

Tablet Formulation of Ethanol– Water Agung Banana var. Semeru (Musa paradisiaca) Peel Extract using Moisture-Activated Dry Granulation (MADG) Method

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Abstract

Purpose Moisture-Activated Dry Granulation (MADG) is a tablet manufacturing method developed from wet granulation method. MADG methods are more efficient and cost-effective in the production of solid dosage forms since they use less fluid and shorter tablet manufacturing time. The MADG method could also be used for water-sensitive or heat-sensitive products where traditional methods may not be suitable. MADG tablet manufacturing is divided into an agglomeration step to activate the granule formation and a moisture absorption step to absorb excess moisture from the granule. This research aims to determine the effect of MADG method on the physical quality of tablet mass and tablet of ethanol–water roasted Agung banana var. Semeru peel extract (RBPE) compared to wet granulation method.

Methods The tablets were prepared by using wet granulation and MADG method.

Results Through the statistical analysis, the granules manufactured using MADG and wet granulation methods have a similar flowability, but those manufactured using MADG method have a higher moisture content. Tablets manufactured using MADG and wet granulation methods have a similar hardness. On the other hand, tablets manufactured using MADG method have lower friability and easier to be disintegrated compared to tablets manufactured using wet granulation method.

Conclusion The experimental data shows that MADG is a better method than wet granulation in manufacturing RBPE tablets.

Keywords Tablet · MADG · Wet Granulation · Roasted Banana Peel Extract · Moisture Absorption

Abbreviations

BPE	Banana peel extract
FST	Forced swimming test
LC–MS/MS–QTOF	Liquid chromatography–tandem mass spectrometry–quadrupole time of flight
LOD	Loss on drying
MADG	Moisture-activated dry granulation
RBPE	Roasted banana peel extract
SEM	Scanning electron microscope
SLS	Sodium lauryl sulfate
SSG	Sodium starch glycolate
TLC	Thin layer chromatography
TST	Tail suspension test

XRD

X-ray diffraction

WG

Wet granulation

Introduction

Mental illness is a disorder that could affect the psychological condition of the sufferer. Anxiety and depression are some of many mental disorders that occur in children, adults, and elders. Data retrieved from the World Health Organization (WHO) show that, during the COVID-19 pandemic, the occurrence of depression and anxiety increased by 28% and 26%, respectively. On the other hand, using natural materials in the health sector has increased and attracted attention. The medicines made from natural ingredients are quite economical and reduce the side effects due to the use of synthetic drugs [1].

Banana is a fruit commonly consumed by a wide community. Bananas are very popular because they are easy to find and contain nutritional substances [2]. One of banana types

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is Agung banana var. Semeru; the fruit can be consumed, while the peel can be processed into extracts [3].

Banana peels are the outer part of banana and are commonly used as animal food, cooking ingredients, and water purification. Moreover, banana peels have many nutritional compounds, as found in the banana fruit. The content of banana peels includes carbohydrates, amino acids (phenylalanine, valine, leucine, etc.), fatty acids (palmitic acid and 12-hydroxystearic acid), and minerals (phosphorous, sodium, calcium, etc.) [4]. Banana peels have been proven to be effective in treating anxiety and depression due to their tryptophan compound, which tryptophan is a precursor of Serotonin [5–7]. The use of Banana Peel Extract (BPE) requires a dose of 200–400 mg/kg in mice to obtain an optimal antidepressant effect, as mentioned by Tan and Halijah in 2011. In an FST test, BPE could reduce the immobility time by 17.36% (dose of 200 mg/Kg) and 19.38% (dose of 400 mg/Kg). On the other hand, in the TST test, BPE could reduce the immobility time by 24.11% (dose of 200 mg/Kg) and 44.16% (dose of 400 mg/Kg) [5].

Roasting is a dry heat treatment of extracts [8] to increase the concentration of most flavonoid compounds, phenolic acid, essential fatty acids, and major minerals [9]. In this research, the banana peel extract was roasted to increase its flavonoid levels.

Tablets are one of pharmaceutical preparations frequently used in formulation. In addition to ease of its manufacturing, tablets are pharmaceutically stable and easy to travel with [10]. Wet granulation, dry granulation, and direct compression are the three tablet manufacturing methods commonly used. With advances in technology, formulation methods continue to improve. Moisture-activated dry granulation is one of the developments in wet granulation method. This method involves two steps: agglomeration and moisture absorption [11]. Compared to wet granulation, the MADG method is more time-efficient and does not require a drying process. Tablets produced by this method will have good flowability, compressibility, and uniform size. The excipients needed in this method are binder, disintegrant, water absorbent, and lubricant [12, 13].

In manufacturing tablets, wet granulation method requires the addition of a binder solution as the natural ingredient extract often causes a sticky mass that is difficult to granule. Besides, the wet granulation requires a heating process, which affects the stability of extract content. The manufacture of tablets using the MADG method does not require large amounts of liquid and does not involve a drying process. Therefore, it can overcome the problems faced in the wet granulation method.

As approved concept, in this study, RBPE tablet was manufactured using the MADG method and compared with RBPE tablet manufactured using the wet granulation method to see the effect of the MADG method on the physical quality of RBPE granules and tablets.

Method and Material

Material

The materials used include Roasted Agung Banana Peel Extract (RBPE) which extraction process is carried out by PT. Phytochemindo Reksa, Bogor, West Java, Avicel PH-102 from PT. Megasetia Agung Kimia. Tbk., sodium starch glycolate from Gujarat Overseas INC., India, and sodium lauryl sulfate from BASF, Germany.

The equipment used includes a roaster, Mettler Toledo analytical weighing equipment AL204, cube mixer, sievers, Ohaus moisture analyzer MB25, Erweka tapped volumeter SVM12, Erweka single punch tablet machine, Erweka hardness tester, Erweka friability tester TAR220, and Erweka disintegration tester.

Roasting Process

The roasting methods refer to research by Hadisoewignyo et al., 2023 [14].

Extract Crystallinity, Size, and Particle Morphology

The crystallinity, size, and particle morphology of BPE and RBPE were checked using XRD and SEM instruments.

RBPE Content Identification

The flavonoid compound of RBPE was determined using LC–MS/MS–QTOF with ESI as a sample converter.

Tablet Manufacturing with Wet Granulation Method

The RBPE was mixed with Avicel PH-102 and SSG in a cube mixer. Then, 2.5 mL of water is added drop by drop until granules formed. Granules are sieved with a No. 16 sieve. The mixture is dried in an oven at 50 °C for 15 min. Then, SLS is added, and the mixture was homogenized in the 68 rpm cube mixer for 1 min. The mixture is sieved with No. 20 sieves. The physical quality of the granules is tested after the mixture is sieved. After passing the granules quality test, it is compressed into a tablet using single punch tablet machine with a 15 mm diameter and flat face shape. Then, the physical quality of the tablet was tested.

Tablet Manufacturing with MADG Method

The first step of this method is to determine the LOD of each ingredient and then count the amount of water needed (2.094 mL). After that, RBPE is mixed with Avicel

PH-102 and SSG in a cube mixer for 5 min. Then, the water that had counted before is sprayed into the mixture as an agglomeration step to make the granules. Avicel PH-102 in the mixture aims to examine the granule's humidity. After that, SLS is added to the mixture in a 68 rpm cube mixer for 1 min, and the granules are sieved with a No. 24 sieve. The physical quality of the granules is tested after the mixture is sieved. After passing the granules quality test, it is compressed into a tablet using a single punch tablet machine with a 15 mm diameter and flat face shape angle of rep. Then, the physical quality of the tablet is tested. The tablet formula and water calculation could be seen in Table 1.

Dry Extract Standardization

The dry extract standardization carried out in this research includes organoleptic, water content, and total ash content. The organoleptic test is carried out by visually checking the form, color, odor, and taste of the extract. The water content analysis is conducted by accurately weighing a 3 g dry extract sample and subsequently heating it at 105 °C in a moisture analyzer. The total ash content is determined by keeping the constant of the crus, weighing a 2 g dry extract sample, and heating it at 675 ± 25 °C in a Furnace burner.

Physical Quality Test of Granules

In this study, we assessed the physical quality of granules, explicitly focusing on granules' moisture content and flowability. Moisture content is determined by weighing 3 g of granules and heating them at 105 °C in the moisture analyzer, and the flowability test is determined by counting Carr's index and Hausner ratio. Carr's index and Hausner ratio were determined by weighing the 100 mL measuring cylinder and filling the samples into it. The total weight is determined. Then, the

measuring cylinder is put in a tapped volumeter and tapped 1250 times. The volume of the sample is measured after tapping.

Physical Quality Test of Tablets

The physical quality tests determined in this study include weight uniformity, tablet hardness, tablet friability, and tablet disintegration times. The weight uniformity test is carried out by randomly taking 20 tablets and weighing them. Of these, less than two tablets must exceed the deviation limit A (5%), and no tablet must exceed the deviation limit B (10%). Tablet hardness is determined by randomly taking 6 tablets and inserting them into the tablet hardness tester. The friability test is carried out by randomly taking 10 tablets and weighing them. After being weighed, the tablet must be tested in the friability tester for 100 rounds at 25 ± 1 rpm. The tablet disintegration time is determined by randomly taking 6 tablets and inserting them in each apparatus. The apparatus is then inserted into a disintegration tester filled with 37 ± 2 °C warm water as a medium.

Active Ingredient Stability Test using Thin Layer Chromatography (TLC)

Profile determination is carried out by using Thin Layer Chromatography (TLC), the mobile phase benzene: ethyl acetate: formic acid: methanol (60:30:10:5). The mobile phase is moved to the chamber, and the chamber is saturated for a moment. The rutin is weighed 1 g and dissolved in 100 mL 96% ethanol to make a 1% rutin solution; 0.6 g RBPE dissolved in 10 mL 96% ethanol, while granules and tablets are weighed 0.96 g and dissolved in 10 mL 96% ethanol. The 2 µL rutin 1% solution and each 30 µL RBPE, wet granulation granule, MADG granule, wet granulation tablet, and MADG tablet 6% solution are spotted into the silica

Table 1 The formula of tablet and calculation of water required

Ingredient	Function	Amount (mg)	1 Batch (120 g)	Weight (%)	LOD (%)*	% LOD (%)**
RBPE	Active Ingredient+Binder	500	75	62.5	6.75	4.22
SSG	Disintegrant	32	4.8	4	10.50	0.42
Avicel PH-102	Filler+Water absorbent	260	39	32.5	1.94	0.63
SLS	Lubricant	8	1.2	1	0.71	0.01
Total		800	120	100		5.28
Water required	$(7\% - 5.28\%) \times 120 \text{ g} = 2.094 \text{ mL}$					

*LOD refers to each material loss on drying

**%LOD refers to LOD X %weight, therefore, it will represent total tablet LOD

The water amount required to make a 7% LOD of the tablet is counted by the Eq. $(7\% - 5.28\%) \times 120 \text{ g} = 2.094$

gel F_{254} . After that, the silica gel is eluted in the saturated chamber. Finally, the detection of flavonoid was performed with $AlCl_3$ Reagent.

Results and Discussion

Nowadays, banana peel powder has various uses in traditional medicine and culinary practices because of its rich nutritional profile and bioactive compounds. On the other hand, roasting banana peel powder has been proven to increase some of the peel's content, which acts as an antioxidant [14].

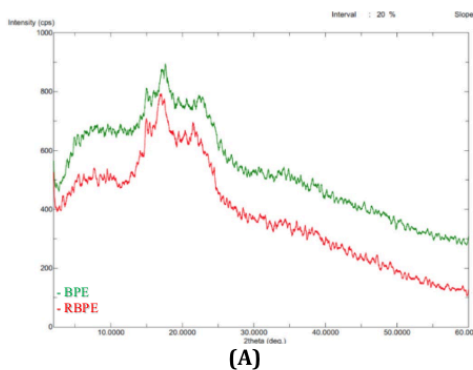
Extract Crystallinity, Size, and Particle Morphology

Roasting banana peel powder increases its solubility by decreasing its crystallinity. The roasting process will affect the particle size, as proven by observations using SEM of

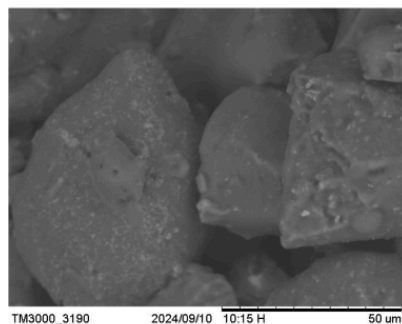
BPE and RBPE. The observation using SEM 1500× magnification showed that the particle size of RBPE is, on average, smaller than the particle size of BPE. This supports the XRD data, which shows that the crystallinity of RBPE is lower than that of BPE. Both results indicate that RBPE tends to have better solubility than BPE (Fig. 1).

RBPE Content Identification

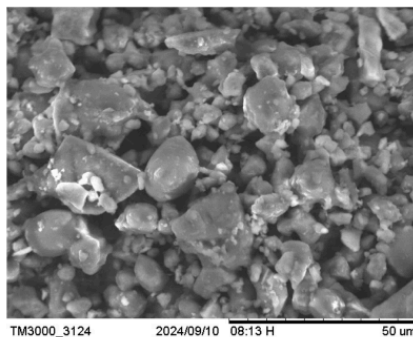
The LC-MS/MS-QTOF was used to identify the flavonoid compounds in RBPE. The result shows that RBPE contains flavonoids with one of the active compounds, i.e., morin which is useful as an antidepressant, both for acute [15] and chronic depression [16–18]. This could be achieved through its ability to regulate endoplasmic reticulum stress [16] and ameliorate oxidative/nitrosative damage in the brain by abolishing stress-induced GSH reduction [17].



(A)



(B1)



(B2)

Fig. 1 A XRD pattern of Agung banana (*Musa paradisiaca*) peel powder; **B1** SEM image of Agung banana peel extract before roasting; and **B2** SEM image of Agung banana peel extract after roasting

Tablet Manufacturing with MADG Method

Tablets should be manufactured using the MADG method in the agglomeration and moisture absorption steps. The pre-experiment shows that RBPE granules containing RBPE and SSG made in this way was very sticky and difficult to sift, so we modified the steps by adding Avicel PH-102 before the agglomeration steps.

Dry Extract Standardization

Dry extract organoleptic checking aims to see simply by using the five senses. The organoleptic test results from RBPE have a powder form, brownish color with a specific taste and odor.

The water content test aims to provide the maximum limit to the amount of water content in the extract and determines the quality of the extract. Extracts with high moisture content could be easily grown by bacteria compared to extracts with low water content. The water content of the dry extract should be less than 10%. The result of the water content test is $6.51 \pm 0.24\%$ and has fulfilled the specification.

Total ash content parameters provide an overview of the internal or external mineral content. The result of total ash content is $16.31 \pm 0.13\%$. This result does not meet the specification ($\leq 10\%$) because of RBPE which contains a lot of mineral contents [4] and the presence of aerosil which contains high silica and silicate [19]. Even if the total ash content does not meet the specification, this parameter does not have a significant impact on the tablet manufacturing process. The result of RBPE standardization can be seen in Table 2.

Table 2 Result of RBPE standardization and specification

Test	Specification	Result
Organoleptic		
Form	Powder	Powder
Color	Brownish	Brownish
Odor	Specific	Specific
Taste	Specific	Specific
Water Content	<10%	$6.51 \pm 0.24\%$
Total Ash Content	<10%	$16.31 \pm 0.13\%$

Table 3 Physical quality test of RBPE granules

Replication	Tablet Manufacturing Method				Specification
	WG	%CV	MADG	%CV	
Moisture content (%)	3.45 ± 0.98	28.38	6.55 ± 0.18	2.75	2–5%
Carr's index (%)	17.32 ± 0.58	3.33	17.66 ± 0.57	3.25	<20%
Hausner ratio	1.21 ± 0.01	0.68	1.22 ± 0.01	0.46	<1.25

^aCV: coefficient of variation

Physical Quality Test of Granules

The moisture content test aims to see the water content of the granules. In general, the specification of moisture content is 2–5%. If the water content is under 2%, the tablet will become more fragile and easily break. Besides, if the water content is too high, it will disturb granule's flowability and make it easy for microorganisms to grow [20, 21]. The resulting test for granules made with the wet granulation method met the specification (2–5%), but the resulting test for granules produced with MADG didn't. No drying process in the MADG method may cause the moisture content of the granule to remain high. Even if the result of moisture content of the MADG method does not meet the specification, granule's flow properties are still good enough to make tablets compressible.

The flowability test aims to see how the granules flow; a bad flow of the granule will cause the distribution of the active ingredient to be ununiform. Flowability of the granules was checked by Carr's index and Hausner ratio [21, 22] using tapped volumeter and tapped for 1250 times. This is sufficient for accurate measurement because, after 500 and 1250 taps, the volume of the granule does not decrease significantly. Carr's index and Hausner ratio result show that all the granules produced with wet granulation or MADG are good enough to be compressed to a tablet. Table 3 shows the result of the physical quality test of granules.

Physical Quality Test of Tablets

Weight variation aims to ensure that the tablet's weight does not deviate too much and maintains the active ingredient to meet the specification. The tablet used in this experiment weighs 800 mg. Indonesian National Food and Drug Agency regulation in 2023 specified the weight variation is no two or more tablets deviated from the average by 5%, and no tablets deviated from the average by 10%.

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. The wet granulation method has a significant value of 0.052 and F_{value} of $3.106 < F_{(0.05)(2.57)} 3.16$; and the MADG method has a significant value of 0.295 and F_{value} of $1.247 < F_{(0.05)(2.57)} 3.16$. The statistical data

analysis (Independent Sample t-Test) between the manufacturing methods has a significant value of 0.037 and t_{value} of $2.111 > t_{(0.05)(118)} 1.984$. This result shows if there is a significant difference in tablet weight produced with the MADG and wet granulation method, with the weight produced with the MADG method being lower but having a lower deviation compared to the wet granulation method.

Hardness test aims to determine whether the tablets have sufficient hardness to withstand mechanical shock during packaging, distribution, and storage. The specification of tablet hardness is 4–8kp. The result of the hardness test is shown in Table 4.

The test results show that all the tablets met the specifications. The results of statistical data analysis (One-Way ANOVA) show no significant differences between batches. The wet granulation method has a significant value of 0.792 and F_{value} of $0.236 < F_{(0.05)(2,27)} 3.35$; and the MADG method has a significant value of 0.645 and F_{value} of $0.466 < F_{(0.05)(2,27)} 3.35$. The statistical data analysis (Independent Sample t-Test) between the manufacturing methods have a significant value of 0.895 and t_{value} of $0.133 > t_{(0.05)(58)} 2.000$. This result shows that there are no significant differences in tablet hardness produced with MADG and wet granulation method, which means the compatibility of tablets produced with the two methods is equal.

Moreover, friability test aims to determine tablets' ability to withstand mechanical shock during packaging and distribution. Based on USP 47 NF 42, the specification for the friability test is $\leq 1\%$. The result of the friability test can be seen in Table 4.

The test results show that all the tablets met the specifications. The results of statistical data analysis (One-Way ANOVA) show no significant differences between batches. The wet granulation method has a significant value of 0.350 and F_{value} of $1.256 < F_{(0.05)(2,6)} 5.14$; and the MADG method has a significant value of 0.110 and F_{value} of $3.257 < F_{(0.05)(2,6)} 5.14$. The statistical data analysis (Independent Sample t-Test) between the manufacturing methods has a significant value of < 0.001 and t_{value} of $8.601 > t_{(0.05)(16)} 2.12$. This result shows a significant difference in tablet friability produced with MADG and wet granulation methods. This is because the granule produced with MADG method has more

moisture content than the granule produced with wet granulation method. The more moisture content could increase the strength of the tablet, making the tablet less fragile [23].

Moreover, tablet disintegration test aims to see the time needed for tablet to disintegrate completely. The specification for RBPE tablet disintegration time is ≤ 30 min [24].

Table 4 shows that all the tablets meet the specifications. The results of statistical data analysis (One-Way ANOVA) show no significant differences between batches. The wet granulation method has a significant value of 0.919 and F_{value} of $0.086 < F_{(0.05)(2,6)} 5.14$; while the MADG method has a significant value of 0.299 and F_{value} of $1.486 < F_{(0.05)(2,6)} 5.14$. The statistical data analysis (Independent Sample t-Test) between the manufacturing methods has a significant value of 0.003 and t_{value} of $3.496 > t_{(0.05)(16)} 2.12$. This result shows a significant difference in tablet disintegration time produced with MADG and wet granulation methods. This is because the granule produced with wet granulation method uses a liquid that forms a liquid bridge and makes a solid bridge after being taken from the oven, whereas MADG method only uses water for the granule manufacture and no drying process make a solid bridge does not occur in this method.

Active Ingredient Stability Test using Thin Layer Chromatography (TLC)

TLC is one of the separation methods using a solid stationary phase and a liquid mobile phase. The mobile phase used in TLC must be stable, and the resulting retention factor (Rf) must be between 0.2–0.8.

The profile determination of roasted Agung banana var. Semeru peel extract aims to determine the active ingredient stability from the beginning (extract) until the end (tablet). The stationary phase used in this experiment is Silica activated in the oven for 15 min, and the mobile phase was benzene: ethyl acetate: formic acid: methanol (60:30:10:5). The stationary phase was made and left for an hour for chamber saturation.

After saturation was done, the test solution (2 μL rutin 1%, each 30 μL RBPE, wet granulation granule, MADG granule, wet granulation tablet, and MADG tablet 6% solution) was spotted into a silica gel 60 F₂₅₄ plate with a

Table 4 Physical quality test of RBPE tablets

Replication	Weigh uniformity (mg)		Tablet Hardness (kp)		Tablet Friability (%)		Tablet disintegration time (Min)	
	WG	MADG	WG	MADG	WG	MADG	WG	MADG
Specification	$\pm 5\%$		4–8		$\leq 1\%$		≤ 30 min	
I	805.9 \pm 4.0	802.7 \pm 6.2	7.2 \pm 0.5	7.2 \pm 0.3	0.2 \pm 0.0	0.2 \pm 0.0	14.2 \pm 0.7	13.7 \pm 0.4
II	802.5 \pm 4.8	800.2 \pm 6.2	7.2 \pm 0.3	7.1 \pm 0.5	0.3 \pm 0.0	0.2 \pm 0.0	14.3 \pm 0.6	13.2 \pm 0.6
III	803.5 \pm 4.4	802.9 \pm 5.8	7.1 \pm 0.4	7.1 \pm 0.3	0.2 \pm 0.0	0.2 \pm 0.0	14.6 \pm 0.4	13.7 \pm 0.2
Mean \pm SD	804.0 \pm 1.7	801.9 \pm 1.5	7.2 \pm 0.1	7.1 \pm 0.1	0.2 \pm 0.0	0.2 \pm 0.0	14.4 \pm 0.2	13.5 \pm 0.3

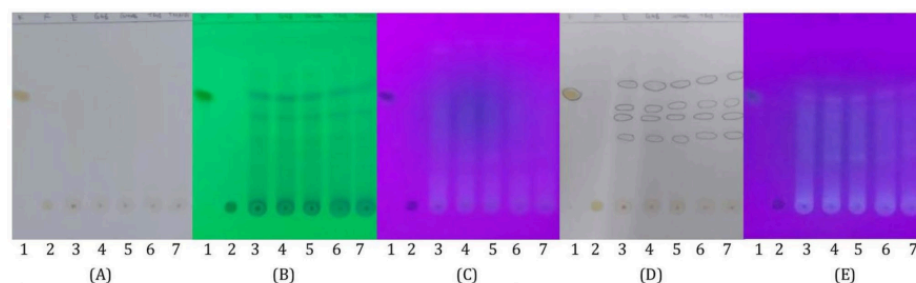


Fig. 2 TLC observation result of extract, granule, tablet stability test by using mobile phase benzene: ethyl acetate: formic acid: methanol (60:30:10:5) with 6% concentration and 30 μ L spotted before and after sprayed by AlCl_3 ; 1: Quercetin; 2: Rutin; 3: Extract; 4: Wet granulation granule; 5: MADG granule; 6: Wet granulation tablet; 7: MADG tablet; A: Visual observation before sprayed by AlCl_3 ; B: UV-254 observation before sprayed by AlCl_3 ; C: UV-366 observation before sprayed by AlCl_3 ; D: Visual observation after sprayed by AlCl_3 ; E: UV-366 observation after sprayed by AlCl_3

distance of 1 cm for each spot. Then, the plate was eluted in the saturated chamber until the upper limit was obtained. This test aims to ensure that the tablet manufacturing process does not remove the active ingredient compound from the extract.

The plate was sprayed with AlCl_3 after elution. Then, TLC plate was dried and observed in a UV366 nm lamp. The TLC result can be seen in Fig. 2.

The results of TLC before being sprayed with AlCl_3 show a node with R_f scores of 0.45; 0.525; 0.625 in UV-254. It shows that there are several active compounds in RBPE. After being sprayed with AlCl_3 , the node with R_f scores of 0.45; 0.5375; 0.575; 0.725 could be seen visually where the first and last nodes look clear, while the middle nodes look vague. Aguiar et al. in 2017 show that the R_f value of morin was 0.75 [25]. The result observation with TLC after being sprayed with AlCl_3 at UV 254 nm visually showed four spots, with one of which having an R_f value of 0.725, which is suspected to be a morin compound. The difference in R_f value can be caused by different test conditions (plat activity, plat thickness and flatness, degree of saturation, and steam in the developer vessel used). The TLC test results show that the wet granulation and MADG manufacturing methods do not affect the stability of RBPE because the intensity and the R_f score made by the node are the same.

Conclusion

In this study, tablets were manufactured using the MADG method and compared with the wet granulation method to evaluate the impact of those manufacturing methods on the physical quality of granules and tablets. The results indicate that the MADG method does not affect Carr's index and

Hausner ratio but affects moisture content when compared to the wet granulation method. Moreover, the MADG method does not affect tablet hardness, instead of affecting tablet weight uniformity, tablet friability, and tablet disintegration time. Finally, the MADG method is more recommended compared to wet granulation for its time efficiency.

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Data Availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Conflict of Interest All authors declare that they do not have a conflict of interest.

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