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Formula Optimization of Propolis Transfersome Gel, Aloe Vera, Gotu Extract: Formula Design, Formulation Evaluation and Cell Regeneration Test in Diabetic Wounds

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Abstract: The study was conducted to determine the optimal formula of transfersome propolis gel, aloe vera extract and gotu gotu leaf extract and test it against diabetic wounds in male white rats *(Rattus norvegicus)*. The gel was created with an optimal formulation resulting from the application of a *Design Expert* with Cutimed as a positive control of burns on the backs of male white *rats (Rattus norvegicus)*. Formula optimization was carried out using a *Simple Lattice Design* with variations of carbopol, TEA and glycerin. Activity tests of propolis transferosome gel, aloe vera extract and gotu gotu extract were conducted on 20 rats. The data results were statistically analyzed using the SPSS *One Way* ANOVA method. Phytochemical screening on aloe vera and gotu gotu showed the presence of flavonoid compounds, tannins and saponins. Transfersome propolis has a particle size of 88.55 nm and a zeta potential of -24.13 mV. The optimal formula produces a clear preparation in white, a distinctive odour, a stable viscosity of 19980 cps, dispersion power of 6.67 cm, adhesion of 4.07 seconds and pH of 6.45. The burn activity test had the fastest effectiveness on day 12 but did not differ significantly from the customized control.

Keywords: Aloe vera L; Diabetes wounds; Gel; Gotu-gotu leaf; Propolis

Introduction

Diabetes is a metabolic disorder characterized by high blood sugar levels or hyperglycemic related to metabolic abnormalities to carbohydrates, fats and proteins caused by the body's inability to secrete insulin or decreased sensitivity to insulin (Ristanti et al., 2021). Chronic hyperglycemic states in people with diabetes can cause damage to body systems, especially in the peripheral nervous system and blood vessels (Li et al., 2023; Vinik et al., 2020). One of the complications resulting from acute hyperglycemia is diabetic foot wounds.

The International Diabetes Foundation estimates that 40 million to 60 million people worldwide are affected by DFU, a noticeable increase from the 2015 estimate, which ranged from 9 million to 26 million (McDermott et al., 2023). Diabetic foot wounds can cause active ulceration related to infection, which causes the wound to widen so that ulcers and gangrene occur. If the treatment is not good, amputation is carried out to avoid the spread of wounds and wider nerve damage to nephropathy (Riani, 2017).

Based on the above phenomenon, treatment is needed to reduce the risk of amputation and accelerate wound healing. Researchers are starting to look for alternative treatments using herbal ingredients with a lower risk of side effects than chemical drugs. In this study, the herbal ingredients developed to treat diabetic wounds include propolis, aloe vera and gotu grain.

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Propolis has flavonoid content that is anti-inflammatory, antibacterial, antiviral, etc (Bhatti et al., 2024; Chavda et al., 2023). Propolis also contains arginine and ferulic acid, which can spur collagen formation and accelerate wound healing. However, propolis has low bioavailability, so technology is needed to be more optimal in its absorption, namely transfersome technology. Aloe vera contains aloesin, an anti-inflammatory, antiseptic (Yusriyani & Nurhidaya, 2020), and antioxidants. Meanwhile, gotu gotu has anti-inflammatory activity in wounds (Fernenda et al., 2023).

The transdermal route is the delivery of drugs through the skin to the systemic, which can avoid the first pass of metabolism, the release of the drug is constrained: it reduces the side effects of the drug, improves the pharmacological effect of the drug, convenient to use, and the treatment directly works on the wound site. One of the preparations that the transdermal route can use is gel. The gel has much water and does not leave a layer of oil on the skin, minimizing inflammation (Denni, 2023).

Therefore, the author chose "Optimization of Propolis Transfersome Gel Formula, Aloe Vera, Gotu Extract: Formula Design, Preparation Evaluation and Cell Regeneration Test in Diabetic Wounds." This study aims to determine the preparation's physical properties, the appropriate formulation, and the level of effectiveness of the active ingredients in the gel against diabetic wounds.

Method

Sample Preparation

Propolis extract, aloe vera extract, and gotu gotu extract were obtained from PT. Kaffah Berkah Bersama and Sentana Sempurna, as evidenced by a Certificate of Analysis (CoA) certificate.

Creation and Characterization of Propolis Transfersomes

Transfersome is made using the thin-layer hydration method. Mixed soy phosphatidylcholine and tween 80 as surfactants (75:25). the mixture is dissolved with chloroform and methanol (2:1). 300µL of propolis is put into a mixture of phospholipids and tween 80. The mixture is evaporated using a rotary evaporator at a temperature of 56° C at 75-130 rpm to remove organic solvents. Then, it is left for 24 hours to perfect the formation of vesicles. The resulting thin layer is hydrated using a solution of 100ml of pH 7.4 phosphate solution at a temperature of 56° C at 75 rpm for 30 minutes (Ambarwati & Susilo, 2019). The solution is sonicated with a sonicator bath for 30 minutes. Characterization of transferosomes propolis includes organoleptics, pH, particle size and zeta potential.

Phytochemical Screening of Aloe Vera and Gotu
Flavonoid

This test was carried out by inserting 2 mg of aloe vera extract into a test tube, dissolved with 1-2 ml of ethanol, several magnesium grains, and 4-5 drops of HCL. If the colour of the precipitate turns yellow, it proves that aloe vera extract contains flavonoid compounds (Dewi et al., 2022). Gotu is characterized by the presence of a red colour on the mail alcohol layer (Djoko et al., 2020).

Saponins

The sample is inserted into the test tube, shaken for 10 seconds, and left for 10 seconds. The saponin content is evidenced by the appearance of foam in the sample, and when HCL 2N is added, the foam does not disappear (Yasir et al., 2021).

Tannins

The sample is inserted into a test tube, and a few drops of 1% iron (III) chloride solution are added. Observe the changes that occur; if a dark blue or greenish-black colour appears, the sample contains tannin compounds (Yasir et al., 2021).

Propolis Transfersome Gel Formulation, Aloe Vera and Gotu Extract

The formulation was obtained from the results of formula optimization using a *Simplex Lattice Design* so that the optimal formula was obtained and developed into a gel preparation.

Physical Evaluation of Transfersome Propolis Gel, Aloe Vera and Gotu Gotu Extract
Organoleptic

Organoleptic observations include odour, colour, and the presence or absence of phase separation.

Homogeneity

This is done by placing a sample between two glass objects and then looking at them in a beam to determine whether or not there are particles.

pH Measurement

It is done by diluting 0.5 g of gel in 50 ml aquadest. pH measurement using a pH meter that has been calibrated in advance.

Viscosity

Viscosity measurement uses *a Brookfield* viscometer with a speed of 30 rpm and spindle 4 (Tajudin et al., 2023). A suitable viscosity for gel preparations is 3000-50,000 cps (Chandra & Rahmah, 2022).

Spreadability

It is done to determine the ability to spread the gel. The gel preparation is weighed by 0.5 grams, then applied to a graph glass and covered with transparent glass. Wait for 60 seconds and record the resulting diameter. Then, put on a load of 200 grams, leave for 60 seconds, and record the resulting diameter. The characteristics of good dispersion in gel preparations are 5-7 cm (Yati et al., 2018).

Adhesivity

The gel preparation is weighed by 0.5 grams, placed on one of the object glasses, and then closed with the other. The glass of the object is given a load of 500 grams for 5 minutes. After that, remove the object glass using the tool contained in the adhesion test tool and calculate the time required for the 2 object glasses to fall off each other. Good adhesion is not less than 4 seconds (Yati et al., 2018).

Making diabetic mice by alloxan induction

The test animals used 20 male rats (*Rattus novergicus)*, who had previously been acclimatized for 7 days. Furthermore, the mice were induced with aloxan at a dose of 150 mb/KgBB intraperitonally. After 3 days, fasting blood sugar levels were examined to find out if the rats had developed a condition of diabetes mellitus, which was characterized by a fasting sugar level of more than 200 mg/dL (Swastini, 2018).

Gel Activity Test Against Wound Healing

As many as 20 rats were shaved on their backs and anaesthetized using ethyl chloride. The mice were divided into 4 observation groups: positive control, negative control, base control and optimal gel formula. The back is cleaned with 70% alcohol and marked 2cm on the area to be cut. The marked area is cut 2 cm long with a sterile scalpel (Amfotis, 2022). Cutting is carried out in the back area to the subcutaneous layer by stretching the skin using the index finger and thumb (Nurafni, 2022). Gel treatment is given after a cut wound using a cotton bud 3 times daily. Measurements of wound length are carried out daily with a calliper. The results of measuring wound length are calculated in the wound healing percentage formula, namely:

$$\%Wound\ Healing: \frac{(wound\ length\ H0 - Wound\ length\ Hn)}{wound\ length\ H0} \times 100\% \quad (1)$$

Result and Discussion

Sample Preparation

Propolis samples were obtained from PT. Kaffah Bersama, accompanied by a CoA (*Certificate of Analysis*) certificate, has a liquid form, a light brown colour and a distinctive smell. Gotu extract and aloe vera extract were obtained from Sentana Sempurna, accompanied by a CoA (*Certificate of Analysis*). Gotu extract is yellow and precise, while aloe vera extract has a clear yellow colour and a distinctive smell.

Creation and Characterization of Propolis Transfersome

Propolis transfersome is made by the decomposition of propolis extract in transfersome delivery media. Transfersomes are elastic lipid vesicles consisting of phosphatidylcholine and surfactants. Transfersome can permeate into the skin through pores that are less than 30 nm in size and can be used for drugs that have low solubility (Nurmahliati et al., 2020).

Organoleptic Test

The organoleptic test was carried out by observing colour, shape, and odour (Lumentut et al., 2020). The results of organoleptic observations on propolis nanoparticles are shown in Table 1.

Table 1. Result in Organoleptic Test of Transfersom

Parameter	Result
Shape	Liquid
Colour	Light chocolate
Smell	Distinctive
Clarity	Clear

pH Test

The pH test uses a pH meter to determine the acid and alkaline levels in the preparation. The optimal pH value is at a vulnerable 4.5-6.5, with the Indonesia National Standard (SNI) for nanoparticle preparations being 4-10. If the pH is too acidic, it can irritate the skin, and too alkaline will cause the skin to become dry (Prasongko et al., 2020). The results of the pH test are shown in Table 2.

Table 2. Result in pH Test of Transfersom

Replication	pH value
1	5.67
2	5.67
3	5.67
Average ±SD	5.67±0.00

The transfersome propolis formulation has an average pH of 5.67 ± 0.00 which means the preparation is at optimal pH susceptibility.

Determination of Droplet Size

The results obtained from *the droplet size* are the *polydispersity index* value, zeta potential value and particle size. The results obtained can be seen in Table 3.

Transfersome propolis has an average of 88.55 nm ± 0.111, which indicates that it corresponds to the size of

the transfersome in order to pass through the stratum corneum, which is <400 nm (Nurmahliati et al., 2020).

Table 3. Droplet Size, Polydispersity Index, and Zeta Potential Value

Replication	Droplet Size (nm)	Polydispersity Index	Zeta Potential Value (mV)
1	110.60	0.348	-24.90
2	74.24	0.250	-23.70
3	80.82	0.471	-23.80
Average ±SD	88.55 ± 19.37	0.356 ± 0.111	-24.13

The Polydispersity Index is a parameter of the particle size distribution in the preparation. According to Kuncahyo et al. (2021) A polydispersity index value of less than 0.5 or even close to 0 will describe a homogeneous particle size range. Based on the table above, the average value of the polydispersity index measurement is 0.356, which indicates that the particle size obtained has a homogeneous dispersion.

Zeta potential is an electrical charge parameter between the surface layers of a particle (Farmasetika, 2024). If the potential value of zeta nanoparticles is less than -30mV and greater than +30 mV, then the degree of stability of the preparation is higher (Rahma et al., 2022). The greater the potential value of the zeta of the nanoparticle preparation, the more stable the nanoparticle system will be formed and prevent flocculation (Kusumawati et al., 2021).

Table 3 shows that the average potential zeta value of transfersome propolis is -24.13. Therefore, it can be concluded that the propolis transfersome preparations obtained are unstable and tend to undergo flocculation. Then, the test results determined that replica 1 has the smallest zeta potential value, indicating that replica 1 has good stability compared to replicas 2 and 3. The negative zeta potential value is due to the phosphatilodicholine used, i.e. soy lecithin. Soybean lecithin is a zwitterionic component with an isoelectric point between 6-7, while the hydration medium used is pH 7.4. Under conditions of pH higher than the isoelectric point, it can result in soybean lecithin having a negative charge (Nurmahliati et al., 2020).

Table 4. Optimization of the Formulation

Formulation	Carbopol	Gliserin	TEA	Viscosity	Adhesion
1	65.9981	16.3515	17.6504	19980	4.34
2	1	1	98	19980	6.26
3	49.8205	1	49.1795	19980	4.19
4	16.5964	16.7397	66.6639	19980	120.16
5	98	1	1	18980	4.45
6	48.8228	49.295	1.88216	18980	4.3
7	1	73.1065	25.8935	19980	4.37
8	48.8228	49.295	1.88216	18980	4.88
9	98	1	1	18980	4.59
10	32.5803	33.328	34.0916	19980	4.37
11	25.5997	73.4003	1	19980	60.32
12	49.8205	1	49.1795	19980	4.54
13	1	49.01	49.99	19980	4.24

Phytochemical Screening

The results were obtained (Table 5) that aloe vera extract contained flavonoid compounds which were characterized by a change in color in the sample to yellow, saponin compounds were characterized by the appearance of foam in the sample and tannin compounds were marked by the appearance of dark blue or blackish-green color in the sample. The results are the same as the results of previous research conducted by Yasir et al. (2021). Then the gotu gotu extract contains flavonoid compounds which are characterized by a change in color in the sample to red, saponin compounds which are characterized by the appearance of foam in the sample and tannin compounds which are marked by the appearance of dark blue or blackish-green in the sample. The results are the same as the results of previous research conducted by Djoko et al. (2020).

Table 5. Result Phytochemical Screening

Secondary Metabolite Compounds	Reagents	Result
Flavonoid	Mg + HCl	+
Saponin	Aquadest + HCl	+
Tannin	FeCl3	+

Gel Creation and Evaluation

To obtain an optimal formulation of gel transfer, some propolis, aloe vera, and gotu gotu extract were optimized. Equation optimization was processed using the Design Expert version 13 application, which then obtained 14 formulations, where the optimized materials included carbopol, glycerin, and TEA. The calculation of the optimization formula can be seen in Table 4.

The gel is made by adding aqua dest that has been heated little by little to the carboxyl and then stirring until homogeneous (mixture A). Next, put methylparaben in TEA and glycerin (mixture B) and stir until dissolved, then add to mixture A and stir until a gel mass is formed.

Adhesion

The table shows that run 4 produces the highest adhesion of 120.16 seconds with a carbazole variation of 16.5964%, glycerin 16.7397%, and TEA 66.6639%. Furthermore, statistical processing was carried out with Simplex Lattice Design to determine the influence of these three factors on gel adhesion. The equation obtained from the program is shown in the Formula 2.

$$Y=+2.74006A +14.9389B +5.71255C -13745AB^2C +3359.5 (ABC^2) \quad (2)$$

Information:
Y= Adhesion response
A= Carbopol
B= Gliserin
C= TEA

The equations obtained through Simplex Lattice Design show that carbohydrates, glycerin, and TEA respond positively to adhesion. The interaction of Carbopol and glycerin with the squared amount of TEA increases the preparation's adhesion value.

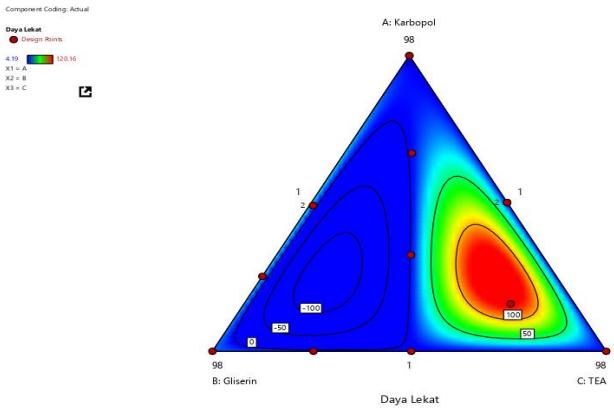

Figure 1. Adhesion

Viscosity

The table shows that several runs have the highest viscosity, 19980 Cp. Furthermore, statistical processing was carried out with Simplex Lattice Design to determine the influence of these three factors on the gel's viscosity. The equation obtained from the program is shown in the Formula 3.

$$Y= +19004.6A +17996.8B +20031.6C +4616.79BC -12589.9AB(A-B) \quad (3)$$

Information:
Y= Adhesion response
A= Carbopol
B= Gliserin
C= TEA

The equations obtained through Simplex Lattice Design show that carbopol, glycerin, and TEA respond positively to viscosity. The interaction of glycerin and tea can increase the preparation's viscosity value.

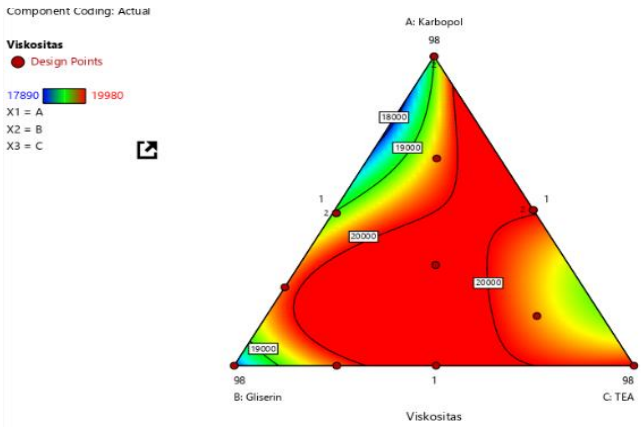

Figure 2. Viscosity

Carbopol, TEA and glycerin are the factors studied to choose the target response in the range. The parameters used to determine the optimal formula in this study are adhesion and viscosity. Adhesion is an essential factor that affects the time of contact of drugs with wounds, so the target response is chosen to maximize (Nam & Mooney, 2021; Wang et al., 2021). Viscosity is a supporting parameter with the target response set to minimize. Software Design Expert version 13.0 provides a solution based on the desired optimization target according to the settings that have been made.

Based on this prediction, a formula with a desirability of 0.821 was produced with Carbopol (71.5604%), Glycerin (24.6837%), and TEA (3.7559%). A desirability value close to 1 indicates the expected formula; conversely, if it gets closer to 0, it indicates an unexpected formula (Santoso & Nurcahyo, 2021).

Table 6. Optimal Formulation

Name	
Carbopol	71.5604
Gliserin	24.6837
TEA	3.7559
Viscosity	18319.5
Adhesion	4.18978

The gel base obtained from the optimal formula was then made with each weight (Arun et al., 2023). Namely, 1,537 grams of carbopol, 5.208 grams of glycerin, 1,037 grams of TEA, 0.18 grams of

methylparaben, and 100 ml of aqua dest add. After the gel mass is formed, 2 ml of propolis transferosome, 1.5 ml of aloe vera extract and 3 gotu gotu extract are added while stirring until a gel and homogeneous preparation is formed.

Physical evaluation of propolis transfersome gel preparations, aloe vera and gotu gotu extract include:

Organoleptic Test

Based on the results of the table 7, it can be concluded that the gel preparation is semisolid, clear, and distinctively smells of a combination of aloe vera extract, gotu gotu extract, and propolis transfersome.

Table 7. Result in Organoleptic Test Gel

Parameter	Result
Shape	Semisolid
Colour	Clear
Smell	Distinctive

Homogeneity Test

Based on the observations made, the gel preparations of propolis transfer some, aloe vera, and gotu gotu extract have a homogeneous result characterized by the absence of coarse granules.

pH Test

Based on the results Table 8, the average pH is 6.28 ± 0.02, which means that it is at the optimal pH vulnerability and does not irritate the skin.

Table 8. Result in pH Test Gel

Replication	pH
1	6.25
2	6.70
3	6.33
Average ±SD	6.28 ± 0.02

Spreadability

Gel preparations have a dispersion power of 6.67 cm, which indicates that the dispersion power of the gel preparations is at a good dispersion vulnerability. The value of the spread power is found in Table 9.

Table 9. Result Spreadability Gel

Replication	Spread Value (cm)
1	6.5
2	6.7
3	6.8
Average ±SD	m ± 0.15

Adhesion test

The results of the adhesion test show that the resulting gel has an average adhesion of 4.07 seconds ± 0.020t and has met the requirements of good adhesion of at least 4 seconds.

Table 10. Result in Adhesion Test Gel

Replication	Adhesion Value (seconds)
1	4.06
2	4.10
3	4.07
Average ±SD	4.07 seconds ± 0.020

Viscosity Test

The viscosity test was carried out using *a Brookfield* viscometer on spindle number 4 and a speed of 30 rpm. A good viscosity value for gel preparations is 3,000-50,000 cps (Chandra & Rahmah, 2022). The gel preparations made have a viscosity value of 19,980 cps, which indicates that they are at a good viscosity vulnerability. The viscosity results are shown in Table 11.

Table 11. Result Viscosity Test Gel

Replication	Viscosity Value
1	19.980 cps
2	19.980 cps
3	19.980 cps
Average ±SD	19.980 cps ± 0.00

Gel Activity Test on Diabetic Wounds

The process of observing diabetic wounds on the back of rats was carried out every day for 21 days by measuring the length of the wound using a ruler every day (Huseini et al., 2020). The results of the wound diameter measurement can be seen in Table 12.

Table 12. Result Wound Healing Percentage

Day	Wound Healing Percentage			
	F1 (cm)	F2 (cm)	F3 (cm)	F4 (cm)
7	16.5	36.5	57	31.5
8	28.5	43.5	66.5	38.5
9	35	53.5	76.5	51.5
10	41.5	63.5	86.5	53.5
11	51.5	73.5	93.5	58.5
12	56.5	80	100	63.5
13	66.5	91.5	100	73.5
14	75	100	100	86.5

Information: F1: Negative control without treatment; F2: Positive control of cutimed gel; F3: Propolis transfersome gel, aloe vera and gotu gotu extract; F4: Base control.

The preparation has a rapid healing effect in the healing process compared to the positive control of cutimed gel (Dutta et al., 2024). The results showed that the preparations of propolis transferosome gel, aloe vera and gotu gotu extract (F3) affected the speed of wound healing. Then, the ANOVA one-way test was continued to determine whether the average data sample was comparable or different. The significance value obtained was 0.003, which means it was smaller than 0.05 ($p<0.05$), and it can be concluded that the result of the

wound diameter has a different average. The results of the ANOVA test were then continued with the LSD test.

Based on the LSD test that has been carried out, it can be found that F3 and F1 are significantly different, with a result of 0.000. The administration of F3 and F2 did not differ significantly, with a result of 0.085. The administration of F3 and F4 differed significantly by 0.007. Thus, it can be concluded that all formulations provide activity towards the comparison between positive controls.

Conclusion

The combination of carbopol, glycerin and TEA in the gel manufacture produced an optimal formula with an ingredient composition of 1,537 grams of carbopol, 5,208 grams of glycerin, and 1,037 grams of TEA. Propolis transferosome gel, aloe vera extract and gotu gotu extract produce a clear, distinctive odour, stable, green preparation with a pH value of 6.28 and a dispersion of 6.67 cm. The adhesion is 4.07 seconds, and the viscosity value is 19980 cps. The gel preparations that have been made have activity on healing diabetic wounds in rats with a better level of effectiveness than other formulas with a wound diameter of 0 cm on the 12th day.

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Conceptualization, A.P., and R.S.; Methodology S.I., and E.I.; Data Analysis A.P.; resources S.N.; data curation A.P., R.S., S.I.; writing original draft preparation E.I; writing a review and editing S.I. all authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest
The authors declare that there are no relevant conflicts of interest related to this research

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