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RESEARCH ARTICLE **Open Access**

Optimizing effervescent granules of butterfly pea (*Clitoria ternatea* L) flower ethanol extract as antioxidant

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ABSTRACT

Background: Butterfly pea (*Clitoria ternatea* L.) contains secondary metabolites include flavonoids, saponins, terpenoids, tannins, and anthocyanins which have antioxidant activity.

Objective: This research aims to produce the effervescent granule preparations of the butterfly pea flower ethanol extract with optimal concentrations of citric acid and tartaric.

Methods: Butterfly pea flower was extracted using 70% ethanol. Effervescent granules were made using the wet granulation method in eight formulas containing citric acid and tartaric acid. The physical properties of granules were evaluated including extract quality, flow rate, dissolution time, and pH.

Results: The concentration of the mixed components of citric acid 48.65 mg and tartaric acid 576.30 mg was the most optimal combination of acid sources for effervescent granules of butterfly pea flower extract with a desirability value of 1,000.

Conclusion: The variation of citric acid and tartaric acid affected the flow rate, dissolution time, and pH of effervescent granule preparation.

Keyword: Clitoria ternatea, butterfly pea, effervescent, citric acid, tartaric acid, simplex lattice design

Introduction

An antioxidant is needed by the body to counteract and prevent oxidative stress. Numerous indigenous materials of Indonesia have antioxidant among their active ingredients. It is necessary to use natural materials as antioxidants to improve the people's health quality at a reasonable cost. Butterfly pea (*Clitoria ternatea* L. or blue pea, or telang flower) is one of the natural sources of antioxidant [1,2]. Butterfly pea flower is rich in the anthocyanin, a naturally occuring flavonoid pigment [3].

In the future, properly formulated herbal medicines will be a health solution, given the rising popularity of herbal medicine. People primarily use traditional medicines as *Jamu*, which was prepared by boiling or brewing the ingredients, making it less favorable. In addition, its preparation has several weaknesses, including a less practical and stable preparation as well as an unclear dose. As the sciences and technologies in pharmacy advance, there is an increasing demand to formulate these natural materials into more proper preparations, including the effervescent granule [4–6]. In addition, the preparation of medications has evolved from basic mixing to the use of drug delivery system technologies [7].

Finding the optimal formula in effervescent granule preparation largely depends on optimizing the acid and base components. The optimization process uses simplex lattice design method to determine the most optimal ratio of citric to tartaric acid concentration [8]. Citric and tartaric acids are employed as acid sources in this investigation. Used alone, citric acid renders the mixture sticky and difficult to granulate. In contrast, tartaric acid alone makes the granule clump easily.

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Table 1. Formulation of butterfly pea flower extract effervescent granule

Material	Formula (mg)							
	F1	F2	F3	F4	F5	F6	F7	F8
Butterfly pea extract	200	200	200	200	200	200	200	200
Citric acid	50	45	47.5	48.75	46.25	50	45	47.5
Tartaric acid	575	580	577.5	576.25	578.75	575	580	577.5
Sodium bicarbonate	625	625	625	625	625	625	625	625
Aspartame	40	40	40	40	40	40	40	40
PEG 6000	75	75	75	75	75	75	75	75
Lactose	935	935	935	935	935	935	935	935
Total	2500	2500	2500	2500	2500	2500	2500	2500

Methods

Materials

Butterfly pea flower obtained from the local garden of Rejasari Subdistrict, West Purwokerto District, Banyumas Regency. Ethanol 70% was used to extract the butterfly pea flowers. Citric acid, tartaric acid, sodium bicarbonate, PEG 6000, aspartame, lactose, and aqua dest were used to manufacture effervescent granule.

Extraction

The butterfly pea flower was extracted using 70% ethanol for three times twenty-four hours. Furthermore, the macerated flower was concentrated using rotary evaporator at 50°-60°C until a viscous ethanol extract of butterfly pea flower was obtained. The quality of the extract was evaluated based on its moisture content and drying mass reduction.

Formulation of butterfly pea flower extract effervescent granule

The formula for effervescent granule was designed with acid and base contents of 50% of each. Using Design Expert software, the optimum combination of citric acid and tartaric acid was determined by simplex lattice design. The effervescent granule was made using wet granulation. This method employed a separate granulation procedure between acidic and basic components. The citric and tartaric acids were varied in eight formulas of the effervescent granule. Formula 6, 7, 8 were replication of Formula 1, 2, 3, respectively (Table 1).

The citric and tartaric acids were finely crushed before the butterfly pea flower ethanol extract, PEG 6000, and aspartame were added. Some lactose was added until a clenched mass was formed. The acid portion was then sieved using a mesh 14 sieve before being oven-dried at 40°C for 24 hours. The next step was to make the base component, which consisted of sodium bicarbonate, lactose, and PEG 6000. Gradually, ethanol was added until a clenched mass was produced. The mass of the base portion was sieved through a mesh 14 sieve and oven-dried at 40°C for 24 hours.

Optimizing the formula using simplex lattice design

The effervescent granule was tested to determine its physical properties, including its flow rate, dissolution time, and pH. Further analysis was performed using software design expert version 13.0 to obtain a mathematical equation and the contour plot for each response. The optimum area in the selected area was obtained by combining the contour plot diagram. One point with the highest desirability score was selected to determine the proportion of each optimum formula component. The software-predicted physical property test scores of the optimal formula were compared to the actual observation result scores using the one-sample t-test (IBM SPSS Statistics software). $P < 0.05$ is categorized as significant.

Results

Extraction result

The weight of the powdered simplicia was 500 g, whereas the weight of the extracted material was 70 g. This extraction produced thick butterfly pea flower extract with 14% yield. The drying mass reduction rate of butterfly pea flower powder was 23.47± 1.48%.

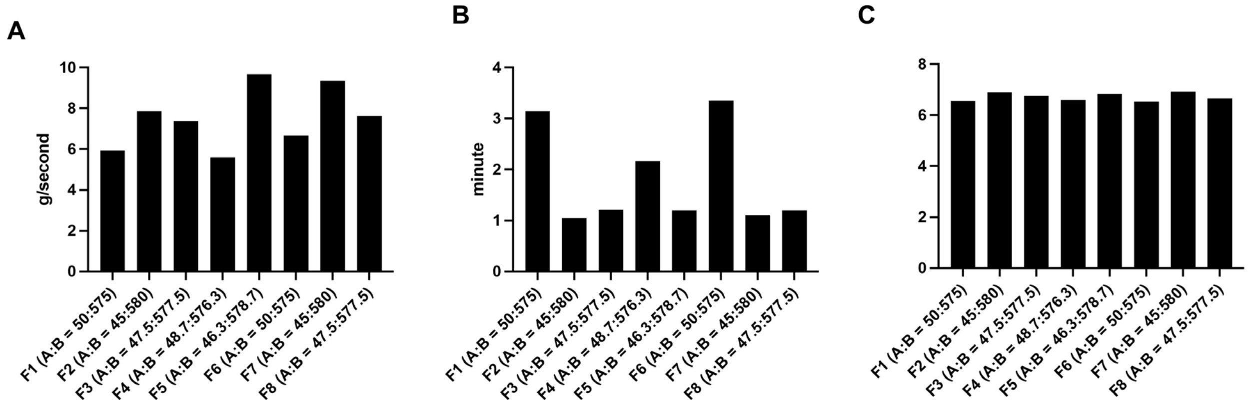

Figure 1. Data of formula experiment response using design expert. Component (X), A: citric acid, B: tartaric acid. (A) Flow rate. (B) Dissolution time. (C) pH

Flow rate analysis results

The physical properties of effervescent granule, including its flow rate, dissolution time, and pH, were evaluated. These physical features of the granule were evaluated to determine if the manufactured granule met the requirements and could be used as a high-quality effervescent granule preparation. Flow rate is one of the parameters that influence the package preparation process. The flow rates of all formulas were deemed to be satisfactory, with a score of 4-10 g/second (Figure 1). The citric and tartaric acid variations may affect the flow property of an effervescent granule product, with the tartaric acid concentration having a positive effect on the flow rate (Figure 2).

The relationship between response and the acid component was represented by the equation Y = 6.32(A) + 8.62(B) + 0.40(AB) – 15.63(AB(A-B)). Based on the equation, the components A (concentration of citric acid) and B (concentration of tartaric acid) had positive values, indicating that they contributed to the increase in flow rate. Component B had a greater impact on the flow rate rise than component A, as its value was greater than component A's.

Dissolution time testing result

The dissolution time was tested to determine how long it took for the granule to dissolve in water completely. The evaluation of each formulation's effervescent dissolution time satisfied the criteria, as the good dissolution time of the effervescent granule was less than five minutes (Table 2). According to Figure 1, Formula 2 dissolved faster than Formula 3. The varied amounts of tartaric acid affected the outcome, in which the dissolution rate is proportional to the concentration of tartaric acid (Figure 3).

The ANOVA analysis of the dissolution time response showed a significant result with $p<0.05$, indicating that all optimization formulas produced significantly different response scores for dissolution time. The relationship between response and the acid components was represented by the equation Y = 3.25(A) + 1.11(B) - 3.45(AB).

pH value optimization result

In order to ensure that the effervescent solution has a tend neutral pH range, measuring pH was needed. When it was extremely acidic, it could cause gastrointestinal irritation, and when it was excessively basic, it had a bitter and unpleasant taste. pH 6-7 was optimal for the effervescent solution. The result indicated that the quantities of citric and tartaric acid affected the pH of the effervescent granule preparation. The higher the concentration of citric acid, the lower the pH value.

The equation of relationship between response and the varied components was Y = 6.53(A) + 6.91 (B). Component A (citric acid concentration) and B (tartaric acid concentration) had positive values, indicating that they contributed to the increase in pH. Component B had a bigger effect on the pH increase, as its value was greater than that of component A (Figure 4).

Optimizing the effervescent granule formula using simplex lattice design

The effervescent granule formula was optimized by determining the minimum and maximum standard range of the components. The process was performed using a theoretical approach and resulted in the value range used in this study. The granule formula optimization was determined by setting the expected

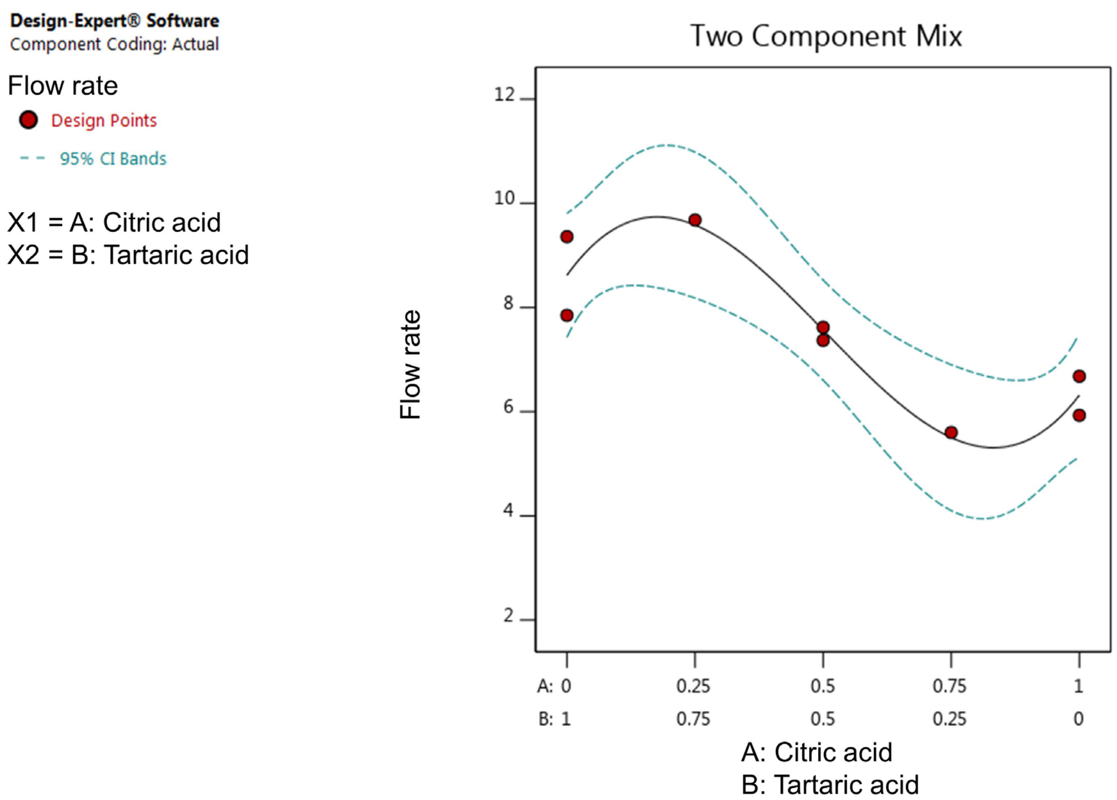

Figure 2. Relationship between granule component and flow rate. The ANOVA statistical analysis of the flow rate response showed a significant result with $p < 0.05$, suggesting the response scores for flow rate produced by the eight optimization formulas were significantly different from one another

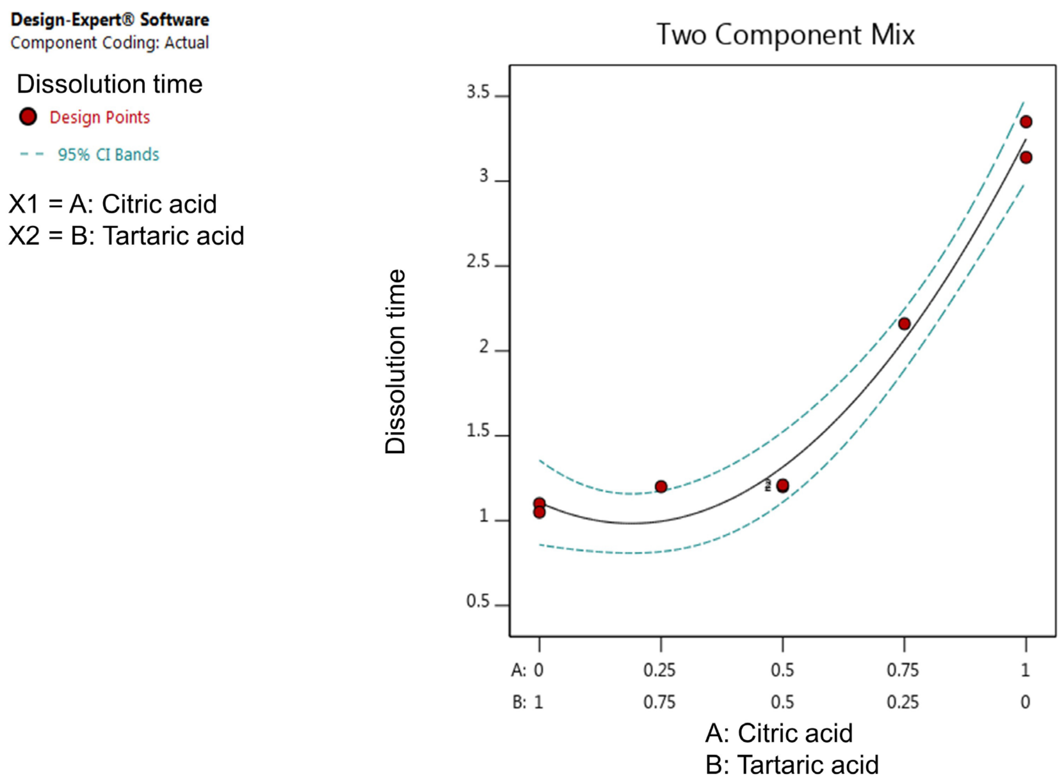

Figure 3. Relationship between granule component and dissolution time. The ANOVA statistical analysis of the dissolution time response showed a significant result with $p < 0.05$, suggesting that the response scores for dissolution time produced by all optimization formulas were significantly different from one another

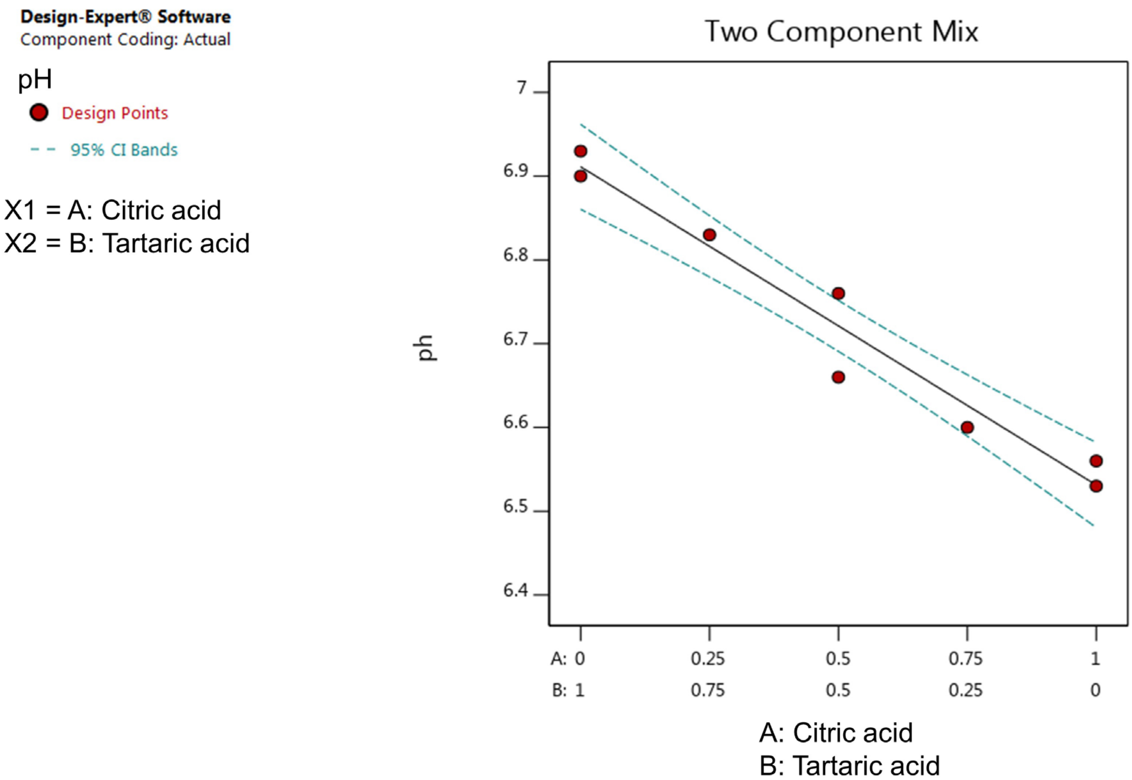

Figure 4. pH test result. The equation of relationship between response and the varied components was Y = 6.53(A) + 6.91 (B)

optimum formula criteria. The optimum formula criteria was presented in Table 2.

The optimum formula was validated by comparing the predicted value to obtained from the Design expert program and the data from the physical test result. The concentration of component mixture of citric acid 48.65 mg and tartaric acid 576.30 mg is the most optimum combination of acid sources for the butterfly pea flower extract effervescent granule at a desirability score of 1.000 (Figure 5).

Discussion

Tartaric acid had greater density than citric acid [9]. Therefore, the effervescent granule containing tartaric acid would produce greater density. A high density would result in a high molecular weight, which would make it easier to flow due to the high gravity [9].

The effervescent granule was produced using wet granulation method, by separating the acid and base part granules to avoid an early effervescent reaction. The additional materials used were combination between citric acid and tartaric acid, sodium bicarbonate, PEG 6000, aspartame, and lactose. As a base component, sodium bicarbonate was good to use in 25-50% range. Meanwhile, the acid component used was the combination of citric acid and tartaric acid.

The concentration of butterfly pea flower extract used in the optimization of the effervescent formula was 200 mg. This was due to the antioxidant and anti-diabetic activities of butterfly pea flower extract at this dose [10]. The optimum formula of effervescent granule was determined based on response data assessed using ANOVA Design Expert. The data was then processed to determine the optimal formula, considering the criteria for the various components and the determined responses.

The optimum formula was determined by examining the close to 1 desirability score. The optimum formula solution selected would produce the predicted proportions of each intervention and response. At a desirability score close to 1, the suggested optimal formula was reached, with citric acid 48.65 mg: tartaric acid 576.30 mg constituting the optimal formula. Predicting the physical property parameters yielded a flow rate score of 5.58 g/second, a dissolution time of 2.00 minutes, and a pH of 6.64. Incorporating the values of flow rate, dissolution time, and pH factors, the predicted value was subsequently validated using a one-sample *t*-test.

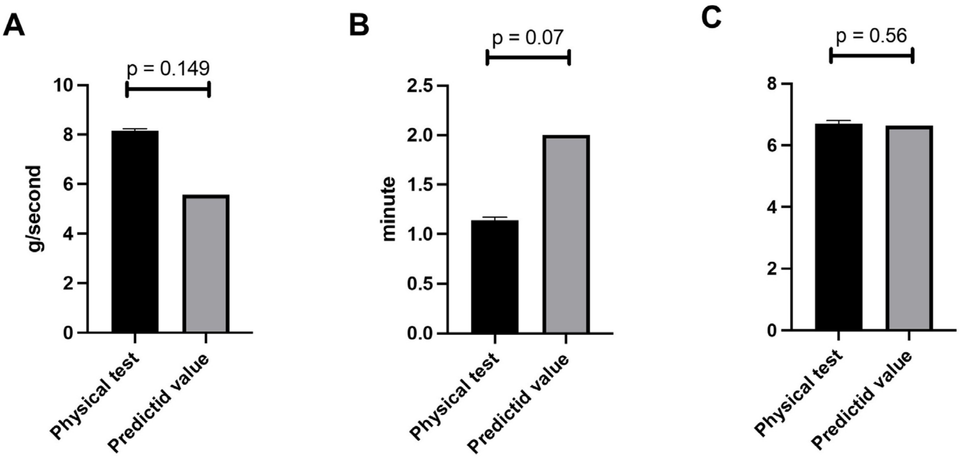

Figure 5. Optimum formula validation test. (A) Flow rate. (B) Dissolution time. (C) pH. All physical property parameters compared to predicted value showed significance values of $p > 0.05$

Table 2. Optimum formula criteria

No	Component	Target	Lower limit	Upper limit
1	Citric acid	In range	45	50
2	Tartaric acid	In range	575	580
3	Flow rate	In range	4	10
4	Dissolution time	In range	2	5
5	pH	In range	6	7

This calculation was intended to determine the difference between the physical property test of effervescent granule optimal formula and the result predicted by the program/software. The validation of the optimum formula revealed that the produced formula possessed the predicted physical features. All physical property parameters showed significance values of $p > 0.05$, thus it was possible to infer that the comparison of program prediction data and the physical property test of the optimal formula for butterfly pea flower effervescent granules did not differ significantly.

Conclusion

The obtained optimum formula was a ratio of amount of citric acid component at 48.65 mg and tartaric acid at 576.30 mg, at desirability score 1,000. This formula had the predicted points of flow rate 5.58 g/second (4-10 g/second), dissolution time 2.00 minutes (<5 minutes), and pH 6.64 (6-7).

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Author contributions

TS, W design the study; TS, W, PW contribute to data acquisition; PW, TS write the first draft; PW, W performed analytical statistic; TS, W finalize and revise final manuscript; all authors agree to the last version manuscript.

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