

Development and optimization of curcumin transfersomes in gel formulations as an antioxidant

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ABSTRACT

Curcumin, a natural compound with potent antioxidant properties, faces challenges in pharmaceutical use due to its poor water solubility and low bioavailability. To overcome these limitations, curcumin was encapsulated in a transfersome drug delivery system and subsequently incorporated into a gel to enhance topical delivery and improve drug release efficiency. This study aimed to evaluate the influence of phospholipid, Tween 80, and cholesterol ratios on the physicochemical properties of curcumin-loaded transfersomes and to assess the antioxidant activity of the optimized transfersome gel. A Simplex Lattice Design (SLD) using Design Expert software generated 14 formulations varying in the three components. Transfersomes were produced via the thin layer hydration method and analyzed for particle size, zeta potential, and entrapment efficiency (%EE). The resulting gel was characterized for pH, viscosity, spreadability, adhesiveness, diffusion behavior using Franz cells, and antioxidant activity through the DPPH assay. Statistical analyses employed ANOVA, Wilcoxon, and T-tests. The optimized formulation containing 700 mg phospholipid, 200 mg Tween 80, and 50 mg cholesterol yielded particles of 134.627 nm, zeta potential -8.924 mV, and 93.656% EE. Antioxidant evaluation showed IC_{50} values of 24 ± 1.78 ppm (transfersome) and 42 ± 2.5 ppm (gel), both indicating very strong antioxidant activity. The gel released $23.12 \mu\text{g}/\text{cm}^2$ curcumin within 150 minutes.

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INTRODUCTION

The skin, as the largest organ of the human body, functions as a vital protective barrier against physical injury, pathogens, and harmful chemicals. Skin aging arises from two main sources: intrinsic factors, which involve collagen and elastin degradation, and extrinsic factors, such as exposure to ultraviolet (UV) radiation (Messire et al., 2023). UV radiation triggers the formation of reactive oxygen species (ROS), leading to oxidative stress that manifests as wrinkles, dryness, roughness, and loss of elasticity, with severe cases resulting in skin cancer. Particularly, UVB rays induce damage to deoxyribonucleic acid (DNA) and structural proteins in the epidermis, causing local inflammation and degradation of skin structure (Frei et al., 2023).

Natural-based treatments have increasingly gained attention as safer alternatives for both therapeutic and preventive applications. According to the World Health Organization (WHO), approximately 80% of the global population relies on natural remedies for health treatments (Frei et al., 2023). Among these, *Curcuma longa* (Turmeric) has been widely utilized for its numerous pharmacological benefits. Its active compound, curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione), demonstrates a wide range of biological activities including antioxidant, anti-inflammatory, neuroprotective, antitumor, and cardioprotective properties (Józsa et al., 2022). Studies have revealed that curcumin exhibits high radical scavenging activity, with one study reporting up to 78% activity at 0.5% concentration based on the DPPH assay (Ruggeri et al., 2022). Frei et al., (2023) also showed that a curcumin-based gel formulation demonstrated $32.87 \pm 2.05\%$ radical scavenging activity, confirming its potential as an antioxidant and anti-inflammatory agent.

Despite its therapeutic promise, curcumin suffers from poor water solubility and low permeability, classifying it under Biopharmaceutical Classification System (BCS) Class IV drugs (Frei et al., 2023). This hydrophobicity significantly reduces its bioavailability, especially for transdermal delivery. Nanotechnology-based topical delivery systems, particularly transfersomes, have been introduced to overcome this limitation due to their highly elastic membrane properties that enable penetration through microscopic skin pores. Studies by Abdelmonem et al., (2020) demonstrated that transfersomal gels could effectively enhance drug bioavailability, while Patel et al., (2009) confirmed improved sustained release profiles of curcumin-loaded transfersomal hydrogels. Gel formulations are further supported for their viscosity and hydration benefits, which facilitate deeper drug penetration into the stratum corneum (Vasanth et al., 2019; Siti Fatimah Zahro et al., 2024).

Transfersome characterization can be influenced by the ratio of its components, particularly phospholipids, surfactants, and cholesterol. Ambarwati & Yulianita, (2022) found that an 80:20 phospholipid-to-Tween 80 ratio produced optimal transfersome characteristics, including 437.77 nm particle size and 74.172% entrapment efficiency. Cholesterol addition enhances vesicle rigidity and stability (Rosalina et al., 2023). Previous studies have shown that excessive use of surfactants will reduce particle size and affect the polydispersity index value because the smaller the particle size, the better. Excessive use of phospholipids will increase particle size but decrease the zeta potential value because phospholipids are zwitterionic components with an isoelectric point between 6-7. The hydration medium used has a pH of 7.4. A pH higher than the isoelectric point will decrease the zeta potential value (causing it to become negative) (Ambarwati & Yulianita, 2022). The addition of cholesterol to Transfersom can increase the absorption efficiency of drug preparations. The absorption efficiency of this drug is an important component in Transfersom formulation, as it is related to the bioavailability and concentration of the drug, which are useful in determining the dosage for therapy and preventing color changes in Transfersom during storage (Febryenti et al, 2018).

The present study employs Design Expert software using the Simplex Lattice Design (SLD) method to optimize transfersome formulation. The SLD method efficiently determines the best formulation proportions with fewer experimental runs. This research aims to develop and optimize curcumin-loaded transfersomes, evaluate their physicochemical characteristics, and assess antioxidant potential using the DPPH method. The optimized formulation will then be converted into a transfersomal gel and tested for its physical quality and curcumin release profile via the Franz diffusion method.

RESEARCH METHOD

This study applied an experimental design to develop and optimize Curcumin Transfersomes in gel dosage form as an antioxidant using the Simplex Lattice Design (SLD) method with Design Expert software to determine the ideal ratios of phospholipid, Tween 80, and cholesterol. Evaluation parameters included entrapment efficiency (%EE), particle size, and zeta potential, supported by antioxidant and physical stability tests (Ambarwati & Yulianita, 2022). The research was sequentially conducted through analytical method validation, formulation, statistical

optimization, and gel incorporation to ensure reproducibility (Yuliana et al., 2025). Conducted at Universitas Setia Budi Surakarta and PT DKSH Indonesia between March and June 2025 (Yuliana et al., 2025), the study analyzed formulations generated by the SLD model using ANOVA and response contour plots. Independent variables were phospholipid, Tween 80, and cholesterol concentrations, while dependent variables included %EE, particle size, and zeta potential, supported by various analytical instruments and pharmaceutical-grade materials ((Raymond C Rowe, P.J.S 2009 ; Yuliana et al., 2025)).

The materials used in this study were as follows: methanol (pro analysis), DPPH (obtained from Sigma Aldrich), curcumin isolate (pharmaceutical primary standard from Sigma Aldrich), phospholipid (from Sigma Aldrich), Tween 80 (USP, Sigma Aldrich), cholesterol (pharmaceutical primary standard from Sigma Aldrich), HPMC, propylene glycol, methyl paraben, propyl paraben, and distilled water sourced from the USB Pharmaceutical Technology Laboratory. The tools used include a set of glassware, (Pirex), analytical balance (Ohaus), UV-Vis Spectrophotometer (Shimadzu), IR Spectrophotometer (Shimadzu), Rotary Evaporator (Ika RV 10), Particle Size and Zeta Potential Analyzer (Malvern), pH meter (Horiba), vials, Viscometer, glass object, deck glass, dark bottle, and moisture balance.

The experimental process began with FTIR characterization of curcumin (Harvey, 2000) and analytical validation via UV-Vis spectrophotometry (Yuliana et al., 2025). Transfersomes were prepared through the thin film hydration method involving solvent evaporation, hydration, and sonication (K P et al., 2024), then optimized using response surface and overlay plots. Antioxidant activity was determined by the DPPH method (Ruggeri et al., 2022), and the optimal formula was incorporated into a gel base of HPMC and propylene glycol for stability and diffusion evaluation using Franz diffusion cells ((Siti Fatimah Zahro et al., 2024; Wulandari et al., 2019)). Data were analyzed using ANOVA, Wilcoxon, and T-tests with Design Expert 13 and SPSS software at a 95% confidence level to validate the optimization results.

RESULTS AND DISCUSSIONS

FTIR

FTIR spectroscopy is a fast, simple, and non-destructive analytical technique that allows all chemical properties of a sample to be traced and displayed in the spectra. FTIR is performed in the infrared wavelength range (wavenumbers 1500-800 cm^{-1}). FTIR analysis is used to observe the absorption spectrum of each sample, where the absorption data is detected at wavenumbers 1500-800 cm^{-1} (Puspitasari et al., 2021).

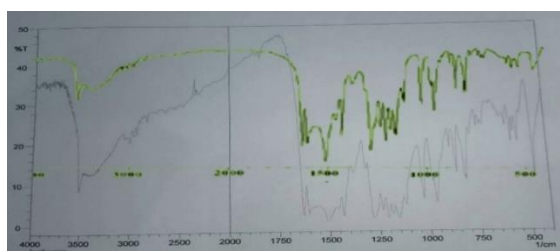


Figure 1. Research and literature results of FTIR spectrum of curcumin

Note: a) The black graph shows the research results spectrum; b) The green graph shows the literature spectrum.

A comparison between the FTIR results from the study and the spectrum from the literature shows a significant similarity in peak patterns. Minor differences in wave positions are likely due to differences in testing conditions, such as sample shape and the sensitivity of the equipment used. However, the similarity of these absorption patterns confirms that the chemical structure of curcumin is preserved and the presence of the main functional groups can be detected.

Thus, this FTIR analysis supports the successful isolation of curcumin and provides a strong basis for further development of the Transfersom formulation.

Calibration Curve Construction and Curcumin Analysis Method

The UV-Vis spectrophotometric analysis of curcumin showed a maximum wavelength (λ_{\max}) at 421 nm, indicating the highest absorbance and maximum sensitivity to concentration changes. The optimum operating time for stable absorption was found between the 23rd and 26th minute, which was used for determining curcumin concentration. A calibration curve was then prepared using six standard concentrations (2.5–7.5 ppm) measured at 421 nm, yielding a regression coefficient (r) of 0.9994, indicating excellent linearity. The absorbance results of the stock solution are presented in the corresponding figure.

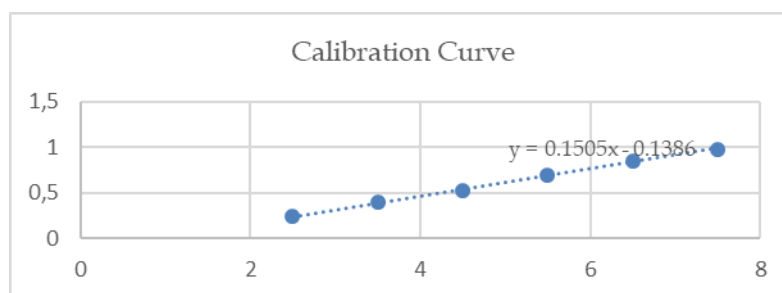


Figure 2. Curcumin standard curve series graph

Note: The Y-axis represents the absorbance of the pure curcumin isolate. The X-axis represents the concentration of the pure curcumin isolate.

Validation of the Curcumin Analysis Method

The validation of the curcumin analysis method included tests for specificity, linearity, accuracy, precision, LOD, and LOQ. Specificity was confirmed by identifying the maximum wavelength of curcumin at 421 nm using p.a. methanol, showing that the UV-VIS spectrophotometer provided accurate and selective measurements. Linearity evaluation using curcumin solutions at concentrations of 2.5–7.5 ppm produced a correlation coefficient (r) of 0.9994, indicating excellent linearity. Accuracy and precision tests using curcumin concentrations of 2.5, 4.5, and 6.5 ppm resulted in percent recoveries of 98–102% and a relative standard deviation (RSD) of 0.79%, both within acceptable limits (Harmita et al., 2004). The limit of detection (LOD) and limit of quantification (LOQ) values were 0.228 and 0.693, respectively, demonstrating the method's sensitivity and reliability for curcumin quantification.

Characterization of the Optimum Curcumin Transfersome Formula

- Percentage Entrapment Efficiency, the adsorption efficiency analysis used a quadratic model based on the simplex lattice design (SLD) method, with ANOVA results showing statistical significance ($p = 0.0348 < 0.05$; $F = 4.25$), indicating that variations in independent variables affected %EP. The non-significant lack of fit confirmed a good model fit, with $R^2 = 0.7266$ and adjusted $R^2 = 0.5558$ explaining most response variation, though predicted $R^2 = -0.8533$ suggested weak predictive ability. Nevertheless, Adeq Precision = 6.3397 (>4) indicated an adequate signal-to-noise ratio, so despite the negative predicted R^2 , the model remained valid for interpreting variable relationships.

Table 1. %EP model equation

| Response | Equation |
|----------|--|
| %EP | $Y = 86.64A + 93.66B + 90.20C - 32.83AB - 37.74AC - 26.87BC$ |

Based on the SLD model equation, all components – phospholipid (A), Tween 80 (B), and cholesterol (C) – individually exhibited positive effects on entrapment efficiency, with Tween 80

showing the highest coefficient. As a non-ionic surfactant, Tween 80 functions as an edge activator that enhances the flexibility and deformability of the vesicle membrane. Increasing Tween 80 concentration improves membrane permeability and makes vesicle formation more efficient in entrapping curcumin. The high coefficient indicates that Tween 80 is the most dominant variable influencing %EE. The negative interaction coefficients between phospholipid and the other components indicate that simultaneous increases in phospholipid with Tween 80 or cholesterol reduce %EE. This aligns with formulation principles, where excessive component combinations can cause vesicle structure imbalance, increased viscosity, and reduced membrane capability to entrap the active compound.

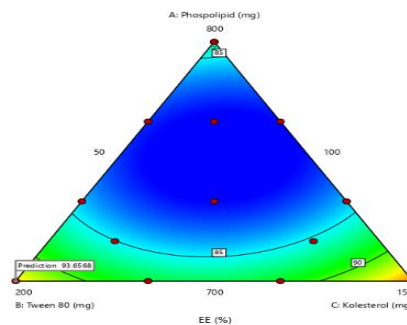


Figure 3. Contour Plot % Entrapment Efficiency

The contour plot of %EP indicates that dark blue areas represent the lowest entrapment efficiency values, while green to bright yellow regions signify the highest. The plot reveals a significant increase in entrapment efficiency at higher concentrations of Tween 80 and lower levels of phospholipid. This trend is attributed to the role of Tween 80, a nonionic surfactant that enhances curcumin solubility and stabilizes vesicle formation.

In this study, an increase in phospholipid levels tended to decrease absorption efficiency, especially when used in high concentrations. This is consistent with previous research by Dwifendi et al (2020), which stated that excessive phospholipid concentrations can cause the formation of larger vesicles, increasing viscosity and inhibiting curcumin absorption due to limitations in capturing active substances. In addition, the graph shows that an increase in Tween 80 increases absorption efficiency. This has been proven in previous research by Shinde et al (2014), which states that Tween 80 as an activator helps increase membrane fluidity, thereby increasing the ability of vesicles to absorb active substances. Similarly, cholesterol shows that the addition of cholesterol serves to increase the stability of the lipid membrane and prevent leakage of active substances.

Particle Size

The optimum formula showed a predicted particle size of 134.627 nm, confirming that the curcumin transfersomes met the <800 nm range for transfersome-based drug delivery systems. Phospholipids and Tween 80 were identified as key variables affecting particle size, where higher phospholipid content increased size, while higher Tween 80 concentration reduced it; cholesterol strengthened the molecular bonds and curcumin binding. ANOVA results ($p = 0.0272 < 0.05$) indicated significant effects of these variables, with a non-significant lack of fit confirming model suitability. The model achieved an R^2 of 0.7447, Adjusted R^2 of 0.5852, and Adequate Precision of 5.9171 (>4), demonstrating reliability despite a negative Predicted R^2 (-0.0461), thus validating its statistical relevance in assessing particle size behavior

Table 2. Particle size model equation

| Response | Equation |
|-----------------|--|
| Ukuran Partikel | $Y = 371.93A + 134.63B + 177.39C - 351.05AB - 5.04AC - 148.76BC$ |

The particle size model equation indicates that the positive coefficients of A, B, and C suggest that increasing the concentrations of phospholipid, Tween 80, and cholesterol tends to enlarge the particle size. The highest coefficient is observed for phospholipid (371.93), signifying that it is the most dominant factor influencing particle growth, as a higher phospholipid content increases the lipid bilayer thickness and vesicle size (Khan et al., 2021). Meanwhile, the negative interaction coefficients of AB (-351.05) and BC (-148.76) indicate that the combined presence of phospholipid with Tween 80 and Tween 80 with cholesterol reduces particle size, likely due to the formation of a more stable and flexible membrane structure.

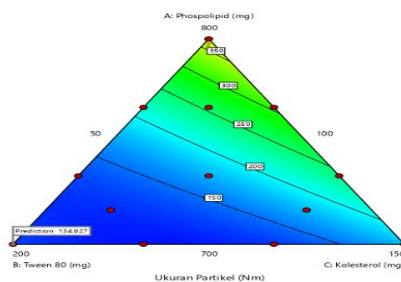


Figure 4. Countour plot PSA

The contour plot illustrates the relationship between phospholipid, Tween 80, and cholesterol concentrations on the particle size of curcumin transfersomes. The color gradient in the plot ranges from blue, indicating the smallest particle size, to yellow-green, representing larger particles. The smallest particle size of 134 nm is observed at high Tween 80, low phospholipid, and high cholesterol concentrations, while particle size increases with higher phospholipid and lower Tween 80 levels. This indicates that phospholipids, as the main vesicle matrix, contribute to thicker bilayer formation, resulting in larger vesicles; Tween 80, as an edge activator, enhances bilayer fluidity, thereby reducing particle size; and cholesterol, in combination with Tween 80, stabilizes the system at smaller dimensions. These findings are consistent with Shaker et al., (2017), who reported that increasing Tween 80 reduces particle size, whereas excessive phospholipid significantly increases it to over 400 nm.

Potential Zeta

Zeta potential is a key indicator of transfersome stability, representing surface charge that influences colloidal behavior. A high absolute value (positive or negative) indicates strong repulsive forces preventing agglomeration, while values near zero promote aggregation (Honary & Zahir, 2013). ANOVA analysis showed a significant model ($p = 0.0272 < 0.05$), meaning phospholipid composition, Tween 80, and cholesterol significantly affect particle size, with a non-significant lack of fit indicating good model agreement. The model exhibited strong statistical performance ($R^2 = 0.9182$; Adjusted $R^2 = 0.8671$), though the lower Predicted R^2 (0.4870) suggests limited predictive ability. With an Adeq Precision of 13.5922 (>4), the model is valid, reliable, and suitable for formulation optimization.

Table 3. Zeta potential equation

| Response | Equation |
|----------------|---|
| Zeta Potensial | $Y = -15.99A - 8.92B - 11.52C + 4.59AB + 8.90AC - 1.67(BC)$ |

The zeta potential model equation ($Y = -15.99A - 8.92B - 11.52C + 4.59AB + 8.90AC - 1.67BC$) indicates that phospholipid (A), Tween 80 (B), and cholesterol (C) exhibit negative coefficients, implying that higher concentrations of these components lead to more negative zeta potential values. A more negative zeta potential enhances colloidal system stability by increasing particle repulsion and preventing vesicle coalescence. Phospholipid, with the largest coefficient (-15.99), exerts the strongest influence in lowering zeta potential. The positive interaction terms AB (4.59) and AC (8.90) suggest that combinations of phospholipid-Tween 80 and phospholipid-

cholesterol tend to raise the zeta potential toward neutrality, potentially reducing stability if uncontrolled due to charge distribution imbalances between polarity and bilayer structure.

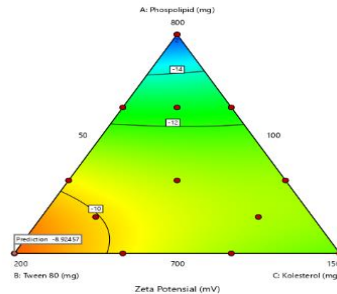


Figure 5. Potential contour plot zeta

The contour plot indicates that the most negative zeta potential (-16.49 mV) occurs at high phospholipid and low cholesterol levels, while the least negative (-8.19 mV) appears at high cholesterol and low phospholipid levels. The low zeta potential in the optimal formula is influenced by phospholipid, cholesterol, and Tween 80 concentrations. Although phospholipid and Tween 80 usually enhance surface charge through electrostatic effects, higher Tween 80 reduces and higher phospholipid increases zeta potential negativity. This inverse pattern is attributed to high cholesterol, which densifies the bilayer, limits charge mobility, and lowers zeta potential (Mozafari et al., 2008; Dianzani et al., 2014).

Determining the Optimum Formula

The optimum formula value was determined using the values from 14 test runs generated by the SLD application. The parameters used to determine the optimum formula were %EP maximized, PSA within range, and Zeta potential maximized. These parameters can be seen in the following table:

Table 4. Parameters used to determine the optimum formula

| Parameter | Target | Lower | Upper |
|----------------|----------|--------|--------|
| Phospholipids | In range | 700 mg | 800 mg |
| Tween 80 | In range | 100 mg | 200 mg |
| Cholesterol | In range | 50 mg | 150 mg |
| PSA | In range | 110 nm | 464 nm |
| % EP | Maximize | 81 % | 97 % |
| Zeta Potential | Maximize | -16.49 | -8.193 |

Table 5. Optimum curcumin transfersome results

| Materials and Response | Results |
|----------------------------------|------------|
| Phospholipids | 700 mg |
| Tween 80 | 200 mg |
| Cholesterol | 50 mg |
| Particle Size | 134.627 nm |
| Zeta Potential | -8.924 mV |
| Percentage Adsorption Efficiency | 93.656 % |

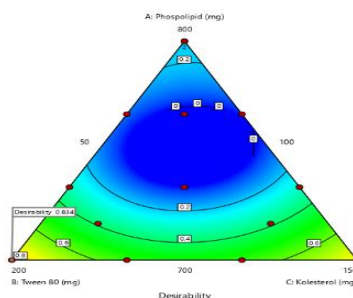


Figure 6. Optimum contour plot zeta

The SLD prediction produced component weights of 700 mg phospholipid, 200 mg Tween 80, and 50 mg cholesterol, with characterization results showing a particle size of 134.627 nm, a zeta potential of -8.924 , and an entrapment efficiency of 93.65%. All characterization results met the requirements for a Transfersome delivery system. The SLD method generated four possible solutions with varying parameters and desirability values, from which the first solution was selected as the optimal formula due to its highest desirability value of 0.834, closest to 1.

Antioxidant Activity of Optimum Curcumin Transfersomes, Optimum Transfersome Gel, and Gel Base

An antioxidant activity test was conducted to evaluate the compound's ability to scavenge free radicals using the DPPH (2,2-diphenyl-1-picrylhydrazyl) method. The parameters observed included the IC_{50} value and the Antioxidant Activity Index (AAI). The IC_{50} value indicates the sample concentration required to inhibit 50% of DPPH free radicals, while the AAI indicates the strength of antioxidant activity based on the ratio of DPPH concentration to the IC_{50} value (Sari et al., 2024). The antioxidant value of the optimum curcumin transfersome sample, optimum transfersome gel, and gel base can be seen in Table 6.

Table 6. Value of IC_{50}

| Sample | IC_{50} Value | Category |
|----------------------------|-----------------|-------------------------|
| Curcumin | 9.27 | Very Strong |
| Curcumin Transfersomes | $24 \pm 1.78^*$ | Very Strong |
| Curcumin Transfersomes Gel | $42 \pm 2.5^*$ | Very Strong |
| Gel Base | -82 ± 23.89 | No Antioxidant Activity |

Note: *= significantly different results from gel base

Table 7. Value of AAI

| Sample | AAI Value | Category |
|----------------------------|-------------------|-------------------------|
| Curcumin | 8.52 | Very Strong |
| Curcumin Transfersomes | $3.33 \pm 0.25^*$ | Very Strong |
| Curcumin Transfersomes Gel | $1.88 \pm 0.11^*$ | Very Strong |
| Gel Base | -1.03 ± 0.35 | No Antioxidant Activity |

Note: *= significantly different results with gel base

The optimized curcumin transfersome showed strong antioxidant activity with an IC_{50} of 24 ± 1.78 ppm and an AAI of 3.33 ± 0.25 , indicating very strong potency. This enhanced efficacy results from the transfersome system, which improves curcumin's solubility, stability, and bioavailability through lipid bilayer encapsulation. FTIR analysis confirmed the presence of phenolic hydroxyl groups responsible for radical scavenging. The curcumin transfersome gel also showed strong activity ($IC_{50} = 42 \pm 2.5$ ppm, AAI = 1.88 ± 0.11), slightly reduced due to the gel matrix limiting active release but still categorized as very strong. The gel base alone exhibited no antioxidant effect, confirming curcumin as the active agent. ANOVA and Post Hoc Tukey tests showed significant differences among formulations ($p < 0.05$), verifying that each preparation had distinct antioxidant efficacy.

Physical Gel Quality Test

The organoleptic and homogeneity evaluations showed distinct physical characteristics between the Transfersome and conventional curcumin gels. The Transfersome gel exhibited a yellow color, typical odor, soft texture, and homogeneous appearance, whereas the conventional gel appeared orange but remained uniform. The yellow hue in the Transfersome formulation resulted from the encapsulation of curcumin within transfersomal vesicles, ensuring even distribution without clumps, while the conventional gel's orange tone reflected unencapsulated curcumin with low solubility and permeability (BCS Class IV). The pH values (6.15 ± 0.04 and 6.09 ± 0.08) met topical standards (4.5–6.5), and the Wilcoxon test ($p > 0.05$) indicated no significant difference, confirming dermatological safety. Viscosity and adhesion tests revealed higher viscosity for the Transfersome gel (5431 ± 1027.15 cP) compared to the conventional gel (1087 ± 75.72 cP),

with a significant difference ($p = 0.002 < 0.05$). This was attributed to interactions between lipid vesicles and the HPMC matrix that enhanced structural density and stability, while stronger adhesion resulted from Tween 80 and lipid components that increased contact duration (Razak et al., 2013)(R. Sari et al., 2016).

The spreadability and stability tests further confirmed the Transfersome gel's superior quality. The Transfersome formulation showed better spreadability (4.83–5.47 cm) than the conventional gel (3.5–4.3 cm), within the optimal range of 5–7 cm for topical use (Sari, 2024). The six-cycle stability test under varying temperatures showed slight pH reductions (6.15 → 5.42; 6.09 → 5.65) and viscosity increases (5431 → 6260 cP; 1087 → 3873 cP), attributed to minor component degradation and structural tightening. However, Wilcoxon analysis ($p > 0.05$) confirmed no significant change, indicating consistent stability. Organoleptic parameters such as color, odor, texture, and homogeneity remained stable, demonstrating that both gels maintained acceptable quality, with the Transfersome curcumin gel showing better mechanical and formulation stability for topical application.

Franz Diffusion Test

A diffusion test was conducted to determine the preparation's ability to release curcumin to the receptor medium through a semi-permeable membrane. The preparation was tested using a Franz Diffusion Cell with a receptor medium volume of 10 mL, a constant temperature of $37 \pm 0.5^\circ\text{C}$, and a semi-permeable HT Tuffryn membrane commonly used for topical testing.

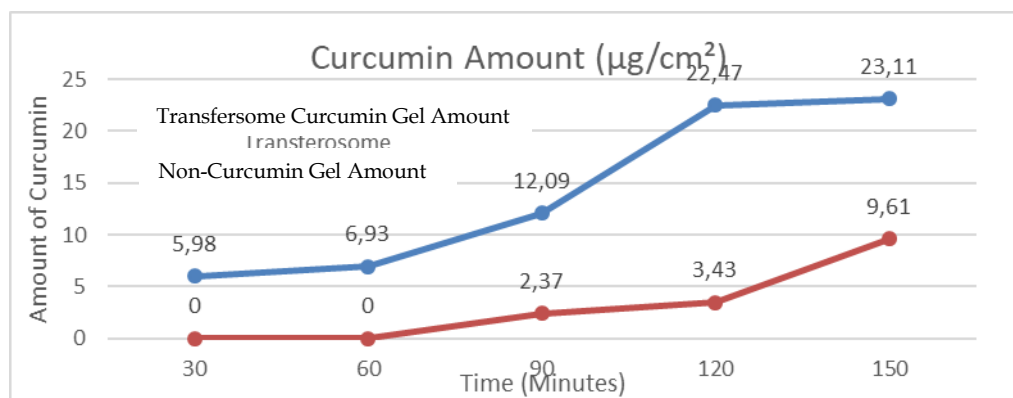


Figure 7. Franz diffusion profile

The diffusion study showed that curcumin transfersomal gel achieved a much higher diffusion rate through the HT Tuffryn membrane than the non-transfersomal gel, indicating superior penetration efficiency. This is attributed to the flexible vesicular structure of transfersomes, small particle size, and high zeta potential. The results support Wulandari et al., (2019), who found higher curcumin release in transethosome gels compared to conventional gels. Statistical analysis ($p < 0.05$) confirmed significant differences between formulations, suggesting transfersomes are an effective topical delivery system for curcumin. Although they enhance skin penetration to deeper layers, systemic absorption remains minimal. Given curcumin's GRAS status and limited systemic exposure, transfersomal curcumin gels are considered safe for topical use.

CONCLUSION

The findings of this study successfully confirm the expectations outlined in the Introduction, demonstrating that variations in the composition of phospholipids, Tween 80, and cholesterol significantly influence the physical characteristics, encapsulation efficiency, and stability of curcumin transfersomes. The optimized formula achieved desirable parameters, including nanoscale particle size, high zeta potential, and strong antioxidant activity, validating the hypothesis regarding its potential as an effective topical drug delivery system. The implication of this research result is that the industry can select more efficient active ingredients and supporting

ingredients in antioxidant gel formulations that can increase the bioavailability of gel formulations in terms of preventing premature aging in humans. These outcomes establish clear compatibility between the research objectives and the obtained results, while also opening promising prospects for further development, such as exploring alternative formulation methods, conducting TEM and in vivo evaluations, and optimizing gel bases to enhance clinical applicability and therapeutic performance in future studies.

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References

- Abdelmonem, R., Hamed, R. R., Abdelhalim, S. A., ElMiligi, M. F., & El-Nabarawi, M. A. (2020). Formulation and Characterization of Cinnarizine Targeted Aural Transfersomal Gel for Vertigo Treatment: A Pharmacokinetic Study on Rabbits. *International Journal of Nanomedicine*, 15, 6211-6223. <https://doi.org/10.2147/IJN.S258764>
- Ambarwati, R., & Yulianita. (2022). Formulasi Transfersom Ekstrak Daun Pandan Wangi (*Pandanus amaryllifolius*. R) dengan Variasi Konsentrasi Fosfolipid dan Tween 80 sebagai Pembentuk Vesikel. *Jurnal Ilmu Kefarmasian*, 3(2), 261-267.
- Dianzani, C., Zara, G. P., Maina, G., Pettazzoni, P., Pizzimenti, S., Rossi, F., Gigliotti, C. L., Ciamporcerro, E. S., Daga, M., & Barrera, G. (2014). Drug delivery nanoparticles in skin cancers. *BioMed Research International*, 2014. <https://doi.org/10.1155/2014/895986>
- Efendi, D., & Sari, P. (2020). SISTEM PAKAR DIAGNOSA PENYAKIT KULIT WAJAH DENGAN METODE CERTAINTY FACTOR PADA KLINIK SKIN RACHEL. *Jurnal Informasi Dan Komputer (JIK)*, 8(1).
- Frei, G., Haimhoffer, Á., Csapó, E., Bodnár, K., Vasvári, G., Nemes, D., Lekli, I., Gyöngyösi, A., Bácskay, I., Fehér, P., & Józsa, L. (2023). In Vitro and In Vivo Efficacy of Topical Dosage Forms Containing Self-Nanoemulsifying Drug Delivery System Loaded with Curcumin. *Pharmaceutics*, 15(8). <https://doi.org/10.3390/pharmaceutics15082054>
- Harmita, H., Mansur, U., & Firnando, F. (2004). Metode Penetapan Kadar Meloxicam Dalam Darah Manusia in Vitro Secara Kromatografi Cair Kinerja Tinggi. *Majalah Ilmu Kefarmasian*, 1(2), 79-92. <https://doi.org/10.7454/psr.v1i2.3372>
- Harvey, D. (2000). Modern Analytical Chemistry. *McGraw-Hill Higher Education*, 273-367.
- Honary, S., & Zahir, F. (2013). Effect of Zeta Potential on the Properties of Nano-Drug Delivery Systems. *Tropical Journal of Pharmaceutical Research*, 12(2), 255-264. <https://doi.org/10.4314/tjpr.v12i2.19>
- Józsa, L., Vasvári, G., Sinka, D., Nemes, D., Ujhelyi, Z., Vecsernyés, M., Váradi, J., Fenyvesi, F., Lekli, I., Gyöngyösi, A., Bácskay, I., & Fehér, P. (2022). Enhanced Antioxidant and Anti-Inflammatory Effects of Self-Nano and Microemulsifying Drug Delivery Systems Containing Curcumin. *Molecules*, 27(19). <https://doi.org/10.3390/molecules27196652>
- K P, M. J., Battu, S., & B A, V. (2024). Transfersomes for Effective Transdermal Drug Delivery. *International Journal of Pharmaceutical Sciences Review and Research*, 84(4), 10-21. <https://doi.org/10.47583/ijpsrr.2024.v84i04.002>
- Khan, I., Needham, R., Yousaf, S., Houacine, C., Islam, Y., Brynan, R., Sadozai, S. K., Elrayess, M. A., & Elhissi, A. (2021). Impact of phospholipids, surfactants and cholesterol selection on the performance of transfersomes vesicles using medical nebulizers for pulmonary drug delivery. *Journal of Drug Delivery Science and Technology*, 66(October), 102822. <https://doi.org/10.1016/j.jddst.2021.102822>
- Messire, G., Serreau, R., & Berteina-Raboin, S. (2023). Antioxidant Effects of Catechins (EGCG), Andrographolide, and Curcuminoids Compounds for Skin Protection, Cosmetics, and Dermatological Uses: An Update. *Antioxidants*, 12(7). <https://doi.org/10.3390/antiox12071317>
- Mozafari, M. R., Johnson, C., Hatziantoniou, S., & Demetzos, C. (2008). Nanoliposomes and their applications in food nanotechnology. *Journal of Liposome Research*, 18(4), 309-327. <https://doi.org/10.1080/08982100802465941>
- Patel, R. K., Singh, S. K., Singh, S. B., Sheth, D. N. R., & Gendle, R. (2009). *Development and Characterization of Curcumin Loaded Transfersome for Transdermal Delivery.*

- <https://api.semanticscholar.org/CorpusID:9518769>
- Puspitasari, L., Mareta, S., & Thalib, A. (2021). Karakterisasi senyawa kimia daun mint (*Mentha sp.*) dengan metode FTIR dan kemometri. *Sfj Sainstech Farma Jurnal Ilmu Kefarmasian*, 14(1), 5–11.
- Raymond C Rowe, Paul J Sheskey, M. E. Q. (2009). Handbook of Pharmaceutical Excipients. *XPharm: The Comprehensive Pharmacology Reference*, 1–3. <https://doi.org/10.1016/B978-008055232-3.62446-8>
- Razak, A., Djamal, A., & Revilla, G. (2013). Uji Daya Hambat Air Perasan Buah Jeruk Nipis (*Citrus aurantifolia s.*) Terhadap Pertumbuhan Bakteri *Staphylococcus Aureus* Secara In Vitro. *Jurnal Kesehatan Andalas*, 2(1), 05. <https://doi.org/10.25077/jka.v2i1.54>
- Rehman, T. R., Bhutto, M. A., Bhutto, M. A., Tunio, A. A., Baig, B. A., Tunio, N. A., & Bhutto, A. A. (2023). Isolation and characterization of curcumin by antisolvent and cooling crystallization method for a potential antimicrobial nanofibrous membrane. *Nanomedicine Research Journal*, 8(3), 246–258. <https://doi.org/10.22034/nmrj.2023.03.003>
- Rosalina, A. I., Sagita, E., & Iskandarsyah. (2023). Penghantaran Obat melalui Kulit: Teknologi Vesikel Liposome dan Analognya. *Jurnal Kedokteran Meditek*, 29(1), 109–120. <https://doi.org/10.36452/jkdoktmeditek.v29i1.2428>
- Ruggeri, M., Sánchez-Espejo, R., Casula, L., Barbosa, R. de M., Sandri, G., Cardia, M. C., Lai, F., & Viseras, C. (2022). Clay-Based Hydrogels as Drug Delivery Vehicles of Curcumin Nanocrystals for Topical Application. *Pharmaceutics*, 14(12). <https://doi.org/10.3390/pharmaceutics14122836>
- Sari, M. H. M., Saccol, C. P., Custódio, V. N., da Rosa, L. S., da Costa, J. S., Fajardo, A. R., Ferreira, L. M., & Cruz, L. (2024). Carrageenan-xanthan nanocomposite film with improved bioadhesion and permeation profile in human skin: A cutaneous-friendly platform for ketoprofen local delivery. *International Journal of Biological Macromolecules*, 265(January). <https://doi.org/10.1016/j.ijbiomac.2024.130864>
- Sari, R., Nurbaeti, S. N., & Pratiwi, L. (2016). Optimasi Kombinasi Karbopol 940 dan HPMC Terhadap Sifat Fisik Gel Ekstrak dan Fraksi Metanol Daun Kesum (*Polygonum minus Huds.*) dengan metode Simplex Lattice Design Abstrak. 72–79.
- Shaker, S., Gardouh, A., & Ghorab, M. (2017). Factors affecting liposomes particle size prepared by ethanol injection method. *Research in Pharmaceutical Sciences*, 12(5), 346–352. <https://doi.org/10.4103/1735-5362.213979>
- Shinde, A. V., & Frangogiannis, N. G. (2014). Fibroblasts in myocardial infarction: A role in inflammation and repair. *Journal of Molecular and Cellular Cardiology*, 70, 74–82. <https://doi.org/https://doi.org/10.1016/j.yjmcc.2013.11.015>
- Siti Fatimah Zahro, Safira Prisia Dewi, Amirah Adlia, & Heni Rachmawati. (2024). Pengembangan Formula Nanoemulsi Minyak Cengkeh (*Syzygium aromaticum L.*) dan Ekstrak Siwak (*Salvadora persica*) serta Uji Aktivitasnya terhadap Bakteri dari Saliva Mencit Galur BALB/c. *Medicinus*, 37(1), 27–43. <https://doi.org/10.56951/jp1ap691>
- Vasanth, V., Chen, Y., Lv, M., Ning, H., Li, C., Feng, S., Wu, Z., & Du, G. (2019). Source Imaging of a Moving Type IV Solar Radio Burst and Its Role in Tracking Coronal Mass Ejection from the Inner to the Outer Corona. *The Astrophysical Journal*, 870(1), 30. <https://doi.org/10.3847/1538-4357/aaeffd>
- Wulandari, A. D., Novianti, A., Andika, M., Amalia Farmasi, A., & Farmasi dan Sains Universitas Muhammadiyah HAMKA, F. D. (2019). Profil Difusi Transethosome Kurkumin Dalam Sediaan Gel Yang Menggunakan Karbomer 934 Sebagai Pembentuk Gel. *Journal Of Current Pharmaceutical Sciences*, 3(1), 2598–2095.
- Yuliana, S., Kuncahyo, I., & Harmastuti, N. (2025). Optimization and Characterization of Naringenin Transfersomes with Simplex Lattice Design and Anti-Aging In Vivo Study. *Jurnal Mandala Pharmacon Indonesia*, 11(1), 208–215. <https://doi.org/10.35311/jmpi.v11i1.782>