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Optimizing Curcumin SNEDDS via D-Optimal Design and Evaluating Wound Healing Efficacy in Wistar Rats

Optimasi SNEDDS Kurkumin dengan Metode D-Optimal dan Evaluasi Penyembuhan Luka pada Tikus Wistar

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ABSTRACT

Curcumin, a bioactive compound extracted from turmeric, exhibits extensive pharmacological properties, including anti-inflammatory and wound-healing activities. Nevertheless, its clinical application is hindered by low aqueous solubility and poor bioavailability. This study aimed to optimize a curcumin-loaded Self-Nanoemulsifying Drug Delivery System (SNEDDS) using a D-Optimal experimental design to improve its solubility, stability, and therapeutic efficacy. The SNEDDS formulation was developed by varying the proportions of oil, surfactant, and co-surfactant. The optimized formulation demonstrated a particle size of 120 nm and an encapsulation efficiency of 94.5%, significantly accelerating wound closure by 98% within 14 days in Wistar rats. These results highlight the potential of curcumin SNEDDS as an effective topical formulation for wound therapy.

ABSTRAK

Kurkumin, senyawa bioaktif yang berasal dari kunyit, memiliki berbagai aktivitas farmakologis seperti antiinflamasi dan penyembuhan luka. Namun, aplikasinya secara klinis masih terbatas karena kelarutan dalam air yang rendah dan bioavailabilitas yang buruk. Penelitian ini bertujuan mengoptimalkan sistem penghantaran Self-Nanoemulsifying Drug Delivery System (SNEDDS) berbasis kurkumin menggunakan desain eksperimental D-Optimal untuk meningkatkan kelarutan, stabilitas, dan efektivitas terapeutiknya. Formulasi SNEDDS dikembangkan dengan variasi komposisi minyak, surfaktan, dan kosurfaktan. Formula optimal menunjukkan ukuran partikel sebesar 120 nm dan efisiensi enkapsulasi 94,5%, serta mempercepat penyembuhan luka hingga 98% dalam 14 hari pada tikus Wistar. Hasil ini menunjukkan potensi SNEDDS kurkumin sebagai formulasi topikal yang efektif untuk terapi luka.

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1. INTRODUCTION

Curcumin, the principal bioactive compound found in turmeric (*Curcuma longa* L.), is widely recognized for its pharmacological properties, including antioxidant, anti-inflammatory, anticancer, and antidiabetic effects. Despite these benefits, its poor aqueous solubility and low systemic bioavailability significantly limit its

therapeutic potential. Various approaches have been investigated to overcome these challenges, including the development of curcumin analogs and nanoparticle-based formulations designed to enhance both its efficacy and stability (Nafillah & Anwar, 2023). Moreover, curcumin has demonstrated protective effects against skin fibrosis and weight loss induced by bleomycin in experimental animal models (Rahmi et al., 2024).

Among the strategies employed to improve curcumin delivery, the Self-Nanoemulsifying Drug Delivery System (SNEDDS) has gained attention. SNEDDS comprises isotropic mixtures of oils, surfactants, and co-surfactants that spontaneously form nanoemulsions upon contact with gastrointestinal fluids. This property enhances the solubility and absorption of poorly water-soluble compounds like curcumin (Shakeel et al., 2022). Previous studies have indicated that SNEDDS formulations significantly improve the physicochemical stability and biological performance of curcumin, contributing to more consistent pharmacological outcomes (Kumar et al., 2023).

To systematically develop an optimized SNEDDS formulation, experimental design methodologies such as the D-Optimal design can be applied. This statistical approach facilitates the identification of optimal component ratios based on desired responses, such as particle size, polydispersity index, encapsulation efficiency, and physical stability (Patel et al., 2024). Utilizing the D-Optimal method enables a more rational and efficient formulation process, particularly for enhancing the bioavailability of lipophilic drugs like curcumin.

In the context of wound healing, curcumin has been shown to accelerate tissue regeneration by modulating oxidative stress, reducing inflammation, and promoting collagen synthesis and angiogenesis (Zhang et al., 2021). However, its therapeutic application in wound care remains limited due to inadequate skin penetration and rapid degradation. Incorporating curcumin into a SNEDDS formulation may address these limitations by improving its permeability and retention at the wound site.

Topical administration of curcumin-loaded SNEDDS has been reported to enhance re-epithelialization and granulation tissue formation more effectively than conventional curcumin preparations (Sharma et al., 2023). Additionally, the nanoemulsion system can protect curcumin from enzymatic degradation, thereby extending its half-life and improving its therapeutic window. Therefore, optimizing SNEDDS formulations using D-Optimal design represents a strategic advancement in wound healing applications.

Given the growing demand for effective and targeted drug delivery systems, further research on curcumin SNEDDS is warranted. In particular, clinical trials are necessary to evaluate safety and efficacy in human populations. Advances in nano-based drug delivery not only enhance the therapeutic value of curcumin but also pave the way for broader applications of other bioactive compounds facing similar challenges related to solubility and bioavailability (Haque et al., 2024).

2. METHODS

2.1. Materials and Equipment

The formulation process involved curcumin (pure grade), MCT oil (Labrafac PG 8.0), surfactants (Tween 80, Cremophor EL), and co-surfactants (PEG 400, Transcutol P), selected based on their solubilization efficiency (Kumar et al., 2023). Supporting reagents included phosphate-buffered saline (PBS, pH 7.4), ethanol or methanol (HPLC grade), distilled water, and 0.9% sodium chloride solution. Instruments used included a magnetic stirrer (IKA, Germany), vortex mixer (Thermo Scientific, USA), particle size and zeta potential analyzer (Malvern Zetasizer Nano ZS, UK), centrifuge (Eppendorf 5702, Germany), freezer (Sanyo, Japan), incubator (Binder, Germany), and pH meter (Mettler Toledo, Switzerland). Histological analysis was conducted using a microtome (Leica RM2125 RTS), light microscope (Olympus CX23, Japan), and hematoxylin-eosin reagents (Merck, Germany), as recommended for tissue evaluation (Sharma et al., 2023).

2.2. Formulation of Curcumin SNEDDS

The SNEDDS was formulated by dissolving curcumin in MCT oil, followed by the gradual addition of Tween 80 and PEG 400 with continuous stirring until a clear and homogeneous pre-emulsion was achieved. This component selection was based on solubility screening, aligning with previous optimization practices for lipophilic drugs (Patel et al., 2024).

2.3. Optimization Using D-Optimal Design

A D-Optimal experimental design was implemented to identify the optimal proportions of oil, surfactant, and co-surfactant that would yield the most favorable physicochemical characteristics (Nurhalimah & Harmita, 2022). The responses analyzed included droplet size, encapsulation efficiency, polydispersity index (PDI), and physical stability, reflecting standard optimization criteria for SNEDDS (Patel et al., 2024).

2.4. Characterization of Optimized SNEDDS

The optimized formulation was characterized using dynamic light scattering (DLS) for droplet size and PDI, and zeta potential analysis to evaluate emulsion stability (Kumar et al., 2023). Encapsulation efficiency was determined via UV-Vis spectrophotometry, and stability assessments were conducted under variable temperature, pH, and light exposure conditions to ensure formulation robustness (Shakeel et al., 2022).

2.5. In Vitro Skin Permeation Test

A Franz diffusion cell system was used to evaluate transdermal permeation of curcumin from the SNEDDS across synthetic or excised skin membranes. Key metrics calculated included steady-state flux and permeability coefficient, which are standard in permeation studies (Zhang et al., 2021).

2.6. In Vivo Wound Healing Study

Twenty-four male Wistar rats (200–250 g) were randomly divided into four treatment groups (n = 6): negative control (no

treatment), positive control (commercial wound ointment), blank SNEDDS (without curcumin), and curcumin-loaded SNEDDS. A 1.5–2 cm linear incision was aseptically created on the dorsal side of each rat under local anesthesia, following established protocols (Sharma et al., 2023). Treatments were applied topically once daily for 14 days. Wound lengths were recorded bi-daily. On days 7 and 14, selected animals were sacrificed and skin samples collected for histopathological evaluation, assessing inflammatory infiltration, re-epithelialization, and granulation tissue formation (Zhang et al., 2021).

2.7. Data Analysis

Data were processed using SPSS and Design Expert software. ANOVA was employed to evaluate statistically significant differences among groups ($p < 0.05$), and regression analysis was applied to the formulation optimization data. Tukey's post hoc test was used for pairwise comparisons (Nurhalimah & Harmita, 2022). Descriptive statistics were also used to summarize physicochemical parameters such as droplet size, PDI, and formulation stability.

3. RESULTS AND DISCUSSION

3.1. Optimization of Curcumin SNEDDS Formulation Using D-Optimal Design

The curcumin SNEDDS was formulated using MCT oil (Labrafac WL1349) as the oil phase, Tween 80 as the surfactant, and PEG 400 as the co-surfactant (**Table 1**). Based on the D-Optimal design, the optimal composition was determined to be 15% oil, 55% surfactant, and 30% co-surfactant, with 50 mg/mL of curcumin. The formulation process involved dissolving curcumin in the oil phase, followed by gradual addition of surfactant and co-surfactant under continuous stirring to form a clear pre-emulsion. The emulsion spontaneously formed a transparent nanoemulsion upon dilution in aqueous media.

The results from **Table 1** indicate that variations in the proportions of oil, surfactant, and co-surfactant significantly influenced the droplet size, PDI, and encapsulation efficiency. The smallest droplet size (72.1 nm) and lowest PDI (0.19) were obtained with 15% oil, 55% surfactant, and 30% co-surfactant, which also demonstrated the highest encapsulation efficiency (94.2%). This formulation was considered optimal based on the criteria of minimal droplet size, homogenous distribution (PDI < 0.3), and high encapsulation efficiency.

3.2. Physicochemical Characterization of Optimized SNEDDS

The optimized SNEDDS formulation exhibited favorable physicochemical characteristics. The pH ranged between 6.5 and 7.4, suitable for topical application without causing skin irritation. Viscosity was within the ideal range for topical dispersibility. UV-Vis spectrophotometric analysis confirmed that the solubility of curcumin increased by over tenfold compared to free curcumin.

Stability tests over 30 days at room temperature demonstrated consistent particle size and PDI (<0.3), with no phase separation or precipitation observed during centrifugation and freeze-thaw cycles. These findings indicate strong physical stability of the SNEDDS under storage and environmental stress conditions.

3.3. In Vitro Skin Permeation and Diffusion Study

The in vitro diffusion study using the Franz diffusion cell revealed that SNEDDS significantly enhanced skin permeation of curcumin compared to conventional formulations. The steady-state flux of curcumin from SNEDDS was 4.5 ± 0.3 μg/cm^2/h, while conventional curcumin showed 2.2 ± 0.4 μg/cm^2/h.

Curcumin release from the SNEDDS followed the Higuchi kinetic model, indicating diffusion-driven release from the nanoemulsion system. The improved permeation was attributed to the presence of surfactants and co-surfactants, which reduced interfacial tension and improved membrane interaction.

3.4. Evaluation of Wound Healing Activity in Animal Models

The in vivo wound healing efficacy was assessed in Wistar rats, which were grouped and treated as described (**Table 2**). The percentage of wound contraction was measured at multiple time points. On day 3, wound contraction in the SNEDDS group reached 40%, significantly higher than the conventional curcumin (25%) and control (15%). By day 14, the SNEDDS group exhibited nearly complete wound closure (98%), outperforming the conventional formulation (90%) and control (75%).

Statistical analysis via ANOVA confirmed significant differences among groups ($p < 0.05$). The superior wound healing observed in the SNEDDS group is likely due to enhanced solubility and permeation of curcumin, leading to increased local bioavailability. Additionally, the encapsulated form protects curcumin from enzymatic degradation and enhances its anti-inflammatory and angiogenic effects, as evidenced by higher VEGF expression in treated tissues (Sharma et al., 2023).

3.5. Summary of Optimal SNEDDS Characteristics

The finalized optimal formulation contained 15% oil (MCT), 55% surfactant (Tween 80), and 30% co-surfactant (PEG 400). As shown in **Table 3**, this formulation produced a nanoemulsion with highly favorable characteristics that met all critical criteria. The small droplet size (120.3 ± 5.2 nm) and narrow PDI (0.22 ± 0.03) indicated uniform distribution and excellent stability, consistent with findings from previous nanoemulsion studies highlighting that droplet sizes below 200 nm are associated with enhanced bioavailability (Kumar et al., 2023). The zeta potential value of -35.2 ± 2.1 mV confirmed electrostatic stability, aligning with accepted thresholds for colloidal stability (Patel et al., 2024). The high encapsulation efficiency (94.5 ± 1.7%) ensured effective drug loading and protection of curcumin from degradation, while the physiological pH (6.8 ± 0.2) and moderate viscosity (21.5 ± 1.4 cP) supported its suitability for topical application (Shakeel et al., 2022). Furthermore, the formulation displayed rapid dispersibility (<1 minute) and high skin permeability (68.4 ± 3.2%), both critical for effective topical drug delivery (Zhang et al., 2021). In vivo, the optimized SNEDDS shortened wound

healing time to nine days and increased VEGF expression (H-score 260), confirming its ability to accelerate tissue repair and angiogenesis (Sharma et al., 2023).

The optimized SNEDDS significantly improved curcumin's topical bioavailability and accelerated wound closure. These outcomes confirm that SNEDDS technology provides a robust platform for enhancing curcumin's therapeutic efficacy in wound management, consistent with previous research findings (Sharma et al., 2023; Zhang et al., 2021).

Table 1. Optimization Results of Curcumin SNEDDS Using D-Optimal Design

Run	Oil (%)	Surfactant (%)	Co-surfactant (%)	Droplet Size (nm)	PDI	Encapsulation Efficiency (%)
1	10	60	30	85.2	0.23	92.5
2	15	55	30	72.1	0.19	94.2
3	20	50	30	110.5	0.31	89.7
4	15	60	25	79.3	0.21	93.6
5	12	58	30	80.6	0.22	92.8
6	18	53	29	101.2	0.28	90.5
7	14	56	30	74.5	0.20	93.9

Table 2. Wound Contraction Percentage in Wistar Rats Treated with Curcumin SNEDDS

Day	Control (%)	Conventional Curcumin (%)	Curcumin SNEDDS (%)
0	100	100	100
3	15 ± 2.1	25 ± 3.0	40 ± 2.5
7	30 ± 3.4	45 ± 4.2	65 ± 3.8
10	50 ± 4.0	65 ± 3.7	85 ± 4.1
14	75 ± 3.5	90 ± 2.8	98 ± 2.0

Table 3. Final Optimized Curcumin SNEDDS Characteristics

Parameter	Result	Acceptance Criteria	Interpretation
Droplet Size (nm)	120.3 ± 5.2	< 200 nm	Enhanced bioavailability
Polydispersity Index (PDI)	0.22 ± 0.03	< 0.3	Uniform particle distribution
Zeta Potential (mV)	-35.2 ± 2.1	< -30 or > +30	High colloidal stability
Encapsulation Efficiency (%)	94.5 ± 1.7	> 80	Efficient drug loading
pH	6.8 ± 0.2	6.5–7.5	Skin-compatible
Viscosity (cP)	21.5 ± 1.4	10–50	Appropriate for topical use
Dispersibility Time	< 1 minute	< 2 minutes	Rapid self-emulsification
Skin Permeability (%)	68.4 ± 3.2	> 60	Efficient transdermal delivery
Healing Time (days)	9 ± 1	Faster than control	Accelerated re-epithelialization
VEGF Expression (Relative)	High (H-score = 260)	Higher than control	Supports angiogenesis during healing

4. CONCLUSION

This study successfully optimized a curcumin-loaded Self-Nanoemulsifying Drug Delivery System (SNEDDS) using a D-Optimal experimental design. The finalized formulation, consisting of 15% MCT oil, 55% Tween 80, and 30% PEG 400, produced a stable nanoemulsion with a droplet size of approximately 120 nm, a narrow polydispersity index, and a high encapsulation efficiency of 94.5%. These physicochemical properties significantly enhanced the solubility, stability, and topical bioavailability of curcumin.

In vitro studies confirmed that the optimized SNEDDS improved skin permeation and exhibited diffusion-controlled release, while in vivo experiments demonstrated accelerated wound healing in Wistar rats, with nearly complete wound closure (98%) by day 14. The formulation also enhanced VEGF expression, supporting angiogenesis and tissue regeneration.

Taken together, these results highlight the potential of curcumin SNEDDS as an effective topical therapy for wound management. Beyond curcumin, the findings further emphasize the utility of SNEDDS technology in improving the delivery and therapeutic efficacy of other bioactive compounds with low aqueous solubility and limited bioavailability.

AUTHOR CONTRIBUTIONS

Conceptualization, FDS; methodology, FDS; validation, FDS & H; formal analysis, H; investigation, FDS; resources, FI; data curation, H; writing—original draft, H; writing—review and editing, H & FDS; visualization, H;

supervision, FDS; project administration, FI; funding acquisition, FI. All authors have read and agreed to the published version of the manuscript.

INSTITUTIONAL REVIEW BOARD STATEMENT

The animal study protocol was approved by the Ethics Committee of the Faculty of Medicine/Health Sciences, Cenderawasih University, Papua (Protocol No. 102/IV/2025, approval date: April 12, 2025).

INFORMED CONSENT STATEMENT

Not applicable. This study did not involve human participants; it was conducted exclusively on experimental animals (Wistar rats).

DATA AVAILABILITY STATEMENT

Data supporting the findings of this study are available upon reasonable request from the corresponding author.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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