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ORIGINAL ARTICLE

Microcrystalline cellulose promotes superior direct compressed *Boesenbergia rotunda* (L.) Mansf. extract tablet properties to spray-dried rice starch and spray-dried lactose

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ABSTRACT

This work aimed to select tablet diluent of *Boesenbergia rotunda* (L.) Mansf. extract tablet. Three tablet diluents, including microcrystalline cellulose (MCC), spray-dried rice starch, and spray-dried lactose were used. MCC exhibited superior performance to the other diluents by providing the hardest tablet, the lowest friability, and the shortest disintegration time. The Box-Behnken design was used to evaluate the effect of hydrophobic excipients when MCC was used as diluent. The optimal formulation was composed of fumed silica 1%, magnesium stearate 1%, and talcum 2%. The tablets had suitable hardness, low friability, and short disintegration time. The marker pinocembrin could be dissolved by 82% within 4 h. Although the marker decreased after three months of stability testing, the antioxidant activity of the formulation remained. In conclusion, MCC was shown to be superior to the other diluents, and the optimal formulation could be used to prepare *Boesenbergia rotunda* (L.) Mansf. extract tablet as a food supplement.

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KEYWORDS
Fumed silica; magnesium stearate; optimization; tablet diluent; talcum

1. Introduction

The size of the antioxidants market will surpass approximately 9,000 million USD by 2026 at a 5.3% compound annual growth rate over the assessment period between 2020 and 2026 (GlobeNewswire, 2021). A natural antioxidant is an interesting source of compounds. *Boesenbergia rotunda* (L.) Mansf. is one of several natural antioxidants that have been marketed recently. *B. rotunda* or fingerroot is a plant that belongs to the Zingiberaceae family. It is used as a food ingredient and herbal medicine in Southeast Asia as well as Indo-China. It possesses several biological and pharmacological activities, i.e. anti-inflammatory effect (Isa et al., 2012), antimicrobial activity (Bhamarapravati, Juthapruth, Mahachai, & Mahady, 2006; Jitvaropas et al., 2012), antioxidant activity (Isa et al., 2012; Jitvaropas et al., 2012), aphrodisiac activity (Ongwisespaiboon & Jiraungkoorskul, 2017), cytotoxic effect (Isa et al., 2012), vasorelaxant effect (Adhikari et al., 2020), wound healing (Jitvaropas et al., 2012; Ruttanapattanakul et al., 2021), treatment of functional dyspepsia (Chitapanarux, Lertprasertsuke, & Toworakul, 2021), etc. During the Covid-19 pandemic, herbal plants were screened for anti-SARS-CoV-2 activity. Among them, *B. rotunda* extract and its isolated compound panduratin A exhibited anti-SARS-CoV-2 activity (Kanjanasirirat et al., 2020). Recently, several fingerroot extract products have been launched in the market. Several products with various doses of *B. rotunda* extract have been registered. The 200 mg *B. rotunda* extract per tablet was selected in this work based on the dose of marketed products that have been sold in Thailand (Thai Food & Drug Administration, 2022). However, there is no regulation concerning the standard dose of *B. rotunda* extract used for food supplements in Thailand (Thai Food & Drug Administration, 2017). In Thailand, numerous products of *B. rotunda* powder as well as its extract are typically prepared in capsule dosage form, due to it being easily operated in small herbal factories or small to medium-sized enterprises. Numerous publications have reported on the biological and pharmacological activities of *B. rotunda* extract. However, there are limited numbers of publications based on the formulation

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development of *B. rotunda* powder or its extract. An innovative product incorporating *B. rotunda* extract with a hydrogel wound dressing has also been reported (Eakwaropas et al., 2019).

Recently, tablets have become the most popular form of solid oral dosage. Direct compression is the first choice for the preparation of tablets. Direct compression exhibits several advantages compared to wet granulation or dry granulation methods, such as saving equipment, energy, space, and time. It also reduces the risk of cross-contamination due to fewer operating procedures, reducing the risk of microbial growth and the risk of degradation of moisture as well as thermal-sensitive drugs due to no water being used. Generally, tablets prepared by direct compression exhibit a faster dissolution rate. However, it requires desired pharmaceutical excipient properties such as good flowability, compressibility, and compactability (Mura, Valleri, Baldanzi, & Mennini, 2019).

The direct compression diluents included in this work were microcrystalline cellulose (MCC), spray-dried rice starch (SRS), and spray-dried lactose (SLT). MCC is one of the most popular cellulose derivatives used as tablet diluent. It exhibits good compressibility, so it is usually included in directly compressed tablet formulations (Zhao, Zhao, Lin, & Shen, 2022). It also exhibits disintegration properties (Rowe, Sheskey, & Quinn, 2009). However, it also displays poor flow properties (Jivraj, Martini, & Thomson, 2000). Its angle of repose, bulk density, and tapped density was 28–29°, 0.34 g/cm^3. and 0.48 g/cm^3, respectively (Rowe et al., 2009). SRS is one of the direct compression fillers. It is an insoluble, neutral, and free-flowing powder (Vongsurakrai & Varavinit, 2010). It also exhibits disintegration properties with a poor flow similar to MCC (Jivraj et al., 2000). Its angle of repose, bulk density, and compressibility were 35–52°, 0.37–0.45 g/cm^3, and 20–36%, respectively (Bergthaller, Varavinit, & Wongsagonsup, 2005). Developed SRS (Era-Tab®) had excellent flowability comparable to dibasic calcium phosphate but superior to MCC, lactose, and pregelatinized starch. However, MCC was superior to other diluents in terms of dilution potential or carrying capacity (Mitrevej, Sinchaipanid, & Faroongsarng, 1996). SLT is usually used as a tablet binder, filler-binder, and flow aid in direct compression tableting. It is a free-flowing powder that disintegrates by dissolution. However, it requires high compressional force to produce hard tablets when compared with MCC (Jivraj et al., 2000). Its angle of repose, bulk density, and tapped density were 28–29°, 0.57–0.67 g/cm^3, and 0.67–0.78 g/cm^3, respectively (Rowe et al., 2009). The selection of direct compression diluents may be an important step to obtain the desired direct compressed tablet properties.

Hydrophobic excipients (e.g. fumed silica, magnesium stearate, and talcum) are also included in tablet formulations to promote desired tablet properties. Lubricants are used to prevent the sticking of the tablet to the punch faces as well as to reduce friction between the tablets and the die wall during the compression and ejection steps. Magnesium stearate is the most common lubricant used in tablet formulation. Other lubricants such as stearic acid and calcium stearate are rarely used. Glidants are used to improve the flowability of the powder blend. Several compounds can be used as glidants such as fumed silica, starch, and talcum. Anti-adherents prevent the tablet from sticking to the die wall and punch faces. Talcum, starch, and magnesium stearate can be used as anti-adherents in tablet formulation (Chowhan, 2020). However, using excessive hydrophobic excipients retarded drug dissolution from a solid dosage form (Rowe et al., 2009). Thus, optimization of hydrophobic excipients is important to obtain suitable tablet properties.

This work aimed to select a tablet diluent of direct compressed *B. rotunda* extract tablet. Three tablet diluents including MCC, SRS, and SLT were included in the simplex lattice design. The most suitable diluent will be used to prepare *B. rotunda* extract tablets by varying hydrophobic excipients including, fumed silica, magnesium stearate, and talcum using the Box-Behnken design. Furthermore, the stability of *B. rotunda* extract tablets was also evaluated. The authors expected that the optimal *B. rotunda* extract tablet formulation could be used to prepare antioxidant food supplement products.

2. Materials and methods

2.1. Materials

Standard pinocembrin was purchased from Chengdu Biopurify Phytochemicals Ltd., Sichuan, China. Fingerroot extract (yellow powder; moisture content of 3.1%; bulk density of 0.45 g/cm^3; flavonoids content of 267.2 mg%) was purchased from Specialty Natural Product Co., Ltd., Chonburi, Thailand. MCC (Comprecel® M102) was purchased from Maxway Co., Ltd., Bangkok, Thailand. SRS (Era-Tab®) was purchased from Erawan Pharmaceutical Research and Laboratory Co., Ltd., Bangkok, Thailand. SLT (FlowLac®) was purchased from Molkerei Meggle Wasserburg GmbH & Co., Wasserburg am Inn, Germany. Magnesium stearate was purchased from Changzhou Kaide Imp. & Exp. Co., Ltd., Changzhou, China. Talcum was purchased from Nitika Pharmaceutical Specialities Pvt. Ltd., Nagpur, India. Fumed silica was purchased from P.C. Drug Center,

Bangkok, Thailand. Sodium lauryl sulphate (SLS) was purchased from EMD Millipore Corporation, Massachusetts, USA. 2,2-diphenyl-1-picrylhydrazyl (DPPH) was purchased from Sigma-Aldrich Pte Ltd., Ascent, Singapore. Acetonitrile (HPLC grade) was purchased from Fisher Chemical, Leicestershire, UK.

2.2. Simplex lattice design for the selection of tablet diluent

A simplex lattice design was applied for the selection of tablet diluent. The ratios of three diluents including MCC, SRS, and SLT were varied for 14 formulations, comprising 9 individual formulations and 5 replicated formulations. The replicated formulations were prepared to check the variation of the design, as shown in Table 1.

The tablet formulations were composed of 33.33% *B. rotunda* extract powder (or 200 mg per tablet), 1% fumed silica, 1% magnesium stearate, 2% talcum, and 62.67% diluents. The total tablet weight was 600 mg. A total of 35 tablets were prepared for each formulation. *B. rotunda* extract powder was mixed with half the content of diluents for 5 min. Premix was prepared by mixing fumed silica, magnesium stearate, and talcum, with diluents. Subsequently, the premix was blended with the mixture of *B. rotunda* extract powder and diluents for 3 min. The obtained mixture was individually weighed for 600 mg, followed by compressing the tablet using 1,000 psi using a hydraulic press connected to a pressure gauge. The tablet properties were evaluated, including weight and weight variation, diameter, thickness, hardness, friability, and disintegration time.

Contour plots were produced using Design-Expert® software (v. 11) (Stat-Ease Inc., Minnesota, USA). Analysis of variance data were reported. Optimization was done using the software – the formulation with minimized friability and minimized disintegration time was selected for the confirmation step. The optimal formulation was prepared again to obtain the experimental values. The experimental values were compared with the predicted values and the percentage error was calculated as Eq. (1).

$$Error\ (\%) = \frac{(Experimental\ value - Predicted\ value)}{Experimental\ value} \times 100 \quad (1)$$

2.3. Box-Behnken design for optimization of the tablet formulation

The Box-Behnken design was applied for optimization of the suitable content of hydrophobic excipients when the most suitable diluent was used. Three hydrophobic excipients including fumed silica, magnesium stearate, and talcum were varied for 17 formulations, 12 individual formulations and 5 replicated formulations, as shown in Table 2.

The tablet formulations were composed of 33.33% *B. rotunda* extract powder (or 200 mg per tablet), 0.5–1.5% fumed silica, 0.5–1.5% magnesium stearate, 2–4% talcum, and 62.67% suitable diluent obtained from the simplex lattice design. The total tablet weight was 600 mg. A total of 35 tablets were prepared for each formulation. The mixing, tableting, and evaluating steps were done according to the simplex lattice design section.

Response surfaces were produced using Design-Expert® software. Analysis of variance data were reported. The design spaces were produced. The criteria of the design spaces were hardness of 5–7 kP, friability of less than 1%, and disintegration time of less than 1 min. Optimization was done using the software – the formulation with minimized friability and within the design space was selected for the confirmation step. The optimal formulation was prepared again to obtain the experimental values. The experimental values were compared with the

Table 1. Factors and responses for the simplex lattice design.

	Factors*			Responses					
Formulations	MCC	SRS	SLT	Weight (mg)	Diameter (mm)	Thickness (mm)	Hardness (kP)	Friability (%)	Disintegration time (min)
1	1	0	0	603.89 ± 1.85	12.82 ± 0.02	4.31 ± 0.06	7.62 ± 0.39	0.27	0.56 ± 0.01
2	0	1	0	600.22 ± 2.64	12.90 ± 0.03	4.42 ± 0.07	2.06 ± 0.20	100.00	6.48 ± 0.05
3	0	0	1	601.78 ± 1.57	12.80 ± 0.02	4.10 ± 0.03	1.28 ± 0.10	100.00	6.71 ± 0.18
4	0.5	0.5	0	604.11 ± 1.34	12.85 ± 0.02	4.25 ± 0.04	4.63 ± 0.20	0.79	1.42 ± 0.09
5	0.5	0	0.5	605.01 ± 1.42	12.81 ± 0.01	4.17 ± 0.02	2.60 ± 0.14	3.03	0.49 ± 0.01
6	0	0.5	0.5	599.98 ± 2.75	12.84 ± 0.02	4.19 ± 0.03	1.77 ± 0.08	100.00	3.39 ± 0.07
7	0.67	0.17	0.17	603.49 ± 1.65	12.84 ± 0.02	4.28 ± 0.03	4.09 ± 0.12	1.69	0.46 ± 0.01
8	0.17	0.67	0.17	601.41 ± 1.69	12.87 ± 0.02	4.32 ± 0.03	1.96 ± 0.17	100.00	4.92 ± 0.04
9	0.17	0.17	0.67	603.33 ± 1.60	12.84 ± 0.02	4.19 ± 0.02	1.66 ± 0.06	100.00	1.55 ± 0.04
10	0.33	0.33	0.33	600.97 ± 2.33	12.86 ± 0.03	4.30 ± 0.03	1.93 ± 0.09	100.00	1.01 ± 0.04
11	0.33	0.33	0.33	600.93 ± 2.30	12.83 ± 0.01	4.25 ± 0.04	2.31 ± 0.12	100.00	1.27 ± 0.01
12	0.33	0.33	0.33	601.97 ± 1.29	12.85 ± 0.01	4.29 ± 0.04	2.03 ± 0.13	100.00	1.10 ± 0.06
13	0.33	0.33	0.33	601.97 ± 1.80	12.87 ± 0.02	4.32 ± 0.04	2.12 ± 0.12	100.00	1.14 ± 0.05
14	0.33	0.33	0.33	601.68 ± 1.76	12.85 ± 0.02	4.31 ± 0.02	2.23 ± 0.08	100.00	1.20 ± 0.06

*MCC = microcrystalline cellulose, SRS = spray-dried rice starch, SLT = spray-dried lactose.

Table 2. Factors and responses for the Box-Behnken design.

	Factors			Responses					
Formulations	Fumed silica (%)	Magnesium stearate (%)	Talcum (%)	Weight (mg)	Diameter (mm)	Thickness (mm)	Hardness (kP)	Friability (%)	Disintegration time (min)
1	0.5	0.5	3	604.25 ± 1.22	12.76 ± 0.03	4.26 ± 0.04	7.78 ± 0.24	0.32	0.44 ± 0.08
2	1.5	0.5	3	604.88 ± 1.63	12.76 ± 0.03	4.35 ± 0.04	5.83 ± 0.20	1.04	0.30 ± 0.02
3	0.5	1.5	3	604.57 ± 1.45	12.76 ± 0.03	4.26 ± 0.03	5.95 ± 0.28	0.87	0.35 ± 0.03
4	1.5	1.5	3	604.02 ± 1.10	12.77 ± 0.03	4.30 ± 0.05	6.10 ± 0.25	0.84	0.39 ± 0.02
5	0.5	1	2	604.68 ± 0.95	12.79 ± 0.02	4.31 ± 0.03	6.82 ± 0.22	0.33	0.48 ± 0.01
6	1.5	1	2	603.92 ± 1.29	12.78 ± 0.03	4.36 ± 0.03	6.52 ± 0.12	0.46	0.36 ± 0.03
7	0.5	1	4	604.63 ± 1.11	12.79 ± 0.04	4.28 ± 0.05	6.73 ± 0.25	0.38	0.40 ± 0.04
8	1.5	1	4	604.32 ± 1.14	12.77 ± 0.05	4.33 ± 0.06	6.40 ± 0.27	0.53	0.40 ± 0.04
9	1	0.5	2	606.59 ± 1.94	12.77 ± 0.03	4.38 ± 0.04	6.95 ± 0.19	0.27	0.30 ± 0.02
10	1	1.5	2	605.16 ± 0.96	12.75 ± 0.04	4.37 ± 0.07	6.20 ± 0.36	0.89	0.37 ± 0.03
11	1	0.5	4	605.64 ± 1.50	12.79 ± 0.03	4.39 ± 0.05	5.97 ± 0.29	0.80	0.37 ± 0.02
12	1	1.5	4	606.45 ± 0.91	12.78 ± 0.03	4.25 ± 0.04	6.36 ± 0.22	0.32	0.61 ± 0.03
13	1	1	3	604.24 ± 1.50	12.78 ± 0.03	4.28 ± 0.06	6.49 ± 0.33	0.43	0.51 ± 0.11
14	1	1	3	604.69 ± 2.73	12.78 ± 0.03	4.28 ± 0.05	7.42 ± 0.29	0.57	0.52 ± 0.10
15	1	1	3	604.03 ± 1.24	12.78 ± 0.03	4.25 ± 0.04	6.76 ± 0.35	0.49	0.60 ± 0.07
16	1	1	3	603.75 ± 2.50	12.79 ± 0.02	4.29 ± 0.05	6.01 ± 0.41	0.44	0.48 ± 0.12
17	1	1	3	605.53 ± 1.59	12.78 ± 0.03	4.30 ± 0.06	7.46 ± 0.68	0.44	0.66 ± 0.19

predicted values and the percentage error was calculated as Eq. (1).

2.4. Evaluation of tablet properties

2.4.1. Weight and weight variation

Twenty tablets were individually weighed using an analytical balance (Entris224i-1S, Sartorius AG, Göttingen, Germany). The average value and SD were reported. Weight variation was calculated as Eq. (2).

$$\textit{Weight variation}\ (\%) = \left(\frac{\textit{Individual weight} - \textit{Average weight}}{\textit{Average weight}}\right) \times 100 \quad (2)$$

2.4.2. Diameter and thickness

Twenty tablets were tested using a thickness gauge. The average value and SD were reported.

2.4.3. Hardness

Ten tablets were tested by a digital hardness tester (TBH 220 TD, Erweka GmbH, Heusenstamm, Germany). The average value and SD were reported.

2.4.4. Friability

The United States Pharmacopeia (USP) specifies that a sample of whole tablets corresponding as near as possible to 6.5 g should be used for the friability test (USP 41/NF 36, 36, 2018). According to this work, a unit weight of 600 mg was prepared, resulting in eleven tablets being sampled for the friability test. Eleven tablets were dedusted and weighed (W_1) using an analytical balance. Friability was tested using a friability tester (K.S.L. Engineering Co. Ltd., Bangkok, Thailand). The drum of the friability tester was rotated at the rate of 25 rpm for 4 min (a total of 100 rounds). Subsequently, the tablets were dedusted and weighed (W_2) again. Friability was calculated using Eq. (3).

$$\textit{Friability}\ (\%) = \left(\frac{W_1 - W_2}{W_1}\right) \times 100 \quad (3)$$

2.4.5. Disintegration time

Six tablets were evaluated for disintegration in water using a disintegration tester (K.S.L. Engineering Co. Ltd., Bangkok, Thailand). The medium was controlled at 37 °C ± 0.5 °C. The average value and SD were reported.

2.5. Dissolution test

Three optimal tablets were tested for pinocembrin dissolution from the fingerroot extract tablets by means of a modified beaker method using a 250-mL beaker. The 0.5% SLS solution (100 mL) was used as a dissolution medium. The temperature was controlled at 37 °C ± 0.5 °C. Tablets were shaken at 100 rpm. The medium was sampled for 3 mL at 15 min, 30 min, 60 min, 120 min, 180 min, and 240 min. The fresh medium was replenished to maintain the volume of the dissolution medium. The withdrawn medium was filtered and analyzed by HPLC to produce the dissolution profile of pinocembrin from the tablets.

2.6. HPLC condition for determination of pinocembrin content

Pinocembrin contained in the optimal tablet and pinocembrin dissolved from the optimal tablet were analyzed by Agilent 1260 Infinity (Agilent Technologies, California, USA). The analytical column was ACE C18-PFP (250 × 4.6 mm, i.d., 5 μm). It was controlled at 25 °C. The mobile phase was composed of water (A) and acetonitrile (B). At 0 to 15 min, B was increased from 50% to 100%; at 15 to 16 min, B

was decreased from 100% to 50% and maintained for 2 min. The flow rate of the mobile phase was 1 mL/min. The injection volume was 10 μL. The detection wavelength for pinocembrin was 288 nm. The HPLC chromatograms, method validation, and system suitability data are shown in the Supplementary Material section.

2.7. DPPH radical scavenging assay

Three optimal tablets were pulverized using a glass mortar and pestle and then accurately weighed to 600 mg, followed by delivery to a 25-mL volumetric flask and adjustment to the volume by methanol. The mixture was sonicated for 5 min and then filtered using a 0.45-μm syringe filter. The filtrate was used to determine DPPH radical scavenging activity. The reaction was done on a 96-well plate. Briefly, 100 μL of samples ($n = 3$) were mixed with 100 μL of 80 μM DPPH in methanol. A blank sample was a mixture of 100 μL of methanol mixed with 100 μL of 80 μM DPPH methanolic solution. They were mixed well and kept in the dark at room temperature for 30 min. Absorbance was measured using a microplate reader (Biorad Laboratories, Inc., California, USA) at 517 nm (Monton et al., 2022). Percentage DPPH radical scavenging was calculated as Eq. (4).

$$DPPH\ radical\ scavenging\ (\%) = \left(\frac{Absorbance_{blank} - Absorbance_{sample}}{Absorbance_{blank}}\right) \times 100 \quad (4)$$

2.8. Stability test

The optimal tablet formulations were packed in a polyethylene terephthalate (PET) bottle with desiccants and sealed with a pressure-sensitive cap seal foam liner before being capped with an aluminium-coated plastic cap. They were stored in a climate chamber (Memmert GmbH + Co. KG, Schwabach, Germany) at 30 °C ± 2 °C/75%RH ± 5%RH and 45 °C ± 2 °C/75%RH ± 5%RH for three months. They have tested tablet properties (including, weight and weight variation, thickness, diameter, hardness, friability, and disintegration time), pinocembrin content, and DPPH radical scavenging activity, compared with an initial time point. The statistical differences between the three groups were analyzed through One-way analysis of variance (One-way ANOVA) using SPSS Statistics 22.0 (IBM, New York, USA) followed by the Tukey HSD post-hoc analysis. Data were significantly different when the *P*-value was less than 0.05 at a 95% confidence interval.

3. Results and discussion

3.1. Optimal tablet diluent of *B. rotunda* extract tablet

The simplex lattice design is a mixture design that varies the ratios for the components of interest (Duangjit & Kraisit, 2018). Thus, a simplex lattice design was applied in the selection of tablet diluents by varying the ratios of three direct compression diluents. Responses to the simplex lattice design are shown in Table 1. The total weight of each tablet was close to 600 mg, due to it being individually weighed during the research and development step. Consequently, the weight variation was acceptable – no tablet had a weight variation exceeding 5%. The diameter of the tablets was between 12.8 and 12.9 mm. Four responses including thickness, hardness, friability, and disintegration time were further analyzed by Design-Expert® software to produce the contour plots. Contour plots of thickness, hardness, friability, and disintegration time of *B. rotunda* extract tablet obtained from the simplex lattice design are shown in Figure 1. Using SRS and SLT provided the thickest and thinnest tablets, respectively (Figure 1a). This occurrence could be described by the highest density of SLT compared with SRS and MCC (Rowe et al., 2009). MCC provided medium thickness though it also showed the hardest tablet compared with SRS and SLT (Figure 1b). This phenomenon reinforced that MCC is the most popular cellulose derivative used as a tablet diluent because of its advantageous compressibility (Rowe et al., 2009). When SRS was used, tablet hardness was slightly higher than that of SLT. The low hardness of tablets containing SRS and SLT provided friable tablets (Figure 1c). Among them, tablets containing MCC exhibited the shortest disintegration time (Figure 1d) because they displayed disintegrant properties (Rowe et al., 2009). The contour plots of the four responses showed that MCC was the most suitable direct compression diluent of the *B. rotunda* extract tablet.

Although MCC showed excellent compactibility at low pressure (Jivraj et al., 2000), it revealed poor flow properties (Jivraj et al., 2000). According to the mechanism of MCC, the high porosity of MCC encourages the swelling and disintegration of tablets, which is due to either water entering the hydrophilic tablet matrix by capillary action of the pores or a breaking down of the hydrogen bonds. Furthermore, MCC demonstrated a rapid water-wicking rate with minimal elastic deformation in its nature. The ability for tablet disintegration is provided by these characteristics (Chaerunisaa, Sriwidodo, & Abdassah, 2019). Various lactoses are free-flowing powders that disintegrate by

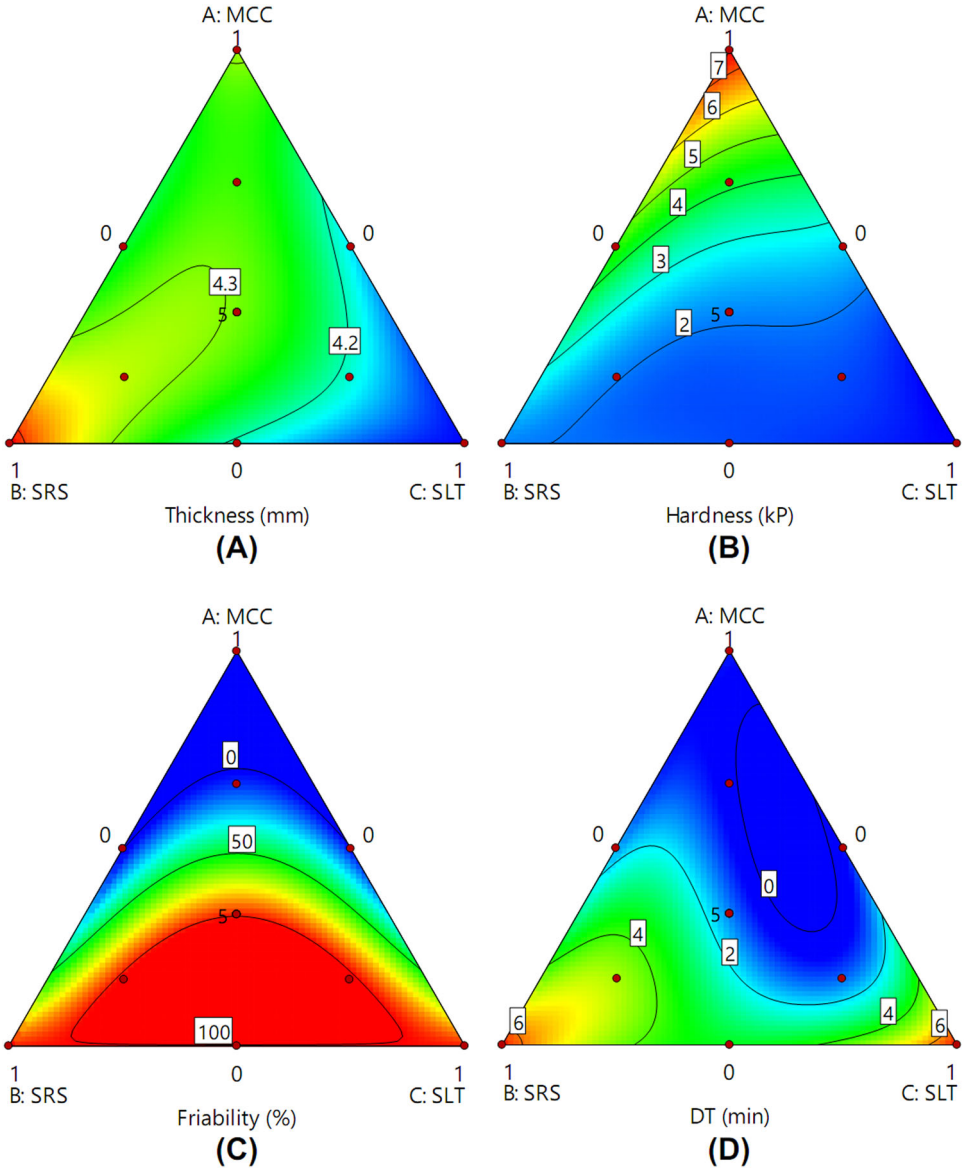

Figure 1. Contour plots of (a) thickness, (b) hardness, (c) friability, and (d) disintegration time of *Boesenbergia rotunda* (L.) Mansf. extract tablet obtained from the simplex lattice design.

dissolution. In the case of SLT, it requires high compressional force to produce hard tablets. Furthermore, a disintegrant is necessary for SLT-based tablets (Jivraj et al., 2000). A diluent SRS also exhibited disintegration properties with a poor flow similar to MCC (Jivraj et al., 2000). Previously, it was reported that SRS with the trade name of Era-Tab® used in this work had superior flowability compared with MCC, lactose, dibasic calcium phosphate, and pregelatinized starch. However, MCC was superior to other diluents in terms of dilution potential or carrying capacity (Mitrevej et al., 1996). One publication suggested that starch is an alternative to MCC and lactose (Jivraj et al., 2000).

Analysis of variance for the simplex lattice design is shown in Table 3. According to tablet thickness, SRS (X_2), MCC (X_1), and SLT (X_3) significantly increased tablet thickness, respectively, due to providing the highest coefficient values. The interaction among the three factors ($X_1X_2X_3$) also significantly increased tablet thickness. The interaction between two factors – X_1X_2, X_1X_3, and X_2X_3, decreased tablet thickness. Only X_1X_2 and X_2X_3 exhibited significant effects. The linear terms of MCC (X_1), SRS (X_2), and SLT (X_3), increased tablet hardness, respectively. The $X_1X_2^2X_3$ and X_1X_3 significantly decreased tablet hardness. The other terms did not significantly affect tablet hardness. However, $X_1X_2X_3^2$ and X_2X_3 seemed to increase while X_1X_2 and $X_1^2X_2X_3$ seemed to decrease tablet hardness. According to friability, MCC (X_1) significantly decreased friability while SRS (X_2) and SLT (X_3) significantly increased friability. The terms $X_1X_2^2X_3$ and $X_1X_2X_3^2$ significantly increased friability, while the other terms decreased friability; among them, only X_1X_2 and X_1X_3 were significant factors. In the case of disintegration time, MCC (X_1), SRS (X_2), and SLT (X_3) significantly increased disintegration time. SRS (X_2) and SLT (X_3) had higher increased disintegration time than MCC (X_1). The terms $X_1^2X_2X_3$ and $X_1X_2^2X_3$ increased disintegration time, but only

Table 3. Analysis of variance for the simplex lattice design.

	Thickness		Hardness		Friability		Disintegration time	
Polynomial terms	Coefficient	*P*-value	Coefficient	*P*-value	Coefficient	*P*-value	Coefficient	*P*-value
Model	–	<0.0001*	–	<0.0001*	–	<0.0001*	–	<0.0001*
Linear Mixture	–	<0.0001*	–	<0.0001*	–	<0.0001*	–	<0.0001*
X_1-MCC	4.31	–	7.61	–	−0.46	–	0.61	–
X_2-SRS	4.42	–	2.05	–	99.27	–	6.53	–
X_3-SLT	4.10	–	1.27	–	99.27	–	6.76	–
X_1X_2	−0.46	0.0024*	−0.89	0.2789	−200.38	0.0001*	−8.19	0.0021*
X_1X_3	−0.14	0.2078	−7.45	0.0002*	−191.42	0.0002*	−12.37	0.0003*
X_2X_3	−0.28	0.0261*	0.35	0.6502	−3.00	0.8823	−12.61	0.0003*
$X_1X_2X_3$	3.10	0.0005*	–	–	–	–	–	–
$X_1^2X_2X_3$	–	–	−38.32	0.0505	−290.17	0.4950	9.18	0.7624
$X_1X_2^2X_3$	–	–	−41.27	0.0398*	3,282.44	0.0004*	175.70	0.0017*
$X_1X_2X_3^2$	–	–	26.74	0.1337	3,202.19	0.0005*	−161.32	0.0025*
Lack of Fit	–	0.9992	–	0.4093	–	–	–	0.0034*

*Significant values.
MCC = microcrystalline cellulose, SRS = spray-dried rice starch, SLT = spray-dried lactose.

Table 4. Confirmation of the prediction by computer software according to the simplex lattice design and Box-Behnken design.

Responses	Predicted values	Experimental values	Error (%)
Simplex lattice design			
Thickness (mm)	4.31	4.26 ± 0.02	−1.17
Hardness (kP)	7.61	7.50 ± 0.27	−1.47
Friability (%)	0.00	0.04	100.00
Disintegration time (min)	0.61	0.58 ± 0.01	−5.17
Box-Behnken design			
Thickness (mm)	4.35	4.38 ± 0.02	0.68
Hardness (kP)	6.83	7.28 ± 0.23	6.18
Friability (%)	0.34	0.37	8.10
Disintegration time (min)	0.47	0.47 ± 0.07	0.00

$X_1X_2^2X_3$ showed a significant effect. The other terms significantly decreased disintegration time.

The formulation with minimized friability and minimized disintegration time was selected for the confirmation step. Thus, MCC was selected as a direct compression diluent. A low percent error was observed for tablet thickness, hardness, and disintegration time. These data indicated that the prediction by Design-Expert® software was accurate. A high percentage error was found for friability. This occurrence could be observed when the predicted value was 0; the percentage error was always 100% for any experimental value. However, the tablet friability was lower than 1%, so it was acceptable (Table 4).

3.2. Optimal hydrophobic excipients of *B. rotunda* extract tablet

The Box-Behnken design was applied for optimization of the suitable content of hydrophobic excipients when MCC was used as a direct compression diluent. Three hydrophobic excipients including fumed silica, magnesium stearate, and talcum were varied. Responses to the Box-Behnken design are shown in Table 2. The total weight of each tablet was close to 600 mg. Moreover, the weight variation was acceptable. The diameter of the tablets was approximately 12.8 mm. Four responses including thickness, hardness, friability, and disintegration time were further analyzed by Design-Expert® software to produce the response surfaces. Response surfaces of thickness, hardness, friability, and disintegration time of *B. rotunda* extract tablet obtained from the Box-Behnken design are shown in Figure 2. Figure 2a shows that increasing fumed silica increased tablet thickness. Increasing magnesium stearate slightly increased tablet thickness at low talcum levels, while decreasing tablet thickness at medium and high talcum levels. Figure 2b shows that maximum hardness was found at a low level of fumed silica and magnesium stearate for all talcum levels. Figure 2c shows that increasing fumed silica increased tablet friability. Increasing magnesium stearate increased friability at low talcum levels while decreasing friability at high talcum levels. Figure 2d shows that the longest disintegration time was found for the medium fumed silica and medium magnesium stearate.

It is well known that the action of fumed silica to enhance the flow characteristics of pharmaceutical powders is based on the disruption of inter-particle forces as well as reduced friction force by silica particles adhering to the particle surface (Paul & Sun, 2018; Tran et al., 2019). Fumed silica is a light and loose material with a very low density of 0.029–0.042 g/cm^3 (Rowe et al., 2009). Thus, increasing fumed silica in the tablet formula made tablets thicker, lowered hardness, raised friability, and shortened disintegration time. In the present work, magnesium stearate varied slightly in a range from 0.5 to 1.5%, which marginally affected the physical properties of tablets. This effect could be found in previous work, hardness and disintegration time of tablets containing spray-dried optimized *Lippia origanoides* extract seemed to not be affected by magnesium stearate content when varied from 0.5% to 1.0% (Coelho et al., 2018). However, magnesium stearate could reduce compactibility, prolong disintegration time, and delay the drug release of chlorpheniramine maleate and prednisolone (Kuncahyo & Choiri, 2014). In many cases, adding talcum to formulations can enhance the hardness, friability, and appearance of

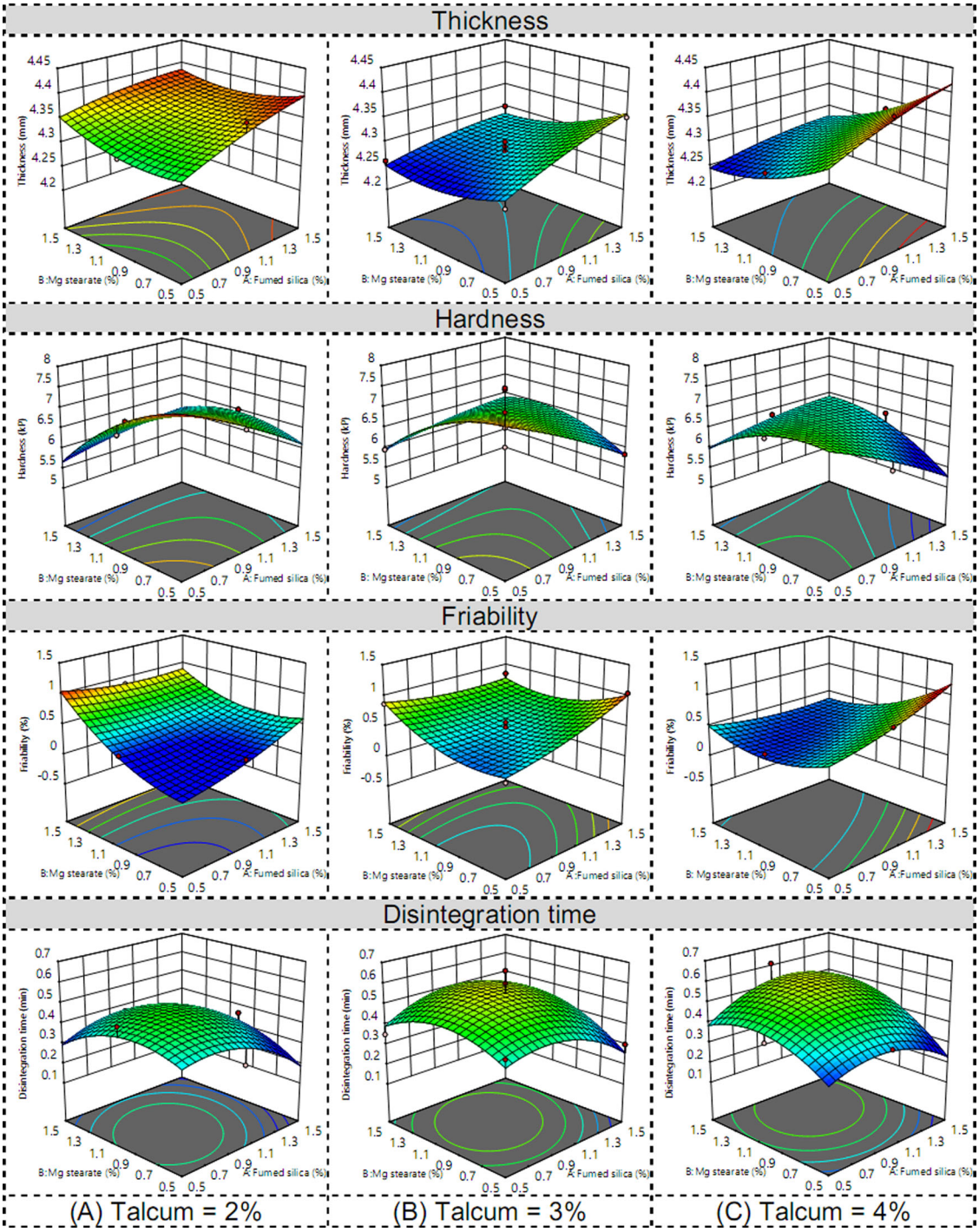

Figure 2. Response surfaces of thickness, hardness, friability, and disintegration time of *Boesenbergia rotunda* (L.) Mansf. extract tablet obtained from the Box-Behnken design when different talcum levels were used: (a) talcum 2%, (b) talcum 3%, and (c) talcum 4%.

tablets (Li & Wu, 2014). In this work, the authors found that complex interactions among several factors could be observed.

Analysis of variance for the Box-Behnken design is shown in Table 5. In the case of tablet thickness, fumed silica (X_1), magnesium stearate (X_2), X_2^2, and X_3^2 increased tablet thickness; among them, X_1, X_2, and X_3^2 were significant terms. The other terms decreased tablet thickness, talcum (X_3) and X_2X_3 were significant terms. According to tablet hardness, three terms – talcum (X_3), X_1X_2, and X_2X_3, insignificantly increased tablet hardness. The other terms insignificantly decreased tablet hardness. In the case of tablet friability, X_1X_2, X_2X_3, and X_3^2 significantly decreased tablet friability. The terms X_1 and X_2^2 have significantly increased tablet friability; while the other terms insignificantly increased tablet friability. According to disintegration time, the terms X_1^2, X_2^2, and X_3^2 insignificantly decreased disintegration time, while the other terms insignificantly increased disintegration time. The statistical experimental design could identify linear, interaction, and quadratic terms of several factors. It is hard to describe compared with one factor at a time, which is done by changing

Table 5. Analysis of variance for the Box-Behnken design.

	Thickness		Hardness		Friability		Disintegration time	
Polynomial terms	Coefficient	*P*-value	Coefficient	*P*-value	Coefficient	*P*-value	Coefficient	*P*-value
Model	–	0.0059*	–	0.3543	–	0.0008*	–	0.1608
Intercept	4.57	–	9.27	–	−2.23	–	−0.15	–
X_1-Fumed silica	0.17	0.0061*	−2.00	0.1463	0.37	0.0033*	0.33	0.3848
X_2-Magnesium stearate	0.04	0.0119*	−1.65	0.2377	0.77	0.0638	0.37	0.2328
X_3-Talcum	−0.24	0.0241*	0.08	0.5109	1.29	0.7302	0.19	0.2927
X_1X_2	−0.05	0.2718	2.10	0.0860	−0.75	0.0021*	0.18	0.3191
X_1X_3	-5.24×10^{-16}	1.0000	−0.02	0.9780	0.01	0.9026	0.06	0.4978
X_2X_3	−0.07	0.0173*	0.57	0.3143	−0.55	0.0002*	0.09	0.3448
X_1^2	−0.03	0.4866	−0.33	0.7562	0.30	0.0944	−0.37	0.0566
X_2^2	0.08	0.0911	−1.32	0.2384	0.88	0.0007*	−0.36	0.0620
X_3^2	0.05	0.0023*	−0.13	0.6334	−0.12	0.0149*	−0.05	0.2546
Lack of Fit	–	0.3234	–	0.7959	–	0.1660	–	0.3101

*Significant values. Coefficient values were based on actual equations.

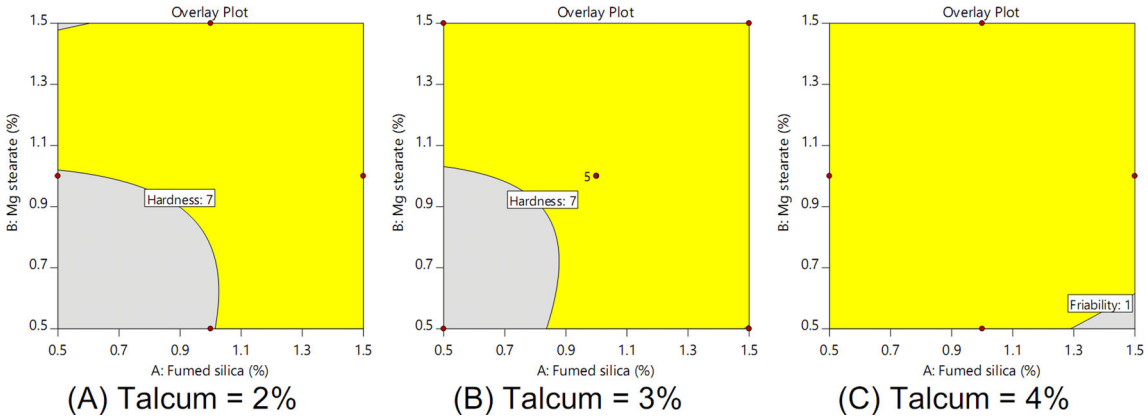

Figure 3. Design spaces that *Boesenbergia rotunda* (L.) Mansf. extract tablet had hardness of 5–7 kP, friability of less than 1%, and disintegration time of less than 1 min at different talcum levels: (a) talcum 2%, (b) talcum 3%, and (c) talcum 4%.

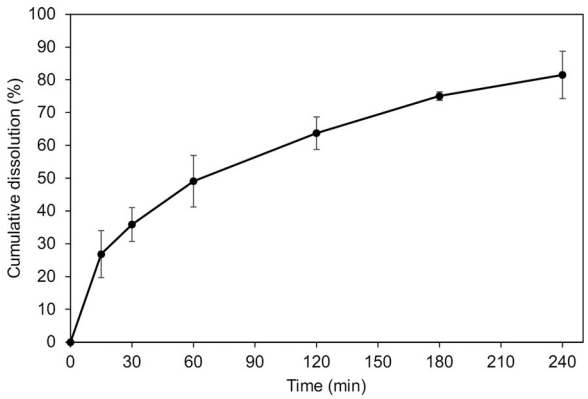

Figure 4. The dissolution profile of pinocembrin from optimal *Boesenbergia rotunda* (L.) Mansf. extract tablets when 0.5% SLS was used as a dissolution medium.

the value of one factor before measuring the response and repeating the process with another factor (JMP Statistical Discovery LLC, 2022). However, the response surface obtained from the Design of Experiment (DOE) approach gave more information about the effect of several factors simultaneously (Gibson, 2016; Steele, 2018).

The optimization data showed that the formulation with minimized friability was found when medium fumed silica, medium magnesium stearate, and low talcum level were used. Moreover, design spaces were constructed to select the formulation in which hardness was 5–7 kP, friability was less than 1%, and disintegration time was less than 1 min. Design spaces are shown in Figure 3.

The formulation with minimized friability and within the design space was selected for the confirmation step. Thus, a tablet formulation containing 1% fumed silica, 1% magnesium stearate, and 2% talcum was selected. A low percent error (less than 10%) was observed for all responses. These data indicated that the prediction by Design-Expert® software was accurate (Table 4). Furthermore, the optimal tablet formulation was sampled for the dissolution test. The dissolution profile in 0.5% SLS of pinocembrin from *B. rotunda* extract tablets is shown in Figure 4. It was found that pinocembrin was dissolved for 81.56 ± 7.23% within 240 min. According to the dissolution test procedure, it was confirmed from previous work that the modified method did not affect the sink condition. The apparent solubility of pinocembrin in water was 48.33 µg/mL at room temperature (Yang et al., 2018). Unfortunately, using 100 mL of water during the dissolution test could not provide certain sink conditions. Therefore, SLS was added to the aqueous medium at a final concentration of 0.5% to increase the solubility of poorly water-soluble pinocembrin, resulting in the promotion of sink conditions (Fotaki et al., 2013).

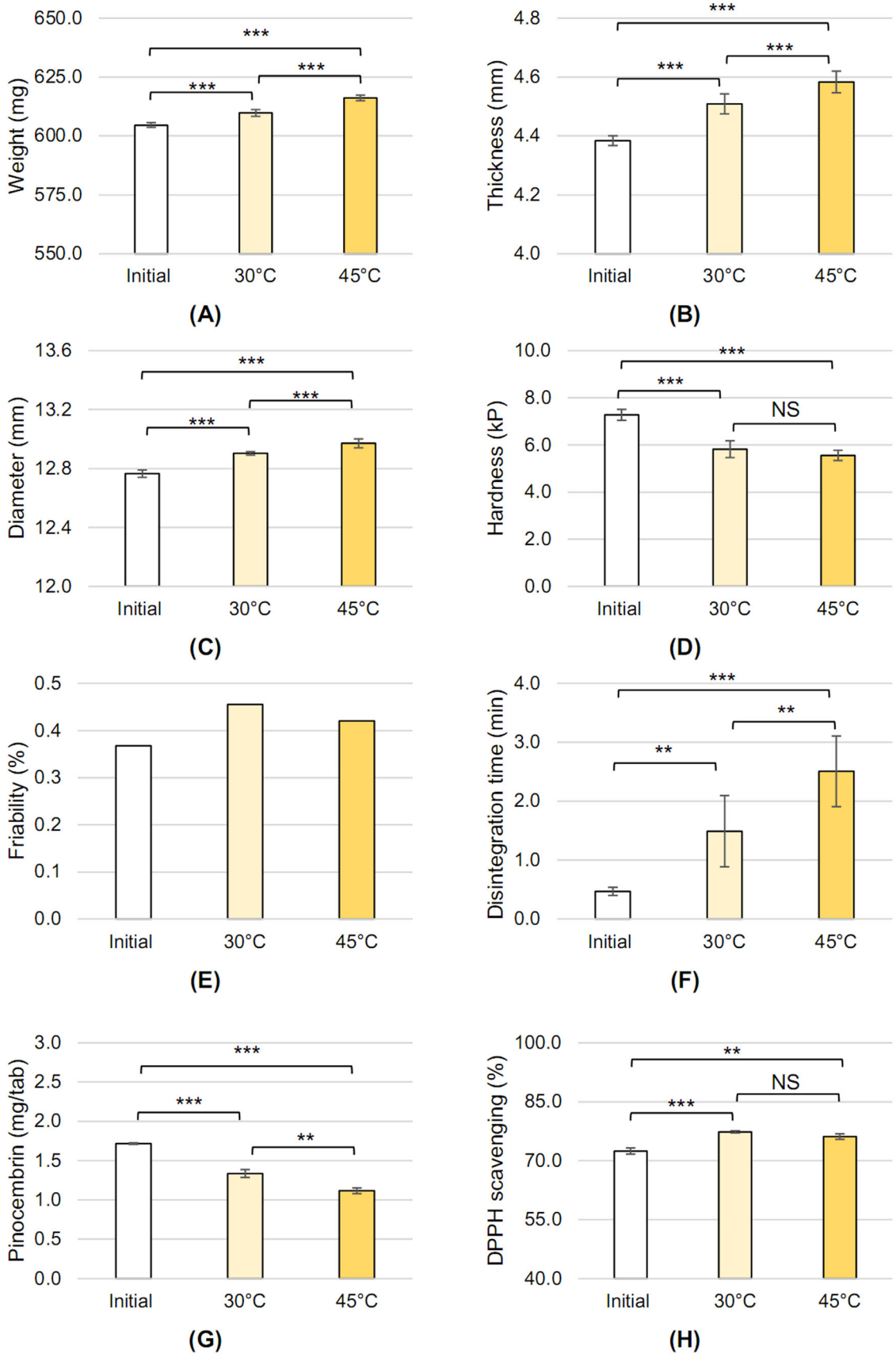

Figure 5. Stability of optimal *Boesenbergia rotunda* (L.) Mansf. extract tablets after being stored at 30 °C ± 2 °C/75%RH ± 5%RH and 45 °C ± 2 °C/75%RH ± 5%RH for three months compared with the initial time. Statistical difference was analyzed by One-way ANOVA with post-hoc analysis using Tukey HSD: which NS = not significant, * = $P < 0.05$, ** = $P < 0.01$, and *** = $P < 0.001$.

3.3. Stability of optimal B. rotunda extract tablet

The optimal *B. rotunda* extract tablets had their stability tested for three months at 30 °C ± 2 °C/75%RH ± 5%RH and 45 °C ± 2 °C/75%RH ± 5%RH. The tablet weight, thickness, diameter, hardness, friability, disintegration time, pinocembrin content, and antioxidant activity were compared with an initial time. The stability data of optimal *B. rotunda* extract tablets are shown in Figure 5. After three months, tablet weight, thickness, and diameter significantly increased, while tablet hardness decreased. Increasing the storage temperature from 30 °C to 45 °C also significantly increased all parameters, but was not significantly different for tablet hardness. The friability remained less than 0.5% for all storage temperatures. The friability of plain tablet dosage form should be less than 1%, so the friability of the *B. rotunda* extract tablets was acceptable. The disintegration time was significantly increased and depended on storage temperature. However, the disintegration time was less than 30 min, indicating that it was acceptable. Pinocembrin content was significantly decreased in a temperature-dependent manner. However, the antioxidant activity of the *B. rotunda* extract tablet was significantly increased.

The optimal *B. rotunda* extract tablets were stored in a PET bottle during the stability test. Plastic bottles are unbreakable, collapsible, and light compared to glass bottles (World Health Organization, 2002). However, PET bottles exhibit higher oxygen permeability than glass bottles (Toussaint, Vidal, & Salmon, 2014). Oxygen and moisture permeation from the environment to drug products could degrade the active compounds as well as their bioactivity (Blessy, Patel, Prajapati, & Agrawal, 2014). Pinocembrin is possibly degraded under excessive heat and exposure duration. The interaction and quadratic terms of temperature and time play a negative role on pinocembrin (Sheng, Wang, Zhao, & Yu, 2017). Moreover, pinocembrin is highly degraded under pH 7.6 conditions (Zhou et al., 2014). So, using a PET bottle could not preserve the stability of the *B. rotunda* extract tablets. This occurrence was related to increasing tablet weight; expanding the tablet promoted the increase of tablet thickness and diameter, consequently decreasing hardness due to loss of compactibility. Furthermore, pinocembrin was also decreased. However, the antioxidant activity was preserved, which indicated that the bioactivity could be promoted by several compounds contained in the *B. rotunda* extract rather than only pinocembrin. The authors mentioned that changing the container for *B. rotunda* extract tablet from PET bottle to glass bottle or the selection of new markers such as pinostrobin, naringenin, alpinetin, 4-hydroxypanduratin A, panduratin A, etc. (Jirakiattikula, Rithichaia, Prachaia, & Itharat, 2021; Tan et al., 2015), might be performed in future work.

4. Conclusion

Tablet diluents including MCC, SRS, SLT, and their mixtures were optimized and selected using the simplex lattice design. Among them, MCC alone exhibited superior performance compared to the other diluents. It provided the hardest tablet, the lowest friability, and the shortest disintegration time, which were the desired tablet properties. Consequently, MCC was used as a diluent for the optimization of hydrophobic excipients by the Box-Behnken design. The three hydrophobic excipients were fumed silica, magnesium stearate, and talcum. The optimal formulation promoted the desired properties (i.e. hardness of 5–7 kP, friability of less than 1%, and disintegration time of less than 1 min), composed of fumed silica 1%, magnesium stearate 1%, and talcum 2%. The marker pinocembrin was selected as a marker for quality control. It could be dissolved by 82% within 4 h of the dissolution test. Stability data showed that the marker content decreased after three months, while antioxidant activity was preserved with a significant increase. In summary, MCC exhibited superior performance compared to the SRS and SLT. The optimal formulation could be used to prepare *B. rotunda* extract tablets as a food supplement with desired properties.

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CRediT authorship contribution statement

Jirapornchai Suksaeree: Methodology, Formal analysis, Investigation, Writing – Original Draft. **Chaowalit Monton:** Conceptualization, Methodology, Formal analysis, Investigation, Resource, Writing – Original Draft, Writing – Review & Editing, Visualization, Supervision, Project administration. **Natawat Chankana:** Methodology, Formal analysis, Investigation, Resource, Writing – Original Draft. **Laksana Charoenchai:** Methodology, Formal analysis, Resource, Writing – Original Draft.

Disclosure statement

No potential conflict of interest was reported by the authors.

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