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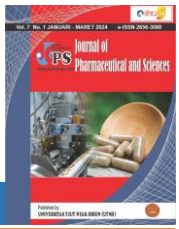

Optimization of the Most Active Fraction Gel Formula of Noni Fruit (*Morinda citrifolia* L.) as a Topical Antioxidant

Optimasi Formula Gel Fraksi Teraktif Buah Mengkudu (*Morinda citrifolia* L.) Sebagai Antioksidan Topikal

Erlinda Novita Sari [a]*, Ika Purwidyaningrum [a], and Iswandi [a]

[a]*Faculty of Pharmacy, Setia Budi University, Surakarta, 57127, Central Java, Indonesia.*

**Corresponding Authors: erlindanovitasa@gmail.com*

Abstract

Introduction: Flavonoid compounds and vitamin C from noni fruit have the potential to be antioxidants. The unpleasant odor, soft texture, and unpleasant taste of noni fruit are minimized through a fractionation process and formulated into a gel preparation, which is expected to increase the acceptance of noni fruit in the community. Objective: to determine the optimal gel formula of the most active fraction of noni fruit with variations of HPMC, Carbopol 940, and propylene glycol through critical parameters of viscosity, pH, and antioxidant activity using the Simplex Lattice Design method. **Method:** The extraction method used is maceration, followed by a fractionation process. Physical property tests include organoleptic, homogeneity, viscosity, adhesiveness, spreadability, and pH determination, as well as the determination of the IC_{50} value of antioxidants with DPPH using a UV-Vis spectrophotometer. The statistical results of the data obtained were processed using ANOVA, Wilcoxon, and the T-test. **Results:** showed that the noni fruit fraction that had the best antioxidant activity was the ethyl acetate fraction (20.35±0.18 ppm), variations of 13 gel formula compositions with the most optimal viscosity, pH, and IC_{50} responses were carbopol 940:HPMC 8060-M: propylene glycol (1.491:0.509:8.000). Variations in the combination of HPMC 8060-M, carbopol 940, and propylene glycol in the gel preparation of the most active noni fruit fraction affected the critical parameters of viscosity, pH, and antioxidant activity. **Conclusion:** The ethyl acetate fraction exhibits the best antioxidant activity, and the optimal gel formula composition is Carbopol 940:HPMC 8060-M: propylene glycol (1.491:0.509:8.000), which is predicted to have a very high desirability value (0.917) and has been validated.

***Keywords*: Antioxidant, Noni fraction, Optimization, pH, Viscosity**

Abstrak

Latar belakang: Senyawa flavonoid dan vitamin C dari buah mengkudu berpotensi sebagai antioksidan. Bau kurang sedap, tekstur lembek, dan rasa tidak enak buah mengkudu diminimalisir melalui proses fraksinasi dan diformulasikan menjadi sediaan gel diharapkan dapat meningkatkan daya penerimaan buah mengkudu di masyarakat. **Tujuan:** mengetahui formula gel fraksi teraktif buah mengkudu teroptimum dengan variasi HPMC, karbopol 940, serta propilen glikol melalui parameter kritis viskositas, *p*H, dan aktivitas antioksidan menggunakan metode *Simplex Lattice Design*. **Metode:** ekstraksi yang digunakan adalah maserasi dan dilanjutkan dengan proses fraksinasi. Uji sifat fisik meliputi organoleptis, homogenitas, viskositas, daya lekat, daya sebar, dan *p*H. Penetapan nilai IC_{50} antioksidan dengan DPPH menggunakan spektofotemeter UV-Vis. Hasil statistik data yang diperoleh diolah menggunakan *Anova*, *Wilcoxon* dan *T-one sample*. **Hasil:** menunjukkan fraksi buah mengkudu yang mempunyai aktivitas sebagai antioksidan terbaik adalah fraksi etil asetat (20,35±0,18 ppm), variasi 13 komposisi formula gel dengan respon viskositas, *p*H, dan IC_{50} teroptimal adalah karbopol 940:HPMC 8060-M:propilen glikol (1,491:0,509:8,000). Variasi kombinasi HPMC 8060-M, karbopol 940, dan propilen glikol dalam sediaan gel fraksi teraktif buah mengkudu mempengaruhi parameter

kritis viskositas, *p*H, dan aktivitas antioksidan. **Kesimpulan:** fraksi etil asetat memiliki aktivitas antioksidan terbaik dan komposisi formula gel teroptimal adalah karbopol 940:HPMC 8060-M:propilen glikol (1.491:0.509:8.000) yang diprediksi dengan nilai desirability sangat tinggi (0.917) dan telah divalidasi.

Kata Kunci: Antioksidan, Fraksi buah mengkudu, Optimasi, pH, Viskositas

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Introduction

Pollutants cause skin exposure to free radicals, thus accelerating premature aging; therefore, exogenous antioxidants are needed. Synthetic antioxidants, such as BHA, BHT, TBHQ, and PG, are carcinogenic when used continuously. [1]. The natural antioxidant content in noni fruit includes flavonoids, alkaloids, vitamin C, and vitamin E. The antioxidant activity of noni fruit extract has varying IC_{50} values, namely 43.14 µg/mL [2]; 24.92 µg/mL [3]; 33.96 µg/mL [4]; and 28.99 µg/mL [5].

Purification of noni fruit extract using the liquid-liquid extraction method is expected to produce a purer compound, thereby reducing the bulk sample mass while improving the therapeutic quality. The ethyl acetate fraction of noni fruit is believed to be rich in phenolics, flavonoids, and coumarins. [6]. These compounds have significant potential as antioxidant agents. However, noni fruit has an unappealing taste, odor, and texture; therefore, processing it into a gel formulation is a breakthrough alternative.

Topical gels have the advantage of being easy to apply, spreading evenly on the skin, drying quickly, providing a cooling sensation, and forming a layer that is easy to clean. [7]. This study utilized HPMC and Carbopol 940 as gelling agents, as they produce neutral, odorless preparations with stable viscosity in the pH range of 2-11, are resistant to microorganisms, and, upon drying, yield a good film strength and a long shelf life at room temperature. [8]The higher the concentration of gelling agent in the gel, the higher the viscosity and adhesiveness values increase, while the spreadability decreases. Propylene glycol, as a humectant in gel preparations, is used to enhance the stability of the preparation over an extended period, thereby protecting the components firmly bound within the material, including water and fat. The accuracy of the variation of HPMC 8060-M, Carbopol 940, and propylene glycol is essential to improve the quality of the gel, which can be done using the SLD (Simplex Lattice Design) method, which has the advantages of being fast and practical because it can avoid determining the formula by trial and error. [9]. HPMC K15M (2%), carbopol 940 (0.5%), and propylene glycol (2.5%) produced an optimum formula with a viscosity of 3,996 cp, a spreadability of 5.80 cm, and an adhesiveness of 63.39 seconds [10]. The most active fraction of the noni fruit gel preparation was tested for its antioxidant activity using the DPPH method. The DPPH method has advantages, including being relatively fast, inexpensive, and effective. The DPPH method involves a stable radical that can react with antioxidants as hydrogen donors to form DPPH, resulting in a decrease in the absorbance of DPPH.

Based on the background that has been described, an optimization test of HPMC 8060-M, carbopol 940, and propylene glycol was carried out on the most active fraction gel of noni fruit as an antioxidant using the DPPH method, so that it is expected to be able to develop a formula for the most active fraction gel preparation of noni fruit as an antioxidant that meets the requirements for optimal physical quality characterization.

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Experimental Section

Research Variables

The independent variables used were Carbopol 940 (0.5-1.5%), HPMC 8060-M (0.5-1.5%), and propylene glycol (7-8%), with target concentrations within the specified range. The dependent variables were viscosity (lower limit: 2,000 cP, upper limit: 5,000 cP, target concentration within range), pH (lower limit: 4, upper limit: 7, target concentration within range), and IC50 (lower limit: 250, upper limit: 2,500, target concentration within range).

Materials and Equipment

The equipment used included a number sieve 60, an oven, an analytical balance, an extensometer, a blender, a water bath, a rotary evaporator, a pH meter, a Brookfield viscometer, a set of glassware, a moisture balance (Ohaus MB23), and a UV-Vis spectrophotometer (Shimadzu). The materials used were noni fruit obtained from Surakarta, Central Java, 70% ethanol (PT. Bratachem), DPPH (Sigma Aldrich), propylene glycol, oleum menthae piperitae, HPMC 8060-M, carbopol 940, nipagin, nipasol, distilled water, ethanol (Merck); HCl, $CHCl_3$, and reagents (Mayer, Dragendorff, Bouchardat, and $FeCl_3$).

Research Procedure

Material Collection and Powder Preparation

Ten kilograms of noni fruit samples were collected from Surakarta, Central Java, meeting the criteria of being ripe, greyish-green, pest-free, and approximately 3 months old. The noni fruit was washed with running water to remove any remaining dirt, then sliced into 3-4 mm thick slices. Then, it was oven-dried at 50°C for several days until completely dry. The dried noni fruit was powdered using a blender and sieved through a 60-mesh sieve to form a fine powder. The identification of the noni fruit powder involved organoleptic testing of the powder, determining the drying loss, measuring the moisture content, assessing the water-soluble extract content, and evaluating the ethanol-soluble extract content. [11].

Extract Preparation and Identification

One kg of noni fruit powder was weighed and macerated with 70% ethanol (1:10) for 5 days. [11]. Afterwards, the macerate was evaporated using a rotary evaporator at 50°C to produce a thick extract. [12]. Identification of the noni fruit extract included an ethanol-free test. [13], a water content test [11], and phytochemical identification of extract compounds (coumarin, polyphenols, flavonoids, and alkaloids) [14].

Fraction Preparation and Identification

Fractionation was carried out by weighing 50 g of the sample, diluting it with 100 mL of distilled water, adding 100 mL of n-hexane, and placing the mixture in a separating funnel. The n-hexane fraction was separated, and the water fraction was fractionated with 100 mL of ethyl acetate to obtain the ethyl acetate and water fractions. Each collected fraction was then concentrated using a rotary evaporator. [13]. The extract and ethyl acetate fraction of noni fruit, believed to possess antioxidant activity, were spotted onto a GF_{254} silica plate using a micropipette with 2 to 3 spots. The plate was then eluted in a chamber previously saturated with a mobile phase of methanol: chloroform (2:8) to the specified limit. The plate was then dried at room temperature and observed under visible light and UV light at two wavelengths: 254 nm and 366 nm. The TLC plate was sprayed with sitroborate reagent to detect flavonoid compounds. [15], and then the resulting Rf value was calculated.

Gel Formulation of the Most Active Fraction of Noni Fruit

The optimal formula design of the most active fraction of the noni fruit gel preparation was determined using the SLD method in Design-Expert software version 12. The gel was prepared by dissolving HPMC 8060-M and Carbopol 940 in hot water at 80°C until they were dispersed entirely in separate mortars. The two gel bases (HPMC and carbopol) were formed separately; the carbopol base, which had been neutralized with TEA, was added slowly to the HPMC base while stirring homogeneously. Methyl paraben and propyl paraben were dissolved in propylene glycol, then added to oleum menthae piperitae and stirred until homogeneous [10]. The most active fraction of noni fruit was subsequently added to the hydrogel base mixture by slowly pouring and mixing until a homogeneous mixture was achieved. The evaluations carried out included physical evaluation and stability during 4 weeks of storage (Daud & Suryanti, 2017). Physical quality tests

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included organoleptic tests, homogeneity, pH, viscosity, spreadability, and adhesiveness, as referenced in the 2018 study by Tambunan & Sulaiman (2018). The physical quality tests were followed by gel stability tests using the stress condition method [18].

Table 1. Design of noni fruit active fraction gel formula

Formula	Composition (%)								
	Fraction	Carbopol 940	HPMC 8060-M	Propylene glycol	TEA	Methyl paraben	Propyl paraben	*Oleum menthae piperitae*	Aquades
1	1.00	1.00	1.50	7.50	0.50	0.18	0.02	0.50	87.80
2	1.00	1.00	1.00	8.00	0.50	0.18	0.02	0.50	87.80
3	1.00	1.50	1.00	7.50	0.50	0.18	0.02	0.50	87.80
4	1.00	1.50	1.50	7.00	0.50	0.18	0.02	0.50	87.80
5	1.00	1.00	1.50	7.50	0.50	0.18	0.02	0.50	87.80
6	1.00	1.50	1.00	7.50	0.50	0.18	0.02	0.50	87.80
7	1.00	1.17	1.17	7.67	0.50	0.18	0.02	0.50	87.80
8	1.00	0.50	1.50	8.00	0.50	0.18	0.02	0.50	87.80
9	1.00	1.00	1.00	8.00	0.50	0.18	0.02	0.50	87.80
10	1.00	1.50	0.50	8.00	0.50	0.18	0.02	0.50	87.80
11	1.00	1.00	1.00	8.00	0.50	0.18	0.02	0.50	87.80
12	1.00	1.50	1.00	7.50	0.50	0.18	0.02	0.50	87.80
13	1.00	1.00	1.50	7.50	0.50	0.18	0.02	0.50	87.80

Antioxidant activity testing with DPPH

The test samples used were 100 ppm of vitamin C, 100 ppm of n-hexane and ethyl acetate fractions of noni fruit, 150 ppm of water extract and fraction, and 10,000 ppm of gel sample. The maximum λ and operating time (OT) were determined by pipetting 1 mL of a 0.2 mM DPPH solution with ethanol PA to the mark, homogenizing it, and then allowing it to stand for 30 minutes. The sample was subsequently measured at λ 400-600 nm. OT was determined by pipetting 1 mL of DPPH, adding 1 mL of sample, and then adding 5 mL of ethanol PA to the mark, followed by reading the absorbance over 60 minutes. The preparation of a sample concentration series was carried out by taking a sample from the stock solution and then adding PA ethanol according to the appropriate dilution volume, then taking a concentration series sample of 1 mL plus 1 mL DPPH, and PA ethanol up to 5 mL in a dark measuring flask, homogenized, waited according to OT, measured absorbance with a UV-Vis spectrophotometer with three replications. The sample concentration value and percent inhibition were plotted on the x and y axes in the linear regression Equation, in the form of y = a + bx, where the y value was set to 50, and the x value obtained is the IC_{50} concentration. [18].

Formula Optimization and Analysis

Formula optimization was performed using Design-Expert software version 12, employing the SLD method. Normality analysis was performed using the Shapiro-Wilk method. If the data were not normally distributed (Sig. < 0.05), a non-parametric test was used. For normal data (Sig. >0.05), a parametric ANOVA test was used. A Dunnett T3 post-hoc test was used to determine differences between samples. A one-sample T-test was used to determine differences between samples before and after testing. The data were then statistically evaluated for formula optimization using Design Expert® version 12.

Results and Discussion

Noni fruit powder characterization test results

Determination at the Batu Herbal Materia Medica Laboratory, through decree number 000.9.3/2565/102.20/2023, confirmed that the plant used was indeed noni (*Morinda citrifolia* L.). Phytochemical tests are used to determine the compounds contained in the extract. The noni fruit extract was declared positive for containing coumarin, polyphenols, flavonoids, and alkaloids. The results of the drying shrinkage test revealed a loss of 4.67 ± 1.15% w/w of compounds, including water molecules, essential oils, flavonols, isoflavones, flavones, and flavonones [19]. The results are in accordance with the standard, which is <10% w/w [11]. The less water contained in the powder after the drying process, the longer the powder's shelf life becomes, because the potential for microbial growth is reduced. The results of the water content of 4.17 ± 0.29%

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w/w have met the standard <10% [11]. The levels of water-soluble and ethanol extracts describe the number of compounds that can be extracted in the solvent, the higher the percentage yield of the extract content produced, the more compounds are extracted, the results show that the water-soluble extract content is 43.32 ± 7.24%w/w (standard >21.3%w/w) [11], while the ethanol-soluble extract content is 25.39 ± 8.48%w/w (standard is >9.8%w/w) [11].

The extract yield exceeded the recommended standard, reaching 24.60% w/w, whereas the standard was 10.1% w/w [11]. The noni extract was declared ethanol-free (no ester odor), making it safe to use as an active gel substance, as it is unlikely to irritate. The extract water content of 0.37 ± 0.11% w/w meets the requirements of <10% w/w [11]. The lower the extract water content, the lower the potential for microbes to grow, thus extending shelf life. [20].

Fraction Preparation

Fractionation is a method of separating compounds based on their polarity. The yield percentages of noni fruit fractions were 66.67% w/w of water, 20% w/w of ethyl acetate, and 5.67% of n-hexane. The water fraction yielded the highest yield, indicating that many compounds in the sample are polar, such as alkaloids, tannins, and saponins. Semi-polar compounds include phenolics and flavonoids, while non-polar compounds include terpenoids and steroids. [21].

The results of the TLC test showed that the extract and ethyl acetate fraction samples of noni fruit were positive for containing flavonoids, which was indicated by the presence of greenish-yellow fluorescence in spots when sprayed with sitroborate reagent in visible light, 254 nm UV light, and 366 nm UV light caused by the presence of complex bonds in the 3-ortho-hydroxy group and a characteristic shift in the high wavelength band. [22]. The Rf of quercetin was 0.76, the extract was 0.8, and the ethyl acetate fraction was 0.78. The results of the n-hexane and water fraction samples did not show any separation spots, as the eluent was unable to elute the compounds in the sample, and the sample did not contain flavonoid compounds.

Antioxidant Vitamin C, Extract, and Fraction of Noni Fruit

The DPPH solution, prepared at a concentration of 0.2 mM, exhibited a maximum λ value of 516 nm, which falls within the required range of 515-520 nm. [23]. The test continued with the determination of the operating time (OT) value to determine the optimal maximum absorbance time for the sample solution mixed with DPPH. The OT values for the samples varied considerably, ranging from 20 to 40 minutes. The IC50 reflects the ability of a test sample to scavenge 50% of DPPH free radicals; the lower the IC50 value, the stronger the antioxidant capacity.

Vitamin C yields the strongest results (14.99 ± 0.74 ppm) because it is a pure synthetic compound that has been extensively tested, resulting in very few by-products or residues. [24]The ethyl acetate fraction has powerful category results (20.35 ± 0.18 ppm). This is thought to be due to the presence of a reasonably potent flavonoid compound contained in the ethyl acetate fraction, as well as previous research, which stated that the flavonoid content of ripe noni fruit is 67.67 ± 1.55 μg QE g−1 FW. [25]. The n-hexane fraction (72.57 ± 2.23 ppm) and extract (77.34 ± 0.34 ppm) have results in the strong category, while the water fraction (116.48 ± 2.91 ppm) falls into the medium category. The IC_{50} results of the n-hexane fraction, extract, and water fraction samples were not as strong as vitamin C or ethyl acetate fractions, which can be influenced by the presence of bulk mass or unwanted residues that were also extracted, these compounds include chlorophyll, because chlorophyll a has a $-CH_3$ group which is less polar, while chlorophyll b is polar because it binds the -CHO group, compounds in the n-hexane fraction, extract, and water fraction have minimal functional groups and do not have aromatic rings, so they are less active in scavenging free radicals. [26]. Based on the ANOVA test followed by the Post Hoc Tukey test, the ethyl acetate fraction is a potential candidate for use as a raw material in active ingredient gel preparations, as it yields the strongest results. Flavonoid compounds in the ethyl acetate fraction can scavenge DPPH free radicals through electron or hydrogen donation.

The IC_{50} results of the gel formula samples showed differences. The higher the Carbopol 940 value, the lower the IC_{50} value. Increasing the concentration of the gelling agent resulted in a higher viscosity, which decreased the drug release from the base. HPMC, carbomer, and propylene glycol all affected drug release [27]. Gels with higher carbomer 940 concentrations had better drug release, especially with the addition of propylene glycol. Higher propylene glycol concentrations decreased the release of the active substance, as did HPMC as a gelling agent. Therefore, the formula used in this study was quite effective because it used propylene glycol with a concentration of <10% [27]. However, the addition of appropriate propylene glycol was able to increase drug release. The carboxyl group of carbomer 940 can ionise, causing the release of H^+

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ions from R-COOH. These H^+ ions play a role in reducing DPPH free radicals [1]. The concentration differences of Carbopol 940, HPMC 8060-M, and propylene glycol affect the antioxidant value, as determined by statistical tests using ANOVA followed by the Post hoc Dunnett T3 test. For future researchers, at least one additional antioxidant assay method should be employed to determine the reduction mechanism using alternative methods.

Gel Physical Quality Test

Organoleptic and Homogeneity Test

The odour, texture, colour, and homogeneity of the gel on days 1 and 21 were stable. The peppermint odour originates from the essential oil of *Mentha piperita*. The soft texture of the gel is attributed to the fully expanded gelling agent and propylene glycol, a humectant that inhibits water evaporation and contributes to a smooth feel when applied to the skin. The yellow colour is due to the addition of the active ingredient ethyl acetate fraction. The gel was considered homogeneous, as indicated by the absence of clumps of base when placed between two glass slides. A homogeneous gel means that the active ingredient and base mix well.

pH Test

The pH test determines the acidity of the gel preparation. A pH that is too alkaline can cause scaly skin, while one that is too acidic can cause dryness and irritation. The pH test results showed that increasing the concentration of Carbomer 940 decreases the pH, as Carbopol is acidic, while HPMC tends to be more stable. [28]. Carbomers have R-COOH groups at each end, which are acidic in nature—some of the carboxyl groups in the carbomer molecular structure form non-ionized coils. Suppose the addition of a base increases the pH of the carbomer dispersion. In that case, the carboxyl groups will progressively ionize, resulting in repulsion between the ionized groups and disrupting hydrogen bonds within the carboxyl groups, which causes an increase in viscosity. The addition of basic TEA functions as a neutralizer and clarifier of the carbomer, increasing pH and viscosity. Based on the test results, it can be seen that all preparations have met the criteria for a good gel, which falls within the range of 4-7 [29]. The results of the pH test on days 1 and 21 showed that the gel preparation met the required standards for safety, indicating it is suitable for the skin. Based on the results of the Wilcoxon test, which showed no significant difference ($p > 0.05$), it can be concluded that storing the gel at room temperature yields a stable pH response. pH test results, gel fraction of ethyl acetate, and noni fruit can be shown in Table 2.

Viscosity Test

The viscosity test was used to determine the viscosity of a gel preparation. All gel formulations met the requirements, ranging from 2,000 to 4,000 cP. [30]. HPMC 8060-M has a viscosity in the range of 65,000 to 80,000 cP, while Carbopol 940 has a viscosity in the range of 40,000 to 60,000 cP [31]. This causes an increase in the concentration of HPMC 8060-M, resulting in a thicker gel, compared to the rise in the concentration of Carbopol 940. The combination of these two gelling agents increases the number of polymer fibers, resulting in more fluid being retained and bound by the gelling agent, which in turn leads to a thicker gel. Hydrogen bonding interactions between TEA carbomers are mediated by the -OH and C=O groups of the gelling agent. The greater the number of hydrogen bonds, the stronger the bonds formed, resulting in higher viscosity. Carbopol 940 is an anionic gelling agent that causes pH-sensitive swelling to increase at neutral/alkaline pH, which can enhance matrix permeability and modulate the release rate. However, electrostatic interactions with charged drugs can inhibit release. HPMC is a non-ionic gelling agent that can provide dominant release control through gel layer formation and erosion, making it more pH-insensitive and resulting in a more reproducible profile across different pH levels [32]. Propylene glycol increases viscosity by binding water, thereby increasing the molecular size. [33]. After 21 days of storage, the Wilcoxon test showed no significant difference ($p > 0.05$). It can be concluded that storage at room temperature resulted in a stable viscosity response for the gel preparation. Viscosity test results and gel fraction of ethyl acetate noni fruit are shown in Table 2.

Spreadability Test

Good gel spreadability is 5-7 cm [31]. Spreadability can decrease due to an increase in molecular size [33]. Variations in Carbopol 940, HPMC 8060-M, and propylene glycol affected spreadability in 13 formulas. Overall, testing on both days 1 and 21 demonstrated that the gel met the requirements for good spreadability.

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Storage increased viscosity, resulting in decreased spreadability. The results of the spreadability test on days 1 and 21, based on the Wilcoxon test, showed no significant difference ($p > 0.05$). Therefore, storage at room temperature results in a stable spreadability response for the gel preparation. The spreadability test results for the gel fraction of ethyl acetate from noni fruit are shown in Table 2.

Adhesion Test

Adhesion refers to a product's ability to adhere to the skin. The longer the gel adheres, the greater the potential for active ingredients to penetrate the skin. Good adhesion is achieved with a value of greater than 1 second. [34]. However, higher adhesion increases the potential for skin pore blockage. However, if the adhesion is too low, the active ingredient's effect will not be achieved. [34]. The adhesion results for 13 formulas tested over 21 days are presented in Table 2, which meets the requirements. The Wilcoxon test showed no significant difference between days 1 and 21. Therefore, it can be concluded that the gel formulation has a stable spreadability response when stored at room temperature.

Table 2a. The test results of *p*H and viscosity gel fraction of ethyl acetate noni fruit

Days to-	1	21	1	21
Formula	*p*H ± SD		Viscosity ± SD (cP)	
1	4,73 ± 0,03	4,83 ± 0,02	3.888 ± 7	6.593 ± 155
2	5,00 ± 0,02	4,59 ± 0,01	2.198 ± 2	4.472 ± 70
3	4,12 ± 0,01	4,10 ± 0,02	3.252 ± 93	6.009 ± 47
4	5,62 ± 0,05	5,45 ± 0,01	3.893 ± 2	6.987 ± 42
5	4,78 ± 0,03	5,00 ± 0,01	3.858 ± 43	6.557 ± 320
6	4,19 ± 0,04	4,11 ± 0,01	3.487 ± 324	5.787 ± 70
7	5,01 ± 0,16	4,77 ± 0,04	2.825 ± 944	5.327 ± 136
8	5,77 ± 0,01	5,80 ± 0,01	2.667 ± 127	4.833 ± 61
9	4,98 ± 0,03	4,64 ± 0,01	2.468 ± 202	4.827 ± 145
10	4,02 ± 0,02	3,73 ± 0,27	2.087 ± 2	4.187 ± 200
11	4,97 ± 0,04	4,62 ± 0,01	2.468 ± 314	4.825 ± 313
12	4,74 ± 0,25	4,05 ± 0,01	3.662 ± 98	5.938 ± 50
13	4,66 ± 0,02	5,00 ± 0,02	3.825 ± 63	6.940 ± 191

Table 2b. The test results of spreadability, stickiness, and IC_{50} gel fraction of ethyl acetate noni fruit

Days to-	1	21	1	21	Antioxidant
Formula	Spreadability ± SD (cm)		Stickiness ± SD (second)		IC_{50} (ppm)
1	5,27 ± 0,14	5,15 ± 0,05	3,22 ± 0,03	3,30 ± 0,04	906,05±50,82
2	6,30 ± 0,07	6,13 ± 0,07	1,27 ± 0,05	1,28 ± 0,05	605,41±19,73
3	5,54 ± 0,19	5,30 ± 0,07	2,08 ± 0,07	2,18 ± 0,03	759,25±18,05
4	5,10 ± 0,07	5,10 ± 0,03	3,43 ± 0,09	3,50 ± 0,06	974,40±32,83
5	5,24 ± 0,08	5,18 ± 0,02	3,37 ± 0,05	3,43 ± 0,06	932,48±28,24
6	5,52 ± 0,11	5,35 ± 0,04	1,93 ± 0,03	1,98 ± 0,03	737,59±66,18
7	5,75 ± 0,03	5,07 ± 0,04	1,92 ± 0,03	1,94 ± 0,03	725,24±91,34
8	6,08 ± 0,02	5,93 ± 0,04	1,92 ± 0,03	1,96 ± 0,03	702,98±23,22
9	6,28 ± 0,09	5,89 ± 0,05	1,91 ± 0,02	2,00 ± 0,03	587,96±4,51
10	6,40 ± 0,07	6,27 ± 0,06	1,12 ± 0,03	1,25 ± 0,04	432,49±44,11
11	6,25 ± 0,10	6,05 ± 0,05	1,84 ± 0,05	1,89 ± 0,06	681,34±36,03
12	5,78 ± 0,09	5,47 ± 0,11	2,59 ± 0,05	2,65 ± 0,05	741,50±7,17
13	5,50 ± 0,13	5,13 ± 0,05	3,26 ± 0,06	3,33 ± 0,09	948,95±86,27

Information:
P = *pippermint*
S = soft
Y = yellow
H = homogeny
* = there are significant differences between the 1st and the 21st

Stability Test

The stability test was used to determine the stability of the gel formula under extreme temperature variations over a six-cycle period. Based on the stability test, it can be observed that the gel preparation exhibits

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organoleptic stability; however, changes in pH and viscosity are evident. The pH and viscosity values show a tendency to increase from cycle 0th to cycle 6th. Based on the ANOVA test followed by the Post hoc Dunnett T3 test, it is stated that variations in the composition of the gelling agent and humectant base can affect the stability test. The changes during the 6-cycle stability process, as determined by Wilcoxon statistical data processing, are known to be insignificant ($p > 0.05$) in both pH and viscosity values. Gel viscosity also affects the pH value, as the increase in pH enhances the ability of carbomer 940 to act as a gelling agent. Carbomer 940 will provide good viscosity at a pH range of 5-7, due to its ability to withstand network formation and interact with HPMC 8060-M through hydrogen bonds. At the same time, the composition of HPMC 8060-M does not alter the pH [33]. Stability test results for the gel fraction of ethyl acetate in noni fruit are presented in Table 3.

Stability testing was conducted for only 21 days under cyclic stress conditions. Long-term stability testing of topical preparations (at least 28 days to 3 months) under ICH-recommended conditions (25 °C ± 2°C/60 % ± 5% RH) is preferred. Furthermore, this study did not include in vitro drug release data, which is a key parameter for predicting gel performance. This discussion has limitations, namely that in vitro release testing has not been conducted. Therefore, in future research, release kinetic studies using diffusion membranes (such as cellophane membranes) can be performed as a next step to evaluate the efficacy of the formula.

Table 3. Gel formula stability test results

Parameters	Odor, texture, color, and homogeneity		*p*H		Viscosity (cP)	
Formula	Average ± SD cycle of					
	0	6	0	6	0	6
1	P, S,Y, H	P, S,Y, H	4.73±0.03*	4.54±0.06*	3,888±7.64*	16,407±4.81*
2	P, S,Y, H	P, S,Y, H	5.00±0.02*	5.52±0.02*	2,198±2.89*	11,373±5.95*
3	P, S,Y, H	P, S,Y, H	4.12±0.01*	4.49±0.01*	3,252±93.05*	13,720±312*
4	P, S,Y, H	P, S,Y, H	5.62±0.05*	5.91±0.05*	3,893±2.89*	17,820± 131*
5	P, S,Y, H	P, S,Y, H	4.78±0.03*	4.78±0.01*	3,858±43.68*	16,513±688*
6	P, S,Y, H	P, S,Y, H	4.19±0.04*	4.15±0.06*	3,487±324.67*	13,787±272*
7	P, S,Y, H	P, S,Y, H	5.01±0.16*	5.45±0.06*	2,825±944.93*	15,667±95*
8	P, S,Y, H	P, S,Y, H	5.77±0.01*	6.07±0.02*	2,667±127.02*	12,613±171*
9	P, S,Y, H	P, S,Y, H	4.98±0.03*	5.04±0.32*	2,468±202.51*	11,160±668*
10	P, S,Y, H	P, S,Y, H	4.01±0.02*	4.02±0.02*	2,087±2.89*	10,520±367*
12	P, S,Y, H	P, S,Y, H	4.97±0.04*	4.85±0.03*	2,468±314.81*	11,193±513*
13	P, S,Y, H	P, S,Y, H	4.66±0.02*	4.53±0.08*	3,825±63,84*	16,673±549*

Information:
P = *Pipermint*
L = Soft
K = Yellow
H = Homogeny
* = significantly different ($p<0.05$) between cycle 0th and cycle 6th for each formula (based on paired statistical test)

Formula Optimization Using Simplex Lattice Design

A good desirability value is close to one, indicating that the results are closer to the target. [35]. The SLD method yielded the predicted optimum gel formula concentration of Carbopol 940 (1.491%): HPMC 8060-M (0.509%): propylene glycol (8.000%), with a desirability of 0.917. The desirability contour plot (orange) indicates the optimum region. The dark blue area indicates the predicted (superimposed) optimum gel formula. The superimposed region represents the desirability. The predicted optimum formula yielded a viscosity of 2,092.011 cP, a pH of 4.00, and an IC_{50} of 437.017 ppm.

The responses of viscosity, pH, and IC_{50} are crucial parameters for determining the gel preparation's ability to spread and provide therapeutic effects when applied to the skin surface. Based on the ANOVA test from Design-Expert software version 12, it is evident that the three responses exhibit a significant linear mixture graphic model ($p < 0.05$), indicating that the variation in the composition of carbopol 940, HPMC 8060-M, and propylene glycol successfully produces different response values between the formulas. The results of the ANOVA test, the SLD Equation, and the t-test are presented in Table 3.

The F-value of lack of fit for the viscosity, pH, and IC_{50} responses indicates that the results are relatively insignificant ($p > 0.05$) compared to the error. Insignificance is required to achieve a suitable model (fit). The higher the lack of fit value, the greater the mismatch, indicating that the gel preparation optimisation research

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model is successful. The lack of fit results show that the viscosities of 0.0514 (5.14%), pH of 0.0757 (7.57%), and IC_{50} of 0.0843 (8.43%) have a good fit value category [36]. The R^2 is used to measure the accuracy of the data in relation to a perceptual map. Adjusted R^2 is used to assess the influence of independent variables on the dependent variable. The closer the R^2 and adjusted R^2 values are to 1, the more perfectly the data is mapped [37]. The predicted R^2 function identifies model overfit. A negative result implies that the overall average of the predictors is likely better than the resulting response. This can be caused by the large amount of data in the model, resulting in excessive noise. The adequate precision value measures the signal-to-noise ratio. Test results showing a value greater than 4 indicate a strong signal and are unaffected by noise, thus allowing the model to be used [36]. A negative predicted R^2 value indicates that the model lacks good predictive ability for new data. This is likely due to high data variation or model complexity that is disproportionate to the amount of available data. Although the T-test results indicate the significance of the variable, interpretation of the model's predictive power should be approached with caution.

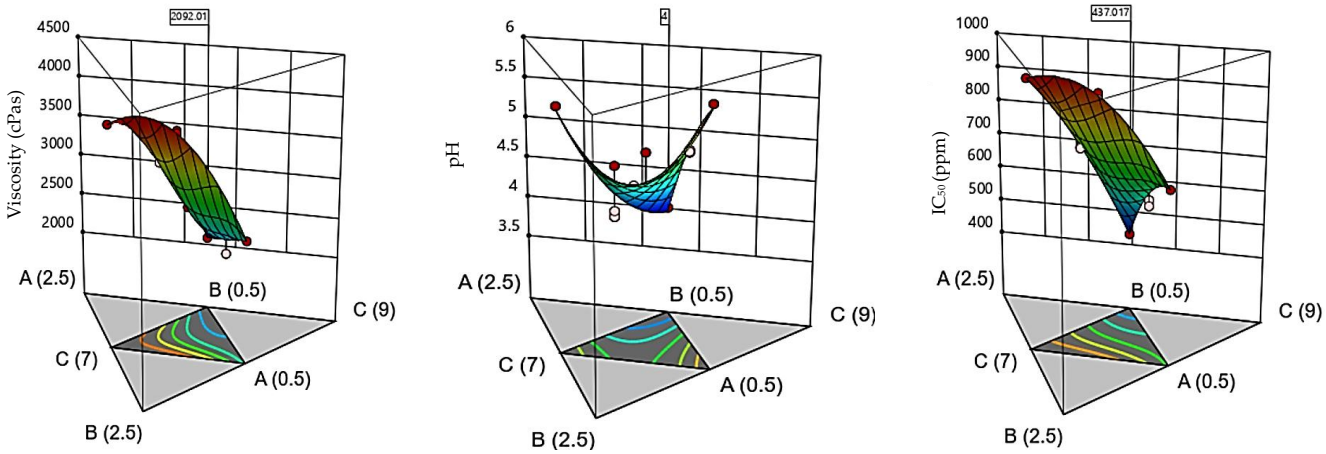

Figure 1. Results of the optimal formula for viscosity, pH, and IC_{50} of the 3D gel formula.

Table 3. Results of ANOVA test, SLD Equation, and T-test

Parameter	Viscosity (cP)	*p*H	IC_{50} (ppm)
Model	<0,0001	0,0053	< 0,0001
Linear mixture	<0,0001	0,0047	< 0,0001
Lack of fit	0,0514	0,0757	0,0843
R^2	0,9813	0,8696	0,9711
Adj. R^2	0,9679	0,7764	0,9505
Predicted R^2	-1,8156	-16,2219	-2,6544
Adequate precision	23,3220	10,5044	22,0491
Respon	Persamaan *Simplex Lattice Design* (Y)		
Viscosity (cP)	17,116.1(A) + 19,080(B) + 10,862.8(C) – 56,820(AB) – 47,611.1(AC) – 49,220 (BC) + 113,693 (ABC)		
*p*H	5,08167(A) + 4,56842(B) + 9,84842(C) + 3,00871(AB) –13,9513(AC) – 5.92462 (BC)		
IC_{50} (ppm)	2.082,18(A) + 3.112,47(B) + 1.655,28(C) – 6.491,71(AB) – 5.744,97(AC) – 6.723,57(BC) + 14.812,7(ABC)		
Respon	Prediction	Result	Significance
Viscosity (cP)	2092,01	2.121,67±71,47	0,547
*p*H	4,0	4,27±0,18	0,37
IC_{50}	437,017	441,93±13,42	0,590

Information :
Y = Response
A = Carbopol 940
B = HPMC 8060-M
C = propylene glycol

The viscosity, pH, and IC_{50} data were normally distributed, as indicated by response values lying around the standard line of the residual plot. The coefficients of Carbopol 940, HPMC 8060-M, and propylene glycol increased the viscosity, pH, and IC_{50} of the gel (positive coefficients A, B, and C). The interaction of

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Carbopol 940 with HPMC 8060-M increased the pH (positive coefficient AB) and decreased the viscosity and IC_{50} (negative coefficient AB). The interaction of Carbopol 940 with propylene glycol and HPMC 8060-M with propylene glycol can reduce the pH, viscosity, and IC_{50} values of the gel (negative AB and BC coefficients). In contrast, the interaction of Carbopol 940, HPMC 8060-M, and propylene glycol increases the viscosity and IC_{50} of the gel (positive ABC coefficient).

Verification of the optimum formula using the T-test showed that the prediction of the optimal gel formula using the SLD method can provide valid predictions for optimising gel preparations. [9], particularly regarding the response to viscosity, pH, and IC_{50} values. The obtained desirability value of 0.917 was also proven in this study, as the closer the value is to 1, the closer the results are to the expected target.

Conclusion

Based on the research conducted, it can be concluded that the ethyl acetate fraction of noni fruit exhibits the best antioxidant activity, specifically 20.35±0.18 ppm (strong category). The most active noni fruit fraction gel formula with the Simplex Lattice Design method that has the most optimal physical quality is Carbopol 940:HPMC 8060-M: propylene glycol (1.491:0.509:8.000). It affects the critical parameters of viscosity, pH, and antioxidant activity, which is predicted to have a very high desirability value (0.917) and has been validated.

Conflict of Interest

No conflict of interest

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Supplementary Materials

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