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Optimization of naringenin sunscreen cream formula using the simplex lattice design method

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ABSTRACT

Naringenin is a pure isolate belonging to a group of flavonoid compounds with pharmacological effects such as anti-inflammatory, anticancer, antiatherogenic, antifibrogenic, and antioxidant properties. The purpose of this study was to determine the effect of variations in the combination of emulator tween 80 and span 80 on physical quality and stability in naringenin sunscreen preparations, obtain the optimum formula composition from emulsifying agents, and activity of naringenin sunscreen cream preparations in terms of their SPF values. The study used Design Expert 7.1.5 software to design the simplex lattice design method. Each formula was tested for the physical properties of the cream to determine dispersal adhesion for 4 weeks. Naringenin sunscreen cream with a combination of emulsifier tween 80 and span 80 in various concentrations gives a significant difference in the physical quality consisting of the parameters of spreadability, adhesion, and viscosity. The optimum formula for naringenin sunscreen cream obtained the proportion of 9% Tween 80 and 5% span 80.
Keywords: Naringenin, Simplex Lattice Design, SPF, Sunscreen.

INTRODUCTION

Naringenin is a pure isolate belonging to the class of flavonoid compounds that have been reported to exhibit broad pharmacological effects on biological systems such as anti-inflammatory, anticancer, antiatherogenic, antifibrogenic, and secondary antioxidants (absorbs UV radiation). Naringenin works as a decomposition of compounds into non-radical compounds, absorption of UV radiation, or deactivation of singlet oxygen so that it can be used as a sunscreen, which has been studied several times (Joshi et al., 2018; Kawakami & Gaspar, 2015). Long-term UV exposure can cause sunburn, hyperpigmentation, skin aging, and cancer (Gromkowska-Kępka et al., 2021). Sunscreen protects the skin from exposure to UV rays by several mechanisms, such as scattering, reflecting, or absorbing UV rays before they penetrate the skin and damage the skin layers (Saffrin M & Sureshkumar, 2019). Using natural ingredients, the solution is to replace synthetic ingredients as active substances in sunscreen cream preparations. Natural ingredients are preferred over synthetic compounds in sunscreen formulations because most natural ingredients can tolerate well on the skin and have a wide absorption spectrum.

Emulsion stability is increased by combining emulsifiers with different properties, namely hydrophilic and hydrophobic emulsifiers (Yamashita et al., 2017). Creams with nonionic emulsifying agents are better than anionic emulsifying agents because anionic emulsifying agents are generally only used as cleansers or detergents so that they can irritate and cause an unpleasant taste on the skin. In contrast, nonionic emulsifying agents are used as products. Cosmetic products because nonionic emulsifying agents can balance the work of hydrophilic and lipophilic molecules so they do not cause irritation to the skin (Tungadi, 2020). Tween 80 is a hydrophilic emulsifying agent, and Span 80 is a hydrophobic nonionic emulsifying agent (Husein & Lestari, 2019).

The Simple Lattice Design (SLD) method is used to optimize formulation in pharmaceuticals for a mixture of materials, with the proportion of the total amount of a different material being 1 (Hidayat et al., 2021). SLD is a mixed design in formulation optimization with the condition that the total amount of ingredients used is always constant (Akbar et al., 2022). This method is also considered much more effective than the trial-and-error method because the SLD method does not require too many materials. SLD is following the manufacturing procedure, which can be used to predict the relationship between causal factors (the relationship between 2 or more variables, namely Tween 80 and Span 80) and the response (the response consists of spreadability, adhesion, and viscosity) and can statistically determine the optimal formula (Duangjit et al., 2014).

The explanation above is the background for the researcher to make a cream formulation with a base type of M/A made from the active substance naringenin as a naringenin sunscreen cream using variations in concentrations from Tween 80 and Span 80, researchers using the simplex lattice design method. The cream formula is the best and physically stable and will be tested for sunscreen activity to obtain the SPF value.

RESEARCH METHOD

Materials

The materials used are Naringenin isolate (Thanen Chemicals), cetyl alcohol, stearic acid, methyl paraben, propyl paraben, tween 80, span 80, glycerin, distilled water, methanol pa. The tools used are a UV-VIS spectrophotometer (Shimadzu UV-1800), magnetic stirrer, viscometer cup, and bob, Design Expert software version 7.1.5.

Methods

1. Design of naringenin sunscreen cream formula

   The design of the Naringenin sunscreen cream formula according to the simplex lattice design per 100 grams is shown in Table 1.

Table 1. Design the Naringenin sunscreen cream formula using the simplex lattice design (100 grams).

No	Nama Bahan	Function	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)
1	Naringenin	Active compound	0.4	0.4	0.4	0.4	0.4
2	Cetyl alkohol	Stiffening agent	4	4	4	4	4
3	Methyl paraben	Preservative	0.2	0.2	0.2	0.2	0.2
4	Propil paraben	Preservative	0.1	0.1	0.1	0.1	0.1
5	Asam stearate	Stiffening agent	3.8	3.8	3.8	3.8	3.8
6	Tween 80	Emulsifier	9	8	7	6	5
7	Span 80	Emulsifier	5	6	7	8	9
8	Gliserin	Humectants	10	10	10	10	10
9	Aquadest	Solvent	add 100	add 100	add 100	add 100	add 100

2. Preparation of naringenin sunscreen cream preparations
   a. Preparation of Naringenin Sunscreen Cream

      The oil phase was prepared by melting a mixture of cetyl alcohol stearic acid and spanned 80 on a water bath. Then, propylparaben was added, and the temperature was maintained at 70ºC. The water phase was prepared by dissolving methylparaben in water heated to 70ºC, then adding glycerin, tween 80, and the remaining water. The temperature was maintained at 70ºC. The cream was prepared by adding the oil to the water phase while stirring until it was homogeneous in the mortar. The mortar used is already warm ± temperature 40℃ so that the preparation does not break or separation occur during the mixing process, then stir again until it is homogeneous. Naringenin was crushed in a mortar, then added to the cream base gradually, and stirred until homogeneous. Then, add the rest of the base to the mortar and stir until homogeneous.

   b. Optimation of Naringenin Sunscreen Cream

      The mixed HLB value can be calculated by the mixture of the two emulsifying agents with the following formula:

$$\%A = \frac{X - HLB0 \times 100}{HLAa - HLAb}$$

$$\%B = 100 - \%A$$

3. Testing the Physical Properties of Sunscreen Naringenin
4. SPF value testing

5. Optimization of Naringenin Sunscreen
   Characterized formula with power parameters spread, power stickiness, and viscosity, then the hail data is characterized and entered in program *simplex lattice design* so that Kim's optimum formula was obtained naringenin *sunscreen. The research* used two mixed emulsifiers, i.e., tween 80 and span 80, to see 3 power test response spreads, adhesiveness, and viscosity tests.

Data Analysis

Differences in physical quality were analyzed using the One-Way Anova test, and the data obtained was used to optimize the optimum formula for the combination of tween 80 and span 80 with the critical parameters of spreadability, adhesion, and viscosity to obtain the prediction results of the optimum formula then analyzed by ANOVA and measuring the SPF value.

RESULT AND DISCUSSION

Design of Sunscreen Formula

Trials or preliminary trials were carried out, which aimed to find out the best conditions for each process to produce preparations in the form of cream, formulated homogeneously with good stability. Some conditions that need to be considered are the mixing between ingredients and the mixing time between the basic ingredients and the active substance. The combination of using tween 80 and span 80 is expected to increase the stability of the preparation. The emulsion system's stability is formed The emulsion system that occurs using these two emulsifying agent combinations is based on the HLB value. In this study, the desired emulsion was O/A, so a combination of emulsifying agents was needed that produced an HLB value between 8-13 because an O/A type emulsion was formed in this HLB range.

Testing the Physical Properties of Sunscreen Naringenin

The results of measuring the spreadability of the cream (Figure 1) on the first day showed that formulas 1, 2, 3, 4, and 5 had different spreading power values. The phase ratio influenced this in the base formation process. The formula with a large amount of water as the material has a wider spreadability value, so formula 5 has the smallest spreadability. The Kolmogorov-Smirnov One-Sample test data obtained $p > 0.05$, namely 0.058 (H0 is accepted), so it was concluded that the data was normally distributed. The results of the homogeneity test showed a value of $p > 0.05$, namely 0.062, so it can be concluded that the data is homogeneous. Furthermore, the One Way analysis shows a significant value of $p < 0.05$, which is 0.000. This means there is a significant difference

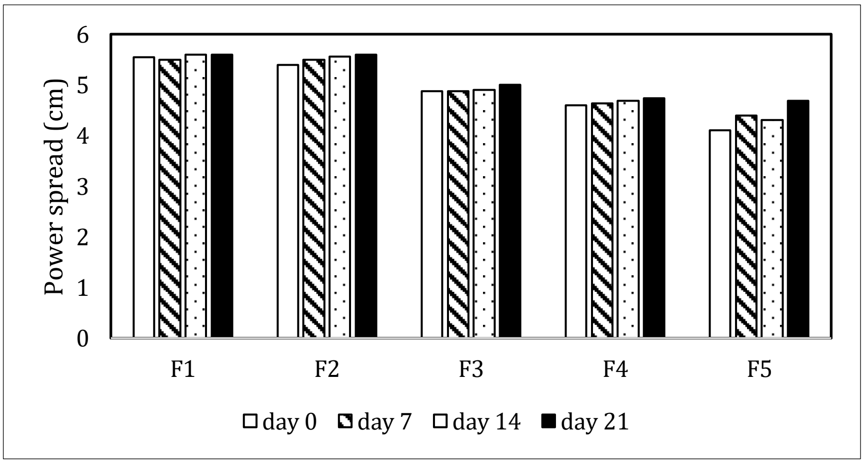

Figure 1. Power Spread Naringenin Sunscreen.

The results of observing the adhesion of the cream every 7 days (Figure 2) showed that each formula from days 0, 7, 14, and 21 tended to be stable. There was a tendency for the concentration of the emulsifying agents Tween 80 and Span 80 to affect the adhesion of the naringenin sunscreen cream, where the greater the concentration of Tween 80 indicates the lower the stickiness time value and the higher the concentration in Span 80 indicates the higher the stickiness time value. The data from the adhesiveness test obtained were analyzed statistically. The Kolmogorov-Smirnov One-Sample test data

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obtained p> 0.05, namely 0.063 (H0 was accepted), so it was concluded that the data was normally distributed, then continued with the homogeneity test showing a value of p> 0.05, namely 0.764 so that it can be concluded that the data is homogeneous. Furthermore, it was analyzed using One Way ANOVA, showing a significant value of p <0.05, namely 0.000. This means that there is a significant difference in the adhesion test parameters.

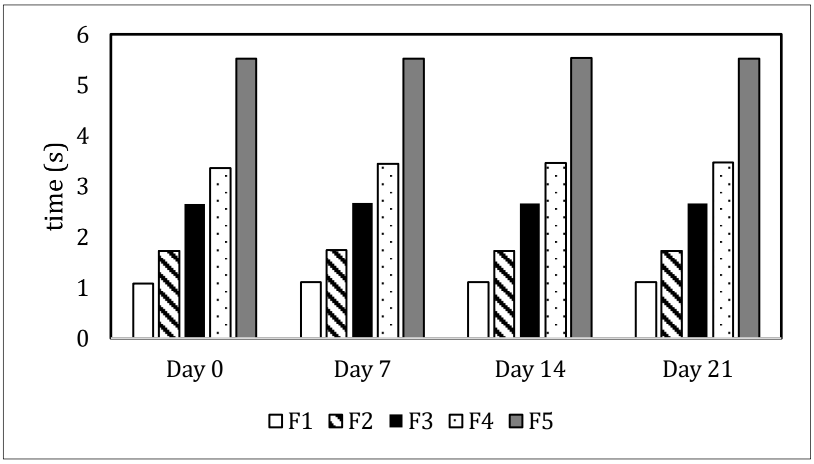

Figure 2. Stickiness of Naringenin Sunscreen.

The observations on the viscosity of naringenin sunscreen cream (Figure 3) showed that the viscosity of the formula from day 1, 7, 14, and 21 was nearly stable or remained the same. Formula 1, 2, 3, 4, and 5 always increase. This can be because of comparing emulsifier concentrations between tween 80 and span 80. Formula 1 has a ratio of tween 80, span 80 (9:5) has the lowest viscosity, while the formula has a ratio of tween 80 and span 80 (5:9) has the highest viscosity. The obtained viscosity test was analyzed statistically. The Kolmogorov-Smirnov One-Sample test data obtained p> 0.05, which is 0.075 (H0 is accepted), so it is concluded that the data is normally distributed. One Way ANOVA analysis showed a significant value of p <0.05, namely 0.000. This means that there is a significant difference in the viscosity test parameters.

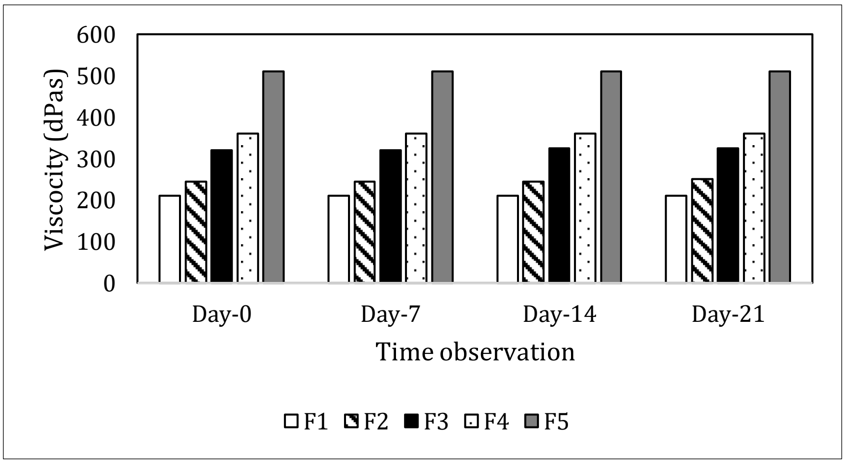

Figure 3. Viscosity of Naringenin Sunscreen.

Optimization Determination of Formulas

Optimization formula determination is carried out to get the optimal formula. Determination of the optimum formula using the method *of Simplex Lattice Design*. Study this optimized influence from variation comparison tween 80 emulator with span 80 obtained from the data of formula 1, formula 2, formula 3, formula 4, and formula 5 with critical parameters power spread, power stickiness, and viscosity, and viscosity replicated for each formula as many as 3 replications so that it has 15 data runs.

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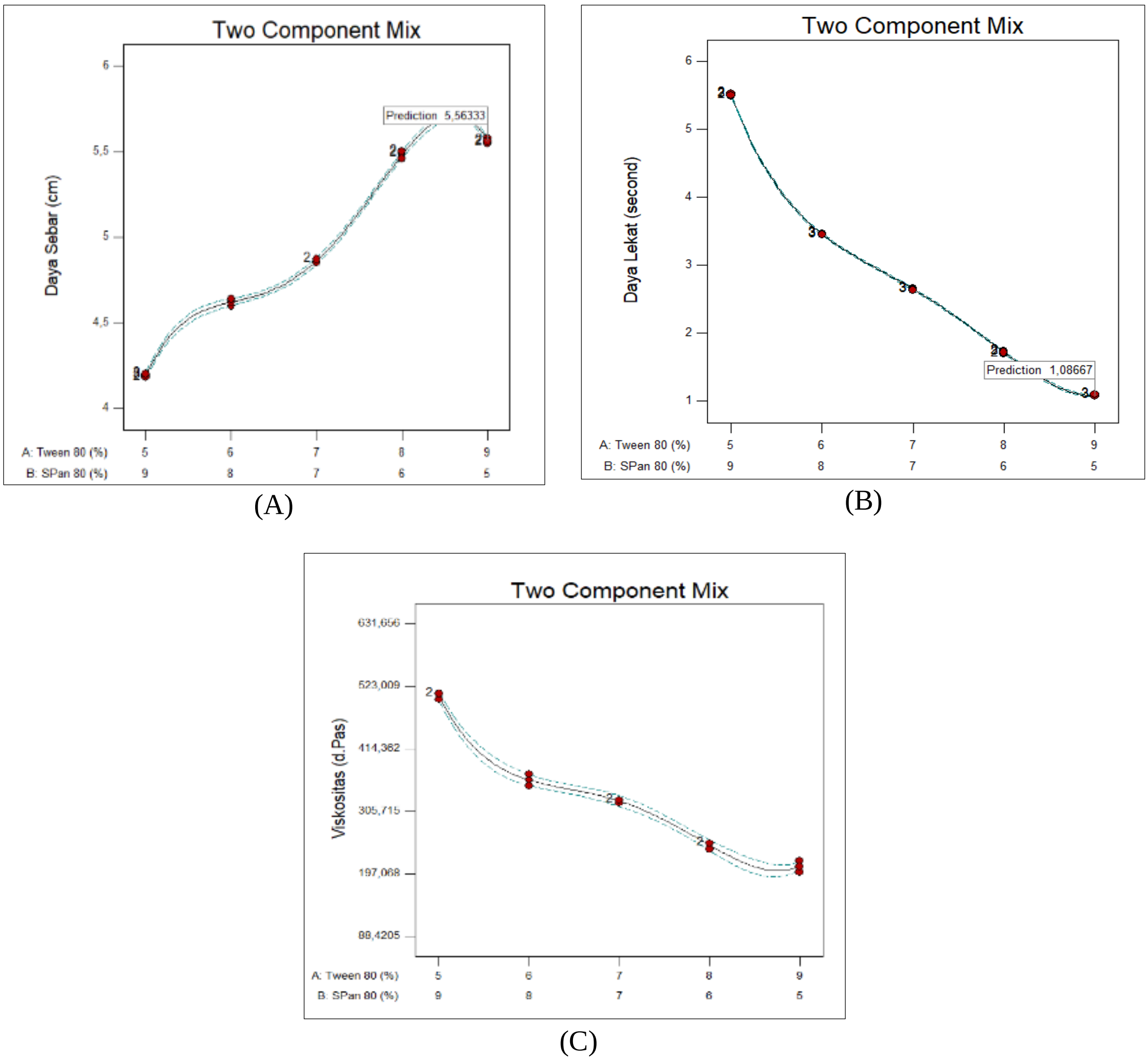

Figure 4. (A) power test result spread method SLD (B) power test result sticky method SLD (C) viscosity test result method SLD.

Figure 4 shows the Spread Power Parameter Test results using the simplex lattice design method from the equation Y = 5.56 (A) + 4.19 (B). The equation shows that the A value is tween 80 and the B value is Span 80, which has a positive result. It means that the addition of tween 80 and span 80 can increase the spreading power on the skin surface. Tween 80 has a greater influence on the spreading power than span 80, so the greater the proportion of tween 80 used will increase the response to the spreading power. Spreadability has an inverse ratio to the viscosity and adhesion of the naringenin sunscreen cream.

In Figure 4, the test of the viscosity adhesion test parameters using the simplex lattice design method forms the equation Y = 1.09 (A) + 5.51 (B), indicating that the values of A tween 80 and span 80 are positive. This means that tween 80 and span 80 can increase the adhesion to the skin surface. The figure also shows that span 80 has a greater effect on adhesion. This causes the adhesive power to be directly proportional to the viscosity. The greater the adhesive power, the greater the resulting viscosity. Stickiness is inversely proportional to spreading power. The greater the adhesion produced, the lower the spreading power value in the naringenin sunscreen cream preparation,

In Figure 4, the viscosity parameter test using the simplex lattice design method forms the equation Y = 210 (A) + 506.67 (B), indicating that the A tween value is 80 and the span 80 is positive. Based on the figure, it shows that the span 80 indicates the greater the proportion of span 80 will increase the viscosity response. This can be caused by the manufacturing process and storage time during parameter observations. The manufacturing process that can have an effect starts from the type of ingredients mixed as ingredients for making cream, the mixing or stirring process in the mortar and stamper, the temperature at the time of stirring, and the ratio between the water and oil phases.

The three parameters, namely spreadability, adhesion, and viscosity had similar results to research conducted by (Wulandari et al., 2022) research conducted using tween 80 and span 80 as emulsifiers in optimizing the simplex lattice design method. The parameters of the spreading power of the equation obtained show that tween 80 is cloudier on cream preparations. The parameters of adhesion and viscosity obtained show that span 80 has more effect on cream preparations. Although the active substance used differs, it shows that tween 80 and span 80 is good for cream preparations for the oil-in-water phase.

The results of the ANOVA test on the Simplex Latte Design program, which was carried out, showed that the value's p-value was significant. Significant means that variations in the tween 80 and span 80 concentration affect the spreadability, adhesion, and viscosity parameters. Adeq precision shows the value of the noise ratio. Numbers more than indicate desirable. The ratio obtained in the optimization of the spreading power parameter is 147.250, the adhesion parameter is 551.422, and the viscosity parameter is 69.286, so it shows the prediction of the optimum formula for the ratio of tween 80 and spa 80 (9:5). The results of the 3 parameter test criteria obtained a solution for each parameter combined to produce a desirability value of 1. A good desirability value is close to 1 to indicate the optimum formula. The Optimum formula in the solution shows the comparison value between tween 80 and span 80, which is 9:5.

Using an emulsifier for sunscreen cream preparations in the form of an oil-in-water phase, the rate of recovery of the oil phase does not necessarily increase even though the concentration is high, but the use of a combination of two emulsifiers, such as span 80 and tween 80, in a combination which is then optimized is the right solution to get the best formula with the best stability of the parameters involved, even though the points and number of parameters studied are different from the research (Sandhi et al., 2022).

CONCLUSION

Naringenin sunscreen cream with a combination of tween 80 and span 80 emulsifiers in different concentrations of emulsifiers in Formulas 1, 2, 3, 4, and 5 in the SPSS test gave significantly different results in the physical quality test with spread ability parameters. In contrast, the adhesion parameters, viscosity, have no significant difference results. Based on results observed in research Formula Optimization and Quality Test physical cream naringenin *sunscreen* with emulsifier Tween 80 and Span 80 with method *simplex lattice design* can it was concluded that the optimum formula was at a ratio of 9% tween 80 and 5% span 80 (Formula 5).

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