

Physical Properties and DPPH Radical-Scavenging Activity of Granules Containing Mango Leaf and Noni Fruit Extracts at Different Primojel® Concentrations

Ni Made Dharma Shantini Suena^{1*}, Ni Komang Sinta Yuli Pratiwi², Kd Dwi Payanti Pitaloka², I Gede Made Suradnyana¹, I Gusti Agung Ayu Kusuma Wardani³, Ni Putu Udayana Antari⁴

¹Department of Pharmaceutics, Faculty of Pharmacy, Universitas Mahasaraswati Denpasar, Jl. Kamboja No.11A, Denpasar, 80233, Indonesia

²Bachelor of Pharmacy Study Program, Faculty of Pharmacy, Universitas Mahasaraswati Denpasar, Jl. Kamboja No.11A, Denpasar, 80233, Indonesia

³Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Universitas Mahasaraswati Denpasar, Jl. Kamboja No.11A, Denpasar, 80233, Indonesia

⁴Department of Social Pharmacy, Faculty of Pharmacy, Universitas Mahasaraswati Denpasar, Jl. Kamboja No.11A, Denpasar, 80233, Indonesia

Submitted : 31-07-2026

Revised : 06-08-2026

Accepted : 30-09-2026

Keywords: DPPH radical-scavenging activity, granule, *Mangifera indica*, *Morinda citrifolia*, physical quality.

Correspondence:

Ni Made Dharma Shantini Suena
dharmashantini@unmas.ac.id



License: CC BY-NC-SA 4.0

Copyright ©2026 Authors

Abstract

Background: Oxidative stress contributes to the pathogenesis of degenerative diseases, highlighting the need for antioxidant-based interventions. Mango leaf (*Mangifera indica* L.) and noni fruit (*Morinda citrifolia* L.) extracts are known to possess antioxidant activity. However, their combination in rapidly disintegrating granule formulations remains limitedly explored.

Objective: This study aimed to evaluate the effect of varying Primojel® concentrations as a superdisintegrant on the physical characteristics and antiradical activity of granules containing combined mango leaf and noni fruit extracts.

Methods: Granules were prepared using five Primojel® concentrations, namely 2%, 4%, 6%, 8%, and 10% for F1 to F5, respectively. Physical evaluations included organoleptic properties, pH, particle size distribution, moisture content, flow rate, angle of repose, compressibility index, and dispersion time. DPPH radical-scavenging activity was evaluated and expressed as IC₅₀ values. Statistical analysis was performed only on parameters with replicated data.

Results: Increasing Primojel® concentration shortened granule dispersion time, with F5 showing the fastest dispersion. Based on descriptive comparison, F5 also showed the lowest IC₅₀ value of 61.33 µg/mL. Several physical parameters, including pH, particle size distribution, and flowability, did not fully meet the required specifications. Varying Primojel® concentrations significantly affected dispersion time and pH, while moisture content and compressibility showed significant but non-linear changes among formulations.

Conclusion: Higher Primojel® concentrations shortened dispersion time, while all formulations exhibited measurable DPPH radical-scavenging activity. These findings contribute to the development of herbal granule formulations. However, further formulation optimization, particularly regarding binder type and concentration, is required to obtain granules with acceptable physical quality for pharmaceutical development.

How to Cite: (citation style AMA 11th Ed.)

Suena NMDS, Pratiwi NKS, Pitaloka KDP, Suradnyana IGM, Wardani IGA, Antari NPU. Physical Properties and DPPH Radical-Scavenging Activity of Granules Containing Mango Leaf and Noni Fruit Extracts at Different Primojel® Concentrations. *J. Ilm. Medicam.*, 2026;12(2): 248-265. doi: [10.36733/medicamento.v12i2.14764](https://doi.org/10.36733/medicamento.v12i2.14764)

INTRODUCTION

As a developing country, Indonesia faces significant challenges in addressing health issues, particularly the increasing prevalence of degenerative diseases. According to the 2018 National Basic Health Research Report (Riskesmas),¹ the prevalence of non-communicable diseases has shown a substantial upward trend, including hypertension (34.1%), followed by stroke, diabetes mellitus, chronic kidney disease (3.8%–10.9%), and cancer (1.8%). Oxidative stress occurs because of excessive production of reactive oxygen species (ROS), leading to oxidative damage, signaling dysfunction, and cellular apoptosis. This imbalance plays a crucial role in the pathophysiology of chronic inflammatory diseases, including cardiovascular diseases, diabetes, cancer, and neurodegenerative disorders.^{2,3} Free radicals, particularly ROS, contribute to oxidative stress that damages cellular components such as DNA, proteins, and lipids.⁴

Cellular damage caused by free radicals can be prevented by antioxidants, which function by scavenging and neutralizing these reactive species. Antioxidants exert their activity by donating hydrogen atoms to reduce the reactivity of free radicals.⁵ Natural antioxidants can be found in various plants, including mango leaves (*Mangifera indica* L.) and noni fruits (*Morinda citrifolia* L.), which are rich in bioactive compounds such as flavonoids, polyphenols, alkaloids, and saponins.^{6,7} Furthermore, in vitro studies have demonstrated very strong antioxidant activity of mango leaf extract, with IC₅₀ values ranging from 25.91 to 37.16 ppm using the DPPH method.⁸ Consistent with these findings, an in vivo study demonstrated the effectiveness of mango leaf extract at a dose of 200 mg/20 g body weight of mice, equivalent to 1,552 mg/70 kg human body weight in humans, in reducing malondialdehyde (MDA) levels.⁹ Similarly, noni fruit exhibited an IC₅₀ value of 22.95 ppm in in vitro assays and demonstrated in vivo effectiveness at a dose equivalent to 1,165 mg/70 kg human body weight.^{10,11} Mango leaf extract is rich in flavonoids and phenolic compounds with well-documented antioxidant properties, while noni fruit extract contains iridoids, flavonoids, and other phytochemicals that also demonstrate substantial antioxidant activity. Therefore, combining these extracts may provide complementary antioxidant constituents that enhance the overall antioxidant potential of the formulation.

The combination of plant extracts with different phytochemicals may provide complementary antioxidant effects through multiple radical-scavenging and oxidative stress-related mechanisms.^{12–14} However, development of a proper pharmaceutical dosage form is needed to obtain acceptable physical characteristics and to allow administration of combined herbal extracts. Among various solid dosage forms, granules are widely used in herbal formulations because they can accommodate relatively high extract loads while providing better flowability, reduced segregation, and improved handling compared with powders.^{15,16} Granulation converts fine powders into larger agglomerates with improved flowability, reduced segregation tendency, and better handling characteristics, which may contribute to improved content uniformity and manufacturing performance.¹⁷ For granules intended for direct administration or dispersion before administration, their ability to rapidly interact with the dispersion medium is also an important formulation consideration.^{18,19} The dispersion behavior of granules is influenced by the type and concentration of excipients used during formulation. Primojel® (sodium starch glycolate), a superdisintegrant with high swelling capacity and rapid water uptake, which can promote the breakup and dispersion of granules upon contact with water.^{20–22} Consequently, variation in Primojel® concentration may influence both the physical characteristics of the granules and the availability of extract constituents during dispersion. However, increasing the Primojel® concentration may not necessarily produce a proportional improvement in granule performance. Therefore, the concentration that provides the most favorable balance among physical quality, dispersion behavior, and measurable DPPH radical-scavenging activity remains to be established within the evaluated range.

In the present study, the total extract loading was fixed at 13% w/w, consisting of 7.5% w/w mango leaf extract (MLE) and 5.5% w/w noni fruit extract (NFE). This extract composition was maintained as a fixed preliminary formulation parameter and was not subjected to formal ratio optimization or synergism testing. In contrast, the concentration of Primojel varied at 2%, 4%, 6%, 8%, and 10% w/w to investigate its effect on the resulting granule characteristics and DPPH radical-scavenging activity. This concentration range was selected to examine whether increasing Primojel® levels could produce differences in granule quality and dispersion-related performance while maintaining the DPPH radical-scavenging activity of the combined extracts.

Limited information is available on the physical characteristics and DPPH radical-scavenging activity of granules containing combined mango leaf and noni fruit extracts formulated with different Primojel® concentrations. Therefore, this exploratory study characterized the physical properties and DPPH radical-scavenging activity of five formulations containing different Primojel® concentrations and compared the antioxidant activity of the individual extracts before their incorporation into the granules.

METHODS

Research Design

This study employed a laboratory-based experimental design with a formulation development approach. The study aimed to develop granules containing a combination of mango leaf extract (MLE) and noni fruit extract (NFE) using different concentrations of Primojel® and to identify the formulation with the most favorable physical characteristics. The antiradical activity of the resulting granules was subsequently evaluated.

Five granule formulations containing varying concentrations of Primojel® as a disintegrant, namely 2%, 4%, 6%, 8%, and 10% (F1–F5), were prepared. Each formulation was prepared as a single batch. All formulations were evaluated

for organoleptic properties, pH, fines content, moisture content, compressibility index, dispersion time, flow rate, and angle of repose. These physical-characteristic measurements were performed in triplicate using samples from the same batch of each formulation. Furthermore, the antiradical activity of all formulations was determined using the DPPH method.

Instruments

The equipment used in this study included a digital balance (Acis BC-6000®), an analytical balance (Ohaus Pioneer PA224C), and standard laboratory glassware.

The instruments employed were a double-beam UV–Visible spectrophotometer (Shimadzu UV-1800®, Japan), an oven (MEMMERT GmbH + Co. KG, Germany), an ultrasonic bath (Elmasonic®, Elma Schmidbauer GmbH, Germany), a rotary evaporator (BUCHI R-300, Switzerland), a granulator (Erweka AR403, Germany), standard test sieves (CV. Total Equipment Pharmacy, Indonesia), a stopwatch, a moisture analyzer (OHAUS MB90, Ohaus Corporation, USA), a flow tester (CV. Mitra Medika Utama Solo, Indonesia), and a tap-density tester (LYCB220S, Linix). Sieves with mesh numbers 16 and 20 were used during granule production, whereas sieves with mesh numbers 30, 40, 50, 60, 80, and 100 were used to determine the particle-size distribution of the five granule formulations.

Materials

The plant materials used in this study were mango leaves (*Mangifera indica* L. var. Arum Manis) and noni fruits (*Morinda citrifolia* L.). The mango leaves were collected from Denpasar, Bali, Indonesia, in January 2024, whereas the noni fruits were collected from Tabanan Regency, Bali, Indonesia, during the same month. Both plant materials were obtained from locally grown, non-cultivated plants. Mature mango leaves were selected based on their uniformly dark-green color, firm and rigid texture, smooth surface, and clearly visible veins protruding from the abaxial surface. Mature noni fruits were identified by their yellowish white to translucent-white peel, soft texture, and characteristic strong fermented aroma. Only plant materials without visible signs of disease, insect damage, or physical deterioration were collected. The materials were harvested manually, placed separately in ventilated plastic containers, protected from direct sunlight, and transported to the Faculty of Pharmacy, Universitas Mahasaraswati Denpasar, for processing. Their botanical identities were confirmed by the Unit Laboratorium MIPA, IAIN Syekh Nurjati Cirebon, Indonesia, under identification document numbers 24/In.08/LB.1.1/PP.009/2/2024 for *M. indica* L. var. Arum Manis and 75/In.08/LB.1.1/PP.009/6/2024 for *M. citrifolia* L.

The formulation excipients, including aspartame (Gsweet Aspartame), microcrystalline cellulose (Avicel® PH 101, MCC NF/Ph. Eur./JPN), sodium starch glycolate (Primojel®, Gujarat Overseas Inc., India), and maltodextrin (Qinhuangdao Lihua Starch Co., Ltd., China), were of pharmaceutical grade. Food-grade orange essence (Cap Kapal Layar) was used as the flavoring agent. The solvents used were analytical-grade 96% ethanol and methanol, and pharmaceutical-grade 70% ethanol (PT Bratachem, Indonesia). The analytical reagents included sodium hydroxide (NaOH; Merck), concentrated hydrochloric acid (HCl; Sekawan Bali Sejahtera, Indonesia), magnesium (Merck), ferric chloride (FeCl₃; Merck), Folin–Ciocalteu reagent (Nitro Kimia), Dragendorff's reagent (CV Faeyza Improchem Lakarya), chloroform (Merck), gallic acid (Sigma), quercetin (Sigma), aluminum chloride, sodium acetate trihydrate (PT Smart Lab Indonesia), Liebermann–Burchard reagent (Sigma), ascorbic acid (Sigma), and 2,2-diphenyl-1-picrylhydrazyl (DPPH; PT Smart Lab Indonesia). All materials were used as received.

Research Procedure

Preparation of the Simplicia

Fresh mango leaves (*Mangifera indica* L.) and noni fruits (*Morinda citrifolia* L.) were washed under running water to remove impurities. The noni fruits were cut into small pieces prior to drying.⁷ Both plant materials were dried in an oven at 55°C for 48 h, ground into powder, and passed through a 30-mesh sieve. The resulting simplicia powders were stored in a dry place protected from direct sunlight until extraction.⁶

Preparation of Extracts

Mango leaf and noni fruit extracts were prepared using ultrasound-assisted maceration with 96% ethanol in an Elmasonic® ultrasonic bath (Elma Schmidbauer GmbH, Germany). Mango leaf powder (600 g) was extracted at a simplicia-to-solvent ratio of 1:10 (w/v) using 6 L of ethanol, whereas noni fruit powder (500 g) was extracted at a ratio

of 1:3 (w/v) using 1.5 L of ethanol. Each material was divided into three equal portions and extracted simultaneously in separate 2-L Beakers.

Ultrasonic extraction was performed at a frequency of 20 kHz. Each extraction cycle consisted of 5 min of sonication followed by manual stirring for 1-3 min, and the procedure was repeated for three cycles. The extracts were filtered through a Büchner funnel, and the residues were re-extracted twice under the same conditions. The combined filtrates were concentrated under reduced pressure using a rotary evaporator at 50°C to obtain viscous mango leaf extract (MLE) and noni fruit extract (NFE).²³ The extraction yield was calculated using formula (1).

$$\text{Yield (\%)} = \frac{\text{weight of extract obtained}}{\text{weight of simplicia extracted}} \times 100 \dots\dots\dots (1)$$

Determination of Total Phenolic Content

Total phenolic content was determined using the Folin-Ciocalteu method. A 400 µg/mL gallic acid stock solution was prepared by dissolving 10 mg of gallic acid in methanol and adjusting the volume to 25 mL. Working standards of 5, 15, 30, 50, 70, and 100 µg/mL were prepared by transferring 0.312, 0.938, 1.875, 3.125, 4.375, and 6.250 mL of the stock solution, respectively, into separate 25-mL volumetric flasks and diluting to volume with 96% ethanol.

The Folin-Ciocalteu reagent was diluted with distilled water at a ratio of 1:20, and a 1% sodium hydroxide solution was prepared in distilled water. For construction of the calibration curve, 1 mL of each gallic acid working standard was mixed with 5 mL of diluted Folin-Ciocalteu reagent and incubated at room temperature for 8 min. Subsequently, 4 mL of 1% sodium hydroxide solution was added, and the mixture was shaken and incubated at room temperature for 1 h. Absorbance was measured using a UV-Visible spectrophotometer at approximately 730 nm. The gallic acid calibration curve was generated by plotting absorbance against concentration.

For preparation of the mango leaf extract test solution, 0.2 g of the ethanolic extract was mixed with 25 mL of methanol, magnetically stirred for 30 min, filtered into a 25-mL volumetric flask, and adjusted to volume with methanol. A 1-mL aliquot of this solution was further diluted to 25 mL with methanol. The noni fruit extract test solution was prepared similarly using 0.2 g of extract, followed by further dilution of a 5-mL aliquot to 25 mL with methanol.

A 1-mL aliquot of each individual test solution was treated under the same conditions used for the gallic acid standards. Absorbance was measured at approximately 730 nm, and total phenolic content was calculated from the gallic acid calibration equation and expressed as milligrams of gallic acid equivalents per gram of extract (mg GAE/g extract).

Determination of Total Flavonoid Content

Total flavonoid content was determined using the aluminum chloride colorimetric method. A 400 µg/mL quercetin stock solution was prepared by dissolving 10 mg of quercetin in 96% ethanol and adjusting the volume to 25 mL. Working standards of 5, 15, 30, 50, 70, and 100 µg/mL were prepared by transferring 0.312, 0.938, 1.875, 3.125, 4.375, and 6.250 mL of the stock solution, respectively, into separate 25-mL volumetric flasks and diluting to volume with 96% ethanol.

A 10% w/v aluminum chloride solution was prepared by dissolving 1 g of aluminum chloride in 10 mL of distilled water. A 1 M sodium acetate solution was prepared by dissolving 8.2 g of sodium acetate trihydrate in distilled water and adjusting the volume to 100 mL. To construct the calibration curve, 0.5 mL of each quercetin working standard was mixed with 1.5 mL of 96% ethanol, 0.1 mL of 10% aluminum chloride, 0.1 mL of 1 M sodium acetate, and 2.8 mL of distilled water. The mixture was shaken and incubated at room temperature for 30 min. Absorbance was measured using a UV-visible spectrophotometer at approximately 415 nm, and the calibration curve was generated by plotting absorbance against quercetin concentration.

For preparation of the mango leaf extract test solution, 0.2 g of the ethanolic extract was mixed with 25 mL of 96% ethanol, magnetically stirred for 30 min, filtered into a 25-mL volumetric flask, and adjusted to volume with 96% ethanol. A 5-mL aliquot of this solution was further diluted to 25 mL with 96% ethanol. The noni fruit extract test solution was prepared by mixing 0.5 g of the ethanolic extract with 25 mL of 96% ethanol, stirring for 30 min, filtering, and adjusting the filtrate to 25 mL with the same solvent.

A 0.5-mL aliquot of each individual or combined extract test solution was treated under the same conditions used for the quercetin standards. Absorbance was measured at approximately 415 nm, and total flavonoid content was calculated from the quercetin calibration equation and expressed as milligrams of quercetin equivalents per gram of extract (mg QE/g extract).

Preparation of MLE-NFE Combination Granules

The granules contained 7.5% w/w mango leaf extract (MLE) and 5.5% w/w noni fruit extract (NFE), corresponding to a total extract loading of 13% w/w and an MLE:NFE ratio of 15:11 w/w. The extract loading and ratio were maintained constant across F1–F5, whereas the Primojel® concentration was varied from 2% to 10%.

Granules were prepared using the wet granulation method, using the ingredients as mentioned in **Table 1**. Wet granulation was selected because the concentrated extracts were cohesive and sticky, making direct conversion into free-flowing granules difficult. The granulating liquid promoted wetting and agglomeration of the extracts with the excipients, followed by drying and sizing to produce more manageable particles. Wet granulation is widely used to improve the flowability, particle-size characteristics, and handling of pharmaceutical powders and has been successfully applied to granules containing ethanolic botanical extracts.²⁴

Table 1. Formulations of Granules Containing Mango Leaf Extract and Noni Fruit Extract

Ingredients	Concentrations (%w/w)					Function
	F1	F2	F3	F4	F5	
Mango Leaf Extract (MLE)	7.5	7.5	7.5	7.5	7.5	Active ingredient
Noni Fruit Extract (NFE)	5.5	5.5	5.5	5.5	5.5	Active ingredient
Aspartame	1.5	1.5	1.5	1.5	1.5	Sweetener
Maltodextrin	5	5	5	5	5	Binder
Primojel®	2	4	6	8	10	Super disintegrant
Orange essences	0.1	0.1	0.1	0.1	0.1	Flavoring agent
Avicel 101	78.4	76.4	74.4	72.4	70.4	Diluent
Ethanol 70%	q.s.	q.s.	q.s.	q.s.	q.s.	Granulating fluid

Notes: q.s. = *quantum satis* (quantity sufficient). Ethanol 70% was used as the granulating fluid in an amount sufficient to achieve granulation, and evaporated during drying; it is not included in the final dry formulation percentage.

The extracts were triturated in a mortar and mixed with 10 mL of ethanol until homogeneous. Avicel® PH 101 was added and mixed thoroughly. Subsequently, maltodextrin, Primojel®, orange essence, and aspartame were incorporated and blended uniformly. After incorporation of the excipients, additional 70% ethanol was added gradually as needed to achieve the wet-massing endpoint, which was assessed using an empirical hand-squeeze test, also known as the banana-breaking test. A small portion of the wet mass was compressed manually to form a cohesive lump and then broken by applying moderate thumb pressure. The wet mass was considered suitable when it retained its shape after compression but broke cleanly without crumbling into dry powder or exhibiting excessive stickiness or plastic deformation. A friable mass that disintegrated immediately indicated insufficient wetting, whereas a sticky or excessively cohesive mass that was difficult to break indicated overwetting.²⁵ The wet mass was passed through a 16-mesh sieve to produce wet granules. The granules were spread evenly on aluminum foil-lined trays and dried in an oven at 50°C for approximately 90 min. After drying, the granules were passed through a 20-mesh sieve to obtain uniform granules. The dried granules were weighed and subjected to physical quality evaluation.^{23,26}

Evaluation of Physical Properties

The physical properties of the granules were evaluated using pharmacopeial procedures where applicable and literature-based formulation-development criteria for attributes without established compendial limits. The granules were visually and organoleptically evaluated for color, odor, taste, and physical appearance.²⁷ For pH determination, 10 g of granules were dispersed in 200 mL of distilled water, and the pH was measured using a calibrated pH meter. A pH range of 6–7 was used as a literature-based formulation target for the aqueous granule dispersion.²⁸ Particle size distribution was determined by analytical sieving according to the general principles of USP General Chapter <786>, Particle Size Distribution Estimation by Analytical Sieving.²⁹ A 100-g sample of granules was placed on a nest of sieves arranged in descending (mesh 30, 40, 50, 60, 80, and 100) aperture size and mechanically shaken for 5 min. The material retained on each sieve was weighed and expressed as a percentage of the total sample mass. Particles passing through the (mesh 100 sieve) were classified as fines. A fines content below 10% was used as a predefined formulation-development target.²⁹ Moisture content was determined using a moisture analyzer. Approximately 3 g of granules were analyzed at 105°C. A moisture content of 1%–5% was used as a literature-based formulation target.³⁰ The untapped bulk volume was determined by transferring a 30-g granule sample into a 100-mL graduated cylinder. The cylinder was subsequently subjected to 500 taps using a tapped-density tester, after which the tapped volume was recorded.²⁶ The compressibility index was calculated using Equation (2):

$$\text{Compressibility index (\%)} = \frac{V_0 - V_f}{V_0} \times 100\% \quad (2)$$

where V_0 is the untapped bulk volume and V_f is the tapped volume. The compressibility index was interpreted as an indicator of granule flowability using the classification described in USP General Chapter (1174), Powder Flow.³¹

Dispersion time was determined by adding 10 g of granules in 200 mL of water and stirring at 50 rpm. The time required for the granules to disperse completely, with no visually detectable agglomerates, was recorded using a stopwatch. A dispersion time of ≤ 5 min was used as a predefined, literature-supported formulation-development target.³² Flowability was additionally evaluated using flow rate and angle-of-repose tests. A 100-g sample of granules was placed in a funnel with the outlet initially closed. After the outlet was opened, the time required for the complete discharge of the sample was recorded, and the flow rate was calculated as the sample mass divided by the discharge time.²⁶ The angle of repose was determined from the height and radius of the resulting granule pile using Equation (3):

$$\alpha = \tan^{-1} \left(\frac{h}{r} \right) \quad (3)$$

where α is the angle of repose ($^\circ$), h is the height of the granule pile, and r is the radius of the granule pile.

Determination of Antiradical Activity

The DPPH radical-scavenging activities of the ethanolic mango leaf extract, ethanolic noni fruit extract, and granule formulations were determined using a UV–visible spectrophotometric method. All solutions were prepared using 96% ethanol and protected from direct light during analysis.

For analysis of the individual extracts, separate stock solutions were prepared by dissolving 25 mg of each ethanolic extract in 96% ethanol and adjusting the volume to 25 mL to obtain a concentration of 1,000 $\mu\text{g/mL}$. Working solutions at concentrations of 5, 10, 15, 20, and 25 $\mu\text{g/mL}$ were prepared by transferring 0.125, 0.250, 0.375, 0.500, and 0.625 mL of the respective stock solutions into separate 25-mL volumetric flasks and diluting to volume with 96% ethanol.

For analysis of the granule formulations, a stock dispersion equivalent to 1,923 $\mu\text{g/mL}$ of granules was prepared by dispersing 192.3 mg of each granule formulation in 96% ethanol and adjusting the volume to 100 mL. The dispersion was filtered through medium-speed qualitative filter paper (Whatman No. 1) to remove insoluble excipients, including microcrystalline cellulose and sodium starch glycolate, and the clear filtrate was used for analysis. Working solutions equivalent to granule concentrations of 25, 50, 75, 100, 125, and 150 $\mu\text{g/mL}$ were prepared by diluting the filtrate with 96% ethanol.

For the individual-extract assays, a 100- $\mu\text{g/mL}$ DPPH stock solution was prepared by dissolving 10 mg of DPPH in 96% ethanol and adjusting the volume to 100 mL. A 50- $\mu\text{g/mL}$ DPPH working solution was prepared by transferring 5 mL of the stock solution into a 10-mL volumetric flask and diluting to volume with 96% ethanol. For the granule assays, a 500- $\mu\text{g/mL}$ DPPH stock solution was prepared by dissolving 25 mg of DPPH in 96% ethanol and adjusting the volume to 50 mL. A 40- $\mu\text{g/mL}$ working solution was subsequently prepared by transferring 2 mL of the stock solution into a 25-mL volumetric flask and diluting to volume with 96% ethanol.

The maximum absorption wavelength was determined by scanning the DPPH working solution over 400–800 nm using 96% ethanol as the instrument blank. The reaction stabilization period was determined by mixing 4 mL of a selected sample solution with 4 mL of the corresponding DPPH working solution and measuring the absorbance at the maximum wavelength at 1-min intervals for 120 min. The period during which the absorbance remained relatively stable was used as the incubation time for subsequent measurements.

For the antiradical assay, 4 mL of each extract or granule sample solution was mixed with 4 mL of the corresponding DPPH working solution, homogenized, and incubated in the dark at room temperature for the predetermined stabilization period. Absorbance was subsequently measured at the maximum absorption wavelength. A control containing 4 mL of the corresponding DPPH working solution and 4 mL of 96% ethanol was prepared and treated under identical conditions.

The percentage of DPPH radical inhibition was calculated using Equation (4):

$$\text{Inhibition percentage (\%)} = \frac{\text{control absorbance} - \text{sample absorbance}}{\text{control absorbance}} \times 100\% \quad (4)$$

A concentration-response curve was constructed by plotting sample concentration (x) against percentage DPPH inhibition (y). The IC_{50} value, defined as the sample concentration required to inhibit 50% of the DPPH radicals, was calculated from the linear regression equation $y = bx + a$ as $\text{IC}_{50} = (50 - a)/b$.³³

Data Analysis

Data obtained from physical quality testing and antiradical activity assays were presented descriptively as tables and figures. Statistical analysis was performed using Microsoft Excel 2019 and IBM SPSS Statistics version 26.0 at a 95% confidence level ($\alpha = 0.05$).

Data normality was assessed using the Shapiro-Wilk test, followed by Levene's test for homogeneity of variance. Data that met the assumptions of normality and homogeneity were analyzed using one-way analysis of variance (ANOVA), followed by Tukey's post hoc test when significant differences were observed ($p < 0.05$). Data that were not normally distributed were analyzed using the Kruskal-Wallis test. When significant differences were detected, pairwise comparisons were performed using the Mann-Whitney U test.

Antiradical activity was expressed as the IC_{50} value, defined as the concentration required to inhibit 50% of DPPH free radicals. IC_{50} values were calculated from the linear regression equation obtained by plotting sample concentration against percentage inhibition.

RESULT AND DISCUSSION

Plant Identification and Extraction

The identification of mango and noni plants was conducted at the MIPA Laboratory, IAIN Syekh Nurjati Cirebon. The results of the identification showed that the sample was the arum manis variety of mango (*Mangifera indica* L. var. arum manis), which belongs to the kingdom Plantae, class Magnoliopsida, order Sapindales, family Anacardiaceae, and genus *Mangifera*. The noni fruit used in the study also yielded similar results, confirming that the plant is indeed the species *Morinda citrifolia*, classified under the kingdom Plantae, class Magnoliopsida, order Rubiales, family Rubiaceae, and genus *Morinda*. Plant identification was performed to verify the authenticity of the plant's identity, thereby ensuring that the extracts used in the study originated from the correct species.^{34,35}

Extraction was performed using the ultrasonic-assisted maceration method to increase yield, reduce extraction time, and minimize solvent use, an ultrasonic-assisted maceration method was employed.^{36,37} The extraction process yielded 152.5 g of concentrated mango leaf extract (MLE) corresponding to a yield of 25.42%, and 122.8 g of concentrated noni fruit extract (NFE) corresponding to a yield of 24.56%. The NFE yield met the requirements of the Herbal Pharmacopoeia, 2nd Edition,³⁸ which states that the yield of noni fruit ethanolic extract should be not less than 10.1%. The MLE yield was higher than that reported by Usman et al.,³⁹ who obtained a mango leaf ethanolic extract yield of more than 12 g per 100 g of starting material, equivalent to approximately 12%. These findings indicate that the extraction procedure used in the present study provided comparatively high extract yields.

The ethanolic mango leaf extract showed a total phenolic content of 31.59 ± 2.84 mg GAE/g extract and a total flavonoid content of 7.16 ± 0.16 mg QE/g extract. In comparison, the ethanolic noni fruit extract had a total phenolic content of 3.72 ± 0.31 mg GAE/g extract and a total flavonoid content of 0.29 ± 0.07 mg QE/g extract. Thus, the total phenolic and flavonoid contents of the mango leaf extract were approximately 8.5-fold and 25.0-fold higher, respectively, than those of the noni fruit extract.

Both extracts exhibited DPPH radical-scavenging activity. The mango leaf extract had an IC_{50} value of 6.42 μ g/mL and an antioxidant activity index of 3.895, whereas the noni fruit extract had an IC_{50} value of 7.57 μ g/mL and an antioxidant activity index of 3.304. The lower IC_{50} and higher AAI of the mango leaf extract indicated slightly greater DPPH radical-scavenging activity than that of the noni fruit extract under the assay conditions.

Formulation and Evaluation of Granule Physical Properties

MLE and NFE combination granules were prepared using the wet granulation method. This method was chosen because it offers technical ease in handling moist or sticky extracts and ensures better flow properties, compressibility, and uniformity.^{17,40,41} The total extract loading and MLE:NFE ratio were maintained as fixed formulation factors throughout the study. The selected composition was not established through systematic optimization of different extract loads or MLE:NFE ratios. Therefore, the present findings do not demonstrate that 13% w/w is the optimum total extract loading or that the 15:11 w/w ratio provides the greatest phytochemical content or antiradical activity. Rather, the results describe the effects of varying Primojel® concentrations within granules containing this specific fixed extract composition. Further studies using mixture-design or response-surface methodology are required to optimize the relative proportions of MLE and NFE. The MLE and NFE combination granules were prepared in five formulations with varying concentrations of Primojel®: F1 (2%), F2 (4%), F3 (6%), F4 (8%), and F5 (10%). Primojel® (sodium starch glycolate)

was selected as the disintegrant due to its ability to absorb water more than 20 times its weight, resulting in strong swelling that accelerates granule dispersion. Furthermore, Primojel® remains effective after the wet granulation process and can be used both intragranularly and extragranularly, thereby increasing the dispersion rate and dissolution rate.^{22,42-45}



Figure 1. Visual Appearance of Granules Combining Mango Leaf Extract (MLE) and Noni Fruit Extract (NFE) with Primojel® Concentration Variation

The results of the organoleptic test on the MLE and NFE combination granule formulation (**Figure 1**) showed a brownish-cream color influenced by the colors of the two extracts, a small granular form, and a faint lemon aroma. The particle size of the granules in all five formulations was relatively small. This condition is likely related to the use of maltodextrin as the sole binder at a 5% concentration, which is thought to be suboptimal for forming bonds between powder particles. Other factors that may have contributed include the limited amount of granulation liquid and the use of a fine sieve (20 mesh). The lemon aroma masks the aromas of both extracts; however, the aroma intensity in all formulations is relatively weak, likely due to the low concentration of the essence (0.1%). The small granule size has the potential to affect flow properties and dissolution time. Small granules tend to have poorer flow properties due to increased interparticle friction but can accelerate dissolution because of their larger surface area.^{17,46}

The formulation of combination granules containing MLE and NFE using varying concentrations of Primojel® (2% to 10%) showed a clear impact on the physical properties of the product (**Table 2**). The non-parametric Kruskal-Wallis test confirmed that changing the Primojel® levels led to significant differences in pH value ($p = 0.009$), moisture content ($p = 0.014$), and compressibility index ($p = 0.010$) across the five formulas. Since there were statistically significant differences across all groups ($p < 0.05$), the analysis was continued with a paired comparison using the Mann-Whitney U test to identify significant differences between formulations.

Table 2. Results of Physical Quality and DPPH Radical-Scavenging Activity Tests (IC_{50}) of MLE-NFE Combination Granules with Variations in Primojel®

Characteristics	MLE-NFE Granules with Primojel® Varying Concentration					Acceptance criterion
	F1	F2	F3	F4	F5	
pH value	4.43±0.021 ^a	4.62±0.015 ^b	4.72±0.006 ^c	4.77±0.017 ^d	4.85±0.015 ^e	6-7 ²⁸
Fines percentage (%)	77.7	87.9	77.68	74.1	73.8	≤10% ²⁹
Moisture content (%) [*]	4.86±0.058 ^a	4.80±0.056 ^a	4.56±0.145 ^b	3.96±0.416 ^c	4.67±0.067 ^b	1-5% ³⁰
Compressibility index (%)	22.276±0.694 ^a	21.020±0.633 ^b	26.335±0.183 ^c	17.157±0.849 ^d	19.907±0.802 ^b	11-15%: Good ^{17,31}
Dispersion time (second) [*]	50±1.00 ^a	46±1.00 ^{ab}	43.33±1.53 ^{bc}	40.67±2.08 ^{cd}	37.67±2.52 ^d	≤5 minutes ³²
IC_{50} value (µg/ml) [*]	65.48	74.31	77.01	72.96	61.33	50-100 µg/mL: strong ⁴⁷

Notes:

F1, F2, F3, F4, F5: Granule formulations combining MLE and NFE with Primojel® levels of 2%, 4%, 6%, 8%, and 10%, respectively. Values are presented as Mean ± SD ($n = 3$) for pH value, moisture content, compressibility index, and dispersion time. Values within the same row sharing different superscript letters (a, b, c, d, e) indicate statistically significant differences ($p \leq 0.05$) based on the Tukey HSD test for dispersion time, and the Mann-Whitney U test for pH, moisture content, and compressibility index. An asterisk (*) indicates that the formulation met the corresponding acceptance criterion or formulation-development target.

Measuring the pH of granule formulations is important because acidity levels can affect drug stability, solubility, and gastrointestinal tolerability. Extreme pH conditions can accelerate degradation through hydrolysis and oxidation

while increasing the risk of gastric discomfort.^{48,49} In this study, an increase in Primojel® concentration resulted in a slight upward shift in granule pH, rising from 4.43 ± 0.021 in F1 (2% Primojel®) to 4.85 ± 0.015 in F5 (10% Primojel®) (**Figure 2**). The results of the normality test showed that the pH data were not normally distributed. Nonparametric analysis using the Kruskal–Wallis test revealed significant variation among the formulations ($p = 0.009$). A subsequent Mann–Whitney post-hoc test confirmed that the pH values of all formulations differed significantly from one another ($p \leq 0.050$).

The acidic pH likely reflects the combined contribution of organic acids, phenolic constituents, and other ionizable compounds present in the botanical extracts.^{50–53} The slight increase in pH observed from F1 to F5 is likely related to the increase in the mass fraction of the superdisintegrant. Sodium glycolate starch generally exhibits a pH close to neutral (5.5–7.5) in aqueous dispersions.⁴² The slight increase in pH with increasing Primojel® concentration may reflect dilution of the acidic extract fraction by an excipient with a comparatively higher dispersion pH. However, this mechanism was not directly investigated. A pH range of 6.0–7.0 was used as a literature-based development target for the aqueous granule dispersion.²⁸ All formulations were below this target. However, product-specific stability, palatability, and tolerability studies would be required to determine the practical significance of the observed acidic pH.

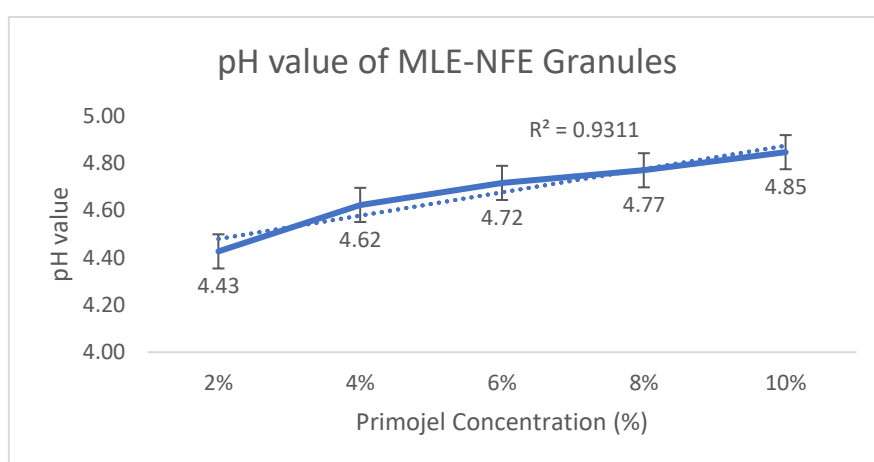


Figure 2. Linear regression analysis shows the effect of Primojel® concentration on the mean pH of granule formulations ($R^2 = 0.9311$).

Particle size distribution was evaluated using a conventional sieve analysis with six graduated sieves (mesh 30, 40, 50, 60, 80, and 100) to determine the proportion of fine particles (fines) and assess granule size uniformity.^{54,55} All formulations were dominated by fine particles, with fines percentages ranging from 73.8% to 87.9% (**Table 2**), considerably exceeding the recommended limit of $\leq 10\%$ for pharmaceutical granules.²⁹ With this particle-size profile, the resulting dosage form technically resembled a coarse powder rather than well-formed granules. This finding indicates inadequate particle agglomeration during wet granulation and suggests that sufficient liquid bridges did not form between the particles to support granule nucleation and growth. The limited granule formation may have resulted from the combined effects of the binder concentration, the amount and distribution of granulating fluid, and the manual mixing process, which may have produced insufficient or nonuniform interparticle bonding.^{54,56} The predominance of fines may also adversely affect flowability and compressibility, consistent with the subsequent physical-quality results.

Moisture content testing was conducted to evaluate the moisture level of the granules, a critical parameter affecting the physical stability and quality of pharmaceutical preparations. The moisture content of the five formulations ranged from 3.96% to 4.86% (**Table 2**), indicating that all formulations were within the recommended limit for pharmaceutical granules ($\leq 5\%$).^{57,58} However, the values approached the upper limit, suggesting that the drying process may require further optimization. The relatively high moisture content may be attributed to insufficient drying conditions, in which the heat transferred to the granules was inadequate to completely remove residual water. Similar findings have been reported by Hadi et al.,⁵⁹ who demonstrated that higher drying temperatures and longer drying times facilitate more effective moisture removal. Excess moisture can promote liquid-bridge formation and interparticle aggregation, thereby reduce flowability and increasing the risk of agglomeration during storage. Consequently, elevated moisture levels may adversely affect downstream manufacturing processes and dosage uniformity.^{60–62}

Statistical analysis indicated differences in moisture content among the formulations. Post hoc Mann-Whitney analysis showed that F1 (2% Primojel®) differed significantly from F3-F5 ($p < 0.05$), whereas no significant differences were observed among F3-F5, containing 6-10% Primojel®. F4 had the lowest mean moisture content at $3.96 \pm 0.42\%$; however, its standard deviation was notably higher than those of other formulations, indicating greater variability among the replicate measurements. This variability may reflect nonuniform moisture distribution within the F4 batch, sampling heterogeneity, or variation during drying and sample handling. Therefore, the lower mean value observed for F4 should be interpreted cautiously. Moisture content increased to $4.67 \pm 0.07\%$ in F5, demonstrating that the response did not follow a consistent concentration-dependent pattern with increasing Primojel® concentration. Although the hydrophilic properties of Primojel® may influence moisture retention,⁶³ the present findings do not establish Primojel® concentration as the sole determinant of moisture content. Drying conditions, granule size distribution, sampling location, and within-batch moisture uniformity may also have contributed to the observed variation. Further process optimization and evaluation using independently prepared batches are required to establish a reproducible moisture-content specification.

The compressibility index was evaluated to assess granule flowability and packing characteristics. Materials with compressibility index values below 10% are generally considered to have excellent flow properties, whereas values above 38% indicate very poor flowability.^{17,26,31} In the present study, the compressibility index ranged from 17.16% to 26.34% (**Table 2**), indicating fair to poor flowability. These results are consistent with the high fines content observed across all formulations, which can reduce mechanical interlocking between particles and compromise granule packing, density, and flow characteristics.⁶⁴

Statistical analysis revealed significant differences among formulations (Kruskal-Wallis, $p = 0.010$). Post hoc Mann-Whitney analysis showed significant differences between most formulation pairs, except F2 and F5 ($p = 0.121$). The lowest compressibility index was observed in F4 ($17.16 \pm 0.85\%$), which coincided with a lower fines content than F1-F3. This result may reflect more favorable packing associated with its particle-size profile; however, the effect of Primojel® concentration was not monotonic. Previous studies have similarly found that intermediate sodium starch glycolate concentrations can provide better compressibility than higher concentrations. Therefore, the F4 result likely arose from the combined effects of particle-size distribution, fines content, moisture, and excipient interactions rather than Primojel® concentration alone.^{63,65} Nevertheless, all formulations remained within the poor-to-moderate flowability range, indicating that factors such as limited binder concentration and insufficient granule growth continued to influence granule quality.

The dispersion test showed that all formulations met the requirement for instant granules, with dispersion times of less than 5 min.³² A very fast dispersion time is necessary to ensure ease of use, especially for products that are dissolved before consumption, and to guarantee optimal availability of the active ingredient.⁶⁶ The mean dispersion time ranged from 38 to 50 seconds (**Table 2** and **Figure 3**), with F5 (10% Primojel®) exhibiting the shortest dispersion time. These results indicate that increasing the concentration of Primojel® tended to accelerate granule dispersion. As a superdisintegrant, sodium starch glycolate facilitates water penetration into the granule matrix through swelling and wicking mechanisms, thereby promoting rapid dispersion.^{22,65}

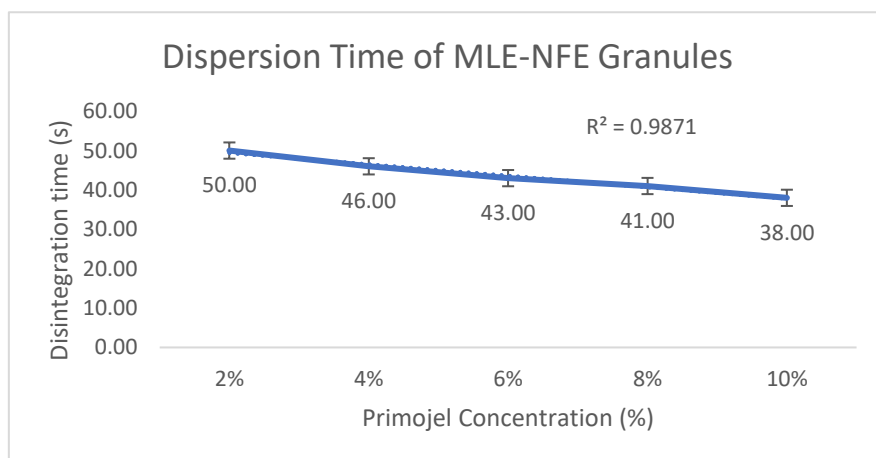


Figure 3. Linear regression analysis shows the effect of Primojel® concentration on the mean dispersion time of granule formulations ($R^2 = 0.9871$).

Statistical analysis confirmed that the data were normally distributed and homogeneous ($p > 0.05$), allowing further evaluation using one-way ANOVA. The ANOVA results revealed significant differences among formulations ($p < 0.001$), indicating that Primojel® concentration significantly affected granule dispersion time. Tukey's post-hoc test showed that F1 differed significantly from F2, F3, F4, and F5, while F2 differed significantly from F4 and F5 ($p < 0.05$). However, no significant difference was observed between F4 and F5, despite the lower mean dispersion time recorded for F5.

These findings suggest that increasing Primojel® concentration up to 8% substantially improved granule dispersion performance. Although the 10% formulation produced the shortest dispersion time, the improvement was not significantly different from that of the 8% formulation. This observation indicates that the disintegrating effect of Primojel® approached a plateau level at higher concentrations. Nevertheless, all formulations exhibited rapid dispersion and complied with the quality requirements for instant granules. At very high concentrations, Primojel® has the potential to cause gelling, which can inhibit dispersion,⁶⁵ so concentration optimization is still necessary to maintain effectiveness. Therefore, when selecting the concentration of Primojel®, it is important to consider the balance between dispersion effectiveness and formulation efficiency.

Flow rate testing was performed to evaluate the ability of the granules to flow freely, an important parameter for ensuring dose uniformity, ease of packaging, and manufacturing efficiency.^{30,56} Granules with good flow properties generally exhibit a flow time of ≤ 10 seconds for a 100-gram sample or a flow rate of ≥ 10 g/second.²⁶ In the present study, none of the formulations were able to flow through the funnel, indicating poor flowability. This result is consistent with the high proportion of fines (73.8–87.9%), relatively high moisture content, and compressibility index values in the poor-to-moderate range. High fines content can reduce powder flow, impair compressibility, and compromise dose uniformity by increasing interparticle cohesion.⁶⁷ Furthermore, the low concentration of maltodextrin as the sole binder and the limited amount of granulation liquid likely restricted granule growth, resulting in small, low-density particles with poor flow characteristics.⁵⁶

The compressibility-index results further supported the suboptimal flow behavior of the formulations. F4 showed the lowest compressibility index, at $17.16 \pm 0.85\%$, coinciding with a lower fines content than F1–F3. This value indicates fair flow according to the compressibility-index classification. The lower index may reflect more favorable particle packing associated with the reduced proportion of fines; however, the effect of Primojel® concentration was not monotonic. A previous wet-granulation study reported that granules containing 4% Primojel® had a lower compressibility index than those containing 8% Primojel® (7.12% versus 16.51%), suggesting that increasing the disintegrant concentration does not necessarily improve packing or flowability. Similarly, a recent study of paracetamol granules containing 2%–6% sodium starch glycolate found the best compressibility index at the intermediate concentration of 4%, rather than at the highest concentration tested. Therefore, the comparatively low compressibility index of F4 may have resulted from the combined effects of particle-size distribution, fines content, moisture, and excipient interactions rather than from the Primojel® concentration alone.^{20,68}

The angle of repose is commonly used as an additional indicator of flowability. However, this test could not be performed because none of the formulations flowed through the funnel, preventing the formation of the conical heap required for measurement. Taken together, these results indicate that the MLE-NFE combination granules met the dispersion-time and moisture content requirement but failed to satisfy the quality criteria for particle size distribution and flow-related properties, including compressibility, flow rate, and angle of repose. Further optimization of formulation and granulation parameters is therefore necessary to improve granule quality.

Antiradical Activity Assay of MLE and NFE Combination Granules

The DPPH assay was used to evaluate the radical-scavenging activity of the individual extracts and MLE–NFE granules. This method is widely used because it is simple, rapid, economical, and provides a quantitative estimate of antiradical activity through the IC_{50} value, with a lower IC_{50} indicating greater activity.^{69–72} The maximum absorption wavelength was 517 nm, at which the DPPH control had an absorbance of 0.495. Absorbance monitoring over 120 min showed a relatively stable reaction period between 15 and 60 min, which was used to establish the incubation period for the assay.⁷³

The baseline phytochemical and antiradical characteristics of the individual extracts are presented in **Table 3**. MLE contained substantially higher total phenolic and flavonoid contents than NFE and exhibited a slightly lower IC_{50} value and higher antioxidant activity index. These findings suggest that the greater abundance of phenolic and flavonoid constituents in MLE may have contributed to its higher DPPH radical-scavenging activity. Nevertheless, the DPPH

response cannot be attributed exclusively to these compound classes because other electron- or hydrogen-donating constituents may also contribute. Although NFE had lower TPC and TFC values, its IC_{50} of 7.57 $\mu\text{g/mL}$ and AAI of 3.304 demonstrated that it also possessed measurable antiradical activity.

Table 3. Total phenolic content, total flavonoid content, and DPPH radical-scavenging activity of the individual extracts (MLE and NFE)

Extract	TPC (mg GAE/g extract)	TFC (mg QE/g extract)	DPPH IC_{50} ($\mu\text{g/mL}$)	AAI
MLE	31.59 ± 2.84	7.16 ± 0.16	6.42	3.895
NFE	3.72 ± 0.31	0.29 ± 0.07	7.57	3.304

Notes: MLE, ethanolic mango leaf extract; NFE, ethanolic noni fruit extract; TPC, total phenolic content; TFC, total flavonoid content; GAE, gallic acid equivalents; QE, quercetin equivalents; IC_{50} , concentration required to inhibit 50% of DPPH radicals; AAI, antioxidant activity index. Values for TPC and TFC are presented as the mean $\pm$ standard deviation of three replicate measurements from the same extract sample.

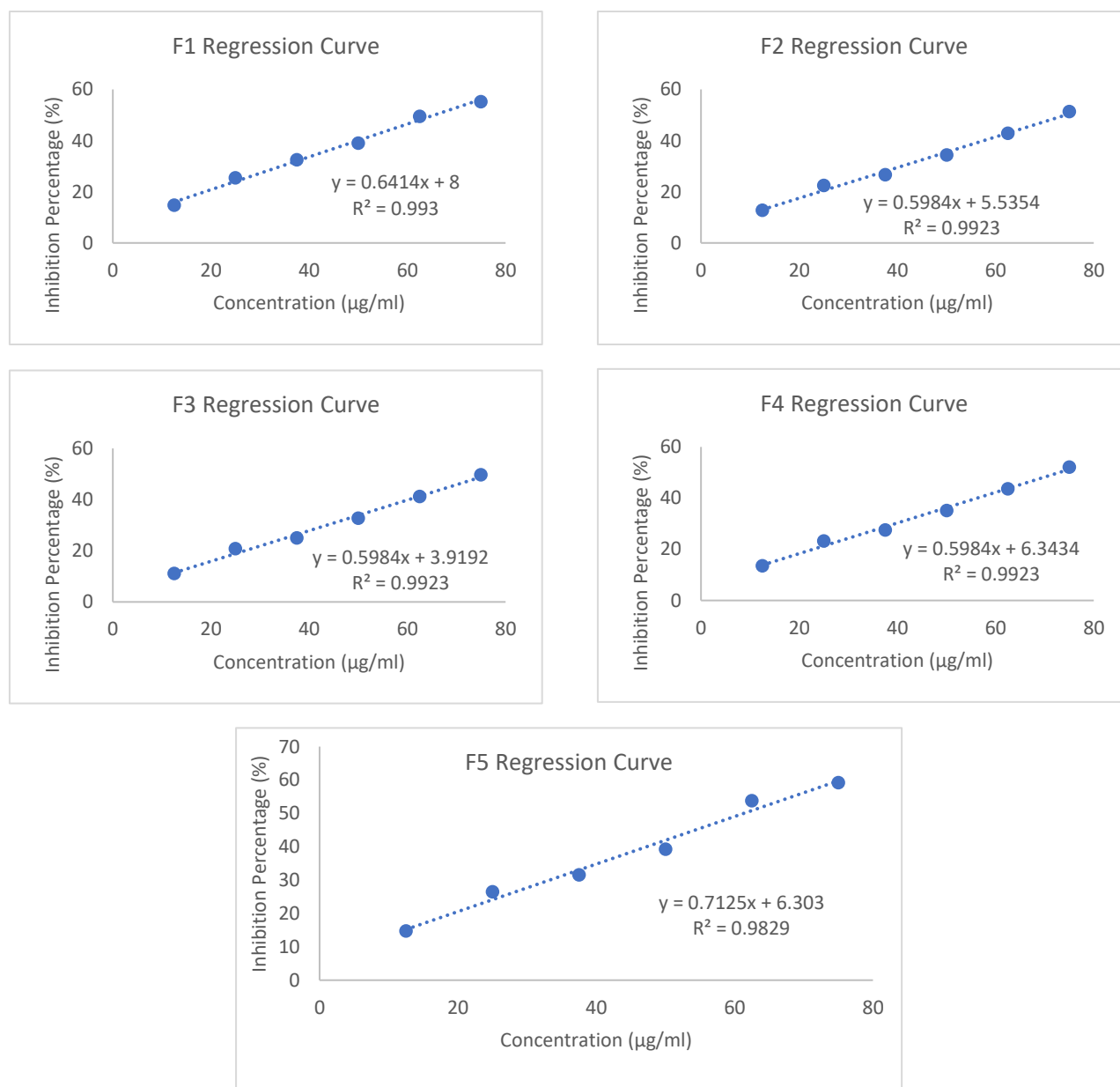


Figure 4. DPPH radical scavenging activity of MLE-NFE granules (F1–F5). Linear regression curves plot granule concentration ($\mu\text{g/mL}$) against the percentage of inhibition (Y) to determine IC_{50} values.

The two extracts were incorporated into the granule formulations at an MLE:NFE ratio of 7.5:5.5 w/w. The IC_{50} values were calculated from the linear regression equations relating sample concentration to percentage DPPH inhibition, with $y = 50$ as the calculation point (Figure 4). The resulting IC_{50} values ranged from 61.33 to 77.01 $\mu\text{g/mL}$ (Table 2), demonstrating measurable DPPH radical-scavenging activity in all formulations.

The observed activity may be associated with the secondary metabolites present in MLE and NFE. MLE contains phenolic compounds, flavonoids, tannins, alkaloids, saponins, and steroids, whereas NFE contains phenolic compounds, flavonoids, tannins, alkaloids, saponins, steroids, and anthraquinones.^{6,74–76} Several of these constituents possess antioxidant properties through mechanisms such as electron or hydrogen donation, free-radical stabilization, metal chelation, and inhibition of oxidative reactions.^{76–82} These constituents may therefore have contributed collectively to the DPPH radical-scavenging activity of the granule formulations. However, the relative contribution of each phytochemical class was not determined in the present study.

The IC₅₀ values did not change linearly with increasing Primojel® concentration. Antiradical activity decreased from F1 to F3, as indicated by the progressive increase in IC₅₀, but subsequently increased in F4 and F5. F5 exhibited the lowest IC₅₀ value and therefore the greatest measured antiradical activity among the granule formulations, whereas F3 exhibited the highest IC₅₀ value. Similar nonlinear effects of superdisintegrant concentration on the release of active constituents have been reported in herbal formulations.⁸³ Differences in wetting, dispersion, and the release or extraction of antioxidant constituents into the analytical medium may have contributed to this pattern. Nevertheless, the present findings do not demonstrate that Primojel® directly changed the intrinsic antiradical activity of the extracts.

The IC₅₀ values of the granules were numerically higher than those of the individual extracts. A reduction in measured antioxidant activity following incorporation of a botanical extract into a granule formulation has also been reported for *Oxalis dehradunensis* effervescent granules, indicating that formulation and processing can influence the activity measured in the finished dosage form.⁸⁴ However, the higher IC₅₀ values observed in the present study should not be interpreted solely as evidence of phytochemical degradation during granulation. DPPH results are influenced by the reaction solvent, incubation time, DPPH concentration, sample concentration range, reaction environment, and calculation method; therefore, direct quantitative comparisons require equivalent assay conditions and concentration bases.⁸⁵

In the present study, the individual-extract concentrations were expressed according to pure-extract mass, whereas the granule concentrations were based on the mass of the complete formulation, including maltodextrin, microcrystalline cellulose, sodium starch glycolate, aspartame, and orange essence. Consequently, the extract content represented only a fraction of the total mass used to prepare the granule test solutions. Dilution by the excipients, together with matrix-dependent differences in the extraction or release of antioxidant constituents into the analytical medium, may therefore have contributed to the higher apparent IC₅₀ values of the granules. Conversely, processing-related changes in antioxidant constituents cannot be excluded because TPC, TFC, and marker-compound contents were not measured in the finished granules.

The individual-extract results provide baseline evidence that MLE and NFE contained phenolic and flavonoid constituents and possessed DPPH radical-scavenging activity before formulation. The finished granules also exhibited measurable activity, showing that radical-scavenging constituents remained detectable after formulation. However, because an unformulated MLE-NFE blend at the same 7.5:5.5 w/w ratio was not evaluated as a matched pregranulation control, the retention of phenolic content, flavonoid content, and antiradical activity after granulation could not be quantified. Furthermore, the use of different sample-mass bases and DPPH conditions limited direct comparison between the individual extracts and the finished granules, consistent with published recommendations emphasizing standardized DPPH reaction conditions for valid quantitative comparisons. Consequently, the results establish measurable DPPH radical-scavenging activity in the finished granules but do not prove either complete preservation or degradation of the original antioxidant constituents.^{85,86}

Limitation

This study was limited by the preparation of only one batch for each formulation. The triplicate physicochemical measurements were technical replicates obtained from the same batch and therefore did not account for batch-to-batch variability. In addition, the DPPH radical-scavenging activity of each granule formulation was measured only once, preventing estimation of analytical variability and valid inferential comparisons among formulations. Consequently, the findings should be interpreted as preliminary and descriptive and cannot establish a causal effect of Primojel® concentration on the physicochemical properties or antioxidant activity of the granules. Inter-batch reproducibility and pilot-scale production were also not evaluated. Furthermore, the extract load and MLE:NFE ratio was fixed as preliminary formulation parameters without systematic optimization; therefore, this study does not establish the 13% extract load or 7.5:5.5 MLE:NFE ratio as optimal. Dissolution testing and antioxidant constituent release profiling were not performed, preventing direct evaluation of the relationship between granule disintegration or dispersion and

antioxidant activity. Finally, antioxidant activity was evaluated solely using the DPPH assay. Future studies should include independently prepared batches, replicated antioxidant assays, complementary in vitro antioxidant methods, dissolution and release studies, systematic formulation optimization, scale-up evaluation, and in vivo validation.

CONCLUSION

Granules containing 7.5% w/w mango leaf extract and 5.5% w/w noni fruit extract exhibited measurable DPPH radical-scavenging activity and met the selected formulation-development targets for moisture content and dispersion time. Increasing the Primojel® concentration was associated with shorter dispersion times, demonstrating its functional contribution to granule dispersion. The formulations containing 8% and 10% Primojel® showed the shortest dispersion times, with no significant difference between them, while F5 had the lowest IC₅₀ value based on descriptive comparison. These findings suggest that higher Primojel® concentrations within the evaluated range provided more favorable dispersion performance without eliminating the measurable antiradical activity of the incorporated extracts. The study therefore provides preliminary evidence for selecting an appropriate Primojel® concentration in combined mango leaf and noni fruit extract formulations. Further optimization of the binder system, granulating-fluid quantity, and processing conditions are required to reduce fines and improve flowability and granule formation.

FUNDING

This work was supported by the Faculty of Pharmacy, Universitas Mahasaraswati Denpasar, Grant No. 1119.12/E.003/FF-UNMAS/XII/2024.

ACKNOWLEDGMENTS

The authors express their profound gratitude to the Faculty of Pharmacy at Mahasaraswati University in Denpasar for providing financial support and logistical assistance, as well as to the research assistants who carried out the study with great diligence, thereby enabling the acquisition of valid research results.

GENERATIVE AI DISCLOSURE STATEMENT

Generative AI tools (Copilot, 2026) were used during the preparation of this manuscript exclusively to improve grammar and language readability. After using the tool, the authors thoroughly reviewed the text and assumed full responsibility for the accuracy, originality, and integrity of the final content.

AUTHOR CONTRIBUTION STATEMENT

Ni Made Dharma Shantini Suena: Conceptualization, Methodology, Formal analysis, Resources, Investigation, Supervision, Writing—Original draft preparation, Writing- Reviewing and Editing; **Ni Komang Sinta Yuli Pratiwi:** Resources, Writing—Original draft preparation; **Kd Dwi Payanti Pitaloka:** Resources, Writing—Original draft preparation; **I Gede Made Suradnyana:** Methodology, Software, Supervision, Data curation, Writing- Reviewing and Editing; **I Gusti Agung Ayu Kusuma Wardani:** Visualization, Writing- Reviewing and Editing; **Ni Putu Udayana Antari:** Validation, Writing- Reviewing and Editing.

CONFLICT OF INTEREST DECLARATION

The authors declare no conflict of interest.

REFERENCE

1. Tim Riskesdas. *Laporan Nasional Riskesdas 2018 [2018 Basic Health Research (Riskesdas): National Report]*. Lembaga Penerbit Badan Penelitian dan Pengembangan Kesehatan (LPB); 2019. http://labdata.litbang.kemkes.go.id/images/download/laporan/RKD/2018/Laporan_Nasional_RKD2018_FINAL.pdf
2. Blagov A V., Summerhill VI, Sukhorukov VN, Zhigmitova EB, Postnov AY, Orekhov AN. Potential use of antioxidants for the treatment of chronic inflammatory diseases. *Front Pharmacol.* 2024;15(May):1-22. doi:[10.3389/fphar.2024.1378335](https://doi.org/10.3389/fphar.2024.1378335)
3. Reddy VP. Oxidative Stress in Health and Disease. *Biomedicines.* 2023;11(11):2925. doi:[10.3390/biomedicines11112925](https://doi.org/10.3390/biomedicines11112925)

4. Jomova K, Raptova R, Alomar SY, Alwasel SH, Nepovimova E, Kuca K, Valko M. Reactive oxygen species, toxicity, oxidative stress, and antioxidants: chronic diseases and aging. *Arch Toxicol.* 2023;97(10):2499-2574. doi:[10.1007/s00204-023-03562-9](https://doi.org/10.1007/s00204-023-03562-9)
5. Tyagi DN, Ismail DMV, Sharma DMK. An Antioxidant: An Overview. *J Surv Fish Sci.* 2023;8(3):142-147. doi:[10.53555/sfs.v8i3.1363](https://doi.org/10.53555/sfs.v8i3.1363)
6. Loan NTT, Long DT, Yen PND, Hanh TTM, Pham TN, Pham DTN. Purification Process of Mangiferin from *Mangifera indica* L. Leaves and Evaluation of Its Bioactivities. *Processes.* 2021;9(5):852. doi:[10.3390/pr9050852](https://doi.org/10.3390/pr9050852)
7. Wang Q, Yang F, Jia D, Wu T. Polysaccharides and polyphenol in dried *Morinda citrifolia* fruit tea after different processing conditions: Optimization analysis using response surface methodology. *PeerJ.* 2021;9:e11507. doi:[10.7717/peerj.11507](https://doi.org/10.7717/peerj.11507)
8. Pulungan MZ, Hamzah F, Harun N, Dewi YK. Aktivitas Antioksidan dan Mutu Teh Herbal Daun Mangga Berdasarkan Letak Daun pada Ranting [Antioxidant Activity and Quality Characteristics of Mango Leaf Herbal Tea as Affected by Leaf Position on the Branch]. *J Teknol Pertan Andalas.* 2022;26(2):248-253. doi:[10.25077/jtpa.26.2.248-253.2022](https://doi.org/10.25077/jtpa.26.2.248-253.2022)
9. Susilawati E, Sulaeman A, Nuur BF. Aktivitas Rebusan Daun Mangga Manalagi (*Mangifera indica* L. var. Manalagi) terhadap Kadar Gula Darah dan MDA Mencit Putih Galur Swiss Webster [Effects of Manalagi Mango Leaf (*Mangifera indica* L. var. Manalagi) Decoction on Blood Glucose and Malondialdehyd. *Lumbung Farm J Ilmu Kefarmasian.* 2023;4(1):41-47. <https://journal.ummat.ac.id/index.php/farmasi/article/view/9901>
10. Satriari PR, Vedawati PPK, Primantara M, Warditiani NK, Wirasuta IMAG, Susanti NM. Potensi Penangkapan Radikal Bebas DPPH dari Ekstrak Mengkudu (*Morinda citrifolia* L), Kelor (*Moringa oleifera*) dan Kedondong Hutan (*Spondias pinnata* (L.f) kurz) [Evaluation of the DPPH Free Radical Scavenging Activity of Noni, Moringa, and Wild Hog Plum Ex. *J Farm Udayana.* 2017;6(1):43-46.
11. Duri ID, Suwondo A, Suhartono S. Efektivitas Ekstrak Buah Mengkudu (*Morinda Citrifolia*) terhadap Kadar MDA sebagai Pemicu Aterosklerosis [Effect of Noni Fruit (*Morinda citrifolia* L.) Extract on Malondialdehyde (MDA) Levels Associated with Atherosclerosis]. *Visikes.* 2020;19(1):109-117. <https://publikasi.dinus.ac.id/visikes/article/view/3766>
12. Zhang Q, Pan J, Liu H, Jiao Z. Characterization of the Synergistic Antioxidant Activity of Epigallocatechin Gallate (EGCG) and Kaempferol. *Molecules.* 2023;28(13):5265. doi:[10.3390/molecules28135265](https://doi.org/10.3390/molecules28135265)
13. Ben Mrid R, Bouchmaa N, Ouedrhiri W, Ennoury A, Zouaoul Z, Kabach I, Nhiri M, El Fatimy R. Synergistic antioxidant effects of natural compounds on H₂O₂-induced cytotoxicity of human monocytes. *Front Pharmacol.* 2022;13(September):1-15. doi:[10.3389/fphar.2022.830323](https://doi.org/10.3389/fphar.2022.830323)
14. Chen X, Li H, Zhang B, Deng Z. The synergistic and antagonistic antioxidant interactions of dietary phytochemical combinations. *Crit Rev Food Sci Nutr.* 2022;62(20):5658-5677. doi:[10.1080/10408398.2021.1888693](https://doi.org/10.1080/10408398.2021.1888693)
15. Saini R, Bajpai M. Formulation and Evaluation of Nutraceutical Dosage Form Derived from *Vigna aconitifolia*, *Eleusine coracana* and *Chenopodium quinoa*. *Int J Pharm Investig.* 2024;14(4):1226-1234. doi:[10.5530/ijpi.14.4.135](https://doi.org/10.5530/ijpi.14.4.135)
16. Al-Hakim NA, Nur Fauziyyah SA, Purnamasari N, Faramayuda F. Formulation and Physical Evaluation of *Orthosiphon aristatus* Leaf Extract Granule Preparation as Herbal Beverage Candidate. *Maj Obat Tradis.* 2024;29(3):286. doi:[10.22146/mot.91009](https://doi.org/10.22146/mot.91009)
17. Aulton ME, Taylor KMG. *Aulton's Pharmaceutics: The Design and Manufacture of Medicines*. 6th ed. (Taylor KMG, Aulton ME, eds.). Elsevier; 2021.
18. Abuhassira-Cohen Y, Edelman R, Abbas R, Kurnik D, Shibel R, Livney YD. Enhancing the oral bioavailability of natural astaxanthin using plant-based micro- and nano-encapsulation materials: Results of an In vitro evaluation and a cross-over study in humans. *Precision Nanomedicine.* 2020;3(3):641-655. doi:doi.org/10.33218/001c.16781
19. Sirame P, Khairnar R, Tasgaonkar R. Granulation. *Int J Res Appl Sci Eng Technol.* 2023;11(1):347-355. doi:[10.22214/ijraset.2023.48564](https://doi.org/10.22214/ijraset.2023.48564)
20. Imtihani HN, Alfreeda S, Arif JRA. Pengaruh Variasi Disintegran Avicel PH-102 dan Primogel terhadap Karakteristik Co-Processed Excipient [The Effect of Disintegrant Variations from Avicel PH-102 and Primogel on the Characteristics of Co-Processed Excipient]. *J Ilm Medicam.* 2023;9(1):9-15. doi:[10.36733/medicamento.v9i1.4635](https://doi.org/10.36733/medicamento.v9i1.4635)
21. Desai PM, Liew CV, Heng PWS. Review of Disintegrants and the Disintegration Phenomena. *J. Pharm. Sci.* 2016;105(9):2545-2555. doi: [10.1016/j.xphs.2015.12.019](https://doi.org/10.1016/j.xphs.2015.12.019)
22. Sheskey PJ, Hancock BC, Moss GP, Goldfarb DJ. *Handbook of Pharmaceutical Excipients*. 9th ed. (Sheskey PJ, Hancock BC, Moss GP, Goldfarb DJ, eds.). Pharmaceutical Press and American Pharmacist Association; 2020.
23. Suena NMDS, Suradnyana IGM, Juanita RA. Formulation and Antioxidant Activity Test of Effervescent Granule from Extract Combination of White Turmeric (*Curcuma zedoaria*) and Turmeric (*Curcuma longa* L.). *J Ilm Medicam.* 2021;7(1):32-40. doi: [10.36733/medicamento.v7i1.1498](https://doi.org/10.36733/medicamento.v7i1.1498)
24. Chen P, Ansari MJ, Bokov D, Suksatan W, Rahman ML, Sarjadi MS. A review on key aspects of wet granulation

- process for continuous pharmaceutical manufacturing of solid dosage oral formulations. *Arab J Chem*. 2022;15(2):103598. doi:[10.1016/j.arabjc.2021.103598](https://doi.org/10.1016/j.arabjc.2021.103598)
25. Zhao J, Tian G, Qu H. Pharmaceutical Application of Process Understanding and Optimization Techniques: A Review on the Continuous Twin-Screw Wet Granulation. *Biomedicines*. 2023;11(7):1923. doi:[10.3390/biomedicines11071923](https://doi.org/10.3390/biomedicines11071923)
 26. Suenam NMD, Adianta KA, Wardani IGA, Antari NPU. Formulation of White Edible Bird's Nest (*Aerodramus fuciphagus*) Granules with Varying Combinations of Maltodextrin and Povidone. *JFOnline | Print ISSN 1412-1107 | e-ISSN 2355-696X*. 2022;14(2):172-189. doi:[10.35617/jfionline.v14i2.90](https://doi.org/10.35617/jfionline.v14i2.90)
 27. Dewi IK, Lestari T. Formulasi dan Uji Hedonik Serbuk Jamu Instan Antioksidan Buah Naga Super Merah (*Hylocereus Costaricensis*) dengan Pemanis Alami Daun Stevia (*Stevia rebaudiana* Bertoni M.) [Formulation and Hedonic Testing of Antioxidant Instant Herbal Powder from Super Red Dragon Fruit (*Hylocereus costaricensis*) Sweetened with Natural Stevia Leaf (*Stevia rebaudiana* Bertoni M.)]. *J Terpadu Ilmu Kesehat*. 2016;5(2):149-156. doi:[10.37341/interest.v5i2.47](https://doi.org/10.37341/interest.v5i2.47)
 28. Syaputri FN, Saila SZ, Tugon TDA, R. AP, Lestari D. Formulation and Physical Characterization of Effervescent Granule Preparations of Ethanol Extract of Red Betel Leaf (*Piper crocatum* Ruiz) as an Antidiabetic Agent. *Lambung Farm J Ilmu Kefarmasian*. 2023;4(1):191-198. doi: [10.31764/lf.v4i1.12215](https://doi.org/10.31764/lf.v4i1.12215)
 29. United States Pharmacopeia Convention. Stage 4 Harmonization: (786) Particle Size Distribution Estimation By Analytical Sieving. *US Pharmacopeia (USP)*. Preprint posted online 2022:1-8. <https://www.usp.org/sites/default/files/usp/document/harmonization/excipients/harmonization-april-2022-m99584.pdf>
 30. Husni P, Fadhiilah ML, Hasanah U. Formulation and Physical Stability Evaluation of Instant Dry Powder Granules of Genjer Stems (*Limnnocharis flava* (L.) Buchenau) as a Fiber Supplement. *J Ilm Farm Farmasyifa*. 2020;3(1):1-8. doi:[10.29313/jiff.v3i1.5163](https://doi.org/10.29313/jiff.v3i1.5163)
 31. United States Pharmacopeial Convention. Stage 4 Harmonization: <1174> Powder Flow. *US Pharmacop. US Pharmacopeia (USP)*. Preprint posted online 2024:1-8. <https://www.usp.org/sites/default/files/usp/document/harmonization/gen-chapter/20230428HSm99885.pdf>
 32. Markl D, Zeitler JA. A Review of Disintegration Mechanisms and Measurement Techniques. *Pharm Res*. 2017;34(5):890-917. doi: [10.1007/s11095-017-2129-z](https://doi.org/10.1007/s11095-017-2129-z)
 33. Adianta KA. Aktivitas Antioksidan Daun Magenta (*Peristrophe bivalvis* (L.) Merr) sebagai Salah Satu Kandidat Pengobatan Bahan Berbasis Herbal serta Bioaktivitasnya sebagai Analgetik [Antioxidant Activity of Magenta Leaves (*Peristrophe bivalvis* (L.) Merr.) as a Potenti. *J Ilm Medicam*. 2020;6(1):33-39. doi:[10.36733/medicamento.v6i1.745](https://doi.org/10.36733/medicamento.v6i1.745)
 34. Ariawa DC, Suradnyana IGM, Suenam NMD. Formulation of Lerak Liquid Extract (*Sapindus rarak* DC.) as a Biosurfactant for Facial Soap. *J Kefarmasian Indones*. 2024;14(February):1-11. doi:[10.22435/jki.v14i1.6614](https://doi.org/10.22435/jki.v14i1.6614)
 35. Suenam NMD, Wardani IGA, Antari NPU. Peel-Off Mask Formulation of Red Dragon Fruit Extract (*Hylocereus lemairei* Hook.) and Corn Starch with Variation of Polyvinyl Alcohol (PVA) Concentration. *J Ilm Medicam*. 2023;9(2):127-136. doi:[10.36733/medicamento.v9i2.3576](https://doi.org/10.36733/medicamento.v9i2.3576)
 36. Goswami MJ, Dutta U, Kakati D. Ultrasound-Assisted Extraction for Food, Pharmacy, and Biotech Industries. In: Sarkar T, Pati S, eds. *Bioactive Extraction and Application in Food and Nutraceutical Industries*. Humana Press; 2024:103-128. doi:[10.1007/978-1-0716-3601-5_5](https://doi.org/10.1007/978-1-0716-3601-5_5)
 37. Momchev P, Ciganović P, Jug M, Marguí E, Jablan J, Zovko Končić M. Comparison of Maceration and Ultrasonication for Green Extraction of Phenolic Acids from *Echinacea purpurea* Aerial Parts. *Molecules*. 2020;25(21):5142. doi:[10.3390/molecules25215142](https://doi.org/10.3390/molecules25215142)
 38. Kementerian Kesehatan Republik Indonesia. *Farmakope Herbal Indonesia Edisi II 2017 [Indonesian Herbal Pharmacopoeia, 2nd Edition, 2017]*. 2nd ed. [Kementerian Kesehatan Republik Indonesia; 2017](https://www.kemkes.go.id/).
 39. Usman A, Kashif AR, Asadullah M, Bibi H, Younas MU. Therapeutic potential of *Mangifera indica* leaves: Antioxidant, cytotoxic, and thrombolytic properties of solvent extracts. *J Pharmacogn Phytochem*. 2025;14(1):373-379. doi:[10.22271/phyto.2025.v14.i1e.15260](https://doi.org/10.22271/phyto.2025.v14.i1e.15260)
 40. Hapgood KP, Smith RM. Wet Granulation and Mixing. In: *Pharmaceutical Blending and Mixing*. Wiley; 2015:153-182. doi:[10.1002/9781118682692.ch8](https://doi.org/10.1002/9781118682692.ch8)
 41. Eremin VA, Blynskaya E V., Alekseev K V., Tishkov S V., Minaev S V. Comparative Analysis of Innovative Wet Granulation Technologies for Pharmaceutical Production (A Review). *Pharm Chem J*. 2024;58(9):1438-1447. doi:[10.1007/s11094-025-03292-5](https://doi.org/10.1007/s11094-025-03292-5)
 42. Primojel®. DFE Pharma. 2023. <https://dfepharma.com/excipients/primojel>
 43. Primojel®. Pharma Excipients. 2025. <https://www.pharmaexcipients.com/product/primogel/>
 44. Lakshmi KNVC, Aminabee S, Shankar KR, Ramana G, Sultana SA, Keerthana DNR, Sri GB, Niharika CS. Formulation and Evaluation of Valsartan Tablets Using Starch Succinate as Novel Super Disintegrant by Using 32 Factorial Design. *Indian J Pharm Educ Res*. 2024;58(2s):s436-s443. doi:[10.5530/ijper.58.2s.47](https://doi.org/10.5530/ijper.58.2s.47)
 45. Wren SAC, Alhusban F, Barry AR, Hughes LP. Mechanistic understanding of the link between Sodium Starch

- Glycolate properties and the performance of tablets made by wet granulation. *Int. J. Pharm.* 2017;529(1-2):319-328. doi: [10.1016/j.ijpharm.2017.07.004](https://doi.org/10.1016/j.ijpharm.2017.07.004)
46. Sinko PJ. *Martin's Physical Pharmacy and Pharmaceutical Sciences: Physical Chemical and Biopharmaceutical Principles in the Pharmaceutical Sciences*. Eighth. (Sinko PJ, Singh Y, eds.). [Lippincott Williams & Wilkins, a Wolters Kluwer business](https://www.lippincottwilliams.com/); 2023.
 47. Molyneux P. The use of the stable free radical diphenylpicryl-hydrazyl (DPPH) for estimating antioxidant activity. *Songklanakarin J Sci Technol.* 2004;26(2):211-219. <https://sjst.psu.ac.th/article/214>
 48. Vázquez-Blanco S, González-Freire L, Dávila-Pousa MC, Crespo-Diz C. pH determination as a quality standard for the elaboration of oral liquid compounding formula. *Farm Hosp.* 2018;42(6):221-227. doi:[10.7399/fh.10932](https://doi.org/10.7399/fh.10932)
 49. Vardan V. Influence of pH on the Stability of Pharmaceutical Compounds in Japan. *J Chem.* 2024;3(2):21-30. doi:[10.47672/jchem.2404](https://doi.org/10.47672/jchem.2404)
 50. Patil JR, Mhatre KJ, Yadav K, Yadav LS, Srivastava S, Nikalje GC. Flavonoids in plant-environment interactions and stress responses. *Discov Plants.* 2024;1(1):68. doi:[10.1007/s44372-024-00063-6](https://doi.org/10.1007/s44372-024-00063-6)
 51. Padhi S, Singh A, Orsat V, Routray W. Flavonoids as Functional Foods and Nutraceuticals: Recent Advances. In: *Functional Foods and Nutraceuticals: Chemistry, Health Benefits and the Way Forward*. Springer International Publishing; 2024:173-198. doi:[10.1007/978-3-031-59365-9_8](https://doi.org/10.1007/978-3-031-59365-9_8)
 52. Parveen Z, Zaidi S, Bajguz A, Arif Y, Hayat S. Comprehensive Insights into Flavonoids: Biosynthesis, Stress Modulation, and Plant Growth Regulation. *J Plant Growth Regul.* Published online August 15, 2025. doi:[10.1007/s00344-025-11841-1](https://doi.org/10.1007/s00344-025-11841-1)
 53. Safe S, Jayaraman A, Chapkin RS, Howard M, Mohankumar K, Shrestha R. Flavonoids: structure–function and mechanisms of action and opportunities for drug development. *Toxicol Res.* 2021;37(2):147-162. doi:[10.1007/s43188-020-00080-z](https://doi.org/10.1007/s43188-020-00080-z)
 54. Meng W, Oka S, Liu X, Omer T, Ramachandran R, Muzzio FJ. Effects of Process and Design Parameters on Granule Size Distribution in a Continuous High Shear Granulation Process. *J Pharm Innov.* 2017;12(4):283-295. doi:[10.1007/s12247-017-9288-7](https://doi.org/10.1007/s12247-017-9288-7)
 55. Allen LVJ, McPherson TB. *Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems*. Vol 12. 12th ed. (Howes S, ed.). [Lippincott Williams & Wilkins, a Wolters Kluwer business](https://www.lippincottwilliams.com/); 2021.
 56. Apeji YE, Olayemi OJ, Anyebe SN, Oparaechi C, Orugun OA, Olowosulu AK, Oyi AR. Impact of binder as a formulation variable on the material and tableting properties of developed co-processed excipients. *SN Appl Sci.* 2019;1(6):561. doi:[10.1007/s42452-019-0585-2](https://doi.org/10.1007/s42452-019-0585-2)
 57. Syam A. Evaluation of the Quality of Pumpkin Seed Flour and Capsules as Food Supplements. *Media Kesehatan Masyarakat Indones.* 2022;18(2):43-49. doi:[10.30597/mkmi.v18i2.20847](https://doi.org/10.30597/mkmi.v18i2.20847)
 58. Voight R. *Buku Pelajaran Teknologi Farmasi (Terjemahan) [Textbook of Pharmaceutical Technology (Translated Edition)]*. (Soewandhi SN, ed.). Gadjah Mada University Press; 1995.
 59. Hadi M, Mufrod, Iksari ED. Optimasi Suhu dan Waktu Pengeringan Granul Tablet Kunyah Bee Polen [Optimization of Drying Temperature and Drying Time of Bee Pollen Chewable Tablet Granules]. *Maj Farm.* 2014;10(1):176-181. <https://jurnal.ugm.ac.id/majalahfarmaseutik/article/view/24108/15765>
 60. Sharma K, Sharma S, Batra S, Kumar S, Kumar P, Moksha L, Das US. Stability of Colloidal Dispersions Using Freeze-Drying Technology. In: *Freeze-Drying Technology in Pharmaceutical and Biomedical Product Development*. Springer Nature Singapore; 2025:121-137. doi:[10.1007/978-981-95-0221-9_5](https://doi.org/10.1007/978-981-95-0221-9_5)
 61. Nitika, Hiti, Sharma S, Singh TG, Dhiman S, Dora CP. Impact of Freeze-Drying on Pharmaceutical Product's Morphology, Physical Characteristics, and In Vitro Release Kinetics. In: *Freeze-Drying Technology in Pharmaceutical and Biomedical Product Development*. Springer Nature Singapore; 2025:101-119. doi:[10.1007/978-981-95-0221-9_4](https://doi.org/10.1007/978-981-95-0221-9_4)
 62. Fule R, Rangurwar A, Nagdeve A, Nagpure P. Use of Freeze Drying for Pharmaceutical Microencapsulation. In: *Freeze-Drying Technology in Pharmaceutical and Biomedical Product Development*. Springer Nature Singapore; 2025:157-179. doi:[10.1007/978-981-95-0221-9_7](https://doi.org/10.1007/978-981-95-0221-9_7)
 63. Bauhuber S, Warnke G, Berardi A. Disintegrant Selection in Hydrophobic Tablet Formulations. *J Pharm Sci.* 2021;110(5):2028-2037. doi:[10.1016/j.xphs.2020.11.002](https://doi.org/10.1016/j.xphs.2020.11.002)
 64. Shi L, Sun CC. Understanding the roles of compaction pressure and crystal hardness on powder tableability through bonding area – Bonding strength interplay. *Int J Pharm.* 2024;659:124253. doi:[10.1016/j.ijpharm.2024.124253](https://doi.org/10.1016/j.ijpharm.2024.124253)
 65. Putra ON, Musfiroh I, Paramitasari D, Pudjianto K, Ikram EHK, Chaidir C, Muchtaridi M. Sago-Starch-Derived Sodium Starch Glycolate: An Effective Superdisintegrant to Enhance Formulation Performance. *Polymers (Basel)*. 2025;17(9):1208. doi:[10.3390/polym17091208](https://doi.org/10.3390/polym17091208)
 66. Zaborenko N, Shi Z, Corredor CC, Smith-Goettler BM, Zhang L, Hermans A, Neu CM, Alam MA, Cohen MJ, Lu X, Xiong L, Zacour BM. First-Principles and Empirical Approaches to Predicting In Vitro Dissolution for Pharmaceutical Formulation and Process Development and for Product Release Testing. *AAPS J.* 2019;21(3):32. doi:[10.1208/s12248-019-0297-y](https://doi.org/10.1208/s12248-019-0297-y)

67. Pazhayattil AB, Sharma S, Philip JP, Gischewski-Silva M, Ingram M. Scaling-Up of Solid Orals: Granulation, Drying, Size Reduction, Blending, Compression, and Coating Technologies. In: *Technology Transfer: Drug Product Manufacturing Process*. Springer; 2023:61-95. doi:[10.1007/978-3-031-32192-4_5](https://doi.org/10.1007/978-3-031-32192-4_5)
68. Safitri NA, Rahayyu AM, Fauziyya R. Evaluasi Sifat Fisik Granul Parasetamol dengan Variasi Konsentrasi Sodium Starch Glycolate (SSG) dari Pati Batang Nanas sebagai Superdisintegran [Evaluation of the Physical Properties of Paracetamol Granules with Varying Concentrations of Sodium Starch Gl. *Jikes J Ilmu Kesehat*. 2025;3(2):309-318. <https://yptb.org/index.php/jik/article/view/1269>
69. Muscolo A, Mariateresa O, Giulio T, Mariateresa R. Oxidative Stress: The Role of Antioxidant Phytochemicals in the Prevention and Treatment of Diseases. *Int J Mol Sci*. 2024;25(6):3264. doi:[10.3390/ijms25063264](https://doi.org/10.3390/ijms25063264)
70. Kedare SB, Singh RP. Genesis and development of DPPH method of antioxidant assay. *J Food Sci Technol*. 2011;48(4):412-422. doi:[10.1007/s13197-011-0251-1](https://doi.org/10.1007/s13197-011-0251-1)
71. Gulcin İ, Alwasel SH. DPPH Radical Scavenging Assay. *Processes*. 2023;11(8):2248. doi:[10.3390/pr11082248](https://doi.org/10.3390/pr11082248)
72. Gulcin İ. Antioxidants and antioxidant methods: an updated overview. *Arch Toxicol*. 2020;94(3):651-715. doi:[10.1007/s00204-020-02689-3](https://doi.org/10.1007/s00204-020-02689-3)
73. Agustiarini V, Wijaya DP. Uji Aktivitas Antioksidan Ekstrak Etanol-Air (1:1) Bunga Rosella (Hibiscus sabdariffa L.) dengan Metode DPPH (1,1-difenil-2-pikrilhidrazil) [DPPH Radical Scavenging Activity of the Ethanol-Water (1:1) Extract of Roselle (Hibiscus sabdariffa L.) Flowers]. *J Penelit Sains*. 2022;24(1):29. doi:[10.56064/jps.v24i1.679](https://doi.org/10.56064/jps.v24i1.679)
74. Ibrahim SN, Haron N, Abdullah A, Sam MFR. A Brief Review on the Phytochemistry and Pharmacological Activities of Morinda citrifolia L. *Malaysian J Med Heal Sci*. 2024;20(3):339-348. doi:[10.47836/mjmhs.20.3.45](https://doi.org/10.47836/mjmhs.20.3.45)
75. Selvam S, Venkatachalam R, Manikandan R. Phytochemical profiling and antioxidant potential of Morinda citrifolia L. fruit extract from Panikondanviduthi, Tamil Nadu, India. *Int J Biosci*. 2025;26(5):13-24. doi:[10.12692/ijb/26.5.13-24](https://doi.org/10.12692/ijb/26.5.13-24)
76. Zhou S, Huang G. The chemical composition and pharmacological activities of Morinda citrifolia. *Appl Biol Chem*. 2024;67(1):104. doi:[10.1186/s13765-024-00960-0](https://doi.org/10.1186/s13765-024-00960-0)
77. Macáková K, Afonso R, Saso L, Mladěnka P. The influence of alkaloids on oxidative stress and related signaling pathways. *Free Radic Biol Med*. 2019;134:429-444. doi:[10.1016/j.freeradbiomed.2019.01.026](https://doi.org/10.1016/j.freeradbiomed.2019.01.026)
78. Kurnia D, Meilinawati D, Marlioni L, Febrina E, Asnawi A. A Review of Tannin Compounds in Avocado as Antioxidants. *Trop J Nat Prod Res*. 2024;8(10):8607-8616. doi:[10.26538/tjnpr/v8i10.1](https://doi.org/10.26538/tjnpr/v8i10.1)
79. Hassanpour SH, Doroudi A. Review of the antioxidant potential of flavonoids as a subgroup of polyphenols and partial substitute for synthetic antioxidants. *Avicenna J Phytomedicine*. 2023;13(4):354-376. doi:[10.22038/AJP.2023.21774](https://doi.org/10.22038/AJP.2023.21774)
80. Wu J, Xi Y, Huang L, Li G, Mao Q, Fang C, Shan T, Jiang W, Zhao M, He W, Dong J, Li X, Qiu P, Yan P. A Steroid-Type Antioxidant Targeting the Keap1/Nrf2/ARE Signaling Pathway from the Soft Coral Dendronephthya gigantea. *J Nat Prod*. 2018;81(11):2567-2575. doi:[10.1021/acs.jnatprod.8b00728](https://doi.org/10.1021/acs.jnatprod.8b00728)
81. Khan M, Karima G, Khan M, Shin J, Kim J. Therapeutic Effects of Saponins for the Prevention and Treatment of Cancer by Ameliorating Inflammation and Angiogenesis and Inducing Antioxidant and Apoptotic Effects in Human Cells. *Int J Mol Sci*. 2022;23(18):10665. doi:[10.3390/ijms231810665](https://doi.org/10.3390/ijms231810665)
82. Kumar N, Goel N. Phenolic acids: Natural versatile molecules with promising therapeutic applications. *Biotechnol Reports*. 2019;24:e00370. doi:[10.1016/j.btre.2019.e00370](https://doi.org/10.1016/j.btre.2019.e00370)
83. Martínez-Morales F, Alonso-Castro AJ, Zapata-Morales JR, Carranza-Álvarez C, Aragon-Martínez OH. Use of standardized units for a correct interpretation of IC50 values obtained from the inhibition of the DPPH radical by natural antioxidants. *Chem Pap*. 2020;74(10):3325-3334. doi:[10.1007/s11696-020-01161-x](https://doi.org/10.1007/s11696-020-01161-x)
84. Mahyuni EL, Harahap U. The Formulation of Effervescent Granules with Oxalis dehradunensis Raizada Ethanol Extract as an Antioxidant. *J Pharm Sci Community*. 2024;21(1):44-50. doi:[10.24071/jpsc.004492](https://doi.org/10.24071/jpsc.004492)
85. Yamauchi M, Kitamura Y, Nagano H, Kawatsu J, Gotoh H. DPPH Measurements and Structure—Activity Relationship Studies on the Antioxidant Capacity of Phenols. *Antioxidants*. 2024;13(3):309. doi:[10.3390/antiox13030309](https://doi.org/10.3390/antiox13030309)
86. Wołosiak R, Drużyńska B, Derewiaka D, Piecyk M, Majewska E, Ciecierska M, Worobiej E, Pakosz P. Verification of the Conditions for Determination of Antioxidant Activity by ABTS and DPPH Assays—A Practical Approach. *Molecules*. 2021;27(1):50. doi:[10.3390/molecules27010050](https://doi.org/10.3390/molecules27010050)