interaction was observed, as indicated by the small coefficient of the interaction term in the model equation. The interaction plot depicted the effect of the rise in tablet disintegration time by the increase in lubricant concentration when the granule mixing time factor was both low and high, although with a slightly different size of slope. This is because the lubricant used is hydrophobic in nature which can inhibit the penetration of water into the tablet by forming a hydrophobic layer which will increase the disintegration time (Syukri, 2018). On the other hand, the use of a lubricant with a low concentration level will increase

the penetration of water into the tablet which causes a decrease in the disintegration time of the tablet so that the disintegration time becomes faster (Puspadina et al., 2021).

Formula optimization

Optimization of process parameters is carried out using the selected model equations and entering the targets for each response and the desired range of criteria as shown in Table 6. The optimization step resulted in an optimum setting of both factors, i.e., 2.5% of lubricant concentration and 5 min of granule mixing time, together with the predicted values of the responses, as presented in Table 7, with desirability index of 0.589. The optimum setting of the factors was verified by measuring the physical properties of new preparation made based on the setting in triplicate, the mean values of wich are presented in **Table 7**.

It can be seen in **Table 7** that the average verification response values for flow rate, angle of repose, tablet hardness and friability are within the prediction interval range (95% PI low and 95% PI high), while the granule compressibility, weight uniformity, and the tablet disintegration time values does not fall within that range.

CONCLUSION

Lubricant concentration tends to increase tablet weigth uniformity, at both low and high mixing time. It has no effect to tablet hardness at low mixing time but decrease it at high or longer mixing time. Tablet friability is more profoundly increased with the rise of lubricant concentration at low mixing time setting compared with at high mixiing time setting. The tablet disintegration time increases quite sharply, both at low and high mixing time in almost parallel manner. The optimum setting of lubricant concentration in the formula of belimbing wuluh leaf extract tablet and its granule mixing time was successfully predicted for the granule flowability and angle of repose, and the tablet hardness, and tablet friability. However, the prediction was missed for the granule compressibility, weight uniformity, and the tablet disintegration time values.

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