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Optimization, Characterization, and Primary Irritation Test of Serum Based on Simplex Lattice Design

Naniek Widyaningrum, Thendi Abdul Arief, Yuyun Darma Ayu Ningrum*

Faculty of Pharmacy, Universitas Islam Sultan Agung, Semarang, Central Java, Indonesia

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*Corresponding author.
E-mail: *naniek@unissula.ac.id*

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ABSTRACT

Using ingredients in cosmetic serum formulation necessitates meticulous consideration to mitigate potential pharmaceutical and clinical issues, and guarantee their safety for application. Xanthan gum functions as a gelling agent, while sodium metabisulfite is an additional antioxidant capable of enhancing formulation viscosity. This research aimed to ascertain the optimal formula's physical characteristics, stability, and irritation potential. The optimal formula was derived through the utilization of the Simple Lattice Design. Physical characterization encompassed parameters such as pH, viscosity, organoleptic properties, adhesion, spreadability, and homogeneity. Stability testing involved a cycling test performed over 24 hours for six cycles under cold and hot temperatures. Subsequently, an analysis was conducted using the paired t-test. In-vitro primary irritation testing was carried out using rabbits and volunteers. The optimal formula was identified to consist of 0.66% xanthan gum and 0.34% sodium metabisulfite, exhibiting favorable physical quality and meeting the requisite standards. The stability testing results revealed that sig. values <0.05 indicated storage temperature's influence on viscosity enhancement while it did not influence pH with sig. values <0.08. The outcomes of the primary irritation test yielded values of 0, signifying the absence of erythema and edema in both rabbits and volunteers. In conclusion, the optimal formula derived from this study exhibits commendable characteristics, stability, and non-irritating attributes, rendering it safe for application.

***Keywords*:** Formulation; Optimization; Characterization; Simplex lattice design; Primary irritation test

INTRODUCTION

Cosmetic serum contains high concentrations of active ingredients to nourish and moisturize the skin, enabling it to address skin issues more rapidly and effectively.[1] To ensure the safe use of serum, the serum must exhibit sound physical stability and non-irritating properties. Several active ingredients in serum formulations include ceramide, niacinamide, alpha-arbutin, and glutathione. Ceramide, for instance, enhances the skin's recovery ratio and facilitates the renewal of compounds within the skin.[2] Niacinamide can stop melanogenesis in the skin, protect it from reactive oxidative stress (ROS), and keep moisture in the skin by increasing the production of ceramides and fatty acids.[3] Alpha-arbutin possesses antioxidant effects and the ability to inhibit the enzyme tyrosinase. These effects synergistically inhibit eumelanin synthesis, effectively addressing skin hyperpigmentation.[4] Glutathione works to lighten skin by

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stopping melanogenesis by lowering the activity of tyrosinase enzyme.[5]

Glutathione and alpha-arbutin have the potential to undergo oxidating. Therefore, the addition of antioxidants is necessary in the serum formulation.[6] An additional water-soluble antioxidant compound investigated in the study is sodium metabisulfite. This study incorporated multiple additional ingredients to attain an optimal formulation. Xanthan gum is utilized in topical preparations such as cosmetic serum formulations. Xanthan gum was employed as a gelling agent, known for its non-toxic properties and compatibility with other pharmaceutical ingredients. Furthermore, xanthan gum boasts commendable stability and a wide range of viscosities. The study's findings[7] indicated increased salt concentration, specifically sodium metabisulfite, and boosted viscosity. Nevertheless, variations in sodium metabisulfite concentration did not impact the physical characteristics of the preparation. They proved effective as an antioxidant cosmetic serum, except for viscosity evaluation.

Physical stability was assessed through Cycling Test method, encompassing various parameters, including organoleptic aspects (color, form, aroma), pH value, and viscosity.[8] The evaluation of spreadability, homogeneity, and adhesion of the serum preparation was undertaken within this research. Furthermore, safety testing was imperative to ascertain the optimal serum formula's suitability. In this study, one approach employed to determine the safety level of the serum was in-vitro testing, assessing parameters such as edema and erythema. As described in the preceding description, the primary objective of this research is to carry out physical characterization, stability testing, and in-vitro primary irritation assessment of the optimal cosmetic serum formulation.

Simplex Lattice Design (SLD) is a suitable method for this research. The formula was obtained through the Simplex Lattice Design method. This method was found in the Design Expert software to determine formulas more quickly, and effectively, and avoid selecting formulas by trial and error.[9] The optimization process obtains the optimum response from a formula when developing dosage forms.[10,11]

METHODS

Equipment and Materials

The research utilized several equipment, including a mortar and stamper, beaker glass 250 mL (Pyrex), pH meter (Hanna HI 98121), homogenizer (IKA 25T Ultra Turrax), brookfield viscometer (Ametek), analytical balance (Ohaus), aluminium foil, handscoon (Altamed), mask (Onemed), and cream pot.

The materials used consisted of ceramide (Merck), niacinamide (Merck), alpha-arbutin (Merck), glutathione (Merck), xanthan gum (Sigma-Aldrich), sodium metabisulfite (Sigma-Aldrich), methylparaben (Sigma-Aldrich), propylparaben (Sigma-Aldrich), propylene glycol (Sigma-Aldrich), and pH five citrate buffer solution (Sigma-Aldrich) obtained from PT Medikalab Indo Raya, Semarang.

Formula Determination Using the Simplex Lattice Design (SLD) Method

The serum formulation began with precisely weighing the materials according to the formula. Xanthan gum was evenly sprinkled across the surface of a mortar containing the citrate buffer solution. Moreover, it was left undisturbed for 15 minutes during which it underwent swelling, and subsequently, it was stirred to form a gel base. Methylparaben and propylparaben were dissolved in propylene glycol, mixed into the gel base, and stirred until homogeneous. Sodium metabisulfite, niacinamide, ceramide, alpha arbutin, and glutathione were each dissolved in the citrate buffer solution and then added to the gel base, followed by homogenization. The remaining citrate buffer solution was added gradually while

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stirring until homogeneity was achieved. The functions of the utilized ingredients are as follows: ceramide, niacinamide, and alpha arbutin serve as active agents; glutathione and sodium metabisulfite function as antioxidants; methyl paraben and propyl paraben act as preservatives; xanthan gum operates as a gelling agent; propylene glycol is employed as a solvent; and the citrate buffer solution acts as a carrier and pH modifier.

Evaluation of the Optimal Formula

The Simplex Lattice Design was used to find the best formula for the serum.[12] It led to the discovery of a single solution with 0.66% xanthan gum and 0.34% sodium metabisulfite as its bases. The formula optimization encompassed several parameters, including pH testing, viscosity assessment, spreadability, and adhesion. Additionally, organoleptic tests, homogeneity testing, and stability analysis were performed.[13]

The pH testing was carried out using a pH meter. A serum sample of 0.5 g was dissolved in distilled water within a glass beaker, and then the electrode was immersed and the pH value was recorded on the monitor. The criteria for the pH value to meet the requirements of the serum formulation were within the range of 4.5-6.0.[8]

The formulation's viscosity was determined using the Brookfield Cone and Plate Viscometer. The preparation was dissolved in 100 ml of distilled water in a glass beaker. Subsequently, the spindle and rotational speed were adjusted to 20 rpm. The serum viscosity values ranged from 800 to 3000 cPs.[14]

The spreadability test was conducted by weighing 0.5 g of serum, and placing it at the center of a circular glass with a 15 cm diameter. Another glass circle and a 150 gram weight were placed atop the serum and left undisturbed for a minute. Subsequently, the spread diameter was measured and recorded. The optimal spreadability range for highly comfortable semisolid usage was 5-7 cm.[15]

The adhesion test involved placing 0.5 g of the preparation in the center of one glass object and covering it with another. A weight of 250 grams was applied to the top glass for 5 minutes. The upper edge of the top object glass and the lower edge of the bottom object glass were clamped using a fixture on the adhesion testing device. The support weight was then released, and the time required for both object glasses to detach from the testing device was

Table 1. Serum Formula Utilizing Simplex Lattice Design

Materials	F1	F2	F3	F4	F5	F6	F7	F8
Ceramide	0,5 %	0,5 %	0,5 %	0,5 %	0,5 %	0,5 %	0,5 %	0,5 %
Niacinamide	5 %	5 %	5 %	5 %	5 %	5 %	5 %	5 %
Alfa arbutin	2 %	2 %	2 %	2 %	2 %	2 %	2 %	2 %
Glutathione	2 %	2 %	2 %	2 %	2 %	2 %	2 %	2 %
Xanthan gum	0.9 %	0.3 %	0.1 %	0.5 %	0.9 %	0.7 %	0.1 %	0.1 %
Sodium metabisulfite	0.1 %	0.7 %	0.9 %	0.5 %	0.1 %	0.3 %	0.9 %	0.9 %
Methylparaben	0,18 %	0,18 %	0,18 %	0,18 %	0,18 %	0,18 %	0,18 %	0,18 %
Propylparaben	0,02 %	0,02 %	0,02 %	0,02 %	0,02 %	0,02 %	0,02 %	0,02 %
Propylene glycol	10 %	10 %	10 %	10 %	10 %	10 %	10 %	10 %
Ad 100 ml citrate buffer solution pH 5	100 %	100 %	100 %	100 %	100 %	100 %	100 %	100 %

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recorded. The adhesion criterion was shown to be greater than one second. Organoleptic testing was performed by observing changes in the preparation's physical shape, smell, and color.[16]

Homogeneity testing entailed weighing 0.5 grams of serum. The preparation was positioned in the center of an object glass, leveled, and covered with another object glass. The homogeneity of the serum was observed in the presence of coarse particles or any lack of mixing between serum components.[17]

Cycling Test

The stability assessment of the preparation employed the Cycling Test method, where the serum formulation was stored at a temperature of (40 ± 2)°C and then transferred to a climatic chamber with temperatures of (40 ± 2)°C and room temperature (25 ± 2)°C for 24 hours. The Cycling Test was conducted to observe any phase separation occurring before and after the testing, with a total of six cycles undertaken to assess the stability of the preparation.[8]

Irritation Testing Using Test Animals

The testing was conducted based on ethical clearance no. 134/III/2023/Komisi Biotik on male albino rabbits weighing approximately 2 kg. The rabbits were shaved in an area on their back, covering approximately 10 x 15 cm or at least 10% of the body surface area designated for applying the serum preparation. After shaving, the test animals were allowed to acclimate for 24 hours. Healthy-skinned animals were chosen for the experiment. The application area consisted of distilled water, a 0.5 gram base control, and serum samples weighing 0.5 gram and 1 gram respectively. The serum application areas were covered with non-irritating gauze and tape, with an exposure time of four hours. The rabbits were observed for erythema and edema on the treated skin. The observation results were summarized in a table, recorded at 1, 24, 48, and 72 hours after the patch removal.[18]

Irritation Testing Using Volunteers

The irritation testing was conducted based on ethical clearance no. 134/III/2023/Komisi on volunteers in a closed manner. The test patches consisted of circular filter paper with a diameter of 2.5 cm and adhesive tape. Formulations containing active substances were applied to the upper right arm and the back of the ear. Observations were performed at 0, 24, 48, and 72 hours. The severity of irritation was assessed by assigning scores ranging from 0 to 4 based on the degree of erythema and edema reactions on the skin.[19,20] The selected respondents adhered to the inclusion criteria, encompassing healthy adults aged 18-35 without skin conditions. Meanwhile, the exclusion criteria for the study encompassed volunteers who were allergic to the substances and those unwilling to participate as volunteers.

Data Analysis

The data in this study were analyzed descriptively. Before and after conducting the Cycling Test, the observations were subjected to a dependent T-test (paired T-test). This test was utilized to compare the paired mean differences of observations, establishing their interrelationship.[21]

Table 4. Observation scale for irritation testing using animals and volunteers

Irritation Index	Erythema	Edema
0	No Irritation	No Irritation
1	Very Slight (diameter <25 mm)	Very Slight
2	Mild (25.1-30 mm)	Mild (< 1 mm)
3	Moderate (30.1-35 mm)	Moderate (raised edge ± 1 mm)
4	Severe (> 35 mm)	Severe (raised edge > 1 mm)

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RESULTS AND DISCUSSION

Evaluation of the Optimal Formula using SLD

In this formulation, eight concentrations of xanthan gum and sodium metabisulfite were employed across the eight formulas. These varying concentrations were employed to assess their influence on serum viscosity. Based on the results of physical quality tests on the eight formulas, the Simplex Lattice Design suggests the best formula, which has 0.66% xanthan gum and 0.34% sodium metabisulfite. This formula underwent sensory evaluation, organoleptic, pH testing, viscosity measurement, homogeneity assessment, spreadability, adhesion testing, and stability evaluation.

Table 5. The Optimal Formula as Recommended by the Simple Lattice Design

Materials	Concentration
Ceramide	0,5%
Niacinamide	5%
Alfa arbutin	2%
Glutathione	2%
Xanthan gum	0.6%
Sodium metabisulfite	0.3%
Methylparaben	0,18%
Propylparaben	0,02%
Propylene glycol	10%
Ad 100 ml Citrate buffer solution pH 5	100%

Characteristics Evaluation

The characterization of the optimal formula is based on recommendations from the Simplex Lattice Design. Several tests were conducted on the optimal formula, including organoleptic evaluation, homogeneity, pH, viscosity, spreadability, and adhesiveness. The test results would be compared before and after undergoing the Cycling Test.

Table 6. The results of the characteristic evaluation of the serum optimal formula

Evaluation	Cycling Test	
	Before (25±5°C)	**After (4±2°C and 40±2°C)**
Organoleptic		
Color	Transparent	Transparent
Form	Liquid	Liquid
Aroma	Distinct Aroma	Distinct Aroma
Homogeneity	Homogenous	Homogenous
pH	4.51 ± 0.0057	4.67 ± 0.01
Viscosity (cP)	1346 ± 17.55	2443 ± 107.5
Spreadability (cm)	7.53 ± 0.208	7.9 ± 0.152
Adhesion (s)	1.08 ± 0.026	1.06 ± 0.011

Organoleptic

The organoleptic observations of the serum revealed that it possessed a distinct aroma, transparent color, and liquid consistency. The results of the organoleptic examination after the Cycling Test indicated no changes in color, form, and aroma.[22] The serum utilized in this study was formulated with a water-based composition, which facilitated the complete solubility of all constituent substances in water. Consequently, the resulting serum exhibited a liquid consistency and possessed a transparent appearance. The distinct aroma of the serum was attributed to the release of H2S from the glutathione component.[23] The production of this serum did not involve the use of fragrance, thereby minimizing the potential for skin issues.

Homogeneity

Homogeneity testing was conducted to ascertain and observe whether the serum was uniformly mixed. The homogeneity testing result of the serum yielded a result indicating its homogeneity, as evidenced by the absence of clumps or coarse particles and an even distribution. According to[24], homogeneity was evidenced by the absence of clumps, coarse particles, and even the distribution of the serum. If the preparation maintained the same color, form, and consistency throughout the serum, it could be categorized as homogeneous.[25]

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pH

The pH testing of the serum formulation resulted in a pH value of 4.5, which fell within the range of skin pH values, namely 4.5-6.[26] The changes in serum pH value could be minimized using a buffer solution.[7] The results of the pH examination after the Cycling Test above stability testing indicated no change in pH values. Subsequently, a paired T-test analysis was performed to understand the impact of storage on pH values. The test results revealed a P-value > 0.05, precisely 0.08, signifying that the storage temperature did not affect the serum pH. The serum remained safe within the acceptable pH range. This phenomenon could be attributed to the use of distinct ingredients in the formulation process. The pH values before and after the stability test were not significantly different.[27]

Viscosity

The viscosity of the serum formula was observed at a stirring speed of 20 rpm, resulting in varying viscosity values that remain within the range of serum viscosity. According to[14], the observed viscosity values fell within the 800-3000 cP range. The results of the viscosity examination after the Cycling Test above stability testing indicated an increase in viscosity following storage at cold and hot temperatures. Subsequently, a paired T-test analysis was conducted to understand the influence of storage on serum viscosity. The test results revealed a P-value < 0.05, precisely 0.013, signifying that storage at cold and hot temperatures affects serum viscosity, making it slightly more viscous. According to the research findings of[28], there were no significant changes in the gel before and after stability. It could be attributed to the use of different ingredients in the formulation process.

Spreadability

The spreadability testing results revealed values exceeding the optimal spreadability range of 7.6-8.1 cm. According to[25], an excellent topical preparation exhibited a spreadability range of 5 to 7 cm. The wider the spreadability of the serum preparation, the faster the active ingredients could penetrate the skin, a preparation would be preferred if it could spread easily on the skin.

Adhesion

The adhesion testing produced a result in the range of 1.05 – 1.10 seconds. The adhesion criterion surpassed one second. Adhesion testing was conducted to illustrate the adherence of the preparation to the skin. Good adhesion enabled the product to remain in place and adhere to the skin, achieving the desired effect over a longer duration.[27]

Skin Irritation Test on Test Animals and Volunteers

Based on the observation data from the control using distilled water, control basis, doses of 0.5 gram and 1 gram, the irritation index was 0, indicating no erythema or edema reactions from the application until day 14. It is demonstrated by the observation table, which indicates no erythema formation or edema in the application area. According to the research findings of, there was no irritation from 1 hour to day 14, and the rabbit fur grew back normally and evenly.

The irritation testing was conducted on 30 volunteer participants, including males and females aged 18-35, as this age range corresponds to students who often use cosmetics. Skin irritation effects were observed at 0 hours before the application of the test substance and at 24, 48, and 72 hours following the application. The observation results indicated an irritation index value of 0, signifying the absence of erythema and edema. The reaction shows irritation can appear 12 to 48 hours after exposure.[29] Research by[30], tested 12 volunteers by applying the red betel leaf extract serum on the skin behind the ear, and it demonstrated that all participants obtained negative results for irritation parameters, including redness, itching, and rough skin.

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Table 7. Irritation test using albino rabbits and volunteers

Symptoms	Dosage	Rabbits	Volunteers
		24-72 Hours	
Erythema	Distilled water	0	0
	Base	0	0
	0.5 g	0	0
	1 g	0	0
Edema	Distilled water	0	0
	base	0	0
	0.5 g	0	0
	1 g	0	0

CONCLUSION

The optimal serum formula obtained through the Simple Lattice Design resulted in a concentration of 0.66% xanthan gum and 0.34% sodium metabisulfite as the base. The physical characteristics revealed transparency in color, a liquid form, and a distinctive aroma and demonstrated good spreadability, adhesion, and homogeneity, rendering it suitable for serum formulation. Stability testing indicated an influence leading to increased viscosity post-testing, yet the serum still fell within the acceptable viscosity ranges with no significant change in pH value. In the in-vitro irritation test, the average result of 0 implied that the serum did not induce erythema and edema effects on both animal and human test subjects.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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