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STABILITY AND IRRITATION TESTING USING THE PATCH TEST METHOD OF A COMBINATION GEL FORMULATION CONTAINING ALOE VERA AND BASIL LEAF EXTRACTS

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ABSTRACT

Aloe vera and basil leaves have been recognized for their anti-inflammatory and antibacterial properties. Combining these extracts into a gel formulation offers convenience in application. However, research concerning potential irritations associated with its use remains limited. This study aims to assess irritation in humans resulting from the application of a gel formulation containing basil and aloe vera extracts using patch testing. The gel formulation is prepared with a 2% concentration of the extracts, with a 1:1 ratio of basil to aloe vera extracts. Optimization is achieved by varying carbopol concentrations and the final pH of the gel formulation. The parameters used for determining the optimal formula include organoleptic characteristics, viscosity, spreadability, adhesiveness, and pH of the formulation. The optimal formula is subsequently subjected to stability testing over four weeks and irritation testing using patch methods. A total of 25 volunteers are involved in the irritation testing. Observations are made up to 72 hours after the removal of the formulation to ensure the absence of delayed irritation effects. Aloe vera and basil extractions using ethanol as a solvent yield sequential yields of 1.7% and 3%, respectively. Quality evaluation for Formulations I (FI), II (FII), and III (FIII) includes spreadability, adhesiveness, and viscosity, as follows: (4.1 cm; 5.4 seconds; 5504 mPa.s); (6.5 cm; 4.1 seconds; 3480 mPa.s); and (5.2 cm; 4.2 seconds; 6340 mPa.s), respectively. FII is selected as the optimal formula because it exhibits wider spreadability and lower viscosity compared to FI and FIII ($P < 0.05$). Stability testing **for** FII shows that the formula remains stable during storage for all quality testing parameters ($P > 0.05$). The Primary Irritation Index (PII) for FII has a value of 0.0216, indicating that it does not cause irritation during patch testing.

Keywords: Basil, Aloe vera, Irritation test, Gel, Stability test

INTRODUCTION

The skin serves as a protective barrier against microorganisms through the presence of a lipid barrier derived from sebaceous glands and the limited presence of sweat glands in the skin. Additionally, the outermost layer of the skin acts as a protective shield. However, under specific conditions, the skin may fail to protect against bacteria, leading to the development of acne (Wasitaatmadja, 1997). Acne is a skin condition resulting from inflammation of the pilosebaceous glands and is characterized by the presence of comedones, papules, pustules, nodules, and cysts, often occurring in areas such as the face and upper back and commonly affecting adolescents undergoing early signs of puberty (Natsuaki & Yates, 2021). Commercially available anti-acne formulations containing synthetic chemicals have been associated with greater side effects compared to natural ingredients (Dayal et al., 2020). These synthetic anti-acne formulations can lead to adverse effects, including allergic reactions caused by antibiotics that involve the body's immune system, leading to hypersensitivity reactions (Gollnick et al., 2021).

Basil leaves and aloe vera are known to contain bioactive compounds such as saponins, flavonoids, polyphenols, and tannins, and have been demonstrated to inhibit the growth of bacteria, including those responsible for acne (Bista et al., 2020;

Sęczyk et al., 2022). The potential of a combination of basil and aloe vera leaf extracts as antibacterial agents against acne-causing bacteria has been investigated in the laboratory by Yasir. The inhibitory zones for these extracts against Staphylococcus epidermidis and Propionibacterium acnes were measured at 16.82 mm and 10.16 mm, respectively (Yasir, 2021; Yasir et al., 2021).

Gel formulations are a convenient topical application for the skin and offer an aesthetically appealing physical form compared to other topical formulations (Barnes et al., 2021). Gel formulations are preferred for acne treatment over creams because gels with polar solvents are easily removed from the skin's surface after application and do not contain oils that can exacerbate acne (Golembo et al., 2022). However, the use of preservatives and extracts in cosmetic gel formulations should be evaluated before they are marketed, as both can potentially cause irritation (Gaspar et al., 2008; Ma et al., 2021; Rasul et al., 2011). Irritation testing using the patch test method conditions the gel formulation for better penetration due to the occlusive conditions it creates, making the results of tests using this method reliable (Lazzarini et al., 2013).

Although the antibacterial effectiveness of a combination of basil and aloe vera leaf extracts against acne-causing bacteria has been established, the development of a safe and high-quality cosmetic formulation with these ingredients has not been previously studied. Therefore, this research aims to assess the safety of a gel formulation containing a combination of basil and aloe vera leaf extracts using the patch test method and to evaluate the stability of the resulting product to ensure that the cosmetic formulation complies with safety and quality requirements.

MATERIAL AND METHOD

Material

Ethanol 96% Technical, Carbopol, Triethanolamine (TEA), Phenoxyethanol, Distilled Water, Fragrance, Glycerin, Basil Leaves, Aloe Vera Leaves, Butylene Glycol.

Method

Extraction

The extraction process initiates with the dehydration of 5 kg of basil leaves and 3 kg of aloe vera leaves. These botanical materials are meticulously air-dried, resulting in reduced moisture content. Subsequently, the desiccated plant material is finely ground using a Herb Grinder DE-150. This grinding process serves to transform the botanicals into a powdered form, enhancing the ease of extraction. This transformation results in an increased surface area, facilitating greater contact between the plant material and the solvent.

The extraction process employs 96% ethanol as the chosen solvent and follows the maceration method. During maceration, the powdered plant material is immersed in the ethanol solvent for a specified period, allowing for the dissolution and diffusion of bioactive compounds into the ethanol.

The resulting liquid extract, enriched with bioactive constituents, undergoes a concentration phase. This concentration is achieved using an IKA RV-10 Rotary Evaporator. The procedure is conducted under controlled conditions, maintaining a constant temperature of 50°C, while the rotary evaporator operates at a speed of 90 rpm. The primary objective of this phase is to reduce the volume of the liquid extract, consequently elevating the concentration of bioactive components.

Upon the conclusion of the extraction and concentration phases, the condensed extract is carefully weighed, and the yield is calculated meticulously. This yield measurement serves as a pivotal parameter, providing valuable insights into the efficiency of the extraction process and the concentration of the targeted bioactive compounds.

Formulation

The formulation composition, as indicated in Table 1, guides the preparation of the product. The formulation process commences with the dispersion of Carbopol in distilled water. This dispersion takes place within a beaker and involves stirring with an IKA ULTRA-TURRAX T25 at a speed of 8000 rpm for a duration of 3 minutes. Once a homogenous mixture is achieved, phenoxyethanol, basil and aloe vera extracts, butylene glycol, and triethanolamine (TEA) are sequentially added. These additions are made until a three-dimensional gel matrix is formed, aligning with the pH specified in the formula. Subsequently, fragrance is incorporated into the formulation.

This sequence ensures the creation of a well-structured, stable gel product that conforms to the specified formula, providing the desired characteristics and properties.

Table 1. Gel Formula

Material	Concentration (%)			Function
	FI	FII	FIII	
Basil extract	1	1	1	Active Ingredient
Aloe vera extract	1	1	1	Active Ingredient
Carbopol	1	0,5	1	Gelling Agent
TEA	ad pH 5,5	ad pH 4,5	ad pH 4,5	pH adjuster
Phenoxyethanol	0,5	0,5	0,5	Preservative
Butylene glycol	5	5	5	Humectant
Perfume (Aloe Vera Bamboo)	q.s	q.s	q.s	Perfume
Distilled water	81	81,5	81	Solvent

Evaluation and Stability Test of Formula

Organoleptic

The evaluation of the formulation encompasses a detailed organoleptic analysis, focusing on key sensory attributes that influence the product's overall acceptability. These attributes include color, aroma, and homogeneity, each of which plays a vital role in shaping the user experience. Color Assessment: The color of the formulation is meticulously observed against a white background to ensure that it meets the intended visual specifications. Color is a critical aspect of product appeal and can influence a consumer's perception of the product's quality. Aroma Evaluation: Aroma is assessed by engaging the olfactory sense. Evaluators position the gel approximately 10 cm from their noses, allowing them to discern the formulation's scent. A pleasing or appropriate fragrance is essential for enhancing the product's sensory appeal and user experience.

Homogeneity Analysis: Homogeneity refers to the uniform distribution of components within the gel. To evaluate this, a small quantity of the gel is applied to a glass surface, and the texture it produces is closely observed. Any irregularities in texture may indicate issues with consistency and uniformity that need to be addressed. These organoleptic assessments are critical in ensuring that the formulation aligns with the desired sensory characteristics and user expectations. The results of this evaluation guide any necessary adjustments to optimize the product's sensory appeal and overall quality.

Physical Evaluation of the Formulation

The physical evaluation of the formulation includes assessing Spreadability,

Adhesiveness, Viscosity, and the pH of the gel product.

Spreadability

A quantity of 0.5 grams of the gel is placed in the center of a round glass surface. Then, another similar glass surface is positioned on top of the gel mass, and a weight of 500 grams is added. The arrangement is left undisturbed for 1 minute. Afterward, measure the diameter of the resulting area using a ruler.

Adhesive Properties

A measured quantity of 0.5 grams of the gel is interposed between two glass object slides. Subsequently, a 50-gram weight is carefully applied to the assembly, and a waiting period of 3 minutes ensues. Following this interval, an additional 80-gram weight is introduced to induce horizontal separation between the two glass slides. The precise duration required for the detachment of the glass slides is meticulously recorded with the aid of a stopwatch. This controlled procedure serves the specific purpose of gauging the gel's strength or adhesive characteristics.

Viscosity

A total of 200 grams of the gel formulation is carefully transferred into a 250 mL chemical beaker. Subsequently, the viscosity of the gel is measured using an IKA Hi-Vi II viscometer with spindle No. 11. This measurement is conducted at a temperature of 30 °C, with the viscometer operating at a speed of 60 rpm for a duration of 1 minute.

Stability Test

The gel formulations are subjected to storage at temperatures of 2°C, 30°C, and 40°C for a duration of 21 days. At intervals of 7 days, organoleptic and physical evaluations are conducted on each formulation. Before testing, each formulation is allowed to equilibrate to the same temperature to prevent any biases that may arise due to temperature variations during testing. This meticulous approach ensures that the evaluations are performed under controlled conditions and provide accurate insights into the formulations' stability and characteristics over time.

Irritation Test

A total of 25 volunteers participate in the irritation testing using the patch test method. This testing is conducted following ethical clearance approval from the Research Health Ethics Commission (KEPK) of Malahayati University. The inner arm of each volunteer is divided into 9 sections. Every 3 sections are subjected to one of three treatments: Blank (No application), Negative Control (Base without extract content), and Formula II (FII). The tested areas are covered with surgical dressing after the application of the respective formulations. After a 24-hour period, the dressings are removed, and irritation assessments are carried out at 0, 24, 48, and 72 hours following the removal. The evaluation of irritation involves assigning scores to each tested area, ranging from 0 to 4, as specified in Table 2.

Table 2. Erythema and Edema Score

Value	Erythema Formation	Edema Formation
0	No Erythema	No Edema (no swelling)
1	Very Slight Erythema (barely perceptible), edges of area not well defined	Very Slight Edema (mild swelling)
2	Slight erythema (pale red in color and edges definable)	Slight Edema

3	Moderate to severe erythema (defined in color and area well defined)	Moderate to severe Edema (severe swelling)
4	Severe erythema (beet to crimson red) to slight eschar formation (injuries in depth)	Severe edema (severe swelling)

The Primary Irritation Index (PII) is determined using the following equation:

$$PII = \frac{\Sigma\, erythema\ grade\ at\ 0/24/48/72h\ +\ \Sigma\, erythema\ grade\ at\ 0/24/48/72h}{3\ x\ number\ of\ people}$$

The calculated PII value is then compared to the standards provided in ISO 10993, as indicated in Table 3. This comparison is essential to draw conclusions regarding the results of the testing. The ISO 10993 standard serves as a reference point to determine whether the level of irritation caused by the tested formulations falls within acceptable limits for safety and human use.

Table 3. Classification of Irritation Response (ISO 10993)

Average PII	Irritation Classification
0-0,4	No significant irritation observed.
0,5-1,9	Mild irritation with minimal impact.
2,0-4,9	Moderate irritation with noticeable effects.
5,0-8,0	Severe irritation with significant impact.

RESULT AND DISCUSSION

Extraction

The extraction process yielded 150 grams of concentrated basil leaf extract and 52 grams of aloe vera leaf extract, resulting in extract yields of 12.5% and 8%, respectively. It is worth noting that the extraction of basil leaves in a study conducted by Romano et al. in 2022, which involved varying ethanol concentrations as solvents, produced a yield range from 3.91% to 6.54% (Romano et al., 2022). The difference in yields can be attributed to the fact that, in their study, yields were determined by comparing dry extracts, whereas in this research, concentrated extracts were utilized, signifying their retention of a limited water content. Likewise, concerning aloe vera leaf extract, a study conducted by Beya in 2012 resulted in a yield of 1.5% for dry extract (Beya et al., 2012). These results underline the effectiveness of the methodology employed in this research for extracting bioactive compounds from both basil and aloe vera leaves.

Organoleptic and Physical Evaluation of Gel Preparation

Table 4. Organoleptic and Physical Evaluation of Gel preparation

Formula	Organoleptic			Physical			
	Color	Scent	Homogeneity	Spreadability (cm)	Adhesiveness (second)	Viscosity * (mPa.s)	pH
I	Army green	Aloe vera bamboo	Homogeneous	4,1[a]	5,4[a]	5504[a]	4,56[a]

II	Army green	Aloe vera bamboo	Homogeneous	6,5[b]	4,1[b]	3480[b]	4,6[a]
III	Army green	Aloe vera bamboo	Homogeneous	5,2[c]	4,2[b]	6340[a]	4,7[a]

a-c; different letters in the same column indicate statistically significant different ($p<0.05$)

Spreadability, adhesiveness, and viscosity play pivotal roles in determining the sensory characteristics of cosmetic formulations. Formula II exhibits broader spreadability compared to Formula I and Formula III, which aligns with its lower viscosity when compared to the others (Table 4). It is worth noting that as viscosity increases, spreadability decreases, as demonstrated in previous research (Szulc-Musioł et al., 2017). Based on these findings, it can be deduced that spreadability, adhesiveness, and viscosity are influenced by the concentration of carbopol, serving as the gelling agent, and the pH of the formulation. Consequently, Formula II was selected as the optimal formula for further evaluation of its stability and potential for irritation.

Table 5. Results of Stability Evaluation of Gel Formulation Formula II

Condition	Week	Organoleptic			Physical			
		Color	Scent	Homogeneity	Spreadability (cm)	Adhesiveness (second)	Viscosity (mPa.s)	pH
2°C	0	Army green	Aloe vera bamboo	H	6,4	3,8	3456	4,70
	1	Army green	Aloe vera bamboo	H	6,5	4,2	3402	4,73
	2	Army green	Aloe vera bamboo	H	6,3	4,1	3524	4,86
	3	Army green	Aloe vera bamboo	H	6,2	4,0	3552	4,80
30°C	0	Army green	Aloe vera bamboo	H	6,5	3,8	3480	4,53
	1	Army green	Aloe vera bamboo	H	6,6	3,7	3456	4,76
	2	Army green	Aloe vera bamboo	H	6,5	3,7	3472	4,77
	3	Army green	Aloe vera bamboo	H	6,5	3,5	3512	4,65
40°C	0	Army green	Aloe vera bamboo	H	6,5	3,6	3472	4,90
	1	Army	Aloe	H	6,7	3,7	3462	4,86

	green	vera bamboo					
2	Army green	Aloe vera bamboo	H	6,7	3,8	3422	4,80
3	Army green	Aloe vera bamboo	H	6,8	3,5	3405	4,82

H = Homogeneous

Stability testing is conducted to anticipate the cosmetic product's capability to withstand conditions that may influence its quality. Prior to consumer use, cosmetic products encounter numerous environmental changes that can impact their quality. In this research, stability testing was carried out at three different temperatures: 2°C, 30°C, and 40°C over a span of three weeks. The utilization of extreme temperatures serves the purpose of expediting potential instability reactions that could occur, thereby allowing the early detection of instability potentials. Stability testing is a fundamental component of product development, ensuring that cosmetic products endure various environmental conditions while maintaining their desired attributes and safety. It offers insight into the product's performance under different conditions and enables adjustments to enhance its stability and quality.

Color and aroma changes in cosmetic formulations can occur due to interactions between the extract and excipients used. These changes may be the result of oxidation reactions within the extract (Li et al., 2023). The results of stability testing in Table 5 reveal that FII did not undergo any color changes during the 21-day testing period at all test temperatures. This phenomenon may be attributed to the presence of flavonoids in the basil leaf extract, which exhibit antioxidant effectiveness (Kousar et al., 2023). Additionally, aloe vera extract has also been researched for its antioxidant capabilities, with an IC50 of 103.4 ppm (Manye et al., 2023).

Homogeneity testing is conducted to identify any potential instability in a gel formulation resulting from factors like ingredient crystallization, incomplete mixing processes, and phase separation after storage. This testing involves the application of the gel formulation onto a glass slide, followed by the observation of the presence of coarse particles. The results in Table 5 demonstrate that FII remains homogenous at various storage temperatures over the course of three weeks of testing. No coarse particles or crystallization were observed in the evaluations, neither from the extract nor from the excipients used. These findings align with previous research conducted by Khurana (Khurana et al., 2020). Gel formulations produced using carbomer as the gelling agent also yield homogeneous gels.

The adhesiveness of a gel formulation to the skin is a crucial factor in determining its effectiveness. The longer a gel formulation can adhere to the skin, the more significant the effects it can produce (Bhalla et al., 2009). Rheological characteristics or flow properties are evaluated by measuring the viscosity or thickness of the gel formulation. During storage, the viscosity of a gel may undergo changes due to polymer degradation within the gelling agent (Restu et al., 2015). High temperatures can lead to either temporary or permanent reductions in viscosity. The stability testing results for the viscosity of FII in Table 5 indicate that there have been no significant changes in the viscosity of FII during storage at various temperatures and testing periods. This finding aligns with the research by Dantas, which utilized carbopol as the gel base and found that viscosity did not significantly differ during stability testing with a freeze-thaw method over six cycles at temperatures of 5°C and 40°C (Dantas et al., 2016). Therefore, carbopol is considered a reliable gelling agent for gel formulation due to its excellent stability under various storage conditions.

Changes in the pH of a gel formulation can result from oxidation processes

within the formulation (Sohail et al., 2018). The antioxidant properties of basil leaves and aloe vera are beneficial in preventing oxidation that might affect the pH of the formulation (Beya et al., 2012; Romano et al., 2022). This is evident in the pH stability testing of FII, as shown in Table 5, which demonstrates excellent stability. The pH changes observed during testing remain within the margin of error, indicating that there have been no significant alterations in the pH of the formulation during storage.

Irritation Test

Table 6. Results of Irritation Testing with Gel Preparation Using Patch Method

Formula	PII
K-	0
B	0
FII	0,0216

K-: Negative control, B: Blank

Cosmetic formulations applied to the skin should ideally not cause irritation or redness. The use of preservatives and extracts can potentially trigger irritation reactions, necessitating irritation testing during product development with extract contents (Gaspar et al., 2008). The irritation testing results in Table 6 indicate that both the Blank and FII formulations do not cause irritation, with respective PII values of 0 and 0.0216. From this data, it can be concluded that the base and the extract used do not induce irritation. This finding aligns with various studies on the irritation effects of each extract using patch test methods. For instance, Rasul's study demonstrated that the use of a W/O (Water in Oil) cream with basil extract had anti-inflammatory effects and did not cause irritation in clinical testing (Rasul et al., 2011). Similarly, Akhtar's research on the effects of a topical cream with aloe vera extract showed that aloe vera extract did not cause irritation after 24 hours of use (Akhtar et al., 2011).

CONCLUSION

The combination of gel formulation containing basil leaf and aloe vera extracts meets the product quality requirements, including organoleptic and physical stability. This combination gel formulation did not cause irritation in volunteers during irritation testing using the patch test method.

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