Food Research 7 (3) : 77 - 87 (June 2023)
Journal homepage: https://www.myfoodresearch.com

FOOD RESEARCH

FULL PAPER

Enhancing the antioxidant activity and manufacturability of the Indonesian traditional herbal beverage, *jamu*, through granule formulation: a case study on *jamu* SIRMA

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Article history:
Received: 1 December 2021
Received in revised form: 4 January 2022
Accepted: 8 April 2022
Available Online: 20 May 2023

Keywords:
Jamu,
Maltodextrin,
Dextrin,
Lactose,
Granules

DOI:
https://doi.org/10.26656/fr.2017.7(3).931

Abstract

Traditional Indonesian *jamu* manufacturers have faced a great challenge regarding their production using more modern techniques. The granulation of *jamu* was implemented to address this issue. The present study aimed to formulate and optimise the granule formulation of *jamu* using various fillers and the simplex lattice design technique. Additionally, the main effect and interaction of the fillers in the formulation were assessed simultaneously. Dextrin, maltodextrin, and lactose were used as fillers and the critical quality attributes of the granule formulation were determined, such as the flowability, density, water retention and sorption, and antioxidant properties. The data were fitted using multiple linear regression analysis in addition to a statistical evaluation using a confidence level of 95% ($p = 0.05$). The results showed that maltodextrin increased the flowability and hygroscopicity of the granules but reduced the antioxidant activity. Furthermore, lactose showed no significant contribution to the critical quality attributes of the granules. Dextrin prolonged the dispersion time of the granules. The formulation was successfully optimised, and it was obtained at 25.81% dextrin, 44.63% maltodextrin, and 29.56% lactose. This formulation produced improved flowability, less hygroscopicity, and denser granules.

1. Introduction

In recent years, the paradigm shift to nature has increased dramatically. The use of herbal medicines to prevent or support the treatment of diseases has been widely applied (Liu, 2021). In particular, the use of a traditional herbal beverage in Indonesia, *jamu*, has increased significantly due to the Coronavirus disease pandemic (Lim and Pranata, 2020). This herbal medicine is used in rural areas and is also a favoured option in urban regions. It is well-known for the preventive treatment of several diseases, boosts the immune system, and maintains a healthy body (Elfahmi *et al*., 2014; Lim and Pranata, 2020; Suparmi *et al*., 2021). Nowadays, the method for consuming *jamu* has been altered to be more practical and efficient. In the past, *jamu* was prepared by boiling the plants and water to obtain a herbal extract (Limyati and Juniar, 1998; Elfahmi *et al*., 2014). However, nowadays, *jamu* can be obtained more efficiently, for example, preconcentrated in a viscous sugar solution, in teabag form, and as candy, lozenges, and ready-to-drink liquids (Surya *et al*., 2021).

The *jamu* manufacturing process has shifted from traditional to more modern techniques. Teabag formulation is generally used by traditional *jamu* manufacturers. This process requires powdered plant material, which is filled into each tea bag. The primary concept of this *jamu* production technique is an infusion of *jamu* powder to obtain the active compound in boiled water (Elfahmi *et al*., 2014; Lim and Pranata, 2020). A manual process is generally applied; however, it is time-consuming. Conversely, the use of an automatic machine filler results in a great challenge. The plant sources have various characteristics regarding the hardness, density, and ease of cutting, for example, in the leaves, bark, pericarps, stems, and rhizomes (Prabakaran *et al*., 2018;

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eISSN: 2550-2166
Published by Rynnye Lyan Resources

Amo-Mensah *et al*., 2020). Therefore, this promotes the segregation of the components due to the various densities of the powdered plant organs. Furthermore, this affects the consistency of the therapeutic effect due to the variation in the bioactive compounds. The efficacy of *jamu* is mainly affected by the composition of the formulation (Afendi *et al*., 2013). Therefore, to address this issue, a simple formulation can be obtained by using a granule formulation instead of the powdered form of the plants.

A granule formulation can enhance the flowability and bulk density and can have a significant effect on the modern *jamu* manufacturing process (Adi-Dako *et al*., 2021). A granule formulation requires filler and binder to form compact granules (Ainurofiq *et al*., 2020). Generally, soluble fillers can be applied to obtain a clear solution when the teabag is placed in hot water. Additionally, this should not alter the taste and colour (Patel *et al*., 2020; Adi-Dako *et al*., 2021). Therefore, several fillers, such as dextrin, maltodextrin, and lactose, can be utilised to achieve granule formulation. These fillers are inexpensive and easy to obtain due to abundant stock. Additionally, these fillers have no meaningful effect on the taste compared to sucrose and other sugars (Jafari *et al*., 2021). Lactose has been widely applied as a filler in solid formulations, i.e., in tablets and capsules (Batra *et al*., 2020). Dextrin and maltodextrin have also been applied in the pharmaceutical industry; however, they are generally recognised as food fillers (Sarifudin and Assiry, 2014; Jafari *et al*., 2021). No previous studies exist regarding the use and combination of these excipients in granule formulations. Moreover, in the present study, we assessed the main effect and interaction of the fillers in a granule formulation simultaneously using a statistical approach. We used a traditional *jamu* product, *jamu* SIRMA, that was produced by PJ. Suti Sehati (Sukoharjo, Indonesia).

The name SIRMA is derived from the words 'Sirsak' (*Annona muricata* L.) and 'Manggis' (*Garcinia mangostana* L.). Both plants have been applied traditionally to prevent degenerative diseases and maintain a healthy body. This type of *jamu* is applied in teabag form. Although there were limitations, i.e., inconsistency in antioxidant activity (prior evaluation) and difficulty regarding the use of automatic machine fillers, the present study aimed to formulate *jamu* SIRMA granules using a combination of fillers, such as dextrin, maltodextrin, and lactose. Furthermore, the goal of the study was to assess the main effect and interaction between the excipients simultaneously, using a simplex lattice design technique.

2. Materials and methods

2.1 Materials

Jamu SIRMA, consisting of *Annona muricata* L. leaves and *Garcinia mangostana* L. pericarps, was obtained from PJ. Suti Sehati (Sukoharjo, Indonesia). Lactose, maltodextrin, and dextrin were obtained from a local supplier. 2,2-diphenyl-1-picrylhydrazyl (DPPH) and methanol were obtained from Sigma Aldrich (St. Louis, MO, USA) and Merck (Darmstadt, Germany), respectively.

2.2 Experimental design

To optimise the composition of the fillers in the granule formulation, a statistical approach through simplex lattice design was applied. Lactose, dextrin, and maltodextrin were selected as fillers and several critical characteristics of the granules were determined. A total of 13 runs of the simplex model comprising seven design points, in addition to three design points of an augmented design, were utilised. All the design points are presented in Table 1.

2.3 Granule preparation

The *jamu* granules were prepared according to the wet granulation technique. An equal amount of the *jamu* powder and excipient mixture (Table 1) were mixed homogeneously using a cube mixer at 30 rpm for 15 mins. Subsequently, water was added as a binder until the desired mass of granules was achieved. The wet mass was passed through a 10-mesh sieve (2 mm). Next, the wet granules were dried in an oven at 50°C for 4 hrs Spheroidization was conducted by passing the granules through a 12-mesh sieve (1.70 mm). The granules were then stored in a desiccator for further evaluation.

2.4 Powder flow evaluation

The flow characteristics of the granules were evaluated using the United States Pharmacopeia through an angle of repose technique. A total of 100 g of the granules was placed in an orifice. When the granules passed through the orifice, they formed a mound. Next, the diameter (d) and height (h) of the mound were measured accurately using a calliper (accuracy of 0.01 mm). The angle of repose (θ) was calculated using Equation 1.

$$\text{Tan}(\theta) = 2h/d \quad (1)$$

2.5 Moisture evaluation

The moisture content of the granule formulation was evaluated using the gravimetric technique and an Ohaus MB-25 (Shanghai, China) moisture analyser balance. A total of 1 g of granules as an initial weight (Wo) was placed in an aluminium pan. The sample was heated at

https://doi.org/10.26656/fr.2017.7(3).931

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Table 1. Experimental design and results on critical quality attributes of granule formulation using simplex lattice design.

Design				Results						
Runs	A (%)	B (%)	C (%)	AoR (°)	MC (%)	AB (%)	BD (g/mL)	DT (s)	AC (%)	ACE (%)
1	100.00	0.00	0.00	44.86±0.75	8.59±0.15	4.75±0.09	0.28±0.10	489±24.45	83.33±0.32	20.49
2	0.00	100.00	0.00	36.84±0.44	6.53±0.22	44.32±1.71	0.51±0.14	356±17.80	32.99±2.39	-52.31
3	0.00	0.00	100.00	43.00±0.65	4.28±0.08	3.82±0.01	0.37±0.08	309±15.45	78.26±1.68	13.15
4	50.00	50.00	0.00	37.84±0.09	5.02±0.11	48.94±0.67	0.46±0.04	348±17.40	72.64±1.02	5.03
5	50.00	0.00	50.00	42.87±1.45	4.67±0.21	20.70±0.38	0.36±0.06	266±13.30	82.60±0.49	19.42
6	0.00	50.00	50.00	40.57±0.16	5.68±0.05	15.21±0.19	0.40±0.02	468±23.40	72.73±0.87	5.15
7	33.33	33.33	33.33	38.00±0.51	6.15±0.06	6.34±0.12	0.40±0.02	129±6.45	76.97±0.43	11.29
8	66.67	16.67	16.67	39.83±0.71	5.70±0.04	23.51±0.90	0.46±0.13	388±19.40	63.64±1.47	-7.99
9	16.67	66.67	16.67	38.71±0.29	6.80±0.35	16.64±0.36	0.41±0.07	103±5.15	83.77±0.66	21.11
10	16.67	16.67	66.67	41.66±0.60	5.62±0.11	15.01±0.51	0.36±0.07	78±3.90	85.41±0.12	23.49
11	100.00	0.00	0.00	43.58±4.31	9.02±0.20	1.68±0.04	0.27±0.07	442±22.10	78.74±2.82	13.85
12	0.00	100.00	0.00	36.38±0.37	5.97±0.23	38.07±1.47	0.54±0.12	313±15.65	26.36±2.83	-61.88
13	0.00	0.00	100.00	42.42±0.58	4.10±0.08	2.56±0.21	0.36±0.84	301±15.10	69.07±2.23	-0.14

A: Dextrin (%), B: Maltodextrin (%), C: Lactose (%), AOR: angle of repose, MC: moisture content, AM: absorbed moisture, BD: bulk density, AC: antioxidant capacity, ACE: antioxidant capacity enhancement, DT: dispersion time

105°C until a constant weight was achieved (Wt). The moisture content was calculated using Equation 2.

$$\text{Moisture content} = \frac{W_0 - W_t}{W_t} \times 100 \quad (2)$$

The granules were stored under ambient conditions (25±1°C, 65±10% RH) for 7 days, after which the absorbed moisture in the granule formulation was evaluated.

2.6 Bulk density

The bulk density was measured using a calibrated cylindrical flask. A total of 40 g of granules (w) was placed into a 100 mL calibrated cylindrical flask. The volume of the granules (v) was used to calculate the bulk density (bd) according to the weight-to-volume ratio.

2.7 Dispersion time

The dispersion time was measured according to the time required for the granules to disperse completely when introduced into 200 mL of water. A sample equivalent to 2 g of *jamu* powder was dispersed into 200 mL of water at 90°C under a constant stirring rate of 50 rpm (stir bar length of 60 mm). The dispersion was evaluated visually, i.e., when the granules had dispersed completely, the dispersion time was noted.

2.8 Antioxidant evaluation

The antioxidant activity was evaluated using a DPPH assay. An equivalent of 1 cup of *jamu* (2 g *jamu* powder) was dispersed and dissolved in 200 mL hot water. Next, the mixture was filtrated and diluted 20 times. A 0.4 mM DPPH solution was prepared by dissolving 7.2 mg DPPH in 50 mL of methanol. A total of 1 mL of sample was added to 1 mL of DPPH 0.4 mM and 3 mL of methanol. A control solution was also prepared along with zero concentration in the sample solution. The sample and control solution was scanned at the maximum wavelength of DPPH (517 nm) after 30 mins of reaction time. The absorbances of the sample (As) and control solution (Ac) were used to calculate the inhibition using Equation 3.

$$\text{Inhibition} = \frac{A_c - A_s}{A_c} \times 100\% \quad (3)$$

Jamu was also prepared without granule formulation, according to the above-mentioned method, and the inhibition was measured at similar concentrations. The antioxidant enhancement was calculated by the percentage of antioxidant capacity of the granule formulation to the antioxidant activity of plain *jamu*.

2.9 Statistical analysis

The obtained data were analysed using Design Expert v12 software (Stat-Ease, Minneapolis, MN, USA). Multiple linear regression analysis (MLRA) was applied for statistical evaluation in addition to a 95% confidence level (p = 0.05). Each model was fitted to the mixture design model along with quadratic and special quartic models (Equation 4).

$$Y = a*A + b*B + c*C + d*A*B + e*A*C + f*B*C + g*A^2*B*C + h*A*B^2*C + i*A*B*C^2 \quad (4)$$

Where Y = response; a,b,c…., i = regression coefficient; and A = dextrin proportion (0-1), B = maltodextrin proportion (0-1), and C = lactose proportion (0-1). An analysis of variance was also applied to evaluate the significant effect and interaction between the factors. The goodness of fit parameters, i.e., the coefficient of determination (R^2), adjusted R^2 (Adj. R^2), and adequate precision (AP), were also implemented in the model evaluation.

3. Results and discussion

3.1 Preparation of the granule formulation

The *jamu*, which consisted of *A. muricata* L. leaves and *G. mangostana* L. pericarps, showed various raw material characteristics. The main issue that occurred when it was filled into the teabags was that segregation of the components occurred. Therefore, a granule formulation was proposed to enhance the flowability and ensure the consistency of the filling, using an automatic teabag machine to avoid segregation of the components (Persson *et al*., 2011; Patel *et al*., 2020). The yield of the granulation process was 90–95% (data not shown). To avoid a prolonged dispersion time, the granulation process was conducted without any binder in the solution. Moreover, the granules were achieved without a binder agent. Additionally, dextrin shows binding characteristics when combined with water. Therefore, the interparticle binding increased in the presence of dextrin in the excipient mixture (Chen *et al*., 2020). Overall, all the granule formulations could be formulated and stored for further evaluation.

3.2 The flowability characteristics

The angle of repose was used to determine the flow characteristics of the *jamu* SIRMA granules. The angle of repose of all the formulations ranged from 36.38° to 44.86°. The flow characteristics were categorised as fair to passable (Ainurofiq *et al*., 2020; Adi-Dako *et al*., 2021). Additionally, a low angle of repose is considered to be a good flow characteristic. However, the better flow characteristics, the more consistent and more straightforward the manufacturing process (Takeuchi *et al*., 2018). The angle of the repose model was evaluated using the MLRA approach. The quadratic model was significant ($p<0.05$), and the lack of fit test was not significant ($p>0.05$). This was the main requirement for a

https://doi.org/10.26656/fr.2017.7(3).931

fitting model. According to the regression coefficient of the angle of repose (Table 2), maltodextrin was the most valuable factor in increasing the flow characteristics. Furthermore, lactose and dextrin showed a similar impact on the enhancement of the flow characteristics. Additionally, the plain *jamu* SIRMA powder did not demonstrate any flow characteristics. All interactions with the powder showed a reduction in the flow characteristics. Moreover, only the interaction between dextrin and maltodextrin showed a significant impact ($p<0.05$). This was due to the cohesivity of the granules in the presence of both the excipients. To further elucidate this interaction, a contour plot of the angle of repose was created and is presented in Figure 1a. According to the contour plot, a higher proportion of maltodextrin was responsible for increasing the flow characteristics. Although, dextrin was shown to reduce the flowability. This phenomenon was caused by the characteristics of the formed granules, i.e., a lower density. The contour plot shows that maltodextrin was the most dominant factor that affected the pattern alteration. The nonparallel lines show the interaction, which occurred through the combination of maltodextrin and lactose. Additionally, the validation of the model was obtained by the actual and predicted plots. A high R^2 (>0.7) and Adj. R^2, as well as AP (>4), were considered

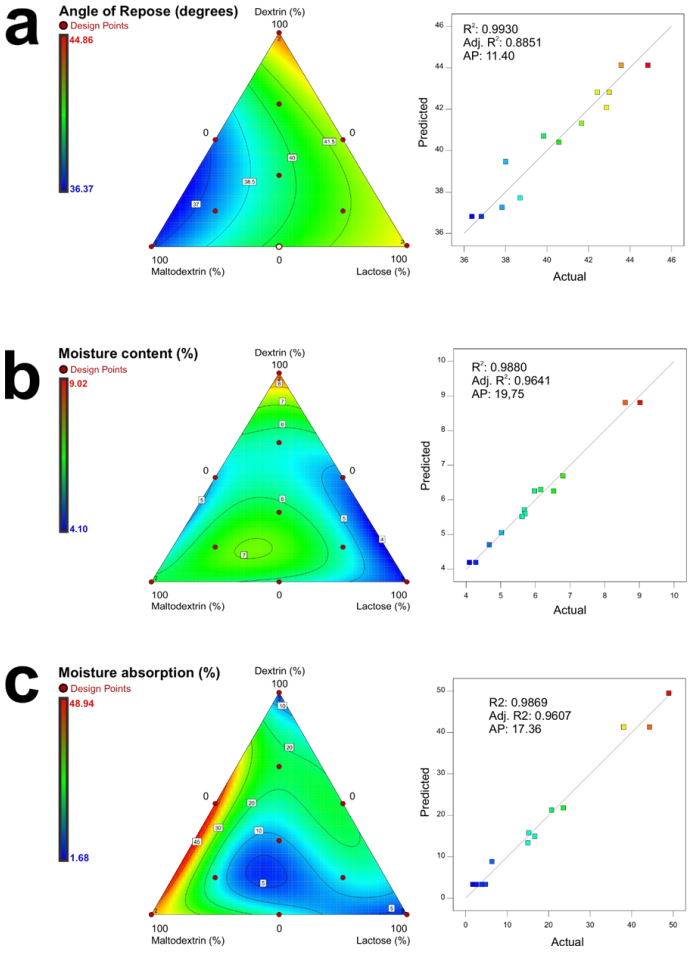

Figure 1. Contour plot and actual vs predicted value plot of angle of repose (a), moisture content (b), and moisture absorbed (c).

to be an adequate model for prediction (Choiri *et al*., 2020). The visual goodness of fit showed a high correlation between the actual and predicted data. This indicated that minimal ambiguity was achieved in the prediction model.

3.3 Moisture evaluation

The moisture content and absorbed moisture of the *jamu* SIRMA granules were also studied. The moisture in the granule formulation depicted the capacity of the excipients to retain water after the granulation process (Veronica *et al*., 2020). Furthermore, the absorbed moisture described the hygroscopicity characteristics of the materials during storage at a predetermined time (Gilda *et al*., 2010; Rajabnezhad *et al*., 2020). The moisture content of all the formulations ranged from 4.10% to 9.02%. The moisture was categorised as a low moisture content because it measured less than 10%. Moreover, it affected the flowability characteristics. To evaluate the effect of the excipient in the granule formulation on the water retention characteristics, a special quartic model of moisture content was constructed. According to the initial statistical evaluation, the model was significant ($p<0.05$), and the lack of fit was not significant ($p>0.05$).

The main effect and interaction of the factors were evaluated based on the regression coefficient of the model (Table 2). Dextrin was the most dominant factor in increasing the moisture content, followed by maltodextrin and lactose. The interaction between the excipient and water promoted water retention during the drying process (Sarifudin and Assiry, 2014). However, the interaction between dextrin and maltodextrin, as well as lactose, reduced the moisture content. This demonstrated that the presence of other excipients in the dextrin mixture reduced the interaction between dextrin and water. The special quartic model was applied for this interaction to obtain the best-fitting model. Furthermore, the presence of maltodextrin was only affected by this exponential effect ($p<0.05$). The contour plot of the moisture content (Figure 2b) was applied to further investigate the interaction between the components. According to the contour plot, the blue colour in the lactose indicated that it had low water retention. This interaction was affected by the presence of maltodextrin. The pattern of the contour showed a change when the maltodextrin proportion increased. A high correlation between the actual and predicted data demonstrated that the model was adequate to predict the moisture content in the excipient mixture in the *jamu* SIRMA granule formulation.

Conversely, the absorbed moisture was also evaluated. This characteristic is dependent on the

https://doi.org/10.26656/fr.2017.7(3).931

https://doi.org/10.26656/fr.2017.7(3).931

Table 2. Statistical parameter of several critical quality attributes of granule formulation using simplex lattice design technique.

Parameter	AoR (°)		MC (%)		AM (%)		BD (g/mL)		AC (%)		ACH (detik)		DT	
	Coef.	p-value	Coef.	p-value	Coef.	p-value	Coef.	p-value	Coef.	p-value	Coef.	p-value	Coef. ($\times 10^2$)	p-value
A	44.13		8.81		3.35		3.61		78.16		13.01		4.63	
B	36.83	0.0001	6.26	0.0004	41.34	0.005	1.90	<0.0001	32.59	0.0077	-52.88	0.0077	3.32	0.0262
C	42.82		4.20		3.33		2.76		74.25		7.35		3.02	
AB	- 12.85	0.0110	-9.92	0.0014	108.61	0.016	-2.37	0.0015	65.94	0.1673	95.35	0.1673	-2.38	0.2748
AC	-5.57	0.1812	-7.20	0.0045	71.66	0.0073	-1.55	0.0071	3.79	0.9318	5.49	0.9318	-5.07	0.0545
BC	2.34	0.5519	1.95	0.1943	-26.24	0.1390	0.7108	0.0809	101.79	0.0490	147.17	0.0490	5.63	0.0404
ABC	-	-	-	-	-	-	-	-	-	-	-	-	-	-
A^2BC	-	-	-60.14	0.1001	-117.04	0.7340	-62.10	0.0008	-	-	-	-	147.19	0.0257
AB^2C	-	-	113.74	0.0157	-2029.14	0.0032	40.97	0.0040	-	-	-	-	-186.17	0.0119
ABC^2	-	-	73.24	0.0604	180.49	0.6041	24.25	0.0246	-	-	-	-	-173.03	0.0152
Model	-	0.0006	-	0.0014	-	0.0017	-	0.0003	-	0.0180		0.0180	-	0.0103
LoF	-	0.1656	-	0.4880	-	0.2623	-	0.5075	-	0.0661		0.0661	-	0.0723
R^2	0.9330		0.9880		0.9869		0.9947		0.8109		0.8109		0.9668	
Adj. R^2	0.8851		0.9641		0.9607		0.9842		0.7658		0.6758		0.9003	
AP	11.40		19.75		17.36		29.93		6.69		6.69		10.77	

A: Dextrin (proportion), B: Maltodextrin (proportion), C: Lactose (proportion), Coef: coefficient regression, LoF: lack of fit test, AOR: angle of repose, MC: moisture content, AM: absorbed moisture, BD: bulk density, AC: antioxidant capacity, ACE: antioxidant capacity enhancement, DT: dispersion time, R^2: coefficient determination, *Adj*. R^2: Adjusted R^2, AP: *adequate precision*

hygroscopicity of the excipients (Rajabnezhad *et al*., 2020). The absorbed moisture of all the formulations ranged from 1.68% to 48.94%. Maltodextrin showed the most significant impact on hygroscopicity ($p<0.05$). However, lactose and dextrin showed a similar effect, i.e., a low impact on an increase in the water content during storage. Both these excipients were non-hygroscopic (Han *et al*., 2018). The interaction effect was the same as that of the moisture content model. A contour plot of the model was created for further analysis. Moreover, lactose was an extremely effective excipient for reducing hygroscopicity (Batra *et al*., 2020). Furthermore, the interaction between maltodextrin and dextrin was observed to increase the hygroscopicity. However, the presence of lactose in the mixture significantly reduced the hygroscopicity. The actual and predicted plots confirmed the validity of the model, which could be applied for response prediction.

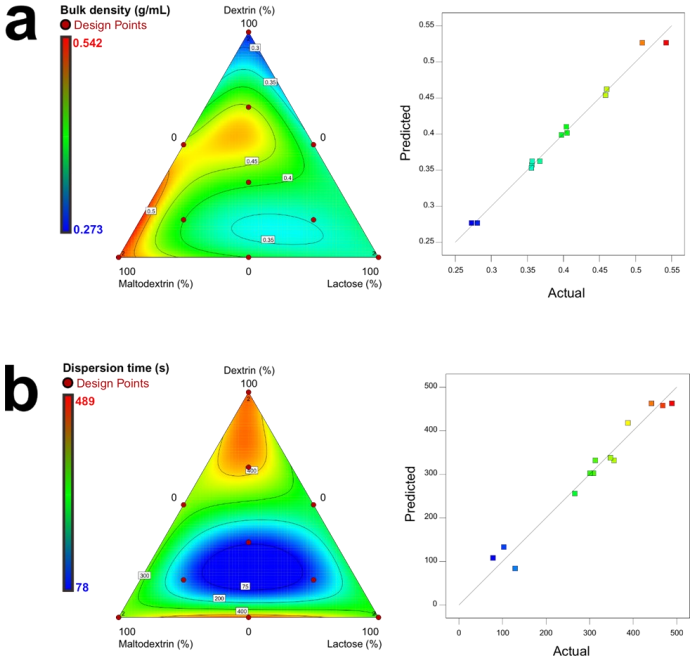

Figure 2. Contour plot and actual vs predicted value plot of bulk density (a) and dispersion time (b).

3.4 Bulk density evaluation

The bulk density was measured to evaluate the factors that affected the flowability and feasibility of the manufacturing process (van den Ban and Goodwin, 2017). The bulkiness of the granule formulation means that it requires larger packaging. The model was converted to the inverse transformation to obtain the best -fitting model. Due to this transformation, the greater the response value, the lower the effect on the bulk density. The bulk density of all the formulations ranged from 0.273 g/mL to 0.542 g/mL. To evaluate the effect of the factors on the granule formulation, MLRA was utilised (Table 2). Dextrin was the most significant excipient that reduced the bulk density, followed by lactose and maltodextrin. The regression coefficient of the interaction between dextrin and maltodextrin, as well as lactose, showed a negative value, indicating that those interactions increased the bulk density. A greater bulk density was a more valuable option and offered flexibility in the manufacturing process. To investigate the effect of the excipient mixture on the bulk density, a contour plot of the bulk density was created and is presented in Figure 2a. Maltodextrin showed the most significant impact on increasing the bulk density of the formulation. This was due to the binding characteristics of maltodextrin. Therefore, maltodextrin produced denser granules compared to the other excipients (Chen *et al*., 2020). The observed high proportion of lactose did not result in a significant impact on the contour alteration. Conversely, the observed high proportion of dextrin showed the lowest bulk density. This interaction was observed in the ternary mixture in the dominant proportion of maltodextrin. The actual and predicted plots showed a perfect correlation; however, the residual was relatively high at higher bulk densities.

3.5 Dispersion behaviour

The dispersion time and disaggregation of the granule formulation were observed, which was followed by the extraction of the components in the *jamu* formulation. This was correlated with the interparticle binding during granulation (Desai *et al*., 2016). The faster the disintegration time, the lower the strength of the interparticle bonding. However, the *jamu* formulation was ready to be extracted into hot water if the formulation had a quicker dispersion time. The dispersion time of the granules ranged from approximately 1 min to 8 mins. The data were modelled into a special quartic model that was significant ($p<0.05$). Additionally, the lack of fit test was insignificant ($p>0.05$). The studied factor affected the response by 96.68%. According to the regression coefficient (Table 2), dextrin with the most robust regarding interparticle bonding provided the longest disintegration time. Moreover, maltodextrin and lactose showed an identic effect on the dispersion time. All the excipients demonstrated good water solubility (Jafari *et al*., 2021). Therefore, the dispersion behaviour was only affected by the interparticle binding during the granulation process. Only the interaction between maltodextrin and lactose significantly increased the dispersion time ($p<0.05$). The contour plot of the dispersion time (Figure 2b) shows that the shortest dispersion time was obtained at the ternary mixture in a low proportion of dextrin. However, the longest dispersion time was observed at a high proportion of dextrin. The interaction was observed around the highest and the lowest dispersion time regions. The actual and predicted plots showed that the model demonstrated a

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high R^2, Adj. R^2, and AP (0.9668, 0.9003, and 10.77, respectively). This indicated that the model was validated and could be utilised for predicting the response.

3.5 Antioxidant activity evaluation

Both the plant components in the *jamu* formulation, i.e., the *A. muricata* L. leaves and *G. mangostana* L. pericarps, were intended to provide antioxidants as highlighted pharmacological benefits (Ibrahim *et al*., 2016; Justino *et al*., 2018). The higher the inhibition value, the greater the potency of the antioxidants. The inhibition of all the formulations ranged from 26.36% to 85.41%. The exact concentrations of all the formulations demonstrated various inhibition values due to the effect of the excipients on the extraction process. Therefore, the effect of excipients should be understood thoroughly. A quadratic model was applied to assess the main effect and interaction of excipients in the granule formulation on the antioxidant activity. The model was considered to be significant ($p<0.05$), and the lack of fit was insignificant ($p>0.05$). Lactose and dextrin did not show an impact on reducing the antioxidant activity; however, maltodextrin was observed to significantly reduce the antioxidant activity ($p<0.05$). This phenomenon could be explained through the interaction of the bioactive compounds contained in *A. muricata* and *G. mangostana*, which predominantly consist of flavonoid and polyphenol compounds. The interaction between active compounds and excipients reduced the interaction between the active compounds and radicals. However, the presence of lactose in the maltodextrin mixture enhanced the antioxidant activity. Thus, it could be inferred that lactose decreased the interaction between the maltodextrin and the active compounds. The other interaction in the simplex lattice design model was insignificant ($p>0.05$). The interaction between the excipients and bioactive compounds plays a fundamental role in the pharmacological effect, which either increases or decreases the activity depending on the interaction (Mor and Raghav, 2021). The contour plot can be applied to obtain various insights into the interactions among factors. The antioxidant activity decreased as the maltodextrin proportion increased. This interaction was also observed in the presence of dextrin and lactose in the binary mixture. No unique interactions were observed in the contour plot (Figure 3). However, the validity of the model was questionable due to a high residual value that was affected by the inadequate distribution of the antioxidant. The antioxidant value of all the formulations was approximately 70–85%. However, in the presence of a high proportion of maltodextrin, the antioxidant value decreased to 20–30%.

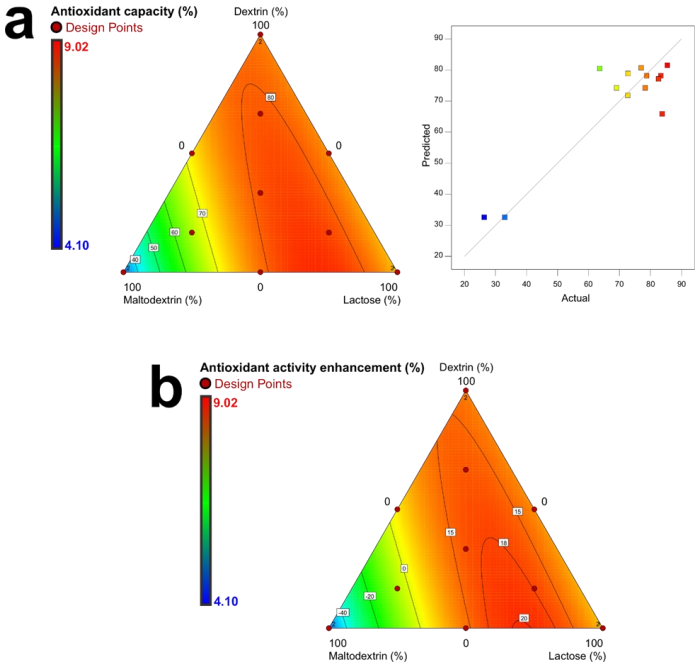

Figure 3. Contour plot and actual vs predicted value plot of antioxidant capacity (a) and contour plot of antioxidant capacity enhancement (b).

The enhancement of antioxidant activity was also evaluated. The data were obtained by comparing the antioxidant activity between the granule formulation and the no granule formulation. The data revealed a decrease in antioxidant activity by -61.88% and an increase in antioxidant activity by 23.49%, respectively. The data pattern was the same as the antioxidant value model. However, additional data demonstrated that dextrin showed a positive effect by increasing the antioxidant value to a higher value than that demonstrated by lactose. The cut-off value, with no alteration of antioxidant effect, was obtained at no more than 80% of maltodextrin in the mixture. Hence, the lower the proportion of maltodextrin, the more influential the antioxidant properties were.

3.6 Determining the optimised formulation

The optimised formulation was determined according to the desired characteristics that presented the critical quality attributes of the *jamu* granule formulation. The quality target product profile for determining the optimised formulation is shown in Table 3. An overlaid contour plot was used to determine the optimised formulation (Figure 4). The optimised formulation consisted of dextrin, maltodextrin, and lactose at compositions of 25.81%, 44.63%, and 29.56%, respectively. The optimised formulation revealed a desirability value of 0.543, and it fulfilled the requirement of the predetermined quality target product profiles by 54.3%. Verification of the optimised formulation was not required because the model validation demonstrated that all the models were accurate. The validation of the model was conducted by

https://doi.org/10.26656/fr.2017.7(3).931

Table 3. Quality target product profile of *jamu* granule formulation

Critical parameters	Goal	Limit	Priority level
Angle of Repose (°)	Minimize	<40	5
Moisture content (%)	Minimize	4.09-9.015	3
Moisture content increment (%)	Minimize	1.68-10	5
Bulk density (g/mL)	Maximize	0.273-0.543	3
Dispersion time (s)	Minimize	78-489	3
Antioxidant capacity (%)	Maximize	50-85.41	5
Antioxidant capacity enhancement (%)	Maximize	0-23.49	5

internal validation using the cross-validation technique and was visualised using actual and predicted plots.

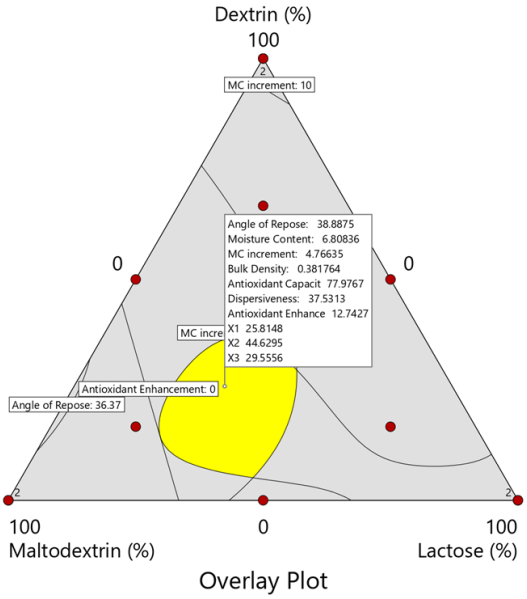

Figure 4. Overlay contour plot for determining the optimized formulation.

4. Conclusion

The *jamu* SIRMA was successfully transformed into granule formulations using various combinations of fillers. The fillers were considered to affect the critical quality attributes of the granule formulations. Maltodextrin demonstrated a positive effect on the powder flowability and a negative effect on antioxidant activity and hygroscopicity. Furthermore, dextrin demonstrated a negative effect on decreasing the dispersion. Moreover, lactose was the most inert filler and showed no significant effect on the critical quality attributes of the granule formulations. An optimised formulation was obtained at 25.81% dextrin, 44.63% maltodextrin, and 29.56% lactose.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

The authors would like to thank the Ministry of Education, Culture, Research, and Technology through Research Group Funding, Universitas Sebelas Maret, along with contract No. 260/UN27.22/HK.07.00/2021.

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