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RESEARCH

Formulation, Optimization, and In Vitro Studies of Roasted Agung Banana var. Semeru Peel Effervescent Antidepressant Tablet

Lannie Hadisoewignyo[1] · Dwi Qonita Safitri[1] · Restry Sinansari[1] · Jefri Prasetyo[1] · Kevin Owen Santoso[1] · Salwa Damayanti[1] · Dilla Sonia Wahyu Afotia[1] · Ivonne Soeliono[1]

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Abstract

Purpose To make effervescent tablet which being able to used for large doses of active ingredient, improve palatability, and simplify the manufacture of an effervescent tablet containing roasted banana peel extract (RBPE) via hot melt extrusion, and to optimise its formulation while assessing its antidepressant activity.

Methods Effervescent granules were produced by hot melt extrusion and compressed directly into tablets. Optimisation employed a two-factor, two-level factorial design, with crospovidone (8–10% w/w) and effervescent base (50–55% w/w) as independent variables. The antidepressant activity of the optimised formulation was evaluated in mice using the forced-swim test (FST) and tail-suspension test (TST).

Results A higher crospovidone concentration significantly shortened disintegration time ($p < 0.05$). The proportion of effervescent base, and its interaction with crospovidone, significantly affected tablet hardness and friability ($p < 0.05$). In both the FST and TST, the optimised RBPE tablet reduced immobility time to the same extent as fluoxetine and crude RBPE, indicating comparable antidepressant efficacy.

Conclusions The optimised RBPE effervescent tablet disintegrated rapidly, met physical quality specifications, and exhibited significant antidepressant activity, supporting its potential as a convenient dosage form for RBPE.

Keywords Effervescent tablet · Roasted banana peel extract · Hot melt extrusion · Factorial design · Antidepressant activity

✉ Lannie Hadisoewignyo
lannie@ukwms.ac.id

Dwi Qonita Safitri
qonitasafitri2804@gmail.com

Restry Sinansari
restry@ukwms.ac.id

Jefri Prasetyo
jefri@ukwms.ac.id

Kevin Owen Santoso
owenkevin2014@gmail.com

Salwa Damayanti
salwadamayanti.SD@gmail.com

Dilla Sonia Wahyu Afotia
dillasonia@gmail.com

Ivonne Soeliono
ivonne-s@ukwms.ac.id

[1] Departement of Pharmacy, Universitas Katolik Widya Mandala Surabaya, Surabaya, Indonesia

Abbreviations

FST	Forced swimming test
LOD	Loss on drying
MC	Methylcellulose
OF	Optimum formula
PVP K-30	Polyvinylpyrrolidone K-30
RBPE	Roasted banana peel extract
SDL	Spray-dried lactose
TLC	Thin layer chromatography
TST	Tail suspension test
Tukey's HSD	Tukey's honestly significant difference

Introduction

Depression is a prevalent mental-health disorder in both adults and adolescents, arising from complex interactions among biological, psychological and social factors, including genetic susceptibility to stress and trauma [1, 2].

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Globally, the number of depression cases rose by 44.8% between 1990 and 2019 [3]. Interest in traditional medicines has grown in parallel, driven by concerns over the adverse effects and cost of synthetic drugs [4].

Banana peel typically discarded as waste contains phyto-antioxidants such as morin that have shown anxiolytic and antidepressant potential [5, 6, 7]. In the present work we used roasted Agung banana peel extract (RBPE), prepared by roasting the peels at 200 °C to enhance antioxidant activity [8]. Tablets were selected as the dosage form because of their stability, low cost and patient acceptance [9].

Previous research have tried to make conventional tablet with MADG method. Even so, the problem regarding patient acceptance is still not solved [7]. Therefore, effervescent is choosen to improve patient palatability and acceptance [10]. The effervescent base was produced by hot melt extrusion (HME), which comprises melting and drying steps that yield granules with excellent flow, enhanced taste and superior dissolution properties [11]. Formulation variables were optimised using a two-level factorial design (2^n), where *n* is the number of factors. This approach generates polynomial equations and contour plots that identify the factor combinations giving the desired responses [10].

The optimised RBPE formulation was evaluated for antidepressant efficacy in mice. The tail-suspension test (TST) and forced-swim test (FST) were employed because they are well-validated, rapid screens of antidepressant activity that measure the duration of behavioural despair [12, 13].

In summary, effervescent RBPE tablets were manufactured by direct compression of an HME produced effervescent base, the formulation was statistically optimised, and the resulting tablets were subjected to pre-clinical antidepressant testing to confirm in-vivo efficacy.

Method and Material

Material

The materials used include Granutech Roasted Agung Banana Peel Extract (RBPE) extracted by PT. Phytochemindo Reksa, Bogor, West Java, Spray Dried Lactose from Foremost Farms USA, citric acid from Shandong Ensign Industry CO., LTD., tartaric acid from Shandong Ensign Industry CO., LTD, sodium bicarbonate from Inner Mongolia Ihjuchem Industrial CO., LTD., PVP K-30 from BASF South East Asia Pte. LTD., crospovidone from JH Nanhang Life Sciences CO., LTD., magnesium stearate from Faci Asia Pacific PTE LTD., stevia, and methylcellulose.

The equipment used includes a roaster, sievers, oven, glass equipment, stopwatch, Saturnus analytical weighing equipment AL-500, Ohaus moisture analyzer MB25, flowability tester, TDT model single punch tablet machine, Erweka hardness tester TBH-125, Erweka friability tester TAR220, and TLC Chamber, Design Expert software, and SPSS software.

Roasting Process

The roasting method refers to the research conducted by Hadisoewignyo et al.., 2023 [8].

Dry Extract Standardization

The dried extract was characterised by organoleptic assessment, loss-on-drying determination, total-ash measurement and phytochemical profiling via thin-layer chromatography (TLC). Organoleptic properties (appearance, colour, odour and taste) were recorded visually. Loss on drying was quantified by heating 2.0 g of extract at 105 °C for 30 min and cooling in a desiccator for 15 min; the percentage mass loss was then calculated. Total ash was determined by incinerating 2.0 g of extract in a muffle furnace at 675 ± 25 °C for 3 h. For phytochemical screening, silica-gel F_{254} plates were developed with benzene/ethyl acetate/formic acid/methanol (60:30:10:5, v/v) and sprayed with Dragendorff, $AlCl_3$, $FeCl_3$ and anisaldehyde reagents to visualise alkaloids, flavonoids, terpenoids and tannins. The TLC sample was prepared by dissolving 3.33 g of roasted banana-peel extract (RBPE) in 10 mL of 96% ethanol (≈ 10% w/v), and 50 µL of this solution was spotted onto each plate before development.

Tablet Manufacturing Method and Optimization Design

The effervescent components (citric acid, tartaric acid, and sodium bicarbonate) are weighed and mixed. The mixture is melted in the oven for 24 h at 50 °C and sieved to make a Mixture (1) The next day, RBPE is mixed with SDL, PVP K-30, crospovidone, and stevia for 3 min to make a Mixture (2) Mixture 1 is weighed and dried in an oven for ± 30 s at 50 °C before being mixed with Mixture 2 for 2 min to make a Mixture (3) Then, magnesium stearate was added to mixture 3, and the mixture was homogenized for 2 min. The final mixture is sieved and then a tablet mass physical quality is carried out. After passing the tablet mass physical quality test, it is compressed into a tablet using a single punch tablet machine, and the tablet physical quality test is carried out. The optimization design in this study uses a 2-factor factorial design. In this study, the effervescent component used was 50%(-1)– 55%(+1), and the crospovidone concentration used was 8%(-1)– 10%(+1). Table 1 shows the formula of the tablets.

Table 1 Tablet formula

No.	Material	Concentration (%)	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	OF (mg)
1.	RBPE		200	200	200	200	200
2.	PVP K-30	10	100	100	100	100	100
3.	Crospovidone	8–10	80	80	100	100	80
4.	Effervescent component	50–55	500	550	500	550	550
5.	Stevia	1	10	10	10	10	10
6.	Magnesium stearate	1	10	10	10	10	10
7.	SDL	ad 100	100	80	50	30	80
	Total		**1000**	**1000**	**1000**	**1000**	**1000**

Tablet Mass Physical Quality Test

Moisture content and flowability of the pre-compression blend were assessed prior to tableting. 3 g samples of the granule were analysed in a moisture analyser at 105 °C until a constant mass was achieved, with results expressed as percentage weight loss. Flowability was evaluated by measuring the time required for 100 g of blend to discharge through a standard funnel, and flow rate (g s^{-1}) was calculated.

Tablets Physical Quality Test

Finished tablets were examined for weight uniformity, tablet hardness, friability and disintegration time. Twenty tablets were individually weighed to determine weight uniformity. Hardness was measured on six randomly selected tablets using a Erweka Hardness Tester. Friability was determined on ten tablets rotated for 100 rounds at 25 ± 1 rpm in a Erweka Friability Tester; the percentage weight loss was recorded. Disintegration time was assessed by placing one tablet in each of six beakers containing 200 mL of distilled water maintained at 15–25 °C and recording the time to complete dispersion of effervescent.

Statistical Analysis

All analysis data were reported as a mean ± SD. The data were analyzed by using SPSS 27.0 software. The statistical significance level was set up at $p < 0.05$.

Active Ingredient Stability Test Using Thin Layer Chromatography (TLC)

Tablet identity was confirmed by thin-layer chromatography (TLC). Silica-gel F_{254} plates were developed with benzene/ethyl acetate/formic acid/methanol (60: 30: 10: 5, v/v). A 0.1% morin reference solution (2 µL), RBPE solution (50 µL), extracts of formulations F1–F4 (50 µL each) and the optimised formulation (50 µL) were spotted and chromatographed in a saturated chamber; plates were visualised by spraying with $AlCl_3$ reagent. Tablet extracts were prepared by dissolving 16.65 g of tablets in 50 mL water, evaporating to dryness and re-dissolving the residue in 10 mL ethanol (96%).

Experimental Animal

All animal procedures were approved by the Health Research Ethics Committee of the Faculty of Medicine, Widya Mandala Surabaya Catholic University (approval code: 0077/WM12/KEPK/MHS/T/2024 and 0078/WM12/KEPK/MHS/T/2024) and conducted from 14 August to 1 December 2024. Male ddY mice (20–30 g, 2–3 months old; Farma Veterinary Center, Surabaya) were acclimatised for seven days under standard conditions (12 h light/12 h dark, lights on 07:00, 20–24 °C, 45–65% humidity, ad libitum food and environmental enrichment). Animals were allocated to five groups ($n = 5$ per group): normal control, negative control, RBPE, fluoxetine and optimised-tablet groups. Inclusion criteria were a coat-condition score and grimace-scale score of 0 and a body-condition score of 3; mice that died during the study or lost > 10% of their initial weight were excluded. All behavioural testing was performed between 08:00 and 12:00.

Test Compound Preparation

Test suspensions of roasted-banana-peel extract (RBPE) were prepared in 0.5% (w/v) methylcellulose (MC) to give an oral dose of 400 mg kg^{-1} body weight (bw). The optimised tablet formulation was triturated (ten tablets, ≈ 2 g extract) and dispersed in 50 mL MC to obtain the same extract concentration. Fluoxetine hydrochloride (20 mg kg^{-1} bw) served as the reference standard. All treatments were administered orally at a volume of 0.5 mL per 20 g bw.

FST Test

Forced-swim testing was performed in transparent cylinders (50 cm height × 20 cm diameter) filled with water (24–25 °C) to a depth of 20 cm. Mice were acclimatized to the test room and exposed to white-noise masking for 60 min, dosed, and then rested for a further 60 min. Each animal was placed in the cylinder for 6 min; the first 2 min

Table 2 Result of RBPE standardization and specification

Test	Specification	Result
Organoleptic		
Form	Powder	Powder
Color	Dark brown	Dark brown
Odor	Specific	Specific
Taste	Specific	Specific
Loss on Drying	< 10%	6.38 ± 0.11%
Total Ash Content	< 10%	19.27 ± 0.13%

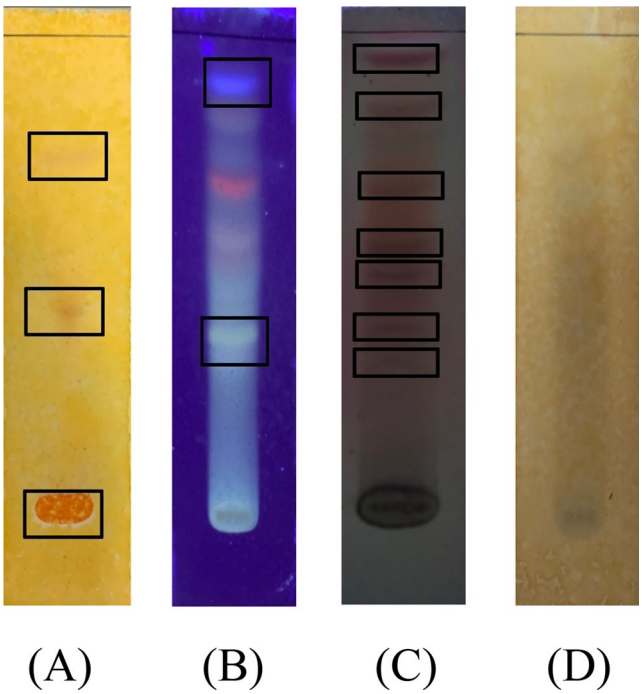

Fig. 1 Phytochemical screening of RBPE by using mobile phase benzene: ethyl acetate: formic acid: methanol (60:30:10:5) with 10% concentration and 50 µL spotted after sprayed by **A**: dragendorff **B**: $AlCl_3$**C**: anisaldehyde **D**: $FeCl_3$ reagent

were regarded as acclimation, and immobility time was calculated as 240 s minus the duration of active swimming.

TST Test

For the tail-suspension test, mice were suspended by the tail (12 cm adhesive tape, affixed 1 cm from the tip) in a sound-attenuated box (55 × 15 × 11.5 cm). After the same acclimation and pre-treatment schedule, each mouse was suspended for 6 min, and immobility was determined as 360 s minus the time spent struggling or making escape-oriented movements.

Result and Discussion

Dry Extract Standardization

Granutech RBPE is a dark brown powder with a specific taste and odor. The LOD test aims to provide a maximum limit regarding the amount of compounds lost during the drying process, which should be less than 10%. The result of the LOD test is 6.38 ± 0.11%, which fulfills the specification.

Total ash content aims to provide an overview of RBPE mineral content. The total ash content of the extract should be less than 10%. Table 2 dispalys the RBPE standardization and specification results. The obtained RBPE ash content was found to be equal to 19.27 ± 0.13%, which does not meet the required specification (total ash content < 10) due to Aerosil and maltodextrin used as dry extract filler with extract: filler ratio of 30: 70. Aerosil contains high amounts of silica and silicates, which have a melting point of 1600 °C [14–15]. Although the total ash content does not meet the specification, it has no effect on the tablet manufacturing process.

RBPE Phytochemical screening aims to analyze the secondary metabolite content of the extract. Figure 1 shows phytochemical screening that are conducted by using TLC and sprayed by dragendorrf, $AlCl_3$, anisaldehyde, and $FeCl_3$. The result shows that the extract contains an alkaloid which is indicated by red nodes with Rf scores of 0.4 and 0.71 (Fig. 1A), flavonoids which are shown by green nodes (Rf 0.38) and blue nodes (Rf 0.87) (Fig. 1B), terpenoids are shown by purple nodes with Rf score of 0.3, 0.38, 0.56, 0.68, 0.71, 0.81, and 0.87 (Fig. 1C). Based on this result, it can be concluded that the RBPE used in this study does not contain a tannin compound, which would be displayed by a dark blue color in $FeCl_3$ reagent (Fig. 1D).

Tablet Mass Physical Quality Test

The moisture content test aims to determine the water content of the granules. In general, the specification of moisture content is 2–5%. Lower moisture content will make tablet mass more fragile and easily break. Besides, Higher moisture content will make the tablet mass sticky and increase the risk of effervescent reaction [10, 16]. Table 3 shows the RBPE tablet mass physical quality test results. The measured moisture content of all the formula (from F1 to OF) meets the required specification. The flowability test carried out in this study is the flow rate test. A faster powder flow

Table 3 RBPE tablet mass physical quality test

Parameters	F1	F2	F3	F4	OF	Specification
Moisture content (%)	3.56 ± 0.13	3.31 ± 0.10	3.31 ± 0.09	3.56 ± 0.13	3.50 ± 0.05	2–5%
Flow rate (g/sec)	23.93 ± 0.05	24.03 ± 0.05	23.81 ± 0.04	23.99 ± 0.12	24.05 ± 0.04	> 10 g/sec

will produce uniform tablet weight. All the formulas pass the flow rate specification (> 10 g/second) [17, 18].

Tablet Physical Quality Test

Weight uniformity test is carried out by weighing 20 tablets randomly with no more than two tablets deviate from the average by 5% and not a single tablet deviates from the average by 10% [19]. This test aims to ensure that the active ingredient meets the specifications. The result shows that all the tablets met the weight variation specification. The results of statistical data analysis (One-Way ANOVA) show no significant differences between batches ($F1_{Fvalue}$ 2.393; $F2_{Fvalue}$ 2.672; $F3_{Fvalue}$ 0.666; $F4_{Fvalue}$ 2.293 < $F_{(0.05)(2,57)}$ 3.160). However, there are significant differences between the formula (F_{value} 3.819 > $F_{(0.05)(3,236)}$ 2.640); it is due to differences in excipient concentration, which causes the difference in compression pressure. Tukey's HSD post hoc test shows that F4 is significantly different from F2 and F3. The average tablet hardness batches were in the range of 8.57 ± 0.01 kp and 8.79 ± 0.05 kp. The results of statistical data analysis (One-Way ANOVA) show no significant differences between batches ($F1_{Fvalue}$ 0.031; $F2_{Fvalue}$ 0.395; $F3_{Fvalue}$ 0.188; $F4_{Fvalue}$ 0.099 < $F_{(0.05)(2,15)}$ 3.680) and no significant differences between the formulas (F_{value} 1.392 < $F_{(0.05)(3,68)}$ 2.740). Crospovidone used in this research 8–10%, increasing the crospovidone concentration will produce a weakers tablets that disintegrate faster [20]. The polynomial equation demonstrating the relationship among independent variables on tablet hardness is: Tablet hardness = 8.6850 + 0.0083 XA– 0.0083 XB + 0.1017 XAXB. The polynomial equation shows the dominant influence of the interaction between crospovidone and the effervescent component (XAXB) on tablet hardness. The statistical data analysis (One-Way ANOVA) shows that the interaction has an F_{value} of 29.710 > $F_{(0.05)(1,8)}$ 5.320. The contour plot shows that the variation of the effervescent component and the crospovidone concentration will always increase the tablet hardness. The average tablet friability batches were in the range of 0.46 ± 0.02% and 0.62 ± 0.01%, and all the formula met the specification ≤ 1% [18]. The results of statistical data analysis (One-Way ANOVA) show no significant differences between batches ($F1_{Fvalue}$ 1.936; $F2_{Fvalue}$ 0.039; $F3_{Fvalue}$ 0.156; $F4_{Fvalue}$ 4.413 < $F_{(0.05)(2,6)}$ 5.140). However, there are significant differences between the formula (F_{value} 68.093 > $F_{(0.05)(3,32)}$ 2.900). Small-size particles such as Crospovidone, increase the total surface area of the powder particle blend, which allows more surface interaction and therefore increases the tablet cohesion [21]. Tukey's HSD post hoc test shows no significant differences between formulas. The polynomial equation demonstrating the relationship among independent variables on tablet friability is: Tablet friability = 0.5275 − 0.0258 XA– 0.0125 XB + 0.0542 XAXB. The polynomial equation shows the dominant influence of the interaction between crospovidone and the effervescent component (XAXB) on tablet friability. The statistical data analysis (One-Way ANOVA) shows that the interaction has an F_{value} of 84.500 > $F_{(0.05)(1,8)}$ 5.320. The contour plot (Fig. 2B) shows that increasing the effervescent component and crospovidone concentration will decrease tablet friability. The average tablet dissolving time batches was in the range of 2.61 ± 0.03 min and 3.01 ± 0.05 min, and all the formulas met the specification ≤ 5 min [19]. The results of statistical data analysis (One-Way ANOVA) show no significant differences between batches ($F1_{Fvalue}$ 1.971; $F2_{Fvalue}$ 0.399; $F3_{Fvalue}$ 0.243; $F4_{Fvalue}$ 0.175 < $F_{(0.05)(2,15)}$ 3.680). However, there are significant differences between the formula (F_{value} 16.294 > $F_{(0.05)(3,68)}$ 3.130). Crospovidone could form a gel-like mass that inhibit water penetration that will increase the tablet dissolving time. Tukey's HSD post hoc test shows that F1 is significantly different from F2 and F4; F2 is significantly different from F1, F3, and F4; F3 is significantly different from F2 and F4; F2 is significantly differences from F1, F3, and F4. The polynomial equation demonstrating the relationship among independent variables on tablet dissolving time is: Tablet dissolving time = 2.8500–0.1417 XA + 0.0550 XB + 0.0400 XAXB. The polynomial equation shows the dominant influence of the effervescent component (XA) on the tablet dissolving time. The statistical data analysis (One-Way ANOVA) shows that the effervescent components have an F_{value} of 47.150 > $F_{(0.05)(1,8)}$ 5.320. The contour plot (Fig. 2C) shows that the increase in effervescent component concentration and decrease in crospovidone concentration will decrease tablet dissolving time (Table 4).

The response-surface model predicted that a formulation containing 55% (w/w) effervescent base and 8% (w/w) crospovidone would yield tablets with a tablet hardness of 8.60 kp, friability of 0.46% and disintegration time of 2.61 min. Experimental manufacture of this "optimum" blend produced tablets exhibiting uniform mass (1.005 ± 0.004 g; $n = 20$), hardness 8.67 ± 0.05 kp, friability 0.47 ± 0.01% and disintegration within 2.56 ± 0.01 min. One-sample t-tests showed no significant deviation of the measured hardness ($t = -1.887$, $df = 17$), friability ($t = 0.983$, $df = 8$) or disintegration time ($t = 0.470$, $df = 17$) from their respective predictions ($p > 0.05$), confirming the validity of the polynomial model.

Active Ingredient Stability Test Using Thin Layer Chromatography (TLC)

Identity testing by thin-layer chromatography (TLC) employed silica-gel F_{254} plates (10 × 10 cm) and a benzene/

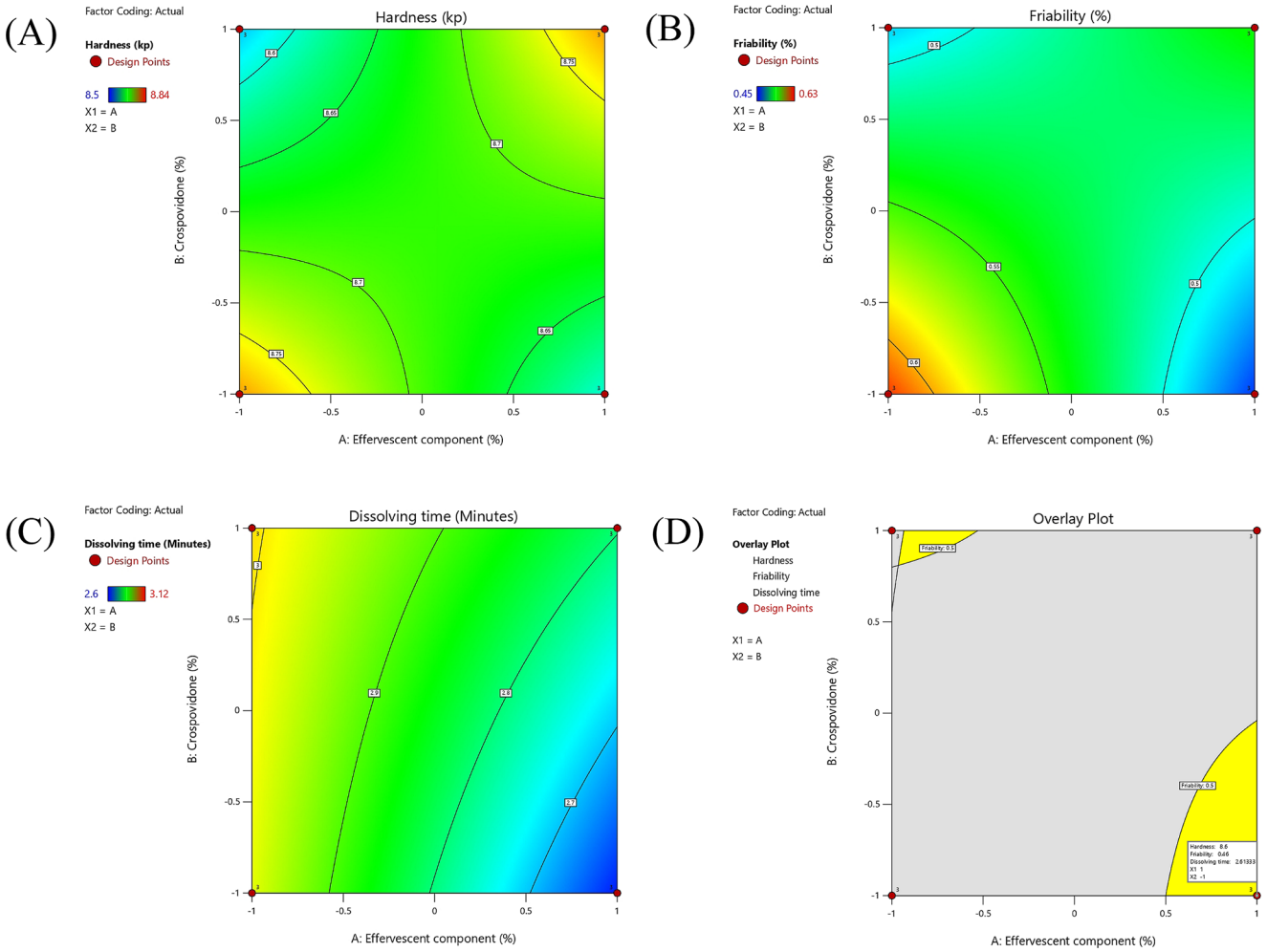

Fig. 2 Contour plot of **A**: tablet hardness **B**: tablet friability **C**: tablet dissolving time **D**: superimposed contour plot

Table 4 RBPE tablet mass physical quality test

Parameters	F1	F2	F3	F4	OF	Specification
Weight uniformity (g)	1.00±0.01	1.00±0.01	1.00±0.00	1.01±0.01	1.01±0.00	±5%
Tablet Hardness (kp)	8.79±0.05	8.60±0.09	8.57±0.01	8.79±0.04	8.67±0.05	7–10 kp
Tablet Friability (%)	0.62±0.01	0.46±0.02	0.49±0.01	0.54±0.03	0.47±0.01	≤1%
Tablet dissolving time (min)	2.98±0.13	2.61±0.03	3.01±0.05	2.80±0.02	2.56±0.01	≤30 min

ethyl acetate/formic acid/methanol mobile phase (60: 30: 10: 5, v/v) [22]. Test and reference solutions (50 µL of 10% RBPE and 2 µL of 0.1% morin, respectively) produced well-resolved spots with an Rf of 0.35. All formulations (F1–F4 and the optimised batch) retained the characteristic morin band, demonstrating that the tableting process did not compromise the phytochemical profile (Fig. 3A-C).

FST Test

In the forced-swim test (FST) the RBPE suspension reduced immobility to 158.6±31.0 s, and the optimised tablet to 166.4±28.7 s, compared with 180.2±30.3 s for fluoxetine (20 mg kg^{-1}) and 236.7±24.5 s in the negative-control group ($p<0.0001$ versus control). Both RBPE treatments were statistically indistinguishable from fluoxetine ($p>0.05$).

TST Test

In the tail-suspension test (TST) the optimised tablet produced the greatest reduction in immobility (210.2±5.2 s), surpassing both RBPE suspension (218.4±9.7 s) and fluoxetine (226.0±31.6 s; $p<0.001$ for all treatments versus control). The differing stress paradigms of the FST and TST, which engage distinct neuroendocrine pathways [23], likely account for the small discrepancies in absolute immobility

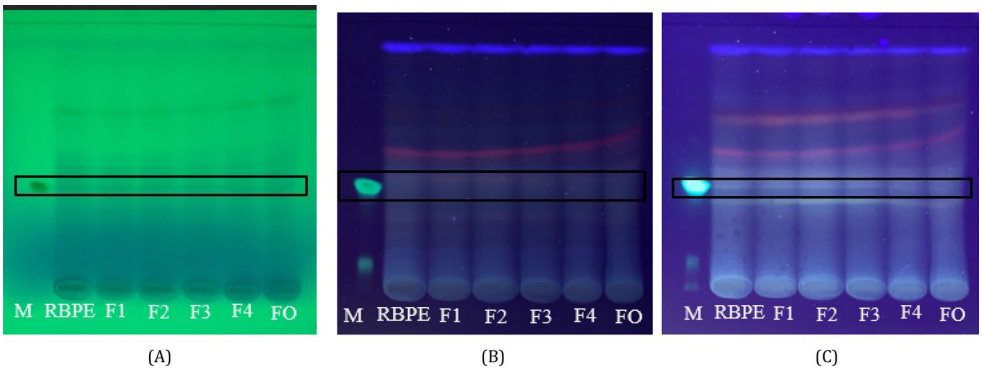

Fig. 3 TLC observation result of extract, granule, tablet stability test by using mobile phase benzene: ethyl acetate: formic acid: methanol (60:30:10:5) with 6% concentration and 30 µL spotted; M: Morin; RBPE: Roasted Banana Peel Extract; F1: Formula 1; F2: Formula 2; F3: Formula 3; F4: Formula 4; FO: Optimum Formula; **A**: UV_{254nm} chromatogram **B**: UV_{366nm} chromatogram **C**: $AlCl_3$ sprayed chromatogram

Table 5 Immobility time result

	Normal Control	Fluoxetine	RBPE	Optimum Formula	Negative Control
TST	311.10±4.55	226.01±31.62	228.95±39.57	210.15±5.22	317.33±7.36
FST	225.12±9.36	180.23±30.25	158.56±30.97	200.24±9.41	210.07±17.02

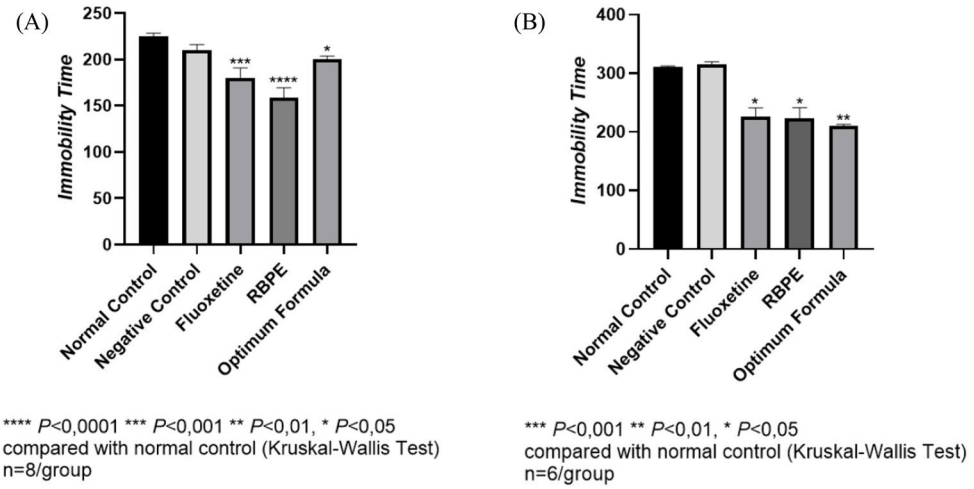

Fig. 4 Comparison of immobility times in the **A**: FST test groups; **B**: TST test groups. Data are expressed as mean±S.E.M. ****$P<0.0001$ versus normal control group; ***$P<0.001$ versus normal control group; **$P<0.01$ versus normal control group; *$P<0.05$ versus normal control group (Kruskal-Wallis Test with post hoc Tukey)

values. Collectively, these findings verify that the optimised effervescent RBPE tablet meets physicochemical quality targets and exerts antidepressant-like activity comparable to fluoxetine in two complementary behavioural models (Table 5) (Fig 4).

Conclusion

Effervescent tablets containing roasted-banana-peel extract were produced by hot-melt extrusion and optimised through a two-level factorial design. The selected formulation fulfilled all physicochemical specifications, retained its phytochemical marker profile, and, when administered orally to mice, significantly reduced immobility in both the tail-suspension and forced-swim tests. Antidepressant-like efficacy was equivalent to that of crude extract and to fluoxetine, indicating that neither the extrusion process nor direct compression compromised bioactivity. These findings support the melt-extruded effervescent tablet as a stable, palatable and pharmacologically effective dosage form for RBPE.

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Author Contributions Lannie Hadisoewignyo: Conceptualization, Supervision, Project Administration, Methodology, Software, Data Curation, Validation, Visualization, Writing - review & editingDwi Qonita Safitri: Investigation, Formal Analysis, Software, Validation, Writing–original draftRestry Sinansari: Methodology, Data CurationJefri Prasetyo: Methodology, Investigation, VisualizationKevin Owen Santoso: Visualization, Writing– original draft, Writing - review & editingSalwa Damayanti: Investigation, Formal AnalysisDilla Sonia Wahyu Afotia: Investigation, Formal AnalysisIvonne Soeliono: Supervision, Methodology, Software, Data Curation, Visualization.

Data Availability The data that support the fndings of this study areavailable from the corresponding author upon reasonable request.

Declarations

Competing Interests The authors declare no competing interests.

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