

Formula Optimization and Evaluation of Synconine Ointment as an Anti-Acne

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ABSTRACT

Acne is a common skin problem that occurs among teenagers and adults, often caused by bacterial activity on facial skin that becomes blocked due to the accumulation of oil and dirt. *Cutibacterium acnes* is one of the bacteria that can infect the skin and trigger acne formation. Synconine is an alkaloid compound that has been proven to inhibit the activity of gram-positive bacteria; therefore, it was formulated into an ointment preparation. An important component in ointment formulations is the base, which functions as a carrier to deliver the drug to its site of action and achieve the desired pharmacological effect. This study aimed to optimize the PEG 400 and PEG 4000 bases in synconine ointment formulations. The optimum concentration was determined using the disc diffusion method for antibacterial activity testing, while formula optimization was carried out using Design Expert® software version 13 with the Simplex Lattice Design method. The results showed that the optimum concentration obtained was 1.5%, producing an inhibition zone of 13.26 mm, which falls into the moderate category (10–15 mm). The optimum ointment formula was achieved with a PEG 400 concentration of 30% and PEG 4000 of 60%, with a desirability value of 0.911. In conclusion, synconine compounds demonstrated potential antibacterial activity against *Cutibacterium acnes*, and formula optimization using the Simplex Lattice Design method with variations of PEG 400 and PEG 4000 significantly influenced viscosity, spreadability, adhesion, and pH responses of the ointment preparation.

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1. INTRODUCTION

Acne is a skin problem that frequently occurs among adolescents and adults¹⁰. Currently, acne is the eighth most common skin disease worldwide, affecting approximately 9.38% of people of all ages globally³. The percentage of acne sufferers has increased by about 10% annually according to cosmetic dermatology research in Indonesia, with 60% of individuals affected in 2006, 80% in 2007, and 90% in 2009⁵. The highest prevalence of acne vulgaris occurs among adolescents, based on dermatological studies in Indonesia, and continues to increase⁷.

One of the causes of acne is bacterial activity on facial skin that becomes clogged due to the accumulation of oil and dirt. *Cutibacterium acnes* is a bacterium that can infect the skin and is one of the causes of acne by breaking down sebum components into fatty acids, resulting in colonization of *C. acnes* and triggering inflammation².

Cinchona plants are known for their antimalarial activity and have been used to treat and cure various health disorders related to malaria. Cinchona extract contains many alkaloids, with the main ones being

cinchonine, cinchonidine, quinidine, and quinine. Cinchona can also be used to treat other diseases because its alkaloids possess antioxidant, anticancer, anti-obesity, anti-inflammatory, and antibacterial activities.

Cinchonine is an alkaloid compound that has been shown to inhibit the activity of gram-positive bacteria. Alkaloid compounds can inhibit bacterial activity by disrupting peptidoglycan components in bacterial cells, preventing proper cell wall formation and causing cell death. In addition, alkaloids can inhibit protein synthesis, thereby disrupting bacterial metabolism¹. Cinchonine alkaloids exhibit antibacterial activity against bacteria, particularly gram-positive *Staphylococcus aureus*, with an inhibition zone of 13.2 mm at a concentration of 125 µg/mL.

The dosage form developed as a delivery system for cinchonine in this study is an ointment preparation. Ointments are semi-solid dosage forms intended for topical application on the skin (Depkes RI, 1995). To deliver the drug to its site of action effectively, the ointment must use an appropriate base, which should be inert so as not to reduce the therapeutic effect of the drug⁶. Ointment preparations offer advantages such as protecting the skin surface and providing good distribution on the skin, resulting in longer effectiveness.

An important component in ointment preparations is the base, which functions as a carrier to deliver the drug to its site of action and achieve pharmacological effects. One of the components used as an ointment base is polyethylene glycol (PEG). This base has good adhesion, is non-irritating, provides good distribution, and offers prolonged effectiveness because PEG can inhibit sweat production and gas exchange. The combination of PEG 400 and PEG 4000 provides advantages since the selected base does not contain fat, thereby preventing the worsening of acne-prone skin.

This study used the Simple Lattice Design method to determine the optimum composition of PEG 400 and PEG 4000. The Simple Lattice Design method can identify the most optimal components based on predetermined responses or variables and is one of the procedures used in formula optimization for pharmaceutical preparations⁴. Based on this rationale, this study was conducted to optimize the formula and evaluate cinchonine ointment preparations as an anti-acne agent in order to determine the most optimal formulation.

2. RESEARCH METHOD

This study employed an experimental design to determine the optimal concentration of cinchonine and to optimize an ointment formulation containing cinchonine as an anti-acne agent. Cinchonine concentrations of 0.18%, 0.5%, 1%, 1.5%, and 2% were evaluated to identify the most effective concentration in inhibiting the growth of *Cutibacterium acnes*. The research also included formulation optimization, antibacterial activity testing of the ointment, irritation testing on rabbits, and diffusion testing using a Franz diffusion cell with mouse skin membranes. The independent variables were cinchonine concentration and base variation, while the dependent variables included physical characteristics (organoleptic properties, homogeneity, adhesion, viscosity, and spreadability), chemical properties (pH), irritation response, and diffusion results. Controlled variables included the bacterial strain (*Cutibacterium acnes*) and the type of rabbits used for irritation testing. The study was conducted from January to May 2023 in the Pharmaceutical Biology, Pharmaceutical Technology, and Microbiology Laboratories of the Biology Study Program, Faculty of Teacher Training and Education, Universitas Muhammadiyah Purwokerto.

The primary materials used in this research included cinchonine obtained from PT. Sinkona Indonesia Lestari and *Cutibacterium acnes* bacteria obtained from the Microbiology Laboratory of Universitas Muhammadiyah Purwokerto. The determination of the optimal cinchonine concentration was carried out using the disc diffusion method with several concentration variations. Bacterial rejuvenation was performed by inoculating *C. acnes* into Nutrient Agar and incubating at 37°C for 24 hours, followed by suspension preparation using sterile NaCl solution. Antibacterial testing involved placing cinchonine-impregnated paper discs onto agar media inoculated with bacteria, and inhibition zones were observed to identify the most effective concentration. This procedure was conducted to determine the optimal antibacterial activity against *Cutibacterium acnes* prior to ointment formulation optimization.

Optimum Concentration Formulated in the Ointment Preparation
a. Formulation**Table 1. Water-soluble ointment base formulation**

Formulation				
Ingredients	Concentration %	Negative Control	Comparator	Function
Cinchonine		Base	Clindamycin 1 %	Active substance
PEG 400	30-60			Base
PEG 4000	30-60			Base
DMDM	0,2			Preservative
Hydantoin				
Oleic Acid	ad 100			Enhancer

b. Optimization of materials

The designed formula was then optimized using the Simplex Lattice Design Mixture method in Design Expert® software version 13, which was expected to obtain responses in the form of pH value, viscosity, spreadability, and adhesion. The formula run setting with 4 responses (viscosity, pH, spreadability, and adhesion) used 3 optimizations, namely PEG 400 (lower limit 30% and upper limit 60%) and PEG 4000 (upper limit 30% and lower limit 60%), resulting in a total of 8 runs.

Table 1. Formulation Design

Run	Component 1 PEG 400	Component 2 PEG 4000
1	45	45
2	60	30
3	60	30
4	30	60
5	30	60
6	52.5	37.5
7	45	45
8	37.5	52.5

c. Preparation of the ointment

All required materials were weighed. Cinchonine and oleic acid were heated in a porcelain dish at 70°C over a water bath. The PEG 4000 base was melted in another porcelain dish over a water bath. The melted PEG 4000 was poured into a warm mortar, followed by the addition of PEG 400 base and mixed until homogeneous. The dissolved cinchonine was gradually added into the base, and finally DMDM Hydantoin was incorporated until a thick consistency was formed.

The evaluation of the cinchonine ointment preparation included physical, stability, chemical, and safety assessments. Physical tests consisted of organoleptic evaluation (observing color, odor, and semi-solid form), homogeneity testing by spreading the ointment on a glass slide to ensure uniform structure without lumps, spreadability testing using a specified weight to measure diameter (acceptable range 5–7 cm), adhesion testing by measuring the separation time between two glass slides under load, and viscosity measurement using a Brookfield viscometer with spindle number 4 at 12 rpm. Stability testing was conducted using a cycling test method by storing the preparation alternately at 4°C and 40°C for 24 hours each over six cycles while observing organoleptic properties, homogeneity, pH, and spreadability. Chemical evaluation included pH measurement, with an acceptable range of 4.5–6.5. Safety evaluation was performed through an irritation test on rabbit skin by applying 0.5 g of ointment to a shaved area and observing erythema and edema responses at specified time intervals according to BPOM guidelines. Data analysis included measuring antibacterial inhibition zones followed by one-way ANOVA and Tukey tests using SPSS, formula optimization using Design Expert® version 13 to

determine the optimal PEG 400 and PEG 4000 composition, verification of the optimum formula using a one-sample t-test, irritation score analysis based on erythema and edema observations, and diffusion test analysis using one-way ANOVA with LSD testing.

3. RESULT AND DISCUSSIONS

3.1 Determination of Cinchonine Concentration

The determination of cinchonine concentration was carried out to ensure its ability to inhibit *Cutibacterium acnes*, a bacterium that causes acne, using the disc diffusion method. This method was selected because it is simple, rapid, and does not require specialized equipment. The formation of a clear inhibition zone around the disc indicated antibacterial activity. The results showed that cinchonine exhibited antibacterial activity at several concentrations with varying inhibition zones. The best inhibition was observed at a concentration of 1.5%, with an inhibition diameter of 13.26 mm, categorized as moderate (10–15 mm), while clindamycin as the positive control produced an inhibition zone of 26.54 mm, categorized as very strong (>20 mm). A decrease in the inhibition zone at the 2% concentration was attributed to a paradoxical antimicrobial effect, where higher concentrations resulted in reduced activity. Additionally, the inhibition zones decreased after 24 hours of observation, likely due to factors such as contact time, concentration, and bacterial characteristics. Statistical analysis using one-way ANOVA showed a p-value <0.05, indicating significant differences in inhibition zone diameters among the tested concentrations, which was further confirmed by Tukey's test showing significant differences between the positive control and each cinchonine concentration. Overall, cinchonine demonstrated positive antibacterial activity against *C. acnes*, likely due to alkaloid mechanisms that disrupt bacterial cell wall peptidoglycan, leading to incomplete cell formation and bacterial death¹.

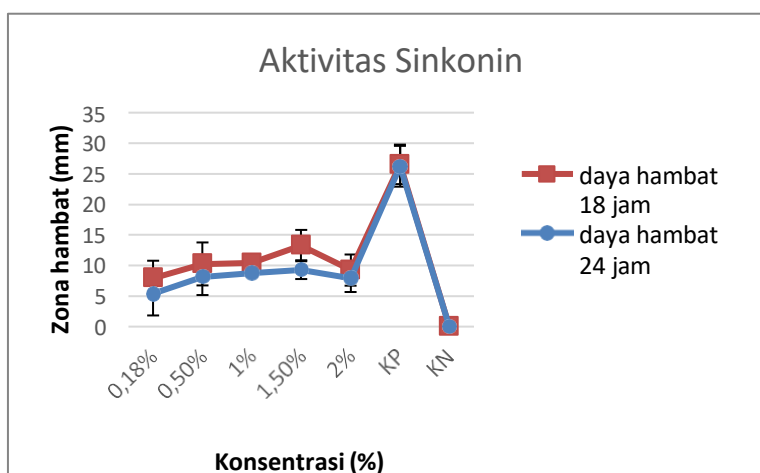


Figure 1. Antibacterial Activity Test after 18 Hours and 24 Hours

3.2 Determination of Cinchonine Concentration

The determination of cinchonine concentration was conducted to evaluate its antibacterial activity against *Cutibacterium acnes* using the disc diffusion method. The results showed that cinchonine produced inhibition zones at several concentrations, with the optimal concentration observed at 1.5%, yielding an inhibition diameter of 13.26 mm, categorized as moderate activity, while clindamycin as the positive control showed a very strong inhibition zone of 26.54 mm. A decrease in activity at the 2% concentration was attributed to a paradoxical antimicrobial effect. Statistical analysis using one-way ANOVA ($p < 0.05$) followed by Tukey's test indicated significant differences between the positive control and each cinchonine concentration. These findings confirm that cinchonine possesses antibacterial activity against *C. acnes*, likely through alkaloid mechanisms that disrupt bacterial cell wall formation, leading to bacterial death.

3.3 Evaluation of Physical Properties

a. Organoleptic Test

The organoleptic test was conducted to observe the odor, shape, and color of the ointment preparation to assess its physical quality. A good ointment should have a semi-solid form, no rancid odor, and a color consistent with the initial formulation. The cinchonine ointment formulated with PEG 400 and PEG 4000 bases produced a semi-solid preparation with a white color that met the initial specifications.

Table 3. Organoleptic Test Results of Ointment Preparation

Run	Form	Color	Smell
1	Semi-solid	White	Characteristic smell
2	Semi-solid	White	Characteristic smell
3	Semi-solid	White	Characteristic smell
4	Semi-solid	White	Characteristic smell
5	Semi-solid	White	Characteristic smell
6	Semi-solid	White	Characteristic smell
7	Semi-solid	White	Characteristic smell
8	Semi-solid	White	Characteristic smell

b. Homogeneousity Test

The homogeneousity test was performed to determine whether the ointment preparation was uniformly mixed between the active substance and the base⁹. A homogeneous ointment is characterized by the absence of lumps, uniform color, and smooth structure. The results showed that all formulations were homogeneous, with no coarse particles, uniform color, and consistent structure.

Table 4. Homogeneousity Test Results of Ointment Preparation

Run	Homogeneousitas
1	Homogeneous
2	Homogeneous
3	Homogeneous
4	Homogeneous
5	Homogeneous
6	Homogeneous
7	Homogeneous
8	Homogeneous

3.4 Optimization Responses and Determination of Optimum Formula

The optimization responses included pH, viscosity, spreadability, and adhesion of the cinchonine ointment formulations. The pH values ranged from 5.08 to 5.62, meeting the acceptable skin pH range (4.5–6.5), and were influenced by PEG components, with PEG 400 showing a greater effect on increasing pH. Viscosity values ranged from 22,100 to 27,050 cP, also meeting the required standards (2,000–50,000 cP), with PEG 4000 having a stronger influence due to its higher molecular weight. Spreadability values ranged from 5.0 to 6.1 cm, fulfilling topical preparation requirements (5–7 cm), and were more affected by PEG 400 concentration, while adhesion values ranged from 4.98 to 7.53 seconds, exceeding the minimum requirement (>4 seconds), with PEG 4000 contributing more significantly to increased adhesion. Statistical analysis using Design Expert® software version 13 demonstrated good model suitability for all responses. Based on optimization using the Simplex Lattice Design method, the optimum formulation consisted of 30% PEG 400 and 60% PEG 4000 with a desirability value of 0.911. Verification using SPSS showed no significant difference between predicted and experimental values ($p > 0.05$), confirming the reliability of the optimized formula.

3.5 Stability and Irritation Test

The stability test using the cycling test method for six cycles showed no significant changes in organoleptic properties, homogeneousity, pH, spreadability, or adhesion, indicating good formulation stability under different temperature conditions. Minor fluctuations in pH, spreadability, and adhesion were influenced by temperature changes affecting viscosity but remained within acceptable limits. The acute dermal irritation

test on rabbits showed an irritation index score of 0, with no erythema or edema observed up to 72 hours, confirming that the cinchonine ointment was safe and non-irritating for topical use.

3.6 Strengths and Limitations

The strength of this study lies in the novelty of optimizing and evaluating a cinchonine ointment formulation as an anti-acne agent using PEG 400 and PEG 4000 as variables. However, the limitations include the absence of diffusion testing using the open and close hair follicle method and antibacterial testing using the well diffusion method.

5. CONCLUSION AND RECOMMENDATION

Conclusion

1. Cinchonine compounds showed positive effects with the potential to inhibit the growth of *Cutibacterium acnes*. The largest inhibition zone indicating antibacterial potential was obtained at a concentration of 1.5%, with an inhibition diameter of 13.26 mm.
2. The optimum ointment formulation was obtained from the Design Expert® software version 13 solution with a concentration of PEG 400 at 30% and PEG 4000 at 60%, with a desirability value of 0.911.
3. The optimum ointment formulation had characteristics of a semi-solid dosage form, white color, and a characteristic odor.
4. The optimum cinchonine ointment formulation was physically stable based on the cycling test conducted for 12 days.
5. The cinchonine ointment preparation did not cause skin irritation and was therefore safe for use.

Recommendations

1. Further diffusion testing is needed to determine the penetration ability of the preparation.
2. Antibacterial activity testing should be conducted on the optimized ointment formulation.

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