JURNAL ILMU KEFARMASIAN INDONESIA, April 2023, page 71-79 Vol. 21, No. 1
ISSN 1693-1831

Optimization of CMC-Na and Glycerin in Aloe Vera Extract Gel with Simplex Lattice Design

(Optimasi CMC-Na dan Gliserin dalam Sediaan Gel Ekstrak Lidah Buaya secara *Simplex Lattice Design*)

MARTINA INDAH ANITA[1], AGATHA BUDI SUSIANA LESTARI[1*]

[1]Faculty of Pharmacy, Sanata Dharma University Campus III, Sleman, DIY Yogyakarta 55282, Indonesia

Submitted 13 April 2022, Accepted 24 March 2023

Abstract: Aloe vera (*Aloe barbandesis* Mill.) is a plant with many benefits, such as an antibacterial agent. A gel dosage form has many advantages, such as being easy to use, not sticky, and quickly washed with water. This pure experimental study aims to obtain the optimal composition of CMC-Na as a gelling agent and glycerin as a humectant to produce a gel with good physical properties and physical stability using the Simplex Lattice Design. The results of the responses of spreadability, viscosity, viscosity shift, and spreadability shift were used to determine the optimum formula and were analyzed using Design Expert® v13 trial Software. The results of the research found that the optimum formulas were formulas 1, 2, and 3 with a concentration of CMC-Na and glycerin, respectively, which were 1.500 g and 1.750 g; 1.563 g and 1.688 g; and 1.625 g and 1.625 g. In addition, formulas 1, 2, and 3 fulfill the gel's physical properties and stability parameters.

Keywords: Aloe vera extract, gel, glycerin, Na-CMC, simplex lattice design

Abstrak: Lidah buaya (*Aloe barbandesis* Mill.) merupakan tanaman yang mempunyai banyak manfaat salah satunya sebagai antibakteri. Ekstrak lidah buaya terbukti memiliki aktivitas sebagai antibakteri. Ekstrak lidah buaya dicoba untuk diformulasikan dalam bentuk sediaan gel karena kelebihan dari sediaan gel seperti mudah diaplikasikan pada kulit, tidak lengket dan mudah dicuci dengan air sehingga mempermudah dalam penggunaannya. Penelitian ini merupakan penelitian eksperimental murni yang bertujuan untuk mendapatkan komposisi CMC-Na sebagai *gelling agent* dan gliserin sebagai humektan yang optimal sehingga menghasilkan sifat fisik dan stabilitas fisik sediaan gel yang baik menggunakan metode optimasi *Simplex Lattice Design.* Hasil respon daya sebar, viskositas, pergeseran viskositas, dan pergeseran daya sebar digunakan untuk menentukan formula optimum. Data hasil uji dianalisis dengan ANOVA satu arah menggunakan *Design Expert® v13 trial Software*. Berdasarkan hasil penelitian, ditemukan formula optimum yaitu pada formula 1, 2, dan 3 dengan konsentrasi CMC-Na dan gliserin secara berturut-turut yaitu 1,500 g dan 1,750 g; 1,563 g dan 1,688 g; dan 1,625 g dan 1,625 g. Selain itu, formula 1, 2, dan 3 memenuhi parameter sifat fisik dan stabilitas fisik gel.

Kata kunci: CMC-Na, ekstrak lidah buaya, gel, gliserin, *simplex lattice design*

*Corresponding author
e-mail: a_budi@usd.ac.id

INTRODUCTION

ALOE vera is a plant with many benefits for body care and treatment. It stated aloe vera contains secondary metabolites with antibacterial activity[1]. Antibacterial substances from aloe vera are anthraquinones (aloin, aloe-emodin, and barbaloin). Aloe vera extract inhibits the growth of *Staphylococcus aureus* bacteria with moderate to severe strength[2].

This research aim is to produce antibacterial aloe vera gel to treat infections on the skin surface caused by *Staphylococcus aureus* bacteria. This bacterium can cause an infection in the wound, usually in the form of an abscess, a collection of pus or fluid in the tissue. *Staphylococcus aureus* can be found on the skin surface as normal flora, especially around the nose, mouth, genitals, and anus[3]. The function of the skin is to protect the body from physical disturbances such as bacteria, fungi, or viruses. The skin is very susceptible to infection, mainly caused by bacteria. Therefore, it is necessary to have an antibacterial dosage form suitable for skin application. The selected dosage form is a gel because it is easy to dry when applied to the skin, easily washed, and provides a cooling sensation, which helps increase therapeutic effectiveness and comfort for the user[4].

Gel is one of the most used pharmaceutical dosage forms, in which the gelling agent is used at low concentrations distributed in a liquid medium[5]. The macromolecular materials will form interconnected networks and provide a rigid structure where the active ingredients are located. Humectants maintain the stability of gel form by absorbing moisture and reducing water evaporation from gel form. The gelling agent used in this study was CMC-Na, and the humectant used was glycerin.

Pharmaceutical dosage forms should fulfill the optimum composition of the ingredients used because they will produce good physical quality. In gel formulations, the gelling agent is a critical factor affecting physical properties[6]. The higher the concentration of the gelling agent, the higher the viscosity and the lower the spreading power of the gel. The humectants can keep the gel stable and maintain skin moisture, so the skin is not dry[7]. Therefore, it is necessary to optimize these two compositions in gel form to determine a formula of gel that meets the parameters of physical properties (organoleptic, pH, homogeneity, spreadability, and viscosity) and physical stability (viscosity shift and spreadability shift) of aloe vera extract gel. The method used in this study was the Simplex Lattice Design (SLD) with five modified formulas at varying concentrations of CMC-Na and glycerin. Simplex Lattice Design is a method used to optimize the mixture of ingredients in a formula and can be used to optimize two or more variables[8]. The composition of this mixed material was used to predict the response through the Simplex Lattice Design equation. The data of each response of physical properties and physical stability tests were analyzed with the Design Expert® v13 trial Software Version 13 trial to obtain the optimum formula.

MATERIALS AND METHODS

MATERIALS. Mueller Hinton Agar (Oxoid) powder media, 10% DMSO (Merck), *Staphylococcus aureus* bacterial suspension (ATCC 25923), aloe vera extract (Eteris Nusantara, Indonesia), CMC-Na (pharmaceutical grade, Brataco, Indonesia), glycerin (pharmaceutical grade, Brataco, Indonesia), methylparaben (pharmaceutical grade, Brataco, Indonesia), propylparaben (pharmaceutical grade, Brataco, Indonesia), aquadest.

Tools. Biologycal safety cabinet (ESCO class II LA2-3A1-E), nephelometer (Thermo Scientific), autoclave (ALP K-40), analytical balance (Ohaus), pH-meter (Ohaus ST 10 pH Pen Meter), viscometer (Rheosys Merlin VR), mixer (Hand River), stopwatch (Chronograph), vernier calipers (Kenmaster), glassware (Pyrex).

METHODS. Extract Collection. The aloe vera extract was obtained from the producer Eteris Nusantara in the Gunung Kidul regency, Yogyakarta Special Region, Indonesia.

Antibacterial Activity Test. Antibacterial activity testing was carried out by the disc diffusion method. The *Staphylococcus aureus* bacterial suspension was spread evenly on the surface of the Mueller Hinton Agar medium, then covered for 5-15 minutes. Place a paper disc that previously has been dripped with a solution of aloe vera extract at concentrations of 10%, 15%, 20%, and 25%, then place it on Mueller Hinton Agar media inoculated with the bacteria. Ampicillin 10 mcg and DMSO 10% were positive and negative controls. Incubated the agar at 35-37ºC for 18-24 hours, then measured the zone of inhibition[3].

Data on the inhibition zone of aloe vera extract on the growth of *Staphylococcus aureus* was stated in diameter (mm). The inhibition zone criteria, according to A'lana et al. 2017[1], state that the strength of the antibacterial activity is 20 mm or more, which means very strong, 10-20 mm is firm, 5-10 mm is medium, and 5 mm or less are weak.

Gel Formulation. In this study, the formula was modified with variations in the composition of the CMC-Na (3-3.5%) as a gelling agent and glycerin (3-3.5%) as a humectant using the Simplex Lattice

Table 1. Gel formulation.

Formula (g)	1	2	3	4	5
Aloe vera extract	7.9	7.9	7.9	7.9	7.9
CMC-Na	**1.500**	**1.563**	**1.625**	**1.688**	**1.750**
Glycerin	**1.750**	**1.688**	**1.625**	**1.563**	**1.500**
Methylparaben	0.09	0.09	0.09	0.09	0.09
Prophylparaben	0.01	0.01	0.01	0.01	0.01
Ethanol 96% (mL)	2	2	2	2	2
Aquadest	ad 50	ad 50	ad 50	ad 50	ad 50

Design method. The formula obtained is presented in Table 1.

Gel Preparation. CMC-Na was dispersed in distilled water for 24 hours and homogenized to form a gel base. Add methylparaben and propylparaben in ethanol and homogenized. Add glycerin and aloe vera extract in aqua dest to the mixture and homogenize. The remaining aqua dest was added to the mixture and homogenized. The mixing process uses a mixer in scale 2 for 10 minutes[9].

Gel Physical Properties Test. The organoleptic test was gel consistency, odor, and color. This test was carried out 48 hours after the preparation of the gel[9].

The pH test used a pH meter by weighing 1 g of aloe vera gel, diluted with 10 mL of distilled water. The electrode is dipped into the gel until the screen on the pH meter shows a stable number. The normal pH range for skin is 4.5-6.5[10].

Gel homogeneity was carried out 48 hours after the preparation of the gel by taking a few aloe vera gels, placing them on a glass object, covered with another glass object. The gel form must show a homogeneous mixture, have a consistent color, and there are no visible coarse grains or lumps in the gel form[11].

The spreadability test was carried out by weighing 0.5 g of gel and placed in the middle of a round glass with a scale. On top, place another round glass and add 150 g of weights. We measured the diameter of the gel spread. The expected spread of the gel for topical use ranges from 5-7 cm in diameter[11].

Viscosity measurements were carried out using a Rheosys Merlin VR viscometer connected to Micra software. This test uses a 2/30mm spindle cone and plate. Several gels are placed in a plate and cone, the tool is turned on, and the viscosity is measured at 10 rpm. Preparations are known by observing the measurement results listed on the computer application. The requirement for gel viscosity is 2-4 Pa.s[12].

Gel Stability Test. Gel physical stability test was carried out by storing the preparation at room temperature for 28 days. Data were compared before and after storage for 28 days[13].

The effect of the addition of CMC-Na and glycerin on the tests carried out (viscosity, spreadability, viscosity shift, and spreadability shift) can be seen using Design Expert® v13 trial Software Version 13 trial so that the Simplex Lattice Design equation is obtained. A contour plot and optimum area are obtained for each response, which can be seen from the desirability value. The selected formula has a composition of CMC-Na and glycerin with a desirability value of 1. The results were validated by one-way ANOVA using the Design Expert Version 13 trial application to obtain a p-value[14].

Table 2. Inhibition zone of aloe vera extract.

Inhibition zone diameter (mm) ($\bar{x}$ ± SD)	
Aloe vera extract 10%	9.1 ± 0.200
Aloe vera extract 15%	9.9 ± 0.100
Aloe vera extract 20%	10.7 ± 0.200
Aloe vera extract 25%	11.2 ± 0.153
Ampicillin 10 mcg	11.1
DMSO 10%	0

RESULTS AND DISCUSSION

Antibacterial Activity Test. An antibacterial test was conducted to prove that aloe vera extract has antibacterial activity. The results are shown in Table 2.

Based on the average results, the inhibition zone for *Staphylococcus aureus* was classified as moderate to strong. The inhibition zone obtained from the viscous extract of aloe vera at concentrations of 10% and 15%, respectively, were 9.1 mm and 9.9 mm. The inhibition zone obtained from the viscous extract of aloe vera at a concentration of 20% and 25%, respectively, were 10.7 mm and 11.2 mm, showing that it has intense antibacterial activity. The positive control used in this study was ampicillin ten mcg; it is sensitive to *Staphylococcus aureus* when the inhibition zone is ≥29 mm based on the antibiogram table. In this study, ampicillin ten mcg gives an inhibition zone of 11.1 mm. Based on CLSI standard[15], this indicates that ampicillin has resistance to *Staphylococcus aureus* bacteria. In this study, ampicillin was used as a method control to ensure the method used was suitable. DMSO 10% as negative control had no inhibition zone, indicating no antibacterial activity. Linear regression was carried out due to consideration of the formulation aspect so that the concentration of aloe vera extract was obtained into gel preparations. The equation obtained is as follows: $Y= 0.1438X + 7.716$. The y value was plotted in the lower limit of the substantial inhibition zone criteria (10 mm), so an x value of 15.8 was obtained ($r= 0.995$). A combination of preservatives is used to broaden the activity of the spectrum against gram-positive and harmful bacteria.

Table 3. Time and rate mixing data.

Formula	Formula 1				Formula 5			
Rate	Scale 1		Scale 2		Scale 1		Scale 2	
Time (min)	5	10	5	10	5	10	5	10
Spreadability (cm)	5.6	5.7	5.7	**5.8**	3.9	4.1	4.0	**4.1**
Viscosity (Pa.s)	2.412	2.321	2.389	**2.241**	5.592	5.418	5.519	**5.329**

Preparation of Aloe Vera Extract Gel. This study used 7.9 g of aloe vera extract in 50 g of gel. CMC-Na as a gel base has the advantage of providing a stable viscosity to the preparation. CMC-Na must be dispersed with aqua dest for 24 hours to form a gel matrix. Adding glycerin will maintain the stability of the gel preparation by reducing water evaporation from the gel preparation and maintaining skin moisture. Aloe vera extract gel preparations have a high-water content making them susceptible to microbial contamination. Methylparaben and propylparaben are added as preservatives. The combination of the two preservatives is often used in formulations and expands the activity spectrum of preservatives. Methylparaben is used as a preservative in topical preparations at 0.02-0.3%, while propylparaben is at a concentration of 0.01-0.6%[16]. Methylparaben and propylparaben were dissolved in ethanol. Methylparaben is dissolved in ethanol because methylparaben is difficult to dissolve in water and dissolves easily in ethanol. In contrast, propylparaben dissolves easily in ethanol and is very difficult to dissolve in water[17]. Methylparaben and propylparaben each dissolved in 1 mL of ethanol.

All these ingredients are mixed to determine the speed and time of the mixing process. This orientation aims to produce the desired spreadability and viscosity response. Orientation was carried out using formulas 1 and 5 by mixing each gel preparation formula using a mixer with a time of 5 and 10 minutes and mixer speed in scale 1 and 2 and then measuring the spreadability and viscosity after 48 hours after gel preparation. The orientation results are shown in Table 3.

Based on these results, a speed scale of 2 and a time of 10 minutes were chosen to use in the following gel preparations in this study. This is because, at that time and scale, the results are close to the desired range of spreadability (5-7 cm) and viscosity (2-4 Pa.s). In formula 1, the viscosity results are 2.241 Pa.s, and the spreading power is 5.8 cm, while in Formula 5, the viscosity results are 5.329, and the spreading power is 4.1 cm.

Gel Physical Properties. All gel formulas have a semisolid form, yellowish brown color, and smell of aloe vera extract. The organoleptic test results showed no change in the gel's shape, odor, and color during 28 days of storage. It concluded that the gel preparation was stable because it did not experience any changes in terms of shape, odor, and color.

The pH test was carried out to determine the safety of gel preparations when applied to human skin. If the pH of the gel is too acidic, it will cause skin irritation, while if too alkaline, it will cause the skin to dry. The normal pH range for skin is 4.5-6.5[18]. The results of the pH test are shown in Table 4. All formulas have a pH corresponding to the skin's normal pH range. Formula 4 and Formula 5 have the highest pH. The increase in pH is due to the high concentration of CMC-Na in Formula 4 and Formula 5. CMC-Na has a pH of 6.5-8.5[16]. The gel preparation changed in pH 48 hours after manufacture on the 28th day during storage. From the results of the pH test, it can be concluded that the gel preparation is stable because it does not experience changes in pH.

A homogeneity test was carried out to see that all the ingredients, when formulated, were evenly mixed. The gel preparation is homogeneous if it shows an even color and there are no visible coarse grains or lumps in the gel preparation[11]. The results show that all gel formulas had a consistent color, and the gel preparations had no visible coarse grains or lumps that the five aloe vera extract gels have good homogeneity.

A spreadability test was carried out to determine the ability of the preparation to spread on the skin when applied. The greater the distribution area, the easier it is to apply to the skin so that the absorption on

Table 4. pH of aloe vera extract gel.

Formula	pH ($\bar{x}$ ± SD)
1	5.0 ± 0
2	5.0 ± 0
3	5.0 ± 0
4	5.1 ± 0
5	5.1 ± 0

Table 5. Spreadability of aloe vera extract gel.

Formula	Spreadability (cm) ($\bar{x}$ ± SD)
1	6.00 ± 0.100
2	5.63 ± 0.153
3	5.26 ± 0.153
4	4.80 ± 0.100
5	4.23 ± 0.208

the skin is optimized. The expected spreading power of the gel for topical use is 5-7 cm in diameter[11]. The results of the spreading power of each formula are shown in Table 5.

Based on the results obtained, it was shown that formulas 1-3 were included in the range of good spreadability of gel preparations, namely 5-7 cm, while formulas 4-5 had low spreadability and did not fulfill the requirement. All gel formulas showed a decrease in spreadability from formula 1 to formula 5 as the viscosity increased the results obtained by the theory that the spreading power is inversely proportional to the viscosity. The higher the viscosity value, the spreading power will decrease[6]. The effect of adding CMC-Na and glycerin to the spreadability test can be seen using Design Expert® v13 trial Software Version 13 Trial. The Simplex Lattice Design equation obtained for the power response is Y= -54.59A + 42.87B + 9.26AB. The equation shows Y as the value of the spreadability response, while A is the concentration of CMC-Na, and B is the concentration of glycerin. The above equation shows that glycerin has the highest positive coefficient value. This shows that glycerin has the most effective in increasing the spreadability.

The combination of CMC-Na and glycerin also has a positive coefficient value which means it can increase the spreadability of the gel, but the effect is not as significant as glycerin; on the other hand, CMC-Na has a negative coefficient value indicating that CMC-Na plays a role in reducing the spreadability of the gel. Based on the contour plot of the spreadability of the gel preparation in Figure 1, the lower the glycerin concentration, the spreading power will decrease, and

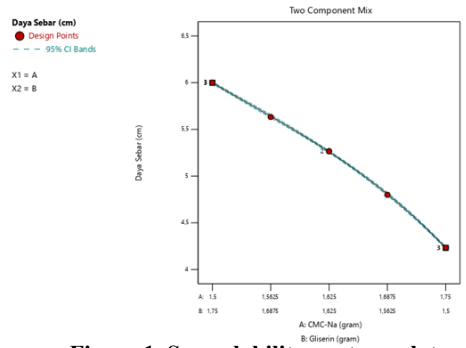

Figure 1. Spreadability contour plot.

vice versa. CMC-Na as a gelling agent, has a high viscosity. Therefore, the addition of CMC-Na has the dominant effect in reducing the spreadability of the gel, and the addition of glycerin has the highest effect in increasing the spreadability.

Viscosity is a statement of the resistance of a preparation that affects its flow properties. The viscosity test is carried out to determine the thickness of the gel preparation so that the gel preparation is expected to have a good consistency and can be easily applied to the skin. The results are shown in Table 6. It shows formulas 1-3 had good viscosity values and

Table 6. Viscosity of aloe vera extract gel.

Formula	Viscosity (Pa.s) ($\bar{x}$ ± SD)
1	2.254 ± 0.093
2	3.047 ± 0.086
3	3.774 ± 0.230
4	4.526 ± 0.174
5	5.227 ± 0.136

were included in the desired viscosity value range, namely 2-4 Pa.s, while formulas 4-5 did not fulfill the excellent viscosity range. The Simplex Lattice Design equation obtained for the viscosity response is as follows: Y = 4.93 A – 6.94 B + 2.66 AB.

The equation shows Y as the viscosity response while A is the concentration of CMC-Na, B is the concentration of glycerin, and AB is the concentration of CMC-Na and glycerin. These data show that CMC-Na has the most significant positive coefficient value. This shows that CMC-Na has the most effective in increasing the viscosity. This is proven because formula 4 and formula 5 have a high concentration of CMC-Na and a high viscosity value. The CMC-Na and glycerin mixture also has a positive coefficient value indicating that the mixture can increase the viscosity, but the effect is not as significant as CMC-Na. When CMC-Na is dispersed into water, polymer molecules from CMC-Na will enter the cavity formed by water molecules which causes hydrogen interactions between the hydroxyl groups of CMC-Na and water molecules. This interaction will help the swelling of CMC-Na so that the higher concentration of CMC-Na causes more hydrogen interactions to form and causes the viscosity of the preparation to increase[19]. Glycerin has a negative coefficient value which indicates that glycerin affects reducing viscosity. The viscosity profile obtained from the Simplex Lattice Design equation using Design Expert® v13 trial Software Version 13 Trial is shown in Figure 2.

Based on the contour plot of the viscosity of the gel preparation in Figure 2, the higher the CMC-Na concentration, the resulting viscosity will increase, and

vice versa. The lower the glycerin concentration, the resulting viscosity will increase. Increasing the use of CMC-Na has a dominant influence in increasing the

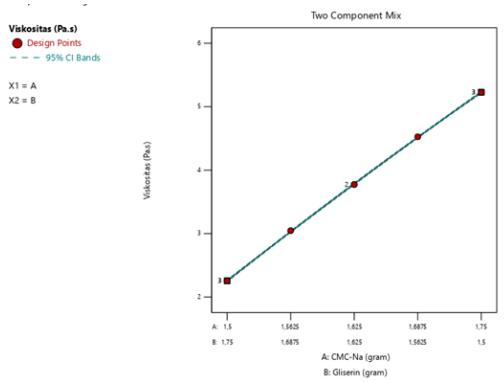

Figure 2. Viscosity contour plot.

viscosity; this is because CMC-Na itself has a high viscosity, while increasing the amount of glycerin affects reducing the viscosity because glycerin is a hygroscopic component that can bind water, so that the consistency of the gel becomes more dilute[20].

Gel Physical Stability Test. A stability test is carried out to determine the physical stability of the gel preparation during the storage period. A preparation must be able to maintain its stability during storage time. The stability of preparation can be seen from the shift in viscosity and spreadability during 28 days of storage. Preparations have good physical stability if they have a shifting percentage of less than 10%. The formula for calculating the shift is:

$$\% \text{ shift } = \frac{|b-a|}{a} \; x \; 100\%$$

a= Viscosity/spreadability in 48 hours after preparation
b= Viscosity/spreadability in 28 days after preparation

The shift in viscosity indicates a change in the viscosity of the gel during storage. Tests were conducted by comparing the viscosity after 48 hours of manufacture with the viscosity during 28 days of storage. This was done to see whether there was a change in the viscosity of the gel during the storage period. The results obtained are shown in Table 7. It shows that all formulas experienced a change in viscosity during 28 days of storage. Each formula has a different viscosity shift. In formula 4, the highest viscosity shift was obtained because there was a significant decrease in viscosity after 28 days of storage. At 48 hours after making the gel, a viscosity value of 4.526 Pa.s was obtained; after 28 days of storage, a viscosity value of 4.153 Pa.s was obtained. The greater the value of the resulting viscosity shift, the viscosity value on the 28th day will decrease. This is caused by the temperature and humidity of the storage room so that when the packaging is less tight, the gel absorbs moisture from the outside and increases the volume of water in the gel, which causes the consistency of the gel to decrease[4]. A preparation is declared to have good stability if there is no significant change in viscosity during storage or the shift value is less than 10%. All formulas have a viscosity shift value of less than 10%. This shows that all formulas fit into the criteria of good viscosity shift. The Simplex Lattice Design

Table 7. Viscosity shift of aloe vera extract gel.

Formula	48 hours (Pa.s) ($\bar{x} \pm SD$)	Day-28 (Pa.s) ($\bar{x} \pm SD$)	Viscosity shift (%)
1	2.254±0.093	2.156±0.123	4.35
2	3.047±0.086	2.874±0.069	5.68
3	3.774±0.230	3.516±0.152	6.84
4	4.526±0.174	4.153±0.110	8.24
5	5.227±0.136	4.913±0.122	6.01

equation is Y = -1641.80 A + 1451.71 B+ 119.66 AB. The above equation shows that Y is the response to a shift in viscosity, while A is the concentration of CMC-Na, B is the concentration of glycerin, and AB is the concentration of CMC-Na and glycerin.

Glycerin has the highest positive coefficient value, which indicates that glycerin has the most significant influence in increasing the viscosity shift. Based on these data, the viscosity shift profile was obtained from the Simplex Lattice Design equation using Design Expert® v13 trial Software Version 13 Trial shown in Figure 3. Based on the figure, it shows that the graph

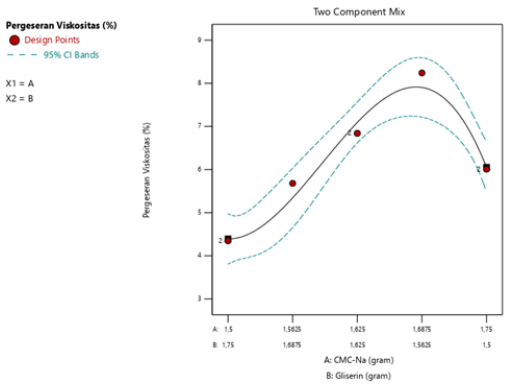

Figure 3. Viscosity shift contour plot.

of the viscosity shift results is not linear because each formula has a different viscosity shift value. From the results of the viscosity shift test, it can be concluded that all formulas have a viscosity shift by the expected criteria, which is less than 10%.

Spreadability shift was measured 48 hours after the gel preparation and after 28 days of storage. Measurement of spreadability after 28 days of storage aims

to see the gel preparation's stability by seeing whether a shift in spreadability occurs or not. The results obtained are shown in Table 8. Based on the results obtained, all formulas experienced different shifts in spreadability. Formula 4 has the most significant shift in spreadability because there is an increase in spreadability after 28 days of storage. Preparation has good physical stability if there is no significant change in spreading power or the spreadability shift value is

Table 8. Spreadability shift of aloe vera extract gel.

Formula	48 hours (Pa.s) (x̄±SD)	Day-28 (Pa.s) (x̄±SD)	Spreadabilityshift (%)
1	6.00±0.100	6.20±0.100	3.33
2	5.63±0.153	5.83±0.153	3.55
3	5.26±0.153	5.50±0.100	4.44
4	4.80±0.100	5.13±0.058	6.94
5	4.23±0.208	4.40±0.100	3.95

less than 10%. The data shows that all formulas have good physical stability because all formulas fall within the range of shifts of good spreadability, which is less than 10%. The Simplex Lattice Design equation is Y = -2819.02 A + 2697.85 B + 76.45 AB.

The equation shows that Y is a response to a shift in spreadability shift, while A is the concentration of CMC-Na, and B is the concentration of glycerin. AB is the concentration of CMC-Na and glycerin. Glycerin has the highest positive coefficient value. This indicates that glycerin has a dominant influence in increasing the shear spread. Glycerin is a hygroscopic component, so when a gel pack is less tight, glycerin will attract water or moisture from the outside so that the consistency of the gel becomes thinner. The spreadability is greater[4]. The combination of CMC-Na and glycerin also has a positive coefficient which means it also influences the increase in the shear spread but not as big as glycerin. CMC-Na has a negative coefficient value. This indicates that CMC-Na influences in reducing the power shift. Based on these data, the profile of the spreadability shift equation is obtained from the Simplex Lattice Design equation using Design Expert® v13 trial Software Version 13 Trial shown in Figure 4. The results of the spreadability shift are not linear because each formula has a different power shift. Formula 4 has the highest shift in spreadability shift, and this is due to a significant shift in viscosity in formula 4 and a large decrease in viscosity after 28 days of storage. It concluded that all gel formulas, less than 10%, fulfill the criteria.

Formula Optimization. Formula optimization aims to determine the optimum composition of the factors used: CMC-Na as a gelling agent and glycerin as a humectant. Optimization of the formula is

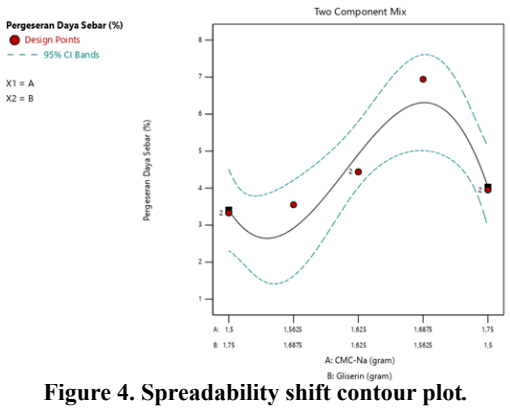

Figure 4. Spreadability shift contour plot.

determined based on physical properties (organoleptic, pH, homogeneity, spreadability, viscosity) and physical stability (viscosity shift and spreadability shift) of the gel preparation by meeting the desired parameters. Optimum formula prediction using Design Expert® v13 trial Software Version 13 Trial on the parameters of physical properties and physical stability of the five modified formulas that have been carried out. The selected formula has a composition of CMC-Na and glycerin with a desirability value close to 1. The highest desirability value is 1. The closer to one, the better the desirability value[21]. The optimum desirability formula results in this study are shown in Figure 5. Based on these results, it can be concluded that the optimum composition is obtained in formulas 1, 2, and 3 because they have a desirability value of 1. In formulas 1, 2, and 3, CMC-Na and

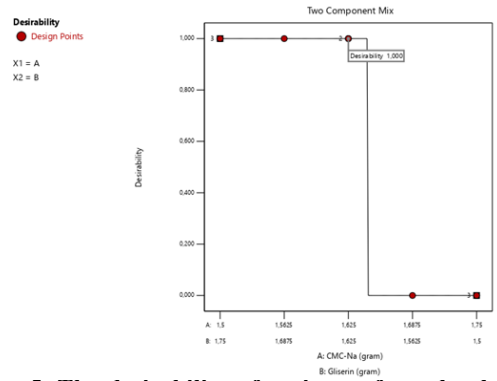

Figure 5. The desirability of optimum formula aloe vera extract gel.

Glycerin compositions are 1.500 g and 1.750g; 1.563g and 1.688g; and 1.625 g and 1.625 g. In addition, the results of testing formulas 1, 2, and 3 met the desired parameters of physical properties (organoleptic, pH, homogeneity, spreadability, viscosity) and physical stability (viscosity shift and spreadability).

Equation Validation. Equation validation was carried out, aiming to see whether the equation from this study's results was valid. The results of this study were validated by one-way ANOVA using Design Expert® v13 trial Software 13 Trial so that the p-value

was obtained, shown in Table 9. Based on the validation results, the p-value was obtained on the ANOVA Design Expert® v13 trial Software results from the 4 tests carried out, namely scattering power, viscosity, viscosity shifting, and spreading power shifting.

Table 9. Equation validation.

Respon	*p-value*
Spreadability (cm)	$p<0.0001$
Viscosity (Pa.s)	$P<0.0001$
Viscosity shift (%)	0.0017
Spreadability shift (%)	0.0308

The p-value <0.05 shows significant results, so the equation obtained from each test response is valid[22]. The validation results from table 9 show that all test responses, namely scatter, viscosity, shear, and viscosity, have p <0.05, so it can be concluded that the equations of all test responses are valid.

CONCLUSION

The optimum composition of aloe vera extract gel preparation (*Aloe barbandesis* Mill.) with Simplex Lattice Design met the parameters of physical properties (organoleptic, pH, spreadability, homogeneity, viscosity) and physical stability (viscosity shift and spreadability) of good gel preparations namely in formulas 1, 2, and 3 with the composition of CMC-Na and glycerin respectively 1.500 g and 1.750 g; 1.563 g and 1.688 g; and 1.625 g and 1.625 g.

REFERENCES

1. A'lana L, Sari R, Apridamayanti P. Penentuan Nilai FICI value determination of combination of *Aloe vera* (L.) Burm.f. ethanol extract with gentamycin sulphate against *Escherichia coli*. Pharm Sci 2017; 4(3):132-42.
2. Puteri T, Milanda T. Inhibition test of aloe vera leaf extract (*Aloe vera* L.) against bacteria *Escherichia coli* and *Staphylococcus aureus: Review*. Farmaka 2016; 14(2):9-17.
3. Prabasari IP, Sumarya IM, Juliasih NKA. In vivo inhibitory power of aloe vera extract (*Aloe barbandesis* Miller) against the growth of *Staphylococcus aureus* bacteria. Jurnal Widya Biologi 2019; 10(1):23-32.
4. Sayuti NA. Formulation and physical stability test of chinese ketepeng leaf extract gel preparation (*Cassia alata* L.). Jurnal Kefarmasian Indonesia 2015; 5(2): 74-82.
5. Taylor KMG, Aulton ME. Aulton's Pharmaceutics The Design and Manufacture of Medicines. 6th ed. Elsevier. Chapter 28, Ointment, pastes, gels, cutaneous patches and topical spray; p.453-4.
6. Afianti HP, Murrukmihadi M. Effect of variation in hpmc gelling agent content on physical properties and antibacterial activity of basil leaf ethanolic extract gel preparations. Majalah Farmaseutik 2015; 11(2): 307-15.
7. Shan WY, Wicaksono IA. Gel formulation of mangosteen peel extract (*Garcinia mangostana*) with variation of base concentration. Farmaka 2018; 16(1):108-16.
8. Kusuma AP. Flexibility of custom design over simplex lattice design in co-processed excipient formulation. Science & Technology Indonesia 2018; 3(1): 30-4
9. Suradnyana IGM, Wirata IK, Suena, NM DS. Optimization of gelling agent and humectant of lime leaf essential oil handsanitizer gel (*Citrus amblycarpa* (Hassk.) Ochse.). Jurnal Ilmiah Medicamento 2020; 6(1): 16-8.
10. Rosida H, Sidiq HBHF, Aprilliyanti IP. Evaluation of physical properties and irritation test of banana peel extract gel (*Musa acuminata* Colla). Journal of Current Pharmaceutical Sciences 2018; 2(1):131-5.
11. Rohana, Stevani H, Dewi R. Hand Sanitizer formulation from pangi seed extract (*Pangium edule* Reinw). Media Farmasi 2019; 15(2):197-204.
12. Ardana M, Aeyni V, Ibrahim A, Formulation and optimization of hpmc (hydroxy proypl methyl cellulose) gel base with various concentration variations. Journal of Tropical Pharmacy and Chemistry 2015; 3(2):101-08
13. Astuti DP, Husni P, Hartono K. Formulation and physical stability test of lavender essential oil hand antiseptic gel preparations (*Lavandula angustifolia* Miller). Farmaka 2017;15(1):176-84
14. Ekowati D, Yuliaswari E, Rejeki ES. noni fruit extract gel formula optimization (*Morinda citrifolia* L.) as antioxidant with simplex lattice design. Jurnal Farmasi Indonesia 2016; 13(1):82-95
15. CLSI. Disc diffusion supplemental tables: performance standards for antimicrobial susceptibility testing. Clinical and Laboratory Standards Institute 2017: 33(7)
16. Sheskey PJ, Cook WG, Cable CG. Handbook of Pharmaceutical Excipients 8th edition. Pharmaceutical Press London and American Pharmacist Association, Washington; 2017
17. Dirjen RI. Farmakope Indonesia, 6th Edition. Jakarta: Kementrian Kesehatan Republik Indonesia; 2020
18. Andini T, Yuliet Y. Optimization of polyvinyl alcohol film formers and propylenglycol humectants in pumpkin fruit juice pell off gel mask formula (*Cucurbita moschata* Duchesne) as antioxidant. Jurnal Farmasi Galenika 2017; 3(2):165-73.
19. Nurdianti L, Rosiana D, Aji N. Evaluation of tea tree (*Melaleuca alternifolia*) oil anti-acne emulgel preparation using hpmc as gelling agent. Journal of Pharmacopolium, 2018; 1(1):23-31
20. Sukmawati A, Laeha NA, Suprapto. Effect of glycerin as humectant on physical properties and stability of vitamin c in solid soap. Pharmacon : Jurnal Farmasi Indonesia, 2017; 14(2):40-7.

21. Hidayat IR, Zuhrotun A, Sopyan I. Design expert software as a pharmaceutical formulation optimization tool. Majalah Farmasetika 2021;6(1):99-120.

22. Maulina L, Sugihartini N. Gel formulation of ethanol extract of mangosteen fruit peel (*Garcinia mangostana* L.) with variation of gelling agent as burnt wound preparation. Pharmaciana 2015; 5(1): 47-9.