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Research Paper

Enhanced Anti-Inflammatory Activity of *Kaempferia galanga* Extract by Solid Self-Nanoemulsifying Drug Delivery System and Its Development in Fast Disintegrating Tablet

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Abstract
The increasing global incidence of osteoarthritis (OA) emphasizes the need for effective treatments, particularly for the elderly. Conventional OA treatments pose administration challenges, leading to patient discomfort due to difficulties in administration. Herbal formulations offer an alternative to mitigate these issues. *Kaempferia galanga* (KG) contains ethyl p-methoxycinnamate, a compound displaying anti-inflammatory properties that hold promise for OA treatment. This study explores the formulation of a solid self-nanoemulsifying drug delivery system (S-SNEDDS) of *Kaempferia galanga* extract (KGE) and evaluates its anti-inflammatory efficacy, subsequently developing it into a fast disintegrating tablet (FDT) dosage form. Initially, a liquid SNEDDS (L-SNEDDS) was prepared with varying surfactant and co-surfactant concentrations. The optimal formula of L-SNEDDS (FL2) using tween 80: cremophor RH 40: PEG 400 in a ratio of 1:1:2 demonstrated favorable characteristics, including transmittance of 86.93 ± 1.16%, emulsification time of 28 ± 2.65 s, particle size of 27.79 ± 2.00 nm, PDI of 0.21 ± 0.014, and zeta potential of -12.57 mV. FL2 was solidified using aerosil 200 to produce S-SNEDDS and tested for anti-inflammatory efficacy *in vivo* using a carrageenan-induced rat model. Results showed enhanced anti-inflammatory efficacy of KGE via S-SNEDDS, marked by reduced edema volume. Afterward, FDT S-SNEDDS were prepared using the direct compression method by comparing different types of superdisintegrants. The formulation using the combination of crospovidone and croscarmellose sodium (FT2) demonstrated excellent flow properties, tablet disintegration time of 63 s, wetting time of 34.01 ± 7.87 s, friability of 0.19%, and hardness of 3.53 ± 6.16 kg/cm^2. The dissolution test indicated a better dissolution profile for FT2 compared to other formulations. In conclusion, this research presents the potential of FDT S-SNEDDS as a promising drug delivery system for enhancing the therapeutic effects of *Kaempferia galanga* extract in treating inflammatory conditions such as osteoarthritis.

Keywords
Anti-Inflammation, Fast Disintegrating Tablet, Solid Self-Nanoemulsifying Drug Delivery System, *Kaempferia galanga*

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1. INTRODUCTION

Osteoarthritis (OA), the most prevalent joint disease worldwide, becoming more prevalent with advancing age and increasing body weight. According to a study, the global prevalence of OA surged by 132% over a span of three decades from 1990 to 2020, resulting in a worldwide incidence of 595 million cases, with 23.24% of them aged 50-69 years and 38.42% aged > 70 years. OA is a degenerative cartilage disease resulting from structural changes in articular cartilage, characterized by pain, stiffness, bone enlargement, and sometimes joint swelling (Chen et al., 2017; Steinmetz et al., 2023). OA is defined as a chronic musculoskeletal disorder affecting the cartilage joint, with inflammation playing a crucial role in its progression by generating inflammatory mediators (Chow and Chin, 2020). Joint damage may degrade the extracellular matrix of the cartilage and trigger the production of inflammatory mediators by activating T cells, fibroblasts, macrophages, or chondrocytes. This, in turn, causes the release of inflammatory mediators such as cytokines, chemokines, and matrix metalloproteinases (MMPs) by directly or indirectly stimulating proteolytic enzymes. Consequently, the inflammation that occurs in the joints worsens and accelerates cartilage damage in progressive OA (Chow and Chin, 2020; Nurul et al., 2021).

Common therapeutic approaches for OA include paracetamol, nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and chondroitin (Maqbool et al., 2021). However, these medications are predominantly available in tablet form,

posing challenges for elderly OA patients who may have difficulty swallowing. This issue raises concerns regarding reduced medication adherence and therapy effectiveness (Aprilianio et al., 2017; Krekeler et al., 2018). Additionally, OA necessitates long-term treatment due to its degenerative nature, which may lead to potentially harmful side effects from prolonged drug use (Maqbool et al., 2021). Hence, there is a growing need for alternative treatments derived from herbal sources.

Kaempferia galanga (KG) is a plant from the Zingiberaceae family, commonly found in Indonesia. KG rhizome is frequently utilized as both a food spice and traditional medicine (Winingsih et al., 2021). It contains ethyl para-methoxycinnamate (EPMC), which exhibits anti-inflammatory properties capable of potentially alleviating the severity of OA. EPMC is known for its ability to systemically inhibit cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). Consequently, it presents itself as a promising alternative therapy for OA. However, EPMC has low solubility in water, which may hinder the absorption process of active substances in the body (Rachmaniar et al., 2020; Umar et al., 2014).

In place of conventional OA therapy, this study aims to develop a fast-disintegrating solid tablet self-nanoemulsifying drug delivery system (FDT S-SNEDDS) incorporating *Kaempferia galanga* extract (KGE). This system offers enhanced stability and efficacy, with its user-friendly administration particularly advantageous for elderly patients. FDT is designed to rapidly disintegrate in the oral cavity within a minute, facilitating quick dissolution and easier swallowing for patients. Furthermore, FDT may enhance bioavailability during pregastric absorption stages, such as in the mouth, pharynx, and esophagus (Parkash et al., 2011). SNEDDS, a lipid-based delivery system, forms oil-in-water nanoemulsions in gastric fluid with droplets below 200 nm (Buya et al., 2020). Comprising oils, surfactants, and cosurfactants or cosolvents, SNEDDS enhances the solubility of drugs in water and oral absorption of lipophilic drugs, such as EPMC found in the aromatic ginger extract. Liquid SNEDDS (L-SNEDDS) is formulated into solid SNEDDS (S-SNEDDS) to enhance product stability and efficacy (Buya et al., 2020; Maji et al., 2021).

Rccent studies have shown the potential for S-SNEDDS to be formulated as tablet dosage form, providing a better alternative to conventional tablet (Bashir et al., 2023; Nair et al., 2022). Hence, the development of FDT S-SNEDDS dosage form may increase patient convenience in drug administration due to the characteristic of FDT and enhance the anti-inflammatory activity of KGE through the SNEDDS formulation. Recent study indicates that investigation into the anti-inflammatory activity of SNEDDS has been confined to liquid formulations (L-SNEDDS) (Frei et al., 2023). To date, there is a lack of available research exploring the anti-inflammatory effects of S-SNEDDS, representing a significant gap in the literature and an opportunity for further study. Therefore, the present study formulates FDT S-SNEDDS incorporating KGE. This formulation is undertaken to evaluate the anti-inflammatory activity of S-SNEDDS, aiming to deliver a treatment for OA that is safe, effective and optimized for efficiency.

2. EXPERIMENTAL SECTION

2.1 *Kaempferia galanga* Rhizome Extraction

The KG rhizome was extracted utilizing the maceration method (Adianingsih et al., 2023). KG rhizome powder was soaked in 96% ethanol at a ratio of 1:10, agitated for 10 minutes using an overhead stirrer, and left for 24 hours. This maceration process was repeated twice. The resulting extract was then concentrated using a rotary evaporator at 50°C, yielding a thick extract subsequently dried in an oven at 60°C. The resultant extract was stored in a sealed container at 4°C for further use.

2.2 L-SNEDDS Formulation

L-SNEDDS formula contains PEG 400, tween 80, cremophor RH 40, and VCO with a concentration based on Table 1. All base ingredients were vortexed for 5 minutes at high speed, heated in a water bath for 5 minutes, and sonicated for 5 minutes. Subsequently, KGE and base were vortexed for 5 minutes at high speed, heated in a water bath for 5 minutes, and sonicated for 10 minutes. The procedure was repeated until the extract was completely dissolved (Indratmoko et al., 2021).

Table 1. L-SNEDDS Formulation

Ingredients	Concentration (%)			
	FL1	FL2	FL3	FL4
KG Extract	20	20	20	20
Tween 80	14.4	17.6	20.8	24
Cremophor RH 40	14.4	17.6	20.8	24
PEG 400	41.6	35.2	28.8	22.4
VCO	9.6	9.6	9.6	9.6

2.3 L-SNEDDS Evaluation

2.3.1 Organoleptic Evaluation

L-SNEDDS was evaluated visually for color and turbidity of the formulation.

2.3.2 Transmittance Evaluation

L-SNEDDS was diluted 1:100 with distilled water and vortexed at low speed for 30 seconds. Subsequently, the transmittance or clarity value of L-SNEDDS was observed with a UV-Vis spectrophotometer at a wavelength of 650 nm. A good transmittance value is considered to fall within the range of 80-100% (Buya et al., 2020; Zhang et al., 2020).

2.3.3 Emulsification Time Evaluation

One mL of L-SNEDDS was diluted at a ratio of 1:100 with distilled water at 37°C and then stirred at 120 rpm. A good emulsification time was determined to be less than 1 minute (Buya et al., 2020).

2.3.4 Determination of Particle Size, Polydispersity Index (PDI), and Zeta Potential

The droplet size, polydispersity index, and zeta potential of all formulations were measured using a dynamic light scattering particle size analyzer. The formulations were diluted at 1:20 %v/v with water and thoroughly mixed. The optimal formulation was characterized by a particle size of < 100 nm, PDI close to 0, and zeta potential ≥ +30 mV or ≤ -30 mV (Zhang et al., 2020).

2.4 L-SNEDDS Solidification

L-SNEDDS was solidified by the absorption method. Gradually, L-SNEDDS was added to the aerosil 200 in a mortar and thoroughly mixed. The resultant S-SNEDDS was then sieved with a mesh number of 60 (Ahmad and Hafeez, 2023). Through optimization of the solidification process, an optimal ratio of L-SNEDDS to aerosil 200 was determined to be 10:8. The solidification process produced solid-SNEDDS (S-SNEDDS) characterized by organoleptic properties, presenting as a yellowish-white dry fine powder.

2.5 *In Vivo* Anti-Inflammatory Test

Twenty-four 12-month-old Wistar rats (*Rattus norvegicus*) weighing 200-250 g were purchased at the Rattus Breeding Centre in Batu, East Java, Indonesia. All experimental procedures received ethical protocols from the Health Research Ethics Committee, Faculty of Medicine, Universitas Brawijaya (169/EC/KEPK/07/2023). The animal study was carried out in the Laboratory of Pharmacology, Faculty of Medicine, Universitas Brawijaya. The animals were acclimated in the laboratory environment for seven days. To induce inflammation, rats received a subcutaneous injection of 0.2 ml of 1% carrageenan solution in phosphate-buffered saline into the paw. The animals were randomly divided into six groups (n=4): (1) the normal group received no treatment or carrageenan induction; (2) the positive or carrageenan group was induced with 1% carrageenan; (3) the KGE group received pre-treatment with 160 mg/kg of KGE suspension orally and was induced with 1% carrageenan; (4) the Carr + S-SNEDDS KGE group received pre-treatment with 160 mg/kg of S-SNEDDS KGE orally and was induced with 1% carrageenan; (5) the Carr + Ibu group received pre-treatment with 20 mg/kg of ibuprofen orally and was induced with 1% carrageenan; and (6) the Carr + S-SNEDDS base group received pre-treatment with 640 mg/kg of S-SNEDDS base orally and was induced with 1% carrageenan. Before inflammation induction, therapy was administered to rats according to each treatment group. The S-SNEDDS formulation evaluated for anti-inflammatory activity was the optimized formula determined through the previous characterization. Paw edema volume was measured immediately after carrageenan injection and at 1, 2, 3, 4, 5, and 6 hours post-injection using a plethysmometer (Saleem et al., 2021).

2.6 FDT S-SNEDDS Formulation

The FDT S-SNEDDS formulations were prepared based on the solidification outcomes of the optimal SNEDDS formulation, employing the direct compression technique along with different types of superdisintegrants, as detailed in Table 2. All ingredients were passed through a mesh 60-sieve and subsequently blended using a turbula mixer for 5 minutes. The mixture was weighed at 300 g and compressed with a compression tool (Khadka et al., 2021).

Table 2. FDT S-SNEDDS Formulation

Ingredients	Concentration (%)		
	FT1	FT2	FT3
S-SNEDDS	4	4	4
Crospovidone	5	2.5	-
Croscarmellose sodium	-	2.5	5
Mannitol	7.5	7.5	7.5
Aspartam	1	1	1
Mg Stearat	1.25	1.25	1.25
Talk	1.25	1.25	1.25
MCC	80	80	80

2.7 FDT S-SNEDDS Evaluation

2.7.1 Angle of Repose

The powder mixture before tablet compression was placed into the funnel and allowed to flow out freely. The angle of repose was determined using the formula $\alpha = \tan^{-1}$ (h/r), where α represents the angle of repose, h denotes the height, and r signifies the radius of the cone formed by the powder pile cone (Swamy et al., 2019). The result was considered to exhibit excellent flowability if the angle of repose value fell within the range of 25-30°, and it was categorized as demonstrating good flowability if the value ranged between 31-35°. The flow rate of the powder mixture was determined as the ratio of mass (g) to time (s).

2.7.2 Organoleptic Evaluation

The tablet was observed according to its shape, color, and odor.

2.7.3 Disintegration Time

The disintegration test was performed using a disintegration tester, with the tablets immersed in distilled water at a temperature of 37 ± 2°C. The disintegration time, defined as the moment when all tablets had completely disintegrated, was recorded. A desirable fast disintegrating tablet (FDT) typically exhibits a disintegration time of less than 3 minutes (Türkmen et al., 2018).

2.7.4 Wetting Time Determination

The tablet was placed on a double-folded tissue in a petri dish containing 10 mL of distilled water. The time when water reached the top of the tablet was recorded as the wetting time (Dasari and Maruvajala, 2020). The result was considered optimal if the tablet exhibited the shortest wetting time.

2.7.5 Friability Test

Tablets weighing up to 6.5 g were tested using a friability tester, with the apparatus set at 25 rpm for four minutes. Following the test, all tablets were dusted and re-weighed, and the percentage of friability was calculated. A tablet meets specifications if the percentage of friability is less than 1% (Türkmen et al., 2018).

2.7.6 Hardness Evaluation

The hardness of 20 tablets was measured with a hardness tester. A tablet is considered to meet specification if it exhibits a hardness within the range of 3-5 kg/cm^2 (Yadav et al., 2022).

2.7.7 Dissolution Test

The dissolution of S-SNEDDS KGE-loaded FDT was assessed using USP dissolution testing apparatus type II at 50 rpm. The test was carried out in 900 mL 0.1 N HCl (pH 1.2) at 37 ± 0.5 °C. Three tablets were used for the test. The sample (5 mL) was withdrawn at specified time intervals of 0, 5, 15, 30, 45, and 60 minutes, with the replacement of the release medium after each withdrawal (Nair et al., 2022). Each 2 mL was dissolved in 10 mL methanol and then sonicated for 5 minutes. Each sample was filtered using a nylon syringe filter of 0.45 μm and analyzed for EPMC content using a validated HPLC method from previous research (Adianingsih et al., 2023).

2.8 Statistical Analysis

The data were expressed as mean ± standard deviation (SD). The data on edema volume was analyzed using one-way ANOVA with IBM SPSS version 25.0, followed by post-hoc Tukey HSD analysis. At a level of $p < 0.05$, differences were considered statistically significant.

3. RESULTS AND DISCUSSION

3.1 Extraction of *Kaempferia galanga* Rhizome

The maceration method was selected for the extraction of *Kaempferia galanga* due to its simplicity and applicability at room temperature, making it ideal for compounds that sensitive to heat (Nurhaslina et al., 2023). The extraction process of KG rhizome yielded 12.12% extract with 4.91% moisture content. Our previous research found that KGE contains 54.13% EPMC, which, with its polar carbonyl group and nonpolar benzene and methoxy groups, allows for extraction using both polar and nonpolar solvents (Adianingsih et al., 2023). The yield meets the Indonesian Herbal Pharmacopoeia (IHP) II requirements of at least 8.3%. The EPMC content in the sample also meets IHP II standards, with at least 4.3% EPMC in the KGE (Ministry of Health of the Republic of Indonesia, 2017). Various factors like plant location, harvest time, extraction method, and solvent selection may influence EPMC content within KGE (Indrayanto, 2022).

3.2 Evaluation of L-SNEDDS

The evaluation of L-SNEDDS incorporating *Kaempferia galanga* extract is summarized in Table 3, presenting data on various formulations FL1 through FL4. The organoleptic evaluation

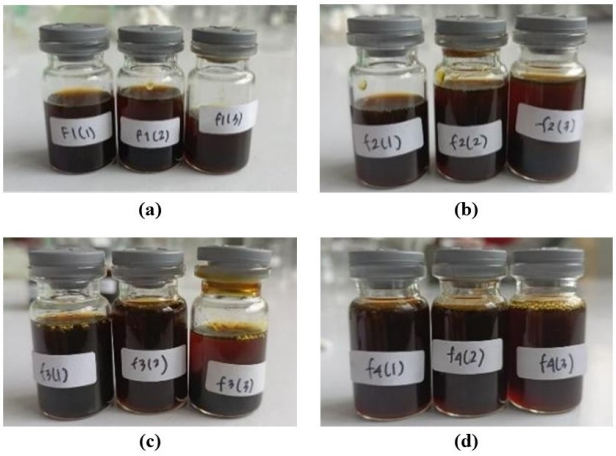

Figure 1. Visual Observation of L-SNEDDS Formulation Using Various Concentrations of Surfactant and Co-Surfactant. (a) FL1, (b) FL2, (c) FL3

of L-SNEDDS revealed that all formulations were dark brown and cloudy, as depicted in Figure 1. All L-SNEDDS formulations with surfactant-cosurfactant variations met the specified criteria for transmittance (80-100%), emulsification time (< 1 minute), and particle size (< 100 nm). Among all parameters examined, FL2 emerged as the optimal L-SNEDDS formulation with a surfactant-cosurfactant ratio of tween 80, cremophor RH 40, and PEG 400 at 1:1:2.

The results indicated that all formulated L-SNEDDS were capable of self-emulsifying to form nanoemulsions. This is demonstrated by the transmittance test results, which show a clear visual appearance and are characterized by a transmittance percentage above the acceptable threshold, ranging from 86.30% in FL1 to 87.17% in FL3. Transmittance values nearing 100% indicate that the dispersion method used in L-SNEDDS formulation can produce transparent nanoemulsions composed of nanometer-scale particles. High transmittance may also ensure good stability in L-SNEDDS, thereby preventing phase separation (Buya et al., 2020). Surfactants are capable of reducing oil content in L-SNEDDS, thus influencing interfacial film distortion, decreasing particle size, and increasing transmittance percentage (Ma'arif et al., 2023).

The optimal L-SNEDDS demonstrates a rapid emulsification time in the stomach, typically under one minute (Detholia et al., 2023). The emulsification time for all formulations fell below one minute, with FL2 showing the fastest emulsification at 28 seconds, which is beneficial for rapid onset of action *in vivo*. The emulsification time observed the ability of SNEDDS to form nanoemulsions with agitation in the digestive tract. Emulsification time describes the ability of surfactants and cosurfactants to produce an oil and water interface layer with low energy in the digestive tract (Buya et al., 2020). In emulsification test, L-SNEDDS was mixed slowly which helps disperse the oil droplets into aqueous phase. The emulsification time

Table 3. L-SNEDDS Evaluation

Parameter	FL1	FL2	FL3	FL4
Organoleptic	Dark brown, cloudy	Dark brown, cloudy	Dark brown, cloudy	Dark brown, cloudy
Transmittance (%)	86.30 ± 0.82	86.93 ± 1.16	87.17 ± 0.55	86.83 ± 0.74
Emulsification Time (s)	28.33 ± 2.08	28 ± 2.65	31.67 ± 2.08	37.33 ± 2.31
Particle Size (nm)	31.81 ± 2.00	27.79 ± 2.00	28.37 ± 0.34	26.91 ± 2.48
Polydispersity Index	0.23 ± 0.003	0.21 ± 0.014	0.22 ± 0.021	0.22 ± 0.037
Zeta Potential (mV)	-7	-12.57	-12.57	-10.93

Data are presented as mean ± SD; FL1: L-SNEDDS 1 formulation; FL2: L-SNEDDS 2 formulation; FL3: L-SNEDDS 3 formulation; FL4: L-SNEDDS 4 formulation.

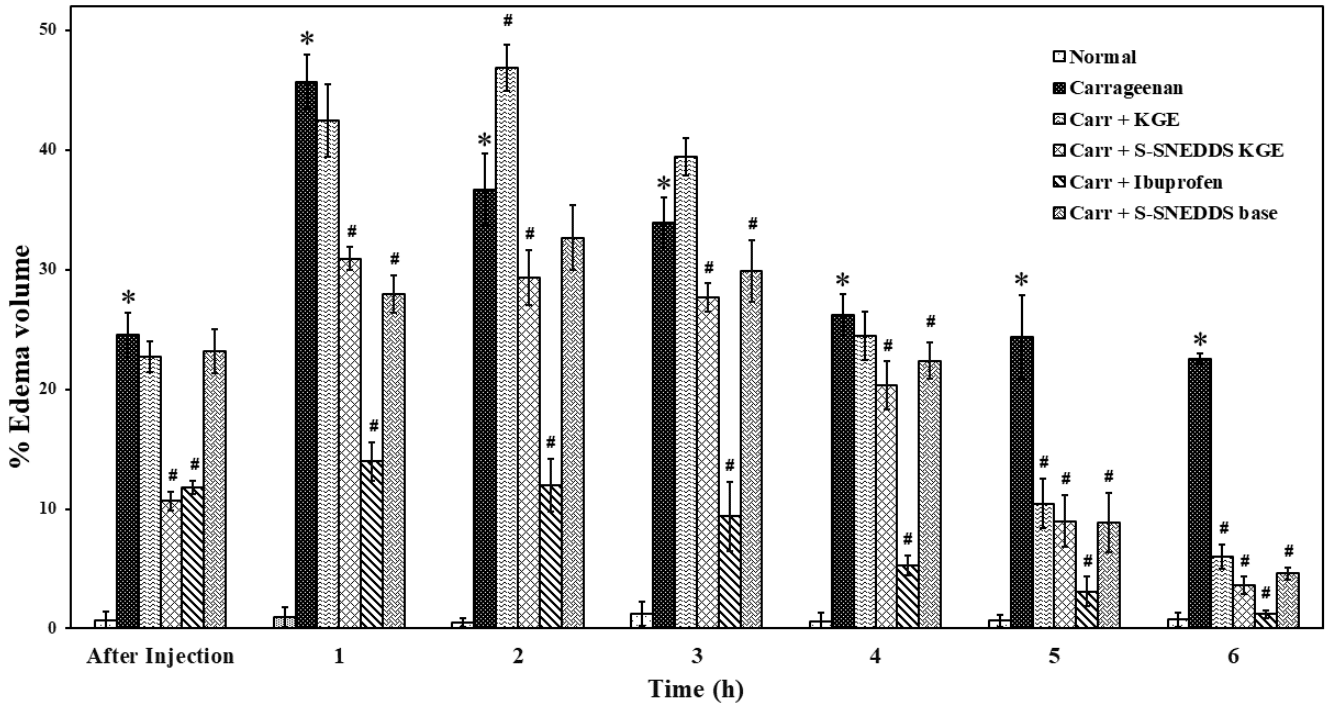

Figure 2. Anti-Inflammatory Activity *In Vivo* Test Result Presented in Percentage of Edema Volume. Data Are Shown as Mean ± SD. *$p < 0.05$ vs Carrageenan Group. #$p < 0.05$ vs Normal Group

influences the stability, homogeneity, and droplet size of the resulting nanoemulsion (Kumar et al., 2019).

The particle size for all L-SNEDDS were well within the nano-range, with FL4 yielding the smallest particles at 26.91 nm. This correlates with the increasing proportion of Tween 80 and Cremophor RH 40 and a corresponding decrease in PEG 400 concentration, facilitating a smaller particle size due to lower interfacial tension. The evaluation of L-SNEDDS indicates that formulations with higher concentrations of co-surfactant and lower concentrations of surfactant yielded poor results. High co-surfactant concentrations may affect the instability of the L-SNEDDS system due to its higher solubility in water, causing an increase in particle size (Kaur et al., 2013). Conversely, reduced surfactant concentrations may result in larger particle sizes due to lower interfacial tension, promoting particle aggregation (Eid et al., 2019). Additionally, the high surfactant concentration causes the interfacial tension of the particles to become greater, making it challenging for the L-SNEDDS particles to emulsify (Khan et al., 2015).

The polydispersity index (PDI) values, which indicate the uniformity of particle sizes, were low for all formulations, with FL2 exhibiting the most uniform distribution at 0.21. This suggests a stable formulation with minimal risk of particle aggregation. The ideal nanoemulsion droplet should have a size below 100 nm and a PDI value less than 1. The size of the nanoemulsion droplets formed from the L-SNEDDS prepa-

ration plays a crucial role in determining drug stability and bioavailability (Detholia et al., 2023). A reduction in particle size signifies a more stable and homogenous formulation, potentially enhancing drug dissolution and absorption within the gastrointestinal tract. Increasing the surfactant composition may decrease interfacial tension, producing a smaller droplet sizes (Baloch et al., 2019). This aligns with the findings of this study. As per Izham et al. (2019), the PDI test assesses the homogeneity of L-SNEDDS formulations, necessitating a monodispersed formulation. A low PDI value indicates good stability and a narrow size distribution within the formulation. Fortunately, the droplet size and polydispersity index values obtained from our research formulation all fall within the specification range (Izham et al., 2019).

Zeta potential values were all negative, with FL2 and FL3 showing the most stability potential at -12.57 mV due to the repulsive forces between similarly charged particles, which may help prevent aggregation. The zeta potential value indicates the electric charge on the surface of the globules. The same charge promotes the repulsive force between the globules, preventing flocculation. An ideal zeta potential value falls below -30 mV or above +30 mV, which suggests that the more negative or positive the globule surface charge, the more stable the dispersion system (Buya et al., 2020). However, the zeta potential values generated by each formulation in this study fail to meet these criteria. This discrepancy may stem from the utilization of nonionic surfactants in the research, which may not significantly influence the zeta potential of the L-SNEDDS. Nonetheless, nonionic surfactants possess a dense hydrophobic domain on their surface, allowing them to interact with hydrophobic functional groups in compounds, thereby stabilizing the L-SNEDDS system by forming a steric barrier between particles and preventing agglomeration (Gao et al., 2008). Ideal zeta potential cannot be reached if systems contain steric stabilizers, as their absorption leads to a reduction in zeta potential attributed to the displacement of the shear plane of the particles (Emerenciano et al., 2019).

In conclusion, the L-SNEDDS evaluation indicates that all formulations have desirable characteristics for a self-nanoemulsifying delivery system. FL2, an L-SNEDDS formulation with tween 80: cremophor RH 40: PEG 400 ratio of 1:1:2 as surfactant and co-surfactants, stands out with the best emulsification time, highly uniform particle size distribution, and strong zeta potential, making it a promising candidate for delivering KG extract for anti-inflammatory purposes. The findings support further investigation into the potential of FL2 L-SNEDDS for enhancing the bioavailability and therapeutic efficacy of KG extract. The optimal L-SNEDDS formulation, FL2, was then solidified using aerosil 200 in a ratio of 10:8. This solidification process was undertaken to enhance the stability of the formula, addressing issues such as rancidity, leakage, or compatibility concerns with the capsule shell, as well as chemical degradation and drug precipitation associated with the lipid components of L-SNEDDS, particularly during manufacturing or storage (Teaima et al., 2022). The adsorption-based solidification method offers several advantages, including a larger surface area for effective physical adsorption, high dissolution rates, and good uniformity (Ahmad and Hafeez, 2023). Aerosil 200 was chosen as an inert adsorbent for loading L-SNEDDS, which serves to enhance the dissolution profile and oral absorption of the formulation (Ahmad and Hafeez, 2023).

3.3 Anti-Inflammation Activity of S-SNEDDS

Figure 2 displays the anti-inflammatory effects of various treatments measured by the percentage of edema volume over time in a carrageenan-induced rat model. Immediately post-injection data served as a baseline to observe the initial inflammatory response. Without any intervention, the normal group demonstrated a consistent low level of inflammation across the timeline, serving as a control for typical edema response. The carrageenan group, which received only carrageenan, showed a significant increase in edema volume, peaking at the first hour and remaining elevated throughout the test period. This elevation represented the expected inflammatory response induced by carrageenan, characterized by an acute swelling phase.

The carrageenan-induced paw edema model is extensively used for its reliable portrayal of acute inflammation and for testing anti-inflammatory effects of various compounds. Carrageenan induces inflammation by activating the complement system and stimulating phospholipase A2, leading to mediator release and inflammation. This process is characterized by a biphasic inflammatory response, with an early phase driven by serotonin and histamine from the injection trauma, and a later phase dominated by prostaglandin activity (Patil et al., 2019). Treatment with *Kaempferia galanga* extract (KGE) alone mitigates the inflammation, with a notable decrease in edema volume compared to the carrageenan group. The anti-inflammatory action of KGE became more pronounced over time, suggesting a delayed but sustained response in reducing edema. The group treated with the S-SNEDDS KGE demonstrated a remarkable reduction in edema, outperforming the group treated with KGE alone. The enhanced anti-inflammatory effect of the S-SNEDDS formulation suggests that the nanoemulsion facilitates better delivery and absorption of the active compounds within KGE, thereby improving its efficacy. Rats administered S-SNEDDS KGE exhibited the highest edema volume in the 1st hour (30.92% ± 0.94), whereas those given KGE showed edema volume peaking in the 2nd hour (46.88% ± 1.94). It is suggested that S-SNEDDS KGE possesses superior anti-inflammatory activity compared to KGE.

The test findings demonstrate that the administration of KGE effectively reduces edema in rats. Edema reduction was notable three hours post-carrageenan injection and significantly pronounced compared to the positive control group after five hours. The anti-inflammatory activity of EPMC found in KG is attributed to its inhibition of cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) in arachidonic acid metabolism, leading to reduced prostaglandin synthesis, which is an inflammatory mediator that induces swelling and pain (Dwita et al., 2021). S-SNEDDS KGE demonstrated faster efficacy com-

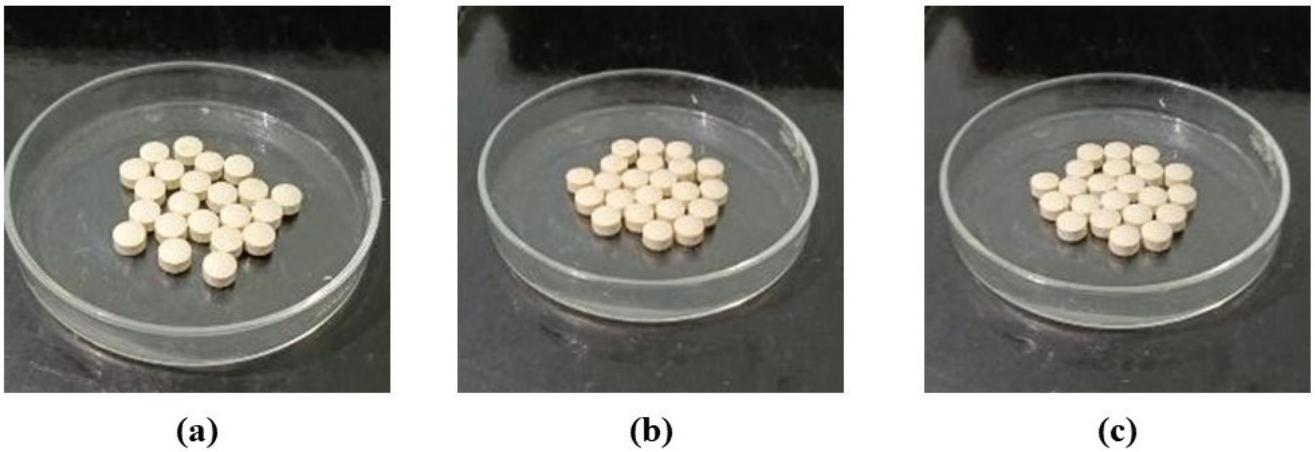

Figure 3. Organoleptic Formulation of FDT S-SNEDDS. The Tablet Was Developed Using Various Superdisintegrants, Including (a) Crospovidone (FT1), (b) Croscarmellose Sodium (FT3), and (c) a Combination of Both (FT2)

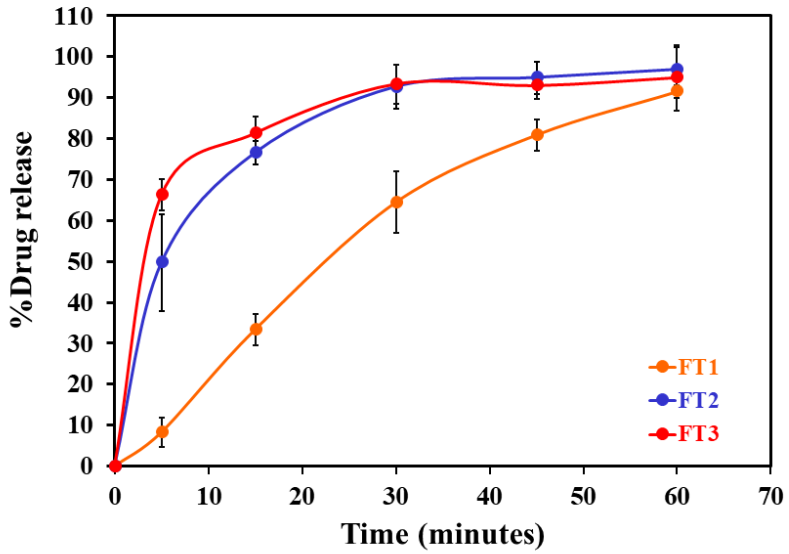

Figure 4. The Dissolution Profile of FDT S-SNEDDS Using Different Superdisintegrants. FT1: Crospovidone; FT2: Combination of Crospovidone and Croscarmellose Sodium; FT3: Croscarmellose Sodium

pared to KGE. Following carrageenan injection, S-SNEDDS mitigated the inflammatory response, which was indicated by a significantly lower percent edema value than the positive control group. S-SNEDDS exhibited edema reduction as early as the 2nd hour, whereas KGE significantly reduced edema by the 5th hour post-injection. This accelerated effect may be attributed to SNEDDS enhancing the solubility of lipophilic compounds and augmenting the bioavailability of active substances (Schmied et al., 2022). Ibuprofen, a standard anti-inflammatory treatment, significantly decreased edema, validating its effectiveness as a comparative control. The reduction in inflammation was swift and remained consistent, highlighting the established role of ibuprofen in acute inflammatory control. Ibuprofen is often used as a positive control in osteoarthritis animal models (Kim et al., 2020).

In summary, this *in vivo* study elucidates the potent anti-inflammatory potential of KGE, which is significantly amplified when delivered through an S-SNEDDS. The results validate the hypothesis that SNEDDS enhances the bioavailability and therapeutic effect of KGE. Future studies should explore the mechanistic pathways of this enhanced activity and consider long-term efficacy and safety profiles for potential clinical ap-

Table 4. FDT S-SNEDDS Evaluation

Parameter	FT1	FT2	FT3
Organoleptic	Cylindrical, Faded Yellow, Pungent Odor	Cylindrical, Faded Yellow, Pungent Odor	Cylindrical, Faded Yellow, Pungent Odor
Angle of Repose (o)	17.24	21.5	11.3
Flow Rate (g/s)	6.29	5.56	4.72
Disintegration Time (s)	57	63	111
Wetting Time (s)	46.12 ± 6.69	34.01 ± 7.87	43.84 ± 1.35
Friability (%)	0.1350%	0.1931%	0.2313%
Hardness (kg/cm^2)	3.55 ± 5.44	3.53 ± 6.16	3.72 ± 5.74

Data are reported as mean ± SD; FT1: FDT S-SNEDDS 1 formulation; FT2: FDT S-SNEDDS 2 formulation; FT3: FDT S-SNEDDS 3 formulation.

plication in managing inflammatory conditions. The study utilized a carrageenan-induced inflammation model in rats, which, although standard, may not fully replicate the complex pathophysiology of human osteoarthritis. Therefore, there is a need to conduct studies in an osteoarthritis-specific animal model to provide a more accurate representation of the formulation's therapeutic potential. Furthermore, the pharmacokinetic profile of the formulation is yet to be characterized, which is vital for understanding how the active ingredients are processed by the body.

3.4 Evaluation of FDT S-SNEDDS

The FDT evaluation results are presented in Table 4 across three different formulations: FT1 (crospovidone), FT2 (crospovidone and croscarmellose sodium), and FT3 (croscarmellose sodium). Organoleptic observations revealed no notable differences in shape, color, and odor attributes among the three FDT tablet formulations. All formulations shared a cylindrical, faded yellow appearance with a pungent odor, indicating uniformity in the tablet appearance and potentially the flavor masking of KG (Figure 3). Regarding physical properties, the powder angle of repose values for each formula consistently fell within the category of excellent flowability, which is critical for manufacturing consistency. Furthermore, the flow times displayed by each formulation aligned with the specified range. Angle of repose assessments involve measuring the angle formed between the surface of a powder mound and the horizontal plane. This parameter acts as a gauge for evaluating the flowability and compressibility of the powder components, ensuring that the powder flows well and produces a homogeneous mass tablet (Humane et al., 2018).

All three formulations met the disintegration time, wetting time, and tablet hardness specifications. The disintegration time of the entire formula is less than 3 minutes indicating it meets the disintegration time requirements for FDT, thus ensuring rapid disintegration after administration. The wetting time was also within a suitable range, indicating good tablet-water interaction, which is crucial for disintegration in the oral cavity. FT2 had the fastest wetting time compared to other formulations because it used a combination of crospovidone and croscarmellose sodium as superdisintegrants. The friability of all three formulations met the specification of being less than 1%, ensuring tablet integrity during handling, and the hardness was adequate, signifying a balance between disintegration efficiency and mechanical strength. Disintegration time, friability, and hardness tests ensured that the FDT exhibits strong resistance during the production process and storage, yet have sufficient friability to disintegrate and dissolve into small particles, thereby facilitating easy swallowing by the patient. The disintegration time was designed to reflect conditions in the human mouth (Kumar and Devi, 2022). Wetting time on FDT represents the contact angle related to the time required for water to penetrate the tablet and disintegrate it in the presence of a minimal volume of saliva. A lower wetting time indicates a faster disintegration time, which may affect the overall disintegration time of the tablet (Aher et al., 2018).

Upon comparison of the three formulations, FT1 exhibited faster disintegration time and lower friability, likely due to the presence of crospovidone, a superdisintegrant that accelerates tablet wetting and disintegration. In contrast, croscarmellose sodium, another superdisintegrant used in FT2 and FT3, can decrease hardness and increase both friability and water absorption (Desai et al., 2014). Crospovidone forms cavities facilitating water penetration and promoting rapid disintegration (Rani et al., 2017). However, disintegration time does not equate to the solubility or dissolution profile of the drug (Gupta et al., 2009).

The dissolution profiles of the FDT S-SNEDDS are shown in Figure 4. FT1, using crospovidone, achieved around 33% drug release within 15 minutes, increased to 64% drug release in 30 minutes, and nearly to 92% in 60 minutes. FT2, combining crospovidone and croscarmellose sodium, showed about 76% drug release within 15 minutes, nearly 92% by 30 minutes, and increased to 97% drug release in 60 minutes. Formulation FT3, using croscarmellose sodium, reached around 81% drug release at 15 minutes, an approximately 93% by 30 minutes, and maintained this rate up to 60 minutes. These results suggest that the combination of crospovidone and croscarmellose

sodium (FT2) provided the most efficient drug release profile, highlighting the synergistic effect of the disintegrants on FDT S-SNEDDS dissolution.

Given the crucial role of dissolution in assessing the absorption and efficacy of solid dosage forms, the selected medium should accurately represent the physiological environment. The dissolution medium used was 0.1N hydrochloric acid (pH 1.2). As per USP guidelines, 0.1N HCl solution is employed as a simulated gastric fluid, mimicking the conditions in the stomach (Shah et al., 2020). In the dissolution medium selection, physical and chemical data for the drug substance and drug product need to be considered. The most common dissolution medium is diluted HCl, however, other media commonly used includes buffers in the physiologic pH of 1.2 to 7.5, simulated gastric or intestinal fluid (with or without enzymes), water and surfactants (with or without acids or buffers) such as polysorbate 80, sodium lauryl sulfate and bile salts (Hasan et al., 2017).

Croscarmellose sodium has a smaller particle size than crospovidone, with particle size of 25-50 μm for croscarmellose sodium and 130-150 μm for crospovidone. Superdisintegrant with smaller particle sizes can be distributed more evenly in the tablet mixture. Consequently, croscarmellose sodium could disintegrate the tablet into smaller particles, increasing the contact surface with the dissolution medium and speeding up the time for tablet dissolution (Berkenkemper et al., 2020). However, this study showed that FT2 had a better dissolution profile compared to FT1 and FT3. This is because the performance of croscarmellose sodium may be influenced by the pH of the media used. It had a better dissolution profile in media with pH 6.8 because the polymer can be ionized. Non-ionized polymers experience less swelling and smaller repulsive forces, leading to slower dissolution in acidic media (Berardi and Janssen, 2022). Therefore, the combination of crospovidone and croscarmellose sodium (FT2) was selected as the optimal formulation due to its ability to balance the characteristics of each superdisintegrant, resulting in a favorable dissolution profile, wetting time, and disintegration time.

This study demonstrates the promising anti-inflammatory benefits of the FDT S-SNEDDS with *Kaempferia galanga* extract for osteoarthritis. Future studies should explore pharmacokinetics, pharmacodynamics, and large-scale manufacturing feasibility to solidify this approach for osteoarthritis treatment.

4. CONCLUSIONS

In conclusion, the study demonstrates a significant enhancement in the anti-inflammatory efficacy of *Kaempferia galanga* extract through the S-SNEDDS formulation. The optimal formulation of FDT S-SNEDDS was determined by comparing surfactant and co-surfactant concentrations alongside selecting an appropriate superdisintegrant. Specifically, the identified optimal formula comprised tween 80 (surfactant), cremophor RH 40 (surfactant), and PEG 400 (co-surfactant) in a ratio of 1:1:2, with the combination of 2.5% crospovidone and 2.5% croscarmellose sodium serving as the superdisintegrant. This result highlights the capacity of S-SNEDDS to enhance the therapeutic properties of *Kaempferia galanga* extract, presenting a promising pathway for advancing the development of enhanced anti-inflammatory pharmaceutical formulations.

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