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Research Article

Formula Optimization of Rosemary (*Rosmarinus officinalis* L.) Extract-loaded Film-forming Spray using Box-Behnken Design

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ABSTRACT

Film-forming sprays are practical and effective in creating a protective film on wounds that evenly distributes active ingredients. Rosmarinic acid in rosemary has antioxidant and anti-inflammatory properties, helping to accelerate wound healing by enhancing macrophage and lymphocyte proliferation and reducing inflammation. This study aims to determine the optimal formulation of a film-forming spray using xanthan gum as a film-forming agent, propylene glycol as a plasticizer, and ethanol as a penetration enhancer. Optimization was carried out using the Box-Behnken design in Design Expert-13, focusing on viscosity, spray diameter, spray angle, area, density, and theoretical film thickness. The optimal base and extract formulas were evaluated for stability over 28 days at room temperature using GraphPad Prism-10. The ideal formula contained 0.1% xanthan gum, 3.6% propylene glycol, and 40% ethanol, with a desirability score of 0.943. The confirmation results showed no significant difference between actual and predicted values, validating the model. The optimal formula had a viscosity of 100 ± 0.00 cps, a spray diameter of 4.52 ± 0.06 cm, a spray angle of 65.70 ± 0.31°, an area of 16.02 ± 0.43 cm², a density of 0.908 ± 0.00 g/ml, and a theoretical film thickness of 0.007 ± 0.00 cm. This formula was then used as the base for the rosemary extract FFS. Stability tests showed that the addition of extracts significantly affected viscosity, spray diameter, spray angle, area, and theoretical film thickness ($p<0.05$), while density was unaffected ($p>0.05$). The study's limitation is the lack of in vivo testing to confirm the formulation's effectiveness in promoting wound healing and its antimicrobial properties.

Keywords: Box-behnken design; film-forming spray; optimization; *Rosmarinus officinalis* L.

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INTRODUCTION

Wounds arise from the deterioration of epithelial tissue, leading to the disruption of tissue continuity and thus impairing its normal structure and function. This damage results from the loss or destruction of tissue components due to pathological processes originating from the internal and external environment (Naziyah, Hidayat, and Maulidya 2022). The most common type of wound is an acute wound, which occurs suddenly and has a predictable healing process. These wounds are generally caused by physical trauma, such as incision wounds, stitches, burns, and stab wounds (Sermatang, Untu, and Lengkey 2021). Wounds necessitate appropriate treatment to avert infection that may impede the healing process. The wound healing process transpires organically through the formation of functional new tissue (Qamarani and Aryani 2023).

Rosmarinus officinalis L., often known as rosemary, possesses natural antioxidants, specifically rosmarinic acid, which can enhance macrophage and lymphocyte proliferation, diminish inflammation in wound sites, and have anti-inflammatory activities to expedite the wound healing process (Nejati, Farahpour, and Nagadehi 2015). Film-forming spray formulations (FFS), now gaining traction in the development of innovative topical medicines, can be utilized to provide rosemary extract as a wound healing agent (Bakhrushina et al. 2023). Based on research conducted by Khalil et al. (2022), in vivo analysis revealed that rosemary extract has potential as an herbal treatment to heal wounds on infected mouse skin through topical cream application. Unlike cream that must be applied topically, FFS offers a more practical use by spraying and prevents contamination because it is used without direct contact with hands (Kresnawati, Fitrianingsih, and Purwaningsih 2022).

FFS is a topical administration technique designed to create a thin film on the skin via a solvent evaporation process (Bakhrushina et al. 2023). FFS has a low risk of irritation, good wound coverage, and uniform distribution of active ingredients. The resulting thin film is non-adhesive and able to conform to the morphology of the skin or wound due to the presence of plasticizers, which also play a role in enhancing the release of active ingredients to the target area through penetration enhancer excipients (Umar et al. 2020). FFS formulas generally contain active substances, polymers, and excipients such as plasticizers and penetration enhancers (Crendhuty, Sriwidodo, and Wardhana 2020). Research conducted by Umar et al. (2021) showed that FFS tested in wound healing activity in rats was able to significantly accelerate the wound closure process. The results indicated that wound closure occurred faster, with complete healing achieved by day 6.

To achieve a particular film, polymers may be combined or utilized separately as film-forming agents. The film production from the polymer solvent is uncomplicated; upon solvent evaporation, the polymer molecules, functioning as chains, will amalgamate to create interconnected polymer complexes on the substrate's surface. The polymer network established on the substrate functions as an external reservoir, regulating the progressive release of active substances to avert excessive discharge that may lead to adverse effects or diminished therapeutic efficacy (Abdullah and Patil 2020). An example of a polymer utilized as a film-forming agent is xanthan gum (Umar et al. 2020).

Xanthan gum is a natural polymer derived from meticulously regulated microbial fermentation, resulting in products with consistent chemical properties. Xanthan gum is widely used as a thickener and stabilizer in oral, topical, or cosmetic pharmaceutical formulations because it is easily accepted by the body and can be degraded naturally without causing adverse reactions (Berninger, Dietz, and López 2021a). Plasticizer excipients serve to provide film properties that are elastic, flexible, and resistant to brittleness; an example is propylene glycol. Propylene glycol contributes to enhancing the flexibility of the resultant film (Yumelisa 2020). Penetration enhancers serve to augment the absorption of active substances into the skin. Penetration enhancers serve to increase the absorption of active substances into the skin. Ethanol increases permeability by decreasing density, shortening protein cross-links, and increasing the porosity of the stratum corneum, thus facilitating penetration (Christinne and Amalia 2023).

This study aims to determine the optimum formula of FFS as a wound healer using Box-Behnken Design (BBD) with desired characteristics. This method evaluates the effect of xanthan gum, propylene glycol, and ethanol as independent variables on viscosity, spray diameter, spray angle, area, specific gravity, and theoretical film thickness as dependent variables (Berninger, Dietz, and López 2021b; Agustiani, Sjahid, and Nursal 2022).

MATERIALS AND METHODS

Materials

The materials used include rosemary (*Rosmarinus officinalis* L.) purchased from the local market in Bandung, West Java, Indonesia, xanthan gum (CV Kimia Subur), propylene glycol (Dwilab Mandiri Scientific), 96% ethanol (Eralika Mitra Persada), ascorbic acid (CV Kimia Subur), triethanolamine (TEA) (Kimia Market), phenoxyethanol (Kimia Market), and distilled water (PT. Amidis Tirta Mulia).

Methods

Extraction

The extraction of rosemary was carried out using the ultrasound-assisted extraction (UAE) method. This extraction begins with soaking the simplisia powder and 96% ethanol in a ratio of 1:20. Then continued with the sonication process using a sonicator for 60 minutes at 50 degrees with a frequency of 40 kHz.

Sedimentation was carried out using centrifugation at 4500 revolutions per minute for 5 minutes. Further centrifugation helped to remove the sediment, leaving only the water-dominated extract, which was evaporated using a water bath (Akmal, Julianti, and Syamsudin 2023).

Optimization using Box-Behnken Design

A response surface methodology (RSM) with box-Behnken design was used with three factors and three levels. Xanthan gum (X1), commonly used as a film-forming agent with a concentration of <0.5%, propylene glycol (X2) as a plasticizer in the concentration range of 0.25-9%, and ethanol (X3) as a penetration enhancer with a concentration of 20-40% were used as independent variables (Table 1) (Hmingthansanga et al. 2022; Umar et al. 2020). The experimental design resulted in 15 formulas obtained from Design Expert version 13 to obtain the optimum FFS formulation (Table 2).

Table 1. Independent and dependent variables with levels and constrains

Variable Independent (X)	**Factor Level**		
	-1	**0**	**1**
X_1 – Xanthan gum (%)	0.1	0.3	0.5
X_2 – Propylene glycol (%)	1	3	5
X_3 – Ethanol (%)	20	30	40
Variable Dependent (Y)	**Constraints**		
Y_1 – Viscosity (cPs)	Minimize		
Y_2 – Spray diameter (cm)	Maximize		
Y_3 – Spray angle (°)	In range		
Y_4 – Area (cm^2)	Maximize		
Y_5 – Density (g/ml)	Minimize		
Y_6 – Theoretical film thickness (cm)	Minimize		

Table 2. Experimental design model with box behnken design

Formula	**Xanthan gum (%)**	**Propylene Glycol (%)**	**Ethanol (%)**
1	0.1	5	30
2	0.5	5	30
3	0.5	3	40
4	0.5	3	20
5	0.3	3	30
6	0.5	1	30
7	0.3	5	40
8	0.1	3	20
9	0.3	5	20
10	0.3	1	40
11	0.3	3	30
12	0.3	1	20
13	0.1	1	30
14	0.1	3	40
15	0.3	3	30

Ascorbic acid is known for its relative safety, stability and non-toxicity. Ascorbic acid is used as a powerful natural antioxidant that plays a role in neutralizing oxidative stress through electron transfer which helps accelerate wound healing (Wibawa, Wati, and Arifin 2020; Safnowandi 2022). Besides that, triethanolamine is used to stabilize the pH of preparations that tend to be acidic so that they can be accepted by the skin without causing irritation (Andaryekti and Munisih 2015). FFS dosage formulations were made using predetermined concentrations of ingredients; the complete formula can be seen in Table 2. Ascorbic acid (0.1%) was dissolved with distilled water and stirred using an overhead stirrer at 600 rpm until dissolved. Xanthan gum was developed into the ascorbic acid solution gradually while stirring at 600 rpm for 30 minutes (Angraini, Asri, and Ariati 2024). Propylene glycol, phenoxyethanol as a preservative (1%), ethanol, and triethanolamine (0.076%) were stirred in another beaker using a magnetic stirrer at 400 rpm for 5 minutes. Then the mixture was added to the FFS base and stirred at 600 rpm for 10 minutes until a homogeneous preparation was formed. For the preparation of rosemary extract (3%) FFS, continue by dissolving the extract with ethanol that has been set aside before. Then the extract solution was added into the base and stirred at 600 rpm until homogeneous.

Evaluation of Film Forming Spray

Organoleptic

Organoleptic evaluation is done visually by observing the physical characteristics of the FFS preparation, such as texture or consistency, color, and odor (Tanjung et al. 2024).

Homogeneity

Homogeneity evaluation is carried out visually by taking a small amount of preparation and then storing it between two transparent glass pieces (Zubaydah et al. 2022).

Viscosity

Viscosity evaluation was carried out using a Brookfield LV viscometer with a suitable spindle. The preparation was poured into a viscosity chamber with a capacity of 200 g, and then the spindle was dipped to the limit mark. Measurements were taken at a certain speed until the viscometer needle showed a constant scale. Viscosity was calculated using the equation (Tanjung et al. 2024):

$$Viscosity = dial\ reading \times factor$$

Spray Diameter

Evaluation of spray diameter is done by spraying the preparation on a piece of paper with a distance of 5 cm. Measure the spray diameter that has been formed using a ruler (Zubaydah, Novianti, and Indalifiany 2022).

Spray Angle

Spray angle testing was carried out with a slight modification: the preparation solution was sprayed directly on a piece of paper at a distance of 5 cm from the spray. The circle formed on the paper was then measured for radius. The spray angle was calculated using the equation:

$$Spray\ angle = tan^{-1}\ ({}^{l}/_{r})$$

Where l is the distance between the paper and the nozzle, and r is the radius of the circle (Abdullah and Patil 2020).

Area

Area evaluation is carried out by spraying FFS onto paper with a distance of 5 cm. After that, measure the radius of the circle formed. Then the area is calculated using the equation:

$$Area\ (cm^2)\ = \pi r_1\, x\, r_2$$

Where r_1 and r_2 are the radii at the horizontal and vertical centers, respectively (Suksaeree et al. 2024).

Density

The evaluation was carried out using a pycnometer that had previously been dried and weighed in an empty condition. The pycnometer is then filled with the preparation and weighed again. Make sure there are no air bubbles trapped before closing the pycnometer. The specific gravity value is calculated by dividing the final liquid weight by the volume used (Abdullah and Patil 2020).

Theoretical Film Thickness

Evaluation The film thickness was calculated with data from the evaluation of spray weight, area, and specific gravity using the equation (Umar et al. 2020).

$$Thickness\ (cm)\ \frac{massa\ (g)}{area\ (cm^2)\ \times\ density\ (g/ml)}$$

Occlusion or Water Vapor Permeability

In this test, the filter paper is placed over the mouth of a beaker containing 50 mL of water without a sample that serves as a control. In another beaker, the FFS was sprayed on the filter paper. After that, the beaker was kept at room temperature and humidity to measure the evaporation of water through the membrane by weighing all samples after 48 hours. Based on the weight loss of water in the beaker, the permeability of the film was calculated.

$$F = 100\,x\left[\frac{A - B}{A}\right]$$

Where A is the weight loss of water from a beaker without a sample, while B is the weight loss of water from a beaker containing a film (Umar et al. 2021).

Stability Test

The stability test of the optimum formula of FFS was carried out by storing the preparation at controlled room temperature with a deviation tolerance between 15^{o} and 30^{o}C (Kemenkes 2020) and evaluated on days 0, 7, 14, 21, and 28. Evaluation of FFS preparation includes organoleptical, homogeneity, viscosity, spray diameter, spray angle, area, density, theoretical film thickness, and occlusion or water vapor permeability (Umar et al. 2021).

Statistical Data Analysis

The data obtained from the test response test results were analyzed using Design Expert version 13.05.0 in 2021. The optimum formula data generated from the stability test was analyzed using GraphPad Prism version 10.4.0.

RESULTS

Extraction of Rosemary

The results of rosemary extraction using the UAE method produced a yield of 23.1% (Table 3). According to Panjaitan and Meze (2023), the extract yield is acceptable if it has a value of more than 10%. Extract yield calculation plays an important role in FFS formulation as it determines the amount of simplisia required to obtain the desired extract concentration in the final preparation. By knowing the yield, the formulation can be designed more accurately to ensure the right amount of active ingredients in the preparation so as to achieve the expected effectiveness.

Table 3. Extraction result of UAE rosemary

Weight of Simplisia (g)	Solvent Volume (mL)	Weight of Extract (g)	Yield (%)
1	20	0.231	23.1%

Optimization using Box-Behnken Design

The formula optimization process was carried out by analyzing response data from 15 formulas (Table 4 and Table 5). Statistical analysis was conducted using ANOVA (Table 6) in Design Expert by identifying the resulting model and paying attention to important parameters to determine the optimum formula. The optimum formula was selected based on the highest desirability value (Table 8), which reflects the closeness of the results to the expected value.

Table 4. Evaluation results of response viscosity, spray diameter, and spray angle

Formula	Viscosity (cPs)	Spray Diameter (cm)	Spray Angle (°)
1	141.60 ± 6.45	4.58 ± 0.28	65.43 ± 1.32
2	4774.58 ± 16.99	1.23 ± 0.03	83.04 ± 0.15
3	402083 ± 29.23	1.44 ± 0.06	81.80 ± 0.32
4	380000 ± 20.92	1.41 ± 0.07	82.00 ± 0.42
5	1616.67 ± 10.21	1.78 ± 0.08	79.88 ± 0.41
6	4366.67 ± 43.06	1.45 ± 0.07	81.75 ± 0.39
7	1300.00 ± 0.00	2.33 ± 0.10	76.86 ± 0.56
8	150.00 ± 0.00	4.56 ± 0.24	65.49 ± 1.14
9	1693.75 ± 6.85	1.97 ± 0.03	78.87 ± 0.13
10	1308.33 ± 6.45	1.78 ± 0.55	79.95 ± 3.06
11	1464.58 ± 12.29	2.28 ± 0.06	77.14 ± 0.32
12	1608.33 ± 6.45	2.1 ± 0.07	78.14 ± 0.38
13	108.33 ± 6.45	4.51 ± 0.24	66.05 ± 0.61
14	85.42 ± 5.10	4.40 ± 0.11	66.26 ± 0.51
15	1418.75 ± 10.46	2.26 ± 0.1	77.28 ± 0.52

Table 5. Evaluation results of response area, density, and theoretical film thickness

Formula	Area (cm²)	Density (g/ml)	Theoretical Film Thickness (cm)
1	16.48 ±1.98	0.936 ± 0.00	0.008 ± 0.00
2	1.18 ± 0.05	0.938 ± 0.00	0.101 ± 0.00
3	1.63 ± 0.13	0.918 ± 0.00	0.068 ± 0.00
4	1.56 ± 0.16	0.935 ± 0.00	0.076 ± 0.00
5	2.50 ± 0.21	0.931 ± 0.00	0.046 ± 0.00
6	1.65 ± 0.16	0.932 ± 0.00	0.070 ± 0.00
7	4.28 ± 0.38	0.917 ± 0.00	0.025 ± 0.00
8	16.35 ± 1.75	0.948 ± 0.00	0.007 ± 0.00
9	3.04 ± 0.08	0.947 ± 0.00	0.039 ± 0.00
10	2.67 ± 1.38	0.908 ± 0.00	0.042 ± 0.00
11	4.10 ± 0.22	0.929 ± 0.00	0.026 ± 0.00
12	3.47 ± 0.23	0.943 ± 0.00	0.034 ± 0.00
13	15.99 ± 1.77	0.928 ± 0.00	0.007 ± 0.00
14	15.21 ± 0.76	0.912± 0.00	0.007 ± 0.00
15	4.01 ± 0.35	0.932 ± 0.00	0.027 ± 0.00

Table 6. Response model and statistical analysis results

Respon	Model	p-value	R^2	Adjusted R^2	Predicted R^2	Adeq Precision	Lack of fit
Viscosity	Quadratic	<0.0001	0.9991	0.9976	0.9910	70.741	1.04
Spray diameter	Quadratic	0.0002	0.9905	0.9735	0.9442	19.2978	0.2404
Spray angle	Quadratic	0.0002	0.9899	0.9718	0.9458	19.0415	0.1970
Area	Quadratic	<0.0001	0.9957	0.9880	0.9731	27.6979	0.2756
Density	Linear	<0.0001	0.8953	0.8668	0.7793	15.8610	7.1237
Thickness	Linear	<0.0001	0.9385	0.9218	0.8899	18.4938	0.4171

Polynomial equation 1. Effect of independent variables on viscosity

$$\text{Viscosity (Y1)} = 1.41478 + 7.83767\ A + 0.001675\ B + 0.004235\ C - 0.048575\ AB + 0.03363\ AC - 0.000316\ BC - 8.03341\ A^2 + 0.005550\ B^2 - 0.000311\ C^2$$

Polynomial equation 2. Effect of independent variables on spray diameter

$$\text{Spray diameter (Y2)} = 6.90208 - 21.04167\ A - 0.130208\ B - 0.018542\ C - 0.182292\ AB, + 0.023958\ AC + 0.008646e\ BC + 21.74479\ A^2 - 0.009635\ B^2 - 0.000260\ C^2$$

Polynomial equation 3. Effect of independent variables on spray angle

$$\text{Spray angle (Y3)} = 53.44520 + 105.35271\ A + 0.563948\ B + 0.131050\ C + 1.19562\ AB - 0.120771\ AC - 0.047750\ BC - 107.46128\ A^2 + 0.067439\ B^2 + 0.000883\ C^2$$

Polynomial equation 4. Effect of independent variables on area

$$\text{Area (Y4)} = 28.05007 - 118.63476\ A - 0.385433\ B - 0.036609\ C - 0.600811\ AB + 0.152216\ AC + 0.025492\ BC + 132.69805\ A^2 - 0.004085\ B^2 - 0.001555\ C^2$$

Polynomial equation 5. Effect of independent variables on density

$$\text{Density (Y5)} = 0.969629 - 0.000413\ A + 0.001646\ B - 0.001471\ C$$

Polynomial equation 6. Effect of independent variables on theoretical film thickness

$$\text{Thickness (Y6)} = 0.044643 + 0.487371\ A + 0.001714\ B - 0.000427\ C$$

Table 7. Organoleptic and homogeneity evaluation results of optimum formula

Evaluation	Optimum Formula FFS Basis	Optimum Formula FFS Basis rosemary extract
Color	Colorless	Green
Consistency	Liquid	Liquid
Odor	Specialty of preparations	Rosemary extract
Homogeneity	Homogeneous	Homogeneous

Table 8. Optimum formula and response results

Optimum Formula			
Xanthan gum (%)	**Propylene glycol (%)**	**Ethanol (%)**	**Desirability**
0.1	3.6	40	0.943
Responses	**Predicted Values**	**Actual Values**	**%Error**
Viscosity (cPs)	87.19	100 ± 0.00	14.69
Spray diameter (cm)	4.54	4.52 ± 0.06	-0.44
Spray angle (°)	65.52	65.70 ± 0.31	0.27
Area (cm²)	15.83	16.02 ± 0.43	1.20
Density (g/ml)	0.92	0.908 ± 0.00	-1.30
Theoretical film thickness (cm)	0.007	0.007 ± 0.00	0

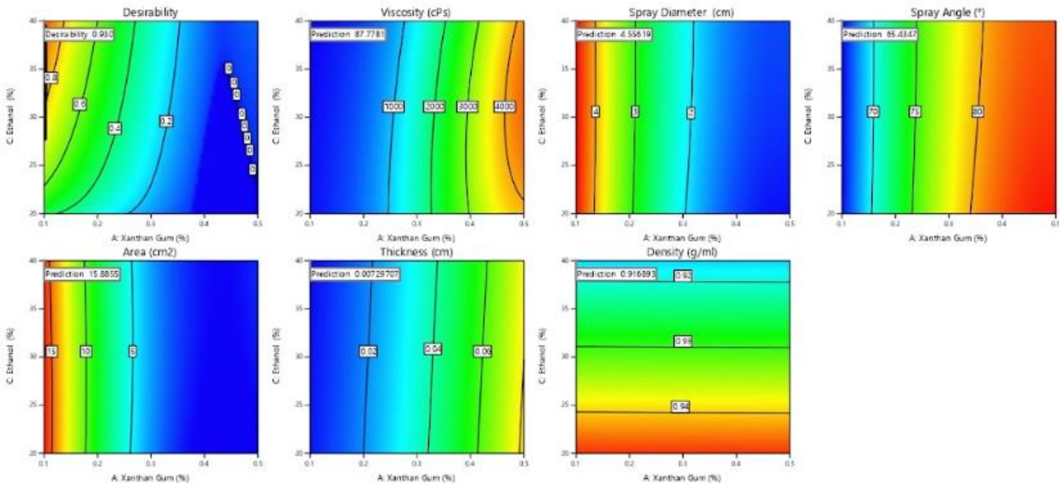

Figure 1. Desirability index plot for optimal formula of FFS

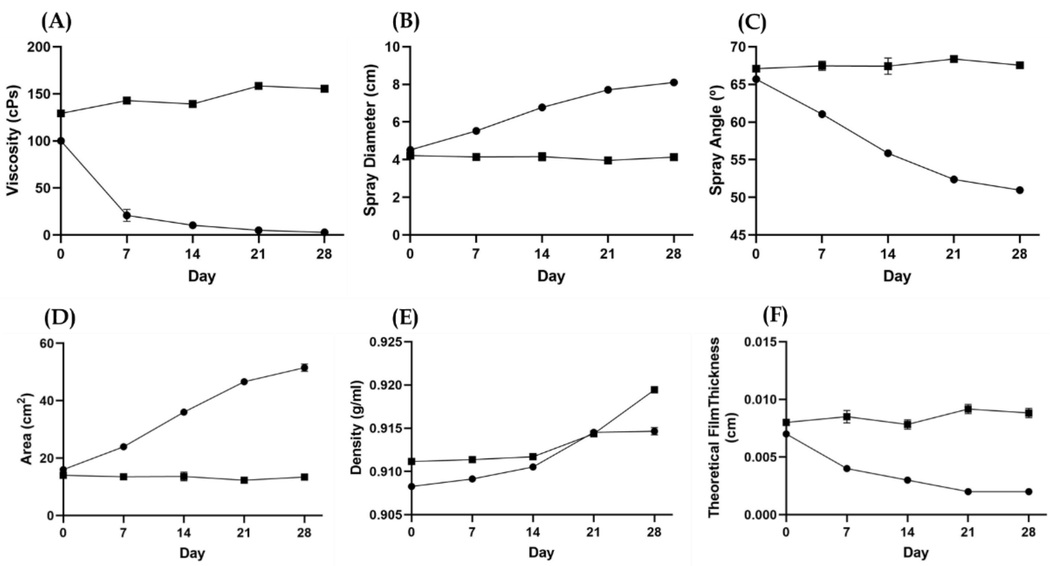

Figure 2. The value of viscosity (A), spray diameter (B), spray angle (C), area (D), desnsity (E), theoretical film thickness (F) Base FFS (●) and FFS rosemary extract (■) for 28 days

DISCUSSION

Extraction

Rosemary extract was obtained using the UAE approach with a simplicia solvent ratio of 1:20 in 96% ethanol. The extraction process was performed at 50°C for 60 minutes. The UAE method was used because it has some advantages, such as lower solvent requirement, higher extract concentration and higher active substance content achieved (Andriani and Murtisiwi 2018). The extraction resulted in a yield of 23.1%. Research conducted by Aprilianti and Esati (2021) produced a rosemary extract yield of 16.87%. The difference in yield value obtained can be influenced by several factors such as time, temperature, and solvent (Siwi, Wardhana, and Septiawati 2023).

Optimization using Box-Behnken Design

Using the factors chosen in the design of the formulas for optimization with Design Expert version 13, the Box-Behnken with 15 runs generated for a formulation containing three factors was done (Table 2). Experimental design is used to analyze the interaction of each formulation variable on the response (Permana and Darusman 2023). This method ensures optimal formulation with a more scientific, structured, and controlled approach, thereby increasing efficiency and accuracy in research. BBD is used because it has various advantages over CCD when applying three variable factors but can achieve comparable results. BBD ensures that extreme test points or axial points are not included in the design (Zahara, Yuniharni, and Arziqni 2023). The test variables used were xanthan gum, propylene glycol, and ethanol and viscosity, spray diameter, spray angle, area, density, and theoretical film thickness as measured response.

Data Compatibility with The Model

Design-Expert encompasses statistical models such as quadratic, linear, two-factor interaction (2FI), and cubic. The most suitable model was chosen to ascertain the optimal formula based on model assessment. The responses of viscosity, spray diameter, spray angle, and spray area were analyzed using a quadratic model based on the recommendations, as the linear and 2FI models did not indicate significance. The theoretical specific density and film thickness responses were investigated using the recommended linear model of the experimental design. (Table 8). All models exhibited a significant effect since the p-value was below 0.05. A p-value below 0.05 signifies a statistically significant model. The R^2 values approaching 1 signify the extent of variance around the mean response to the model equation. In all answers, the predicted R^2 aligns closely with the adjusted R^2, with a difference of less than 0.2, signifying that the model exhibits a strong fit and accurate measurements between predictions and experimental outcomes. The model's precision is greater than 4, signifying its adequacy in fulfilling the specified conditions. The absence of fit with a p-value beyond 0.05 signifies an insignificant outcome. A minimal lack of fit value is very important for an effective model, as this indicates the fit of the response data with the model so that the resulting predictions are more accurate and can be used to determine the optimum conditions (Amani, Pranowo, and Wijana 2024).

Effect of Independent Variable on Dependent Variable

Viscosity

The viscosity values were in the range of 85.42 ± 5.10 cPs to 4774.58 ± 16.99 cPS, as shown in Table 4. The effect of independent variables on viscosity can be explained by Polynomial equation 1. in base log 10 transform. The polynomial equation suggests that xanthan gum exerts the most substantial influence on viscosity, as evidenced by its positive coefficient of +7.83767, signifying that an increase in xanthan gum concentration directly elevates the viscosity of the formulation. Increasing the concentration of xanthan gum from 0.1% (formula 1) to 0.5% (formula 2) results in a viscosity value rise from 141.6±6.45 to 4774.58±16.99 cps. This indicates that an increase in xanthan gum concentration results in a higher viscosity value of the preparation (Nugrahaeni, Srifiana, and Rokhman 2021). This is in accordance with the research conducted by Nugrahaeni, Srifiana, and Rokhman (2021), which shows that the higher the concentration of xanthan gum, the higher the viscosity produced.

Spray Diameter

Spray diameter values were in the range of 1.23 ± 0.003 cm to 4.58 ± 1.28 cm, as shown in Table 4. The effect of independent variables on spray diameter can be explained by Polynomial equation 2. The polynomial equation indicates that xanthan gum exerts the most significant impact on spray diameter, with a value of -21.04167. This suggests that as xanthan gum content rises, viscosity increases, resulting in a decreased spray diameter (Cendana, Adrianta, and Suena 2021). It can be seen when the concentration of xanthan gum is increased from 0.1% (formula 1) to 0.5% (formula 2), showing that the spray diameter decreased from 4.58 ± 0.28 cm to 1.23 ± 0.03 cm. This is in accordance with the research of Tanjung et al. (2024), which showed that with increasing viscosity, the resulting spray diameter is smaller.

Spray Angle

The spray angle values were in the range of 65.05 ± 0.61° to 83.04 ± 0.15°, as shown in Table 4. The effect of independent variables on spray angle can be explained by Polynomial equation 3. The polynomial equation indicates that xanthan gum greatly influences the spray angle, with a value of +105.35271, suggesting that an increase in xanthan gum content will markedly enhance viscosity, hence increasing the spray angle. The increase in xanthan gum concentration from 0.1% (formula 8) to 0.5% (formula 4) results in a spray angle elevation from 65.49 ± 1.14 to 82.00 ± 0.42. This is in accordance with the research of Umar et al. (2021), which shows that viscosity has a significant effect on spray angle. The greater the viscosity, the higher the spray angle produced.

Area

Area values were in the range of 1.18 ± 0.05 cm^2 to 16.48 ± 1.98 cm^2 shown in Table 5. The effect of the independent variables on area can be explained by Polynomial equation 4. The polynomial equation indicates that xanthan gum significantly affects the spray area, with a value of -118.63476, suggesting that an increase in xanthan gum concentration results in a decrease in the spray area. Increasing the concentration of xanthan gum from 0.1% (formula 13) to 0.5% (formula 6) results in a reduction of the area from 15.99 ± 1.77 to 1.65 ± 0.16. Increasing the concentration of xanthan gum elevates viscosity, thereby leading to a reduction in diameter and area generated. This is in conformity with Suksaeree et al. (2024) statement pertaining to the role of xanthan gum in enhancing the viscosity of the formulation as a film-forming agent, it improves the spray dispersion ability.

Density

The density values obtained from the 15-run test are in the range of 0.908 g/ml to 0.948 g/ml, as shown in Table 5. The effect of independent variables on density can be explained by Polynomial equation 5. The polynomial equation indicates that ethanol exerts a more significant effect, with a value of -0.001271, demonstrating that as ethanol concentration increases, the density value diminishes. The increase in ethanol concentration from 20% (formula 4) to 40% (formula 3) results in a drop in density from 0.935 g/ml to 0.918 g/ml. This is in accordance with the statement by Kartika (2022) that increasing the amount of ethanol in the formulation causes a decrease in the density value of the preparation.

Theoretical Film Thickness

The thickness values are in the range of 0.007 cm to 0.101 cm, as shown in Table 5. The effect of the independent variables on theoretical film thickness can be explained by Polynomial equation 6. in square root transform. The polynomial equation demonstrates that xanthan gum exerts a substantial effect, with a value of +0.487371, signifying that an increase in xanthan gum concentration leads to an increase in film thickness. Increasing the concentration of xanthan gum from 0.1% (formula 1) to 0.5% (formula 2) results in an increase in film thickness from 0.008 cm to 0.101 cm. This is in accordance with Deden and Rahim (2020) statement that the higher the concentration of the film-forming polymer, the greater the film thickness.

Confirmation of The Optimum Formula

Desirability denotes the degree of appropriateness or proximity of the test findings to the anticipated value for each response. The nearer it approaches 1, the more favorable the resulting formula. The confirmation results (Table 8) from the response verification indicate that the viscosity response produces the actual value that deviates the most from the prediction compared to the other responses. This figure is acceptable as it satisfies the criteria for optimal spray viscosity, being below 150 cps (Nastiti, Maulida, and Salsabila 2024). This indicates that the model used can accurately predict the optimal formula along with the response (Figure 2).

Stability Test

Organoleptic

Organoleptic evaluation is conducted to provide comfort in the topical use of the preparation. The consistency, color, and aroma of the preparation are observed to carry out this test (Zubaydah, Novianti, and Indalifiany 2022). The FFS base has a liquid consistency with a characteristic odor of the preparation and is colorless. Meanwhile, the FFS preparation with rosemary extract has a liquid consistency, a characteristic smell of rosemary extract, and a green color (Table 7).

Homogeneity

The evaluation of homogeneity seeks to ascertain whether the components utilized in the formulation are adequately blended. The FFS base formula and the rosemary extract FFS exhibited a uniform composition throughout storage, marked by the absence of coarse particles in the gel (Table 7). This complies with the homogeneity criteria, indicating it must exhibit a uniform composition and be free of insoluble particles (Rumanti et al. 2022).

Viscosity

The evaluation of viscosity seeks to ascertain the consistency level of the preparation. FFS is a preparation that is applied through a spraying mechanism, so the viscosity of the preparation has an important role in determining the ease of delivery. High viscosity can make it difficult for the preparation to escape, requiring greater pressure to spray the preparation. This can hinder the release of the preparation from the applicator, affecting the efficiency and convenience of use (Kresnawati, Fitrianingsih, and Puji Purwaningsih 2020). Stability test results on viscosity evaluation both in base form and with extracts varied over the duration of storage. (Figure 2). The viscosity of the base FFS diminishes with storage, but the viscosity of the extract FFS generally escalates. The reduction in viscosity may result from the conditions of the storage environment, where insufficient packing permits the preparation to collect water vapor, thereby elevating the water content in the formulation. Moreover, unmanaged humidity in the room can lead to the preparation absorbing external water vapor, so diminishing its viscosity (Warnida, Oktaviani, and Sukawaty 2016). However, the rise in viscosity may also result from the evaporation of ethanol during the preparation process (Istiana, Fitriani, and Prasetya Fajar 2021). FFS with extracts tends to be more stable due to the addition of active substances that affect the stability of the preparation (Dewi, Anwar, and S, 2014). As the viscosity of the base FFS decreases to a more liquid state, the film formed becomes thinner and reduces its ability to provide good wound protection. FFS with extracts tends to have an increase in viscosity, which will form a thicker film, thus increasing its effectiveness in protecting wounds.

Spray Diameter

The purpose of the evaluation of spray diameter is to check whether the formulation has been delivered adequately to the target area (Zubaydah, Novianti, and Indalifiany 2022). For both the base FFS and FFS with extract, changes occur in line with variations in viscosity (Figure 2). One of the factors influencing the spray pattern is viscosity. Lower viscosity results in a larger spray diameter due to its more liquid consistency, making it easier to spread. Meanwhile, an increase in viscosity causes a decrease in spray diameter. This occurs because more viscous preparations have higher flow resistance when ejected from the nozzle, resulting in more limited liquid dispersion (Kresnawati, Fitrianingsih, and Purwaningsih 2022).

Spray Angle

Evaluation of the spray angle is carried out to determine the magnitude of the angle formed when applied to the skin. In order to cover the maximum surface area, a good spray angle is below 85° (Paradkar et al. 2015). In the preparation of FFS base and FFS with extracts, experienced changes along with changes in viscosity (Figure 2). However, these changes still meet the requirements for a good spray angle. Changes in spray angle are influenced by the viscosity of the preparation. An increase in viscosity leads to a decrease in spray diameter and an increase in spray angle due to higher flow resistance as it is ejected from the nozzle, so the liquid spreads more restricted and concentrated in a smaller area. Conversely, lower viscosity preparations produce larger spray diameters due to their more fluid consistency, allowing for wider dispersion and resulting in larger spray angles.

Area

Area evaluation aims to determine the surface area of the film that can cover the wound area. In FFS base and FFS preparations with extracts, the area produced changes along with changes in the viscosity of the resulting preparation (Figure 2). The viscosity of the preparation is one of the factors that affect spraying patterns such as area. The lower viscosity causes the diameter of the spray produced to be larger so that the area of the film produced is also greater to cover the wound (Kresnawati, Fitrianingsih, and Purwaningsih 2022).

Density

Density evaluation is carried out to determine the density of a preparation. The higher the specific gravity value, the better the level of mixing of the constituent ingredients (Reza, Nurcahyo, and Santosa 2022). Density evaluation was also carried out to be able to calculate the theoretical film thickness. During storage, the results showed that the density value increased as the age of the preparation increased. Evaluation of density is also carried out to be able to calculate the theoretical film thickness. During storage, the results showed that the density value increased as the age of the preparation increased.

Theoretical Film Thickness

This test was conducted to determine the physical characteristics of the film formed, as film thickness plays a role in regulating wound moisture balance. Films with excessive thickness can inhibit water vapor permeability and lead to increased moisture in the wound area. This condition favors the growth of microorganisms, increasing the likelihood of infection and slowing down the wound healing process. In FFS base and FFS preparations with extracts, the film thickness changes along with changes in viscosity (Figure). Viscosity is one of the factors that affect thickness. The lower the viscosity, the thinner the film (Rahardjo, Wiseso Marseno, and Nugroho Wahyu Karyadi 2014). Lower viscosity and lighter density allow the preparation to spread more widely on the surface of the wound area and produce a thinner film. This happens because low-viscosity liquids have better flow, allowing them to spread evenly before drying (Pant, Badola, and Kothiyal 2016).

Occlusion or Water Vapor Permeability (WVP)

WVP is performed to identify the resistance of a film to retain water vapor (Indarti, Marlita, and Zaidiyah 2020). The smaller the occlusion factor value, the better the film permeability to water vapor (Umar et al. 2021). The occlusion value of day 0 base FFS was 4.277%, while after 28 days it decreased to -2.119%. Meanwhile, the occlusion value of FFS with extract on day 0 was 5.50%, decreasing to -4.059% after 28 days. A positive or negative water vapor permeability value simply indicates the direction of the amount of vapor that can pass through the film. It does not determine film quality but reflects its vapor transmission characteristics. A smaller occlusion value means easier vapor passage, while a larger value indicates better resistance to evaporation. The decrease in occlusion value indicates that the ability of the film to retain water vapor is getting better after 28 days of storage due to its ability to retain water vapor transmission (Indarti, Marlita, and Zaidiyah 2020). Films that are able to resist water vapor transmission well can help maintain a balanced moisture content in the wound, which contributes to an optimal healing process. Excessive moisture in a wound can lead to maceration, a condition where the wound edges are damaged by excess fluid. Maceration occurs when the skin's protective function is compromised, especially in acute wounds, causing the skin to become more susceptible to infection due to inflammation and swelling around the wound (Sari, Novitasari, and Ardianapodesta 2024). The decrease in WVP value is due to the interaction of hydrophilic compounds that cause water vapor to easily penetrate the film (Wicakso, Fortuna, and Hernadin 2023).

Statistical Data Analysis

Analysis of stability evaluation data by comparing the optimum formula of FFS base with FFS rosemary extract showed significant results with a p-value <0.05 in the evaluation of viscosity, spray diameter, spray angle, area, and theoretical film thickness. While the density evaluation showed results that had no significant effect with a p-value >0.05.

CONCLUSIONS

Rosemary extract can be developed into an FFS formulation for wound healing. This research demonstrates that the Box-Behnken Design is proficient in optimizing the FFS formulation. The data acquired by Design Expert demonstrate several notable effects of the examined settings on the measured response. The ideal formula was achieved with a xanthan gum content of 0.1%, propylene glycol at 3.6%, and ethanol at 40%, resulting in a desirability value of 0.943. Evaluation of the optimum formula resulted in a viscosity value of 100 cps, spray diameter of 4.52 cm, spray angle of 65.70°, area of 16.02 cm^2, density of 0.908 g/ml, and theoretical film thickness of 0.007 cm. The results of the optimal formula assessment show that the model used can predict the response correctly. The formula is said to be the optimum formula because it meets the predetermined evaluation criteria. The incorporation of extracts into the optimal FFS formulation yielded significant outcomes in the assessment of viscosity, spray diameter, spray angle, area, and theoretical film thickness. Nonetheless, there was no notable impact on density assessment.

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