

Curcumin Transethosome Gel: Anti-inflammatory Activity Test in Carrageenan-Induced Sprague Dawley Rat

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ABSTRACT

Curcumin has anti-inflammatory activities, and is formulated into the transethosome (TE) system to improve penetration. The TE system's stability can be increased by incorporating it into a gel dosage form. This study aims to determine the anti-inflammatory activities of curcumin TE gel. Curcumin TE gel was produced in 3 compositions, each having a curcumin content of 10 mg (F1), 40 mg (F2), or 160 mg (F3). On TE gels, organoleptic, viscosity, pH, particle size, and zeta potential were evaluated. The test animals were divided into five groups for anti-inflammatory activity testing. A 1% carrageenan solution was used to induce edema in the animals, and the volume of edema was measured for comparison with $p < 0.05$ set as significant difference. Curcumin TE gel's physical properties showed a yellow and homogenous gel with viscosity values of 31.173 – 33.626 cPs, pH 4.75 – 4.84, particle size 208.3 – 319.4 nm, and zeta potential (-) 40.03 – (-) 51.12 mV. On anti-inflammatory tests, the edema volume in the group given curcumin TE gel decreased in the 270th minute. According to statistical analysis, the test group had a significant difference ($p < 0.05$) from negative controls and no significant difference ($p > 0.05$) from positive controls in F1 and F2 anti-inflammatory activity. According to these results, the curcumin TE gel exhibited anti-inflammatory activity equivalent to the positive control, while F3 had anti-inflammatory activity better than the positive control.

INTRODUCTION

The turmeric rhizome contains curcumin, which is one of the compounds that has several pharmacological properties, including anti-inflammatory effects (Belma *et al.*, 2021). Inflammation is a self-defense process against harmful stimuli and situations, such as infection and tissue damage, to maintain physiological homeostasis (Peng *et al.*, 2021). According to a study done by Patel *et al.* (2009), curcumin has anti-inflammatory properties at a concentration of 2% in a gel dose form. However, curcumin has a variety of limitations, one of which is its insufficient penetration

(Vijayakumar *et al.*, 2017). According to the Nutraceutical Bioavailability Classification (NuBACS), curcumin's water solubility and stability are limited. Additionally, curcumin undergoes extensive first-pass metabolism. Preclinical and clinical studies have determined that oral administration of curcumin results in inadequate bioavailability. On the other hand, when administered topically, curcumin exhibits adequate bioavailability and bioactivity, particularly when incorporated into new formulations such as nanoparticles (Vollono *et al.*, 2019). Curcumin in the form of a transethosome (TE) system can also be utilized

to enhance the topical penetration of curcumin (Amalia *et al.*, 2021).

The TE is a vesicle-like carrier system of phospholipids, high alcohol concentrations, and water. The benefits of TE include a reduction in the use of large doses, a reduction in toxic effects, and a high level of drug permeation in the skin, allowing it to be turned into transdermal or other topical formulations (Abdulbaqi *et al.*, 2016; Shaji and Bajaj, 2018). According to a study conducted by Srifiana *et al.*, (2020), during the stability test period, the curcumin TE with surfactant ratios of tween 60 and span 60 3:1 was able to retain the physical properties of the system. In the preparation of curcumin TE, the surfactants tween 60 and span 60 were combined to produce a TE system with a higher diffusion rate than a single surfactant system (Amalia *et al.*, 2021). The curcumin phytosome system can be developed into a transdermal dosage form, according to this research.

It can also be used as a transdermal preparation by converting the TE system into a gel dosage form. Enhanced bioavailability of the active components has been demonstrated when the nanoparticle system is formulated into a gel dosage form (Elnaggar *et al.*, 2014). One of the gelling agents that can be utilized in the production of gels is Carbopol 934, which improved the physical stability of microemulsion gel formulations compared to Carbopol 941 (Lestari *et al.*, 2018). The TE gel with Carbopol 934 gel base at a concentration of 1% had the best TE gel diffusion rate (Wulandari *et al.*, 2019). The anti-inflammatory efficacy of curcumin TE gel must be investigated to confirm the formulation's pharmacological effects. The focus of this research was to determine how the anti-inflammatory activity would evolve if the concentration of curcumin TE in the gel mixture was increased.

METHODS

Materials

Curcumin 98% from Matras Exporters (Chennai, India), Lecithin from Solae (St. Louis, MO), Tween 60, Span 60, Ethanol and Carbopol 934 from Shree Chemicals (Pune, India), and Carrageenan from Sigma Aldrich (St. Louis, MO) were employed in this study.

Preparation of Curcumin Transethosome (TE)

The curcumin TE was prepared in a dark environment using the cold method. Ethanol was used to disperse Curcumin (2%) (M1). Tween 60 and lecithin were added to Span 60 and stirred at

30°C (M2). M1 was added to M2, which was then homogenized with a magnetic stirrer (MS-H-PRO) at 750 rpm for 15 minutes, then elevated to 1000 rpm and agitated for 60 minutes, then aquadest was added in a steady stream until a curcumin TE vesicle suspension was produced (Amalia *et al.*, 2021; Srifiana *et al.*, 2020).

Evaluation of the Curcumin Transethosome (TE)

Evaluation of the TE physical properties of curcumin include determining the particle size distribution, zeta potential, pH, and entrapment efficiency (EE). PSA (Particle Size Analyzer) Delsa Nano Beckman Coulter (USA), assessed particle size distribution and zeta potential (Amalia *et al.*, 2021). A Hanna portable pH meter (Jakarta, Indonesia) was used to conduct the test. In the assessment, after calibrating the instrument, the tool's electrode was put into the curcumin TE gel (Srifiana *et al.*, 2020).

The EE test was performed using centrifugation to separate the trapped and non-trapped curcumin in the TE. The EE test was performed using the centrifugation method. The TE was placed in a centrifuge tube and centrifuged at 12,000 rpm for 60 minutes to generate two layers. The amount of curcumin that was not trapped in the supernatant layer was measured as a free drug. The absorbance was measured using a Shimadzu UV-1900 Ultraviolet-Visible (UV-Vis) spectrophotometer (Tokyo, Japan) at a wavelength of 427.2 nm after 1 mL of the supernatant was diluted with ethanol to 100 mL (Wulandari *et al.*, 2019). Equation 1 was used to compute the trapped curcumin percentage.

$$\text{Entrapment Efficiency (\%)} = \frac{\text{Total drug-Free drug}}{\text{Total drug}} \times 100 \dots\dots\dots (1)$$

Preparation of Curcumin Transethosome (TE) Gel

There are three compositions for the curcumin TE gel. Table 1 presents the components for each composition. Curcumin TE comparable to 10 mg curcumin can be found in composition 1 (F1), 40 mg curcumin can be found in composition 2, and 160 mg curcumin can be found in composition 3. Carbopol 934, at a concentration of 1%, was utilized as a gelling agent in the preparation of curcumin TE gel. Carbomer was dispersed in an aqueous solution containing 0.1 percent triethanolamine (TEA) for 24 hours to make a TE curcumin gel (M1). In aqua pervida, nipagin and nipasol were dissolved (M2). M2 was added to M1 and agitated until the

mixture was homogenous and a gel base formed. Following the formation of the gel base, the TE was gradually added while stirring until homogenous (Wulandari *et al.*, 2019).

Evaluation of the Curcumin TE Gel

The organoleptic test evaluated the gel preparation based on its color, shape, and odor (Wulandari *et al.*, 2019). The test procedure is identical to that used to determine the particle size and zeta potential of TE curcumin. The procedure for determining the pH value of TE curcumin is the same as for determining the pH value of TE curcumin. A Brookfield RV DV-E Viscometer (Massachusetts, USA) was used to conduct the viscosity test. The tool's viscosity value was read and recorded in Centipoise (Cps) units (Srifiana *et al.*, 2020).

Study of Anti-Inflammatory Activity

This study employed 25 male Sprague Dawley rats 2-3 months old and weighed between 150 and 250 g. They were bought from CV. Glass World, Solo, Indonesia. Animal Health Certificate number 473/SKKH/VB/2020 was issued to the animals used in this investigation after being examined and confirmed healthy by drh. Fakhur Rakhman. The experimental animals were divided into five groups: (1) the negative control group, which received gel base; (2) the positive control group, which received curcumin gel with a 2 % curcumin concentration; (3) the test group, which received curcumin TE gel F1, (4) the test group 2, which received curcumin TE gel F2, and (5) the test group 3,

which received curcumin TE gel F3. The gel containing 2% curcumin was used as a positive control because, according to Patel *et al.* (2009), the gel containing 2% curcumin has anti-inflammatory properties. Carbopol 934 was used to make the curcumin gel, conducted the same way as the curcumin TE gelling. Each group had five white male rats in it. The mice were given a two-week acclimatization period to help them adjust to their new habitat and treatment. The tails and legs of the experimental animals were marked.

Universitas Muhammadiyah prof. DR. HAMKA Health Research Ethics Commission approved and granted authorization for the anti-inflammatory activity test of curcumin TE gel with Ethics Approval number 02/20.02/0320. Rats were deprived of food for 18 hours and then given water to drink. A boundary was drawn around the rat's right leg, then measured with a pletysmometer. The initial volume of a mouse paw was measured (V_0). The test material was applied topically to each group of rats before intraplantar injection of 0.1 mL carrageenan solution stimulated the rats. A carrageenan solution was made by dissolving 100 mg of carrageenan in a 0.9 % NaCl solution (Zubaydah *et al.*, 2019). The edema volume was measured as V_t at 30, 90, 150, 210, and 270 minutes. Equation 2 was used to determine the percentage of edema volume.

$$\text{Edema percentage} = \frac{V_t - V_0}{V_0} \times 100 \dots\dots (2)$$

Table 1. Composition for curcumin TE gel

Component	Concentration (%)		
	F1	F2	F3
TE Curcumin	0.5	2	8
Carbopol 934	1	1	1
Triethanolamine	0.1	0.1	0.1
Methylparaben	0.18	0.18	0.18
Propylparaben	0.02	0.02	0.02
Aquadest add	100	100	100

Notes: TE: transethosome.

Table 2. Curcumin TE gel average particle size and zeta potential (n = 3)

Composition	Particle Size (nm)	Zeta Potential (mV)
F1	263.1 ± 29.3	(-) 45.12 ± 5.4
F2	319.4 ± 71.5	(-) 51.12 ± 3.2
F3	208.3 ± 6.9	(-) 40.03 ± 3.7

Notes: TE: transethosome.

The trapezoid method was used to determine the total area under the curve (AUC) value. The equation 3 is used to calculate the percentage of edema inhibition. (Aprilianto *et al.*, 2019; Dwita *et al.*, 2019; Zubaydah *et al.*, 2019).

$$\text{Edema Inhibition (\%)} = \frac{Ed_{\text{control}} - Ed_{\text{substance}}}{Ed_{\text{control}}} \times 100 \dots\dots (3)$$

where:

Ed_{control}: Edema volume of negative control

Ed_{substance}: edema volume of test substance

Data Analysis

Data on curcumin EE, pH, viscosity, percentage of inflammation, total AUC, and percentage of edema inhibition were analyzed by one-way ANOVA (SPSS 38 trial version) with $p < 0.05$ as significant.

RESULTS AND DISCUSSION

Physical Properties of Curcumin Transethosome

Because curcumin was light-sensitive, the curcumin transethosome was created using a cold method in the darkness (Edityaningrum and Rachmawati, 2015; Kharat *et al.*, 2017). The produced TE is yellow and homogeneous, with a particle size of pH 5.60 ± 0.01, a particle size of 250.50 ± 16.90 nm with polydispersity index (PDI) 0.57 ± 0.00, zeta potential (-) 41.68 ± 3.45 mV, and 93.29 ± 2.10 % EE. Because the TE system generated is in the 10–1000 nm size range, it is classified as a nanoparticle (Ramadon and Mun'im, 2015). According to these findings, the TE particle size fits within the category of nanoparticles, but it has a PDI that is greater than 0.2, which indicates that it has a larger size distribution (Danaei *et al.*, 2018; Esposito *et al.*, 2022; Strambeanu *et al.*, 2015).

Physical Properties of Curcumin Transethosome (TE) Gel

Organoleptics

Because of the variable quantities of curcumin TE in each formula, organoleptic examinations on the gel preparations revealed that each formula had a different color intensity. F1 forms a yellow gel, F2 a light orange gel, and F3 an orange gel. With a semisolid dose form, all gels have a distinct turmeric odor. Figure 1 describes the result of the organoleptic evaluation of Curcumin TE gel.

Particle Size and Zeta Potential

Physical characteristics such as particle size and zeta potential determine the success of

nanoparticle systems development. If the particle size of a system or preparation is between 1 and 1000 nm, it is considered a nanoparticle system. F1 – F3 is a nanoparticle system with a particle size value of less than 1000 nm, according to the data (Table 2) (Strambeanu *et al.*, 2015). The particle size range of curcumin TE gel was between 208.3 and 319.4. These results suggest that TE gel has the potential to be administered transdermally. Nanovesicles smaller than 300 nm can deliver encapsulating material to the deeper skin layers. In contrast, vesicles with a diameter greater than 600 nm cannot transport the encapsulating material to the deeper layers of the epidermis (Danaei *et al.*, 2018). The surface charge characteristics of the nanoparticles were characterized using the zeta potential of the nanoparticles. The zeta potential is crucial for determining particle surface charge and can be used to predict and control stability. If the zeta potential is more significant than (±) 30 mV, the system is stable (Gondkar *et al.*, 2017). Because the average zeta potential value in each composition is more than (±) 30 mV, the gel created can be considered stable. Curcumin TE gel had a higher zeta potential than curcumin's TE zeta potential. As a result of being created in gel preparations, the possibility of forming aggregates is reduced (Singh and Lillard, 2009). The curcumin TE gel's negative zeta potential suggests that when Carbopol is dispersed in distilled water, the -COOH group ionizes to form -OH (Ben *et al.*, 2013).

pH Value

Curcumin TE gel preparations had pH values of 4.84 ± 0.04 (F1), 4.75 ± 0.01 (F2), and 4.84 ± 0.02 (F3). The pH of the preparation should be within the range of 4.5 – 6.5, which correlates to the skin's pH (Agoes, 2012). According to the statistical analysis, the pH values of the compositions did not differ significantly ($p > 0.05$). This result means that variations in curcumin TE concentration do not affect the pH of the gel.

Viscosity

The viscosity of the curcumin TE gel is shown in Figure 2. The concentration of the gelling agent used affects the viscosity of the gel preparation. Carbopol 934, at a concentration of 1%, was utilized as a gelling agent in the production of the curcumin TE gel. The concentration of 1% was selected due to research conducted by Wulandari *et al.* (2019); compared to the other compositions, the TE

curcumin gel composition with a concentration of Carbopol 934 showed the fastest diffusion rate value. Carbopol 934 has a viscosity of 30,000–39,000 cPs at a concentration of 1% (Rowe *et al.*, 2009). These results indicate that the gel's viscosity matches the properties of the Carbopol 934 gel. The statistical analysis showed a significant difference ($p < 0.05$). These findings suggest that the viscosity of the gel preparation is affected by variations in TE concentration. The viscosity of the gel formulation increases with the concentration of curcumin TE. This finding can be caused by increasing the curcumin TE concentration in the gel preparation; the more curcumin added to the gel preparation, the higher the density of the gel preparation.

Study of Anti-Inflammatory Activity

The volume of rat foot edema after induction with a 1 % carrageenan solution

injected intraplantar was calculated to test the anti-inflammatory activity of curcumin TE gel. The inflammation caused by carrageenan is acute and does not cause tissue damage. A mercury plethysmometer was used to determine edema volume (Dwita *et al.*, 2019). Table 3 shows that the largest average volume of edema is negative control, positive control, curcumin TE gel F1, curcumin TE gel F2, curcumin TE gel F3. TE contained 10 mg (F1), 40 mg (F2), and 160 mg (160 mg) of curcumin. The curcumin content of TE ranges from 10 to 160 mg because the curcumin nanoparticle compositions delivered through the epidermis contain anti-inflammatory substances in the range of 10 to 40 mg. Formula 3 is applied as the highest active testing dosage (El-Mahdy *et al.*, 2020; Gonçalves *et al.*, 2017).



Figure 1. Organoleptic evaluation of curcumin TE gel F1 with TE curcumin 0,5% (A), curcumin TE gel F2 with TE curcumin 2% (B), curcumin TE gel F3 with TE curcumin 8% (C).

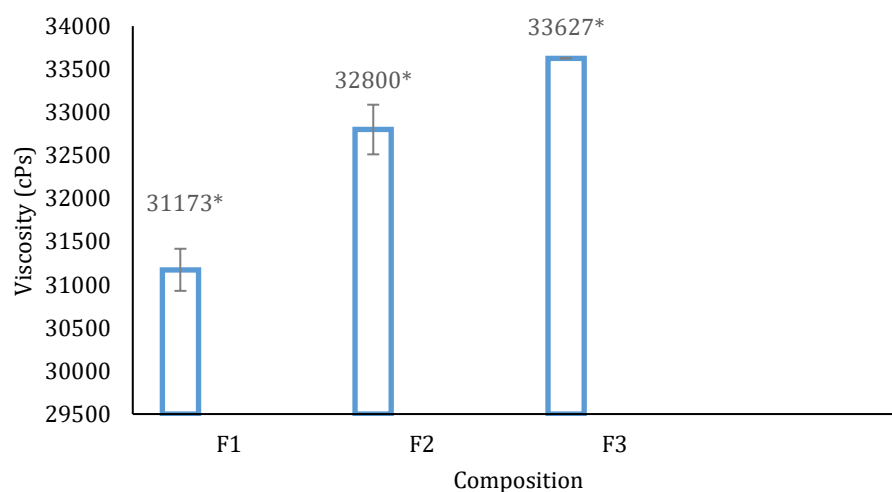


Figure 2. The viscosity of curcumin transethosome gel ($n = 3$). *: significantly different from another composition. Significance level at $p < 0.05$.

Table 3. Average edema volume percentage \pm SD in Rat Paw (n = 5).

Group	Percentage (%) per Minute					
	0	30	90	150	210	270
Curcumin TE Gel F1	0	35.00 \pm 14.91	41.67 \pm 7.80*	56.67 \pm 9.13	61.67 \pm 11.18	35.00 \pm 13.69*
Curcumin TE Gel TE F2	0	36.67 \pm 13.94	53.33 \pm 7.45*	60.00 \pm 9.13	63.33 \pm 7.45	30.00 \pm 7.45*
Curcumin TE Gel TE F3	0	31.67 \pm 12.36	34.17 \pm 1.36*	28.33 \pm 7.45*	27.50 \pm 10.03*	9.17 \pm 8.54*
Negative Control	0	36.67 \pm 12.64	79.17 \pm 5.89	53.33 \pm 7.45	71.67 \pm 9.03	72.50 \pm 16.30
Positive Control	0	40.83 \pm 8.54	56.67 \pm 9.13*	60.00 \pm 9.13	53.33 \pm 7.45*	20.83 \pm 8.33*

SD, standard deviation; TE, transethosome; *: significantly different from the negative control. Significance level at $p < 0.05$.

Table 4. Total AUC value and percentage of edema inhibition (n = 5).

Group	Total AUC (mL/minute)	Edema Inhibition (%)
Curcumin TE Gel F1	14.09 \pm 1.88	13.67 \pm 8.20 ^b
Curcumin TE Gel TE F2	12.05 \pm 0.40 ^b	25.39 \pm 10.49 ^b
Curcumin TE Gel TE F3	10.92 \pm 1.63 ^{a,b}	32.75 \pm 10.28 ^{a,b}
Negative Control	16.32 \pm 1.53 ^a	0.00 \pm 0.00 ^a
Positive Control	13.44 \pm 1.82 ^b	17.30 \pm 11.05 ^b

AUC, area under the curve; TE, transethosome; ^a = significantly different from the positive control, ^b = significantly different from the negative control. Significance level at $p < 0.05$.

At the 30th minute, there was inflammation caused by carrageenan induction which was indicated by an increase in inflammation volume in all groups (Santi, 2015). There are two stages to the inflammation caused by carrageenan. The first phase, which occurs 1-2 hours after carrageenan injection, results in trauma due to carrageenan-induced inflammation. Prostaglandins are released from macrophages during the second phase, occurring 3-4 hours after carrageenan injection. The first phase marks the start of a rise in inflammation, with the second phase being the peak of inflammation following carrageenan injection (Aprilianto *et al.*, 2019).

Compared to other topical preparations, the anti-inflammatory test of curcumin TE gel on white male rats showed that the gel's nature could scatter the medication well and had good absorption, allowing the active substance to enter the skin and disseminate uniformly. Edema volume increased from the 30th minute to the 270th minute in each treatment group, with the most significant volume of edema occurring at the 210th minute, according to the percentage of edema against time (Table 3). The results showed a significant difference ($p < 0.05$) between the Gel TE test group and the negative control group when the data were statistically examined. The percentage of edema in the test group and the positive control did not

significantly differ ($p > 0.05$) compared to the positive control. This result suggests that curcumin TE gels F1, F2, and F3 have anti-inflammatory properties and alleviate edema in male white rats' soles caused by 1% carrageenan.

Because the negative control group was only given a gel base, Table 3 shows that the negative test group had the highest percentage of edema, with a percentage of edema of 79.17%. With an edema percentage of 9.17%, the F3 gel TE had the lowest edema percentage. The observation can explain that F3 has the smallest particle size compared to F1 and F2. The smaller the particles, the easier they become to penetrate (Ramadon and Mun'im, 2015). F3 has had the highest viscosity of all the gel compositions. The gel composition will remain longer, and contact with edema in the rat paw will be prolonged as the viscosity increases (Sweetman, 2009). The gel becomes more successful at reducing the size of edema in experimental animals due to this difference.

The edema volume data for each treatment can be used to calculate the AUC value and the percentage edema inhibition. The parameter described as the AUC value defines the amount of edema that each group generates per unit of time (Anggraeny and Pramitaningastuti, 2016). The AUC value indicates the amount that the sample inhibits the production of edema. The greater the inhibition

of edema production from the sample, the lower the AUC value (Andayani *et al.*, 2018). Based on the results (Table 4), the group that was administered curcumin F3 gel had the least value and a significant difference between the positive and negative controls. The F2 treatment group had the next-lowest inhibitory power; its results revealed a substantial difference from the negative control and similar inhibitory power to the positive control. The results of determining the percentage value of edema inhibition, as displayed in Table 4, validate these findings.

Based on the results, Gel TE curcumin F3 has the highest level of inhibition, followed by F2, the positive control, F1, and the negative control. These results indicate that curcumin can more effectively suppress edema formation by being included into the TE system because the TE gel has a nano size that enables it to more immediately penetrate the area of edema formation. (Abdulbaqi *et al.*, 2016). The results also showed that there was a higher inhibition of edema production with increasing curcumin concentration in the TE gel preparation. This finding is because curcumin has anti-inflammatory properties, which include decreasing the production of prostaglandins by inhibiting the cyclooxygenase enzyme and its ability to bind oxygen free radicals that cause inflammation (Belma *et al.*, 2021; Patel *et al.*, 2009).

CONCLUSIONS

Curcumin transethosome (TE) gels containing 10 mg (F1), 40 mg (F2), and 160 mg (F3) of curcumin were developed to decrease inflammation in rat paws after 0.1 ml carrageenan was applied. Positive control had an inflammatory inhibition of 17.30%, curcumin TE gel F1 had 13.67%, F2 had 25.39%, and F3 had 32.75%. Based on the statistical analysis, there was a significant difference between the inhibition of F3 with the negative control and the positive control ($p < 0.05$). The highest anti-inflammatory effects were the TE gel containing 160 mg of curcumin (F3) indicating the gel's benefits are dose-dependent and increase with the gel's concentration of curcumin along with its viscosity while maintaining stable neutral pH between 4.75-4.84.

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CONFLICT OF INTEREST

The authors declare that this article has no actual, potential, or perceived conflict of interest.

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