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Optimization of Glycerin and Sorbitol in Hand Sanitizer Cream with *Centella asiatica* (L.) Extract

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ABSTRACT

The use of alcohol-based hand sanitizers can cause dry skin. *Centella asiatica* (L.) extract can be used as an alternative to alcohol because it contains triterpenoids, especially asiatic acid, potentially an antibacterial and inhibitor of the SARS-CoV-2 virus. Cream is a preparation that can moisturize and protect the skin. Glycerin and sorbitol are humectants often used in cream preparations and have a large percentage in the cream preparation's formula so that they can affect the physical properties of the cream. This study aims to obtain the optimum composition range of glycerin and sorbitol and determine the effect of glycerin and sorbitol as humectants on the physical properties and stability of the hand sanitizer cream with Centella asiatica (L.) extract. The composition optimization was done using a factorial design method on two factors and two levels using the Design Expert 13 (free trial) application. The data on the physical properties and stability of the cream were statistically analyzed using a two-way ANOVA test at a 95% confidence level. Qualitative phytochemical screening confirmed that the extract contains triterpenoids. The average test of physical properties and stability of physical properties meet the desired criteria: cream type O/W, viscosity 120–170 dPa.s., spreadability of 5-7 cm, shift of spreadability, and shift of viscosity below 10%. The optimum area indicates that formulas F1, FB, and FAB meet the desired criteria.

1. Introduction

At the beginning of 2020, the world was shocked by the news of the Covid-19 outbreak. One of the preventive measures recommended by the Indonesian Ministry of Health to prevent the spread of Covid-19 is to wash our hands more often with soap or alcohol-based hand sanitizer. Alcohol applied to the skin of the hands can denature proteins in the stratum corneum layer and cause dry hands, causing the skin to crack and peel (Jing et al., 2020). One solution to this problem is to use herbal plants as active substances to replace alcohol in hand sanitizers due to its antibacterial and antiviral activities (Listari et al., 2020).

Centella asiatica (L.) is one of the herbal plants that has antibacterial and antiviral potential because it contains triterpenoids especially asiatic acid (Rollando, 2019). Research by Wong and Ramli (2021) showed that the aqueous extract of *Centella asiatica* (L.) with a concentration of 100 mg/mL (10%) had inhibitory power on *B. cereus*, *E. coli*, and *S. Aureus* bacteria with an inhibition zone of 6.5 ± 0.41 mm, respectively. 6.33 ± 0.47 mm, 7.00 ± 0.00 mm. Research conducted in silico molecular docking by (Musfiroh et al., 2020) showed that asiatic acid has a strong binding affinity to the main protease in the SARS-CoV-2, so it was concluded that asiatic acid has the potential to be an inhibitor of the Covid-19 virus (Musfiroh et al., 2020).

Cream preparation is a semi-solid preparation in the form of an emulsion containing not less than 60% water and suitable essential ingredients (Syamsuni, 2006). Cream preparation is preferred because it is easy to remove from the container and has good spreadability. Humectants are important components in cream formulations. Adding humectants to the cream formulation gives the preparation a soft sensation (Santoso et al., 2018).

Glycerin and sorbitol are humectants used in cream preparations. The use of glycerin tends to cause a sticky and heavy sensation but can be subdued by combining glycerin with sorbitol (Barel et al., 2005). In the cream formula, the percentage of glycerin and sorbitol as humectants is large enough to affect the viscosity, spreadability and physical stability of the resulting cream preparation. According to (Rowe et al., 2009), the percentage of glycerin in cream is 30%, and the percentage of sorbitol is 3-15% (Rowe et al., 2009). Therefore, optimization is necessary to determine the optimal composition of glycerin and sorbitol as humectants in the hand sanitizer cream with *Centella asiatica* (L.) extract.

2. Materials and Methods

2.1. Tools and Materials

The tools used in this research were Waterbath (Memmert), pH meter (OHAUS), viscotester Rion VT-04, Ultra turrax (Ystral GmbH D-7801 Dottingen X 1020, Germany), analytical balance (OHAUS), oven (Memmert), refrigerator (Samsung), microscope (OLYMPUS).

The materials used in this research were *Centella asiatica* (L.) dried extract (*Centella asiatica* (L.)) (PT. Phytochemindo Reksa), stearic acid, triethanolamine, cetyl alcohol, glycerin, sorbitol, liquid paraffin, methyl paraben, propyl paraben, distilled water, methylene blue, acetic anhydride, concentrated sulfuric acid.

2.2. Triterpenoid Qualitative Test

The triterpenoid qualitative test was carried out using the Lieberman-Burchard method. The method involves heating 2 mg of dry extract in acetic anhydride. The mixture was then cooled, and 1 mL of concentrated H_2SO_4 was added (Balafif et al., 2013).

2.3. Formulation of Hand Sanitizer Cream with Centella asiatica (L.) Extract

The cream preparations begin with making an oil phase (stearic acid, cetyl alcohol, liquid paraffin, and propylparaben) and an aqueous phase (sorbitol, TEA, glycerin, and methylparaben) by melting each ingredient according to its phase in a water bath at 70 °C. The dry extract was dissolved with 75 mL of distilled water. The mixing process was performed with Ultra Turrax for 10 minutes with a scale of 2.5. The formula used in this study refers to the research conducted by (Utari et al., 2009).

Table 1. Hand Sanitizer Cream Formulation

Composition (%)	Formulas			
	F1	**FA**	**FB**	**FAB**
Dried *Centella asiatica* (L.) Extract	13.75	13.75	13.75	13.75
Sorbitol	6.25	8.75	6.25	8.75
Glycerin	8.75	8.75	11.25	11.25
Stearic acid	10.50	10.50	10.50	10.50
TEA	2.75	2.75	2.75	2.75
Liquid paraffin	10.00	10.00	10.00	10.00
Cetyl alcohol	2.50	2.50	2.50	2.50
Methyl paraben	0.15	0.15	0.15	0.15
Propyl paraben	0.15	0.15	0.15	0.15
Aquadest	Add 75	Add 75	Add 75	Add 75

2.1. Physical Properties test of Hand Sanitizer Cream with *Centella asiatica* (L.) Extract

2.1.1. Organoleptic test

Organoleptic test was carried out by observing the preparation of hand sanitizer cream with *Centella asiatica* (L.) extract visually, such as the color and smell of the cream (Azkiya et al., 2017)

2.1.2. Visual homogeneity test

Visual homogeneity test was carried out by taking the hand sanitizer cream with *Centella asiatica* (L.) extract at the top, middle, and bottom, then smeared on an object glass (Azkiya et al., 2017).

2.1.3. pH test

pH test was carried out by taking 1 gram of hand sanitizer cream with *Centella asiatica* (L.) extract and diluting it with 10 mL of distilled water. Then, the pH was measured using a pH meter (Lumentut et al., 2020).

2.1.4. Viscosity test

Viscosity test was carried out using a Rion viscotester by inserting the hand sanitizer cream with *Centella asiatica* (L.) extract into a portable viscometer and installing a number 2 spindle. The spindle must be wholly immersed at the time of measurement.

2.1.5. Spreadability test

Spreadability test was carried out by taking 1 gram of hand sanitizer cream with *Centella asiatica* (L.) extract and placing it on an object glass that had been coated with millimeter block paper, then placing a piece of glass on it and leaving it for 1 minute, calculating the area reached by the preparation. Then, each preparation was given a load of 50; 100; and 150 grams and left for 1 minute. The diameter achieved by the preparation was calculated (Saryanti et al., 2019).

2.1.6. Cream type test

The cream type test was carried out by placing a certain amount of cream on a drupple plate, dripping it with methylene blue, and observing using a microscope.

2.2. Physical Stability Test of Hand Sanitizer Cream with *Centella asiatica* (L.) Extract using Freeze Thaw Method

The stability test used the freeze and thaw method, where the cream was stored at ± 4^0C in the refrigerator and ± 40^0C in the climatic chamber for 24 hours each condition. The process was replicated three times, and the cream's physical changes were observed, including organoleptic, cream type, pH, visual homogeneity, viscosity, and dispersibility (Falahi et al., 2020).

2.3. Data Analysis

Analysis of physical response data (viscosity, spreadability, viscosity shift, and spreadability shift) was carried out using the Design Expert 13 application in the free trial version. From the factorial design equation, the interaction between glycerin and sorbitol at two levels for each response is found, each response will be made a contour plot. Determination of the optimum area is done using an overlay plot. The significance of the effect and interaction of glycerin and sorbitol was statistically analyzed by a two-way ANOVA test at a 95% confidence level using the Design Expert 13 application (free trial). A factor is said to be influential if it has a *p-value* <0.05. Furthermore, validation of the optimum area is carried out. Validation is done by randomly taking one of the points in the optimum area, followed by an unpaired *T-test*. The equation is said to be valid if it produces a *p-value*> 0.05 (Suradnyana et al., 2020).

3. Results and Discussion

3.1. Triterpenoid Qualitative Test Results

The test results showed that the dry extract of *Centella asiatica* (L.) used was positive for triterpenoids which were indicated by a change in the color of the the extract and reagent solution to red. The color change was caused by condensation and merging with carbocations (Siadi, 2012).

3.2. Physical Properties Test Results of Hand Sanitizer Cream with *Centella asiatica* (L.) Extract

3.2.1. Organoleptic and Visual Homogenity Test Results

The four formulas are semi-solid, have a distinctive smell of *Centella asiatica* (L.) extract, and are light brown. A high percentage of extract (10 grams) causes a light brown color and characteristic odor of the extract in the cream. The test results showed that the cream was homogeneous, with no lumps and coarse particles.

3.2.2. pH Test Results (Table 2)

Test results showed that the pH of the cream preparation ranged ±7 and did not meet the pH requirements for a safe cream. Interaction between the two emulsifiers causes saponification and produces triethanolamine stearate amine soap with a pH of ± 8 (Rowe, Sheskey, & Quinn, 2009). After three cycles of freeze and thaw stability test, the pH of the preparation is around ±7. Cream preparations must follow the physiological pH of the skin, which is in the range of 4-6. The skin needs an acidic pH to maintain skin moisture. The acidic environment allows free fatty acids to persist in a non-ionic form, thereby minimizing the occurrence of head-to-head repulsion to help form a specific bilayer structure in the stratum corneum layer. The acidic pH is also advantageous for the degradation process of proteolytic corneodesmosomes or the final step of differentiation of keratinocyte cells in the stratum corneum, where keratinocyte cells are needed to maintain the water content of the skin (Lukić et al., 2021).

3.2.3. Viscosity Test Results (Table 2)

The 0 cycle viscosity test results show that the F1, FB, and FAB formulas fall into expected ranges of 120 - 170 dPa.s, while the FA formula exceeds the expected range value. A high sorbitol level can increase the viscosity of cream preparations (Barel et al., 2005). After three cycles of freeze and thaw, the viscosity test results showed that the four formulas have decreased viscosity. The cause of the decreased viscosity is the changes in temperature and the use of glycerin as a humectant where glycerin is hygroscopic so that it easily attracts water from the surrounding environment and reduces the viscosity of the cream (Lestari, 2017). The value of the viscosity shift of the four formulas is at the expected value, which is < 10%, so the cream is stable in terms of viscosity (Table 3).

3.2.4. Spreadability Test Results (Table 2)

The four formulas have different dispersion diameters but still fall into the range of good cream spreadability, where the expected dispersion range is 5-7 cm (Purwaningsih et al., 2020). The results of the spreadability test of the four formulations after three cycles of freeze and thaw showed an increase in dispersion but fell into the desired range. The changes in the preparation's viscosity increased the spreadability (Lumentut et al., 2020). The dispersion value of the preparation is related to the viscosity value, namely, the higher the viscosity, the smaller the dispersion produced, and vice versa. The test results show that the spreadability of the cream has shifted after three cycles of freeze and thaw, but the shift experienced by the cream is at the expected value, which is < 10% (Table 3).

3.2.5. Cream Type Test Results

The methods used for the cream type were dispersion and dilution methods. In the cream type test with the dilution method, the cream appears to be soluble in water, so it is known that the outer phase of the preparation is water and the cream is O/W type. According to (Elcistia & Zulkarnain, 2019), only the emulsion's outer phases can be diluted and used as an emulsion type marker. The test results using the dispersion method showed that the four formulations of the hand sanitizer cream with *Centella asiatica* (L.) extract are O/W type creams. The microscope observations showed methylene blue spreads in the cream except for the droplets, and this is because methylene blue is a water-soluble reagent. In contrast, the droplets contained in the cream are oil, so methylene blue cannot mix with droplets. The results of the cream type test show that the hand sanitizer cream is stable because it does not change the type after three cycles of freeze and thaw test.

Table 2. Results of pH, Viscosity, and Spreadability Test (0 and 3rd Cycle)

Formula	Cycle 0 ($\bar{x}$ ± SD)			Cycle 3 ($\bar{x}$ ± SD)		
	pH	Viscosity (dPa.s)	Spreadability (cm)	pH	Viscosity (dPa.s)	Spreadability (cm)
F1	7.4 ± 0.00	166.67 ± 2.89	5.5 ± 0.41	7.3 ± 0.12	156.67 ± 2.89	5.7 ± 0.28
FA	7.3 ± 0.06	176.67 ± 2.89	5.3 ± 0.16	7.5 ± 0.06	166.67 ± 7.64	5.6 ± 0.12
FB	7.3 ± 0.10	153.33 ± 5.77	5.5 ± 0.70	7.3 ± 0.00	141.67 ± 2.89	5.9 ± 0.56
FAB	7.4 ± 0.00	168.33 ± 2.89	5.3 ± 0.18	7.3 ± 0.10	161.67 ± 2.89	5.5 ± 0.15

The data replicated 5 times

Table 3. Viscosity Shift and Spreadability Shift

Formula	Viscosity shift (%)	Spreadability shift (%)
F1	166.67 ± 2.89	5.5 ± 0.41
FA	176.67 ± 2.89	5.3 ± 0.16
FB	153.33 ± 5.77	5.5 ± 0.70
FAB	168.33 ± 2.89	5.3 ± 0.18

The data replicated 5 times

3.3. Data Analysis Test Results

3.3.1. Viscosity Responses

The following equation is the factorial design equation for the viscosity response in this study, $Y = 166.250 + 6.250X_1 - 5.417X_2 + 1.250X_1X_2$. Equation can be used to calculate the viscosity value based on the amount of sorbitol and glycerin and is used to predict the viscosity response. The viscosity response showed the effect and interaction between sorbitol and glycerin. The results of the test of the influence and interaction of the two factors can show in Table 4.

Table 4. Effect of Sorbitol, Glycerin, and their interaction on Viscosity Response

Factor	Effect	Contribution (%)	P-value	P-value Model
Sorbitol	12.500	48.019	0.001	
Glycerin	-10.833	36.819	0.001	0.0005
Interaction	2.500	1.9608	0.281	

Table 4 showed that sorbitol has the most significant effect in influencing the viscosity response with a value of 12,500 and contributes to the viscosity of 48.019%. Sorbitol has a higher molecular weight and viscosity than glycerin, so that it can increase the viscosity of the cream. In addition, sorbitol is a material that can bind water to the material so that the water content decreases and the viscosity decreases (Elfiyani et al., 2015). The effect given by glycerin is -10,833. The negative value indicates that glycerin contributes to reducing the viscosity response. The p-value of sorbitol and glycerin showed that both factors significantly affected the viscosity response. The interaction between the two factors has no significant effect on the viscosity response because the resulting p-value is > 0.05, which is 0.281.

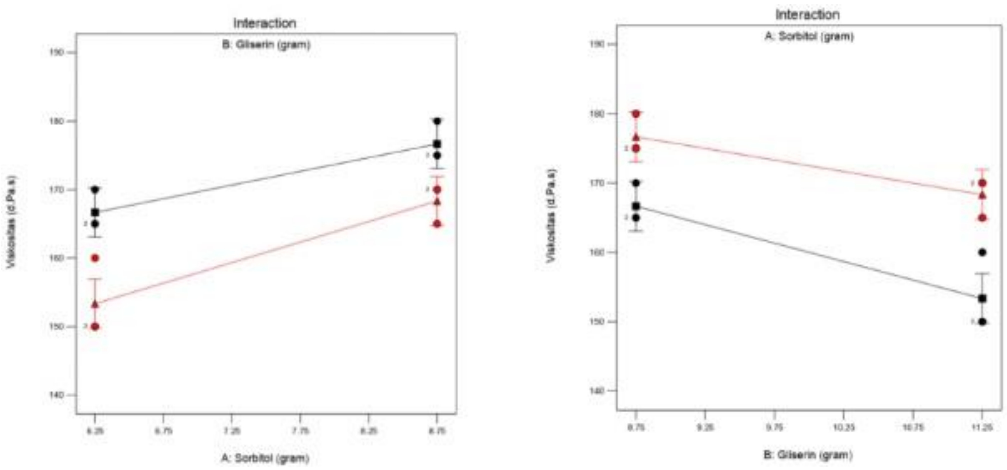

Fig. 1. (a) Interaction of sorbitol to glycerin on viscosity response. (b) Interaction of glycerin to sorbitol on viscosity response

In Figure 1(a), the black line indicates the low level of glycerin, and the red line indicates the high level of glycerin. Figure 1(a) shows that adding sorbitol to low-level glycerin and high-level glycerin can increase the viscosity of the preparation. In Figure 1(b), the black line indicates the low sorbitol level, and the red line indicates the high sorbitol level. From Figure 1(b), it is known that adding glycerin to low-level and high-level sorbitol can reduce the viscosity of the preparation.

Based on the p-value of the significant model equation, it shows that the contour plot formed is valid. The Figure 2 shows that the higher the sorbitol and the lower the glycerin used, the higher the viscosity produced. On the other hand, the higher the glycerin used and the less sorbitol used, the lower the viscosity.

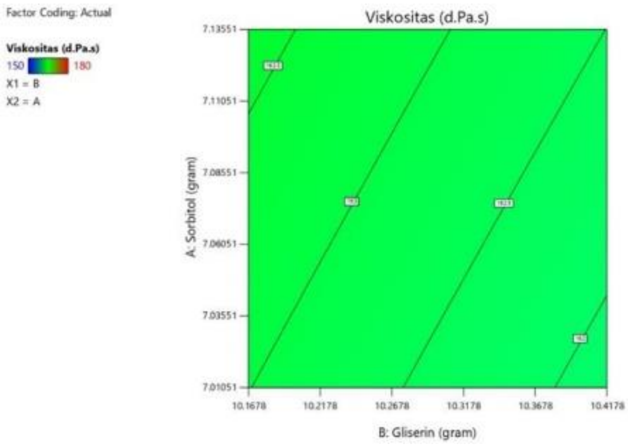

Fig. 2. Contour plot of viscosity response

3.3.2. Spreadability Responses

The following equation is the factorial design equation for the spreadability response in this study, $Y = 5{,}404 - 0{,}100X_1 + 0{,}038X_2 + 0{,}000X_1X_2$. From the results of the calculation of dispersion data on the application design expert version 13 (free trial), it is known that the model obtained is not significant, with a p-value of 0.854. Hence, the regression equation is not valid for predicting the dispersion response, the test results of the effect and interaction of sorbitol and glycerin are shown in Table 5.

Table 5. Effect of sorbitol, glycerin, and their interaction on spreadability response

Factor	Effect	Contribution (%)	P-value	P-value Model
Sorbitol	-0.200	7.706	0.435	
Glycerin	0.075	1.084	0.766	0.854
Interaction	1.026×10^{-15}	2.220×10^{-14}	1.000	

Table 5 shows that the p-value of the two factors and the resulting interaction is insignificant and indicates that the two factors and their interactions do not significantly affect the preparation's dispersion response. In preparations with pseudoplastic flow properties, the dispersion value of the preparation is related to the viscosity value, namely, the higher the viscosity, the smaller the dispersion produced, and vice versa. The slipperness, smoothness, and stiffness of the cream caused both factors, and their interactions had no significant effect on dispersion but a significant effect on viscosity (Nava, 2016).

3.3.3. Viscosity Shift Responses

The following equation is the factorial design equation for the viscosity shift response in this study, $Y = 5{,}802 - 0{,}983X_1 - 0{,}0421X_2 - 0{,}826X_1X_2$. From the results of the calculation of dispersion data on the application design expert version 13 (free trial), it is known that the model obtained is not significant, with a p-value of 0.202. Hence, the equation is not valid for predicting the viscosity shift response. The results of the test of the influence and interaction of the two factors can be seen in Table 5.

Table 6. Effect of sorbitol, glycerin, and their interaction on viscosity shift response

Factor	Effect	Contribution (%)	P-value	P-value Model
Sorbitol	-1.996	24.624	0.102	0.202
Glycerin	-0.084	0.045	0.939	
Interaction	-1.653	17.394	0.160	

Table 6 shows that the *p-value* of the two factors and their interaction is insignificant and indicates that the two factors and their interactions do not significantly affect the viscosity shift response in the preparation.

3.3.4. Spreading Shift Responses

The following equation is the factorial design equation for the spreading shift response in this study, Y = 5,295 – 0,585X1 + 0,107X2 – 1,521X1X2. From the results of the calculation of the scatter power data on the expert version 13 design application (free trial), it is known that the model obtained is not significant, with a p-value of 0.531. Hence, the equation is not valid for predicting the shift in dispersion power response. The test results of the influence and interaction of the two factors can be seen in Table 7.

Table 7. Effect of sorbitol, glycerin, and their interaction on spreadability shift response

Factor	Effect	Contribution (%)	P-value	P-value Model
Sorbitol	0.218	0.129	0.911	0.531 (not significance)
Glycerin	-2.610	18.562	0.202	
Interaction	-1.249	4.241	0.525	

Table 7 shows that the p-value of the two factors and their interaction is insignificant and indicates that the two factors and their interactions do not significantly affect the spreading shift response.

3.3.5. Overlay Plot

This study used the design expert version 13 (free trial) application to determine the optimum area. The overlay plot obtains the optimum area from the viscosity contour plot. The yellow area is the area with an optimal response, and the gray area is the area with a non-optimal response. Formulas F1, FB, and FAB met the expected criteria. The FA formula is in the gray area because the preparation has a viscosity that exceeds the range. The high viscosity is because of the high levels of sorbitol that increase the viscosity of the preparation. One optimum formula was selected from the three that met the standard criteria. The chosen formula is F1, which uses fewer ingredients, with a few ingredients, it can produce hand sanitizer cream preparations that are good in terms of physical properties and stability.

3.3.6. Validation of Response Equation in Optimum Composition Area

This study validates the viscosity equation obtained from the optimum composition area on the overlay plot. The overlay plot obtained one hundred solutions on the point prediction on the software, which is then selected to perform an unpaired *T-test*. The solution selected for the unpaired *T-test* contained 8.134 grams of sorbitol and 10.182 grams of glycerin with a predicted viscosity value of 168.721 dPa.s. The test was carried out with three replications to ensure that the test results were valid. Actual viscosity values and theoretical viscosity values were compared statistically by unpaired *T-test*. The obtained equation is consideredvalid if the *p-value* > 0.05, meaning there is no significant difference between the actual viscosity value and the theoretical viscosity value. The results of the calculation of the actual data validation against theoretical statistical data with the unpaired *T-test* can be shown in Table 8. Table 8 shows that the *p-value* obtained is > 0.05, so the obtained equation is valid.

Table 8. Calculation of validation viscosity response equation against actual data

Response Equation	Teoritical (dPa.s)	Actual (dPa.s)	p-value
Viscosity	168.72	170	0.343
	168.72	165	
	168.72	165	

4. Conclusion

The optimal amount of sorbitol and glycerin as humectants in the preparation hand sanitizer cream with *Centella asiatica* (L.) and produce preparations that meet the physical properties (viscosity) that meet the parameters are in the range of 6.5-7.1 grams for sorbitol and 11.75-11.25 grams for glycerin. Glycerin and sorbitol affect the physical properties in the form of viscosity but do not affect the stability of the hand sanitizer cream with *Centella asiatica* (L.) extract.

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Competing Interests
The authors disclose no conflict of interest.

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