



# PHYSICAL STABILITY TEST, PENETRATION EFFICIENCY AND ABSORPTION OF LEAF ETHOSOME EXTRACTS TEKELAN (*Chromolaena odorata* L.)

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## Abstract

Ethosomes are innovative lipid-based vesicular systems containing relatively high concentrations of phospholipids, ethanol, and relatively high air. The presence of phospholipids and ethanol can enhance the permeation and penetration of the drug more profoundly into the skin layers. This study aimed to test the physical stability, penetration and adsorption efficiency of autosome ethanol extract of tekelan leaves. Methods. The method used in this study was the physical stability test of ethosomal preparations with varying concentrations of F1 (autosome quote without extract), F2 (0.5 g autosome extract in 10 mL ethanol), F3 (2 g autosome extract in 20 mL ethanol) and F4 (1.5 g autosome extract in 30 mL ethanol). Test Physical stability test includes pH, viscosity, storage stability at room temperature, low temperature, high temperature and cycle test. High temperature and cycle test. In addition, the total flavonoid content in the extract was replaced, expressed as mgEQ/g ethosome and entrapment test and penetration efficiency were performed. The results obtained in this study showed that all formulas met the skin pH requirement (4.5-6.5) after 12 weeks of storage and were stable during 12 weeks of storage at room temperature. Stable during 12 weeks of storage at room temperature, low and high temperatures. F4 has the lowest pH after 12 weeks of storage ( $4.10 \pm 0.00$ ) with viscosity ( $3519.33 \pm 55.72$  cP). Per cent binding efficiency in F4 (68.44%) and total quercetin compound collection ( $11210.204 \pm 815.049$  mcg/cm<sup>2</sup>), per cent collection of quercetin compounds ( $38.824 \pm 0.446\%$ ) and flux of inhibition of quercetin compound ( $23.014 \pm 1.732$  mcg.cm<sup>-2</sup>.hour<sup>-1</sup>). This study concluded that the ethanol preparation (1.5 g extract in 30 mL) was physically stable during storage at various temperatures with the best entrapment and penetration efficiency.

**Keywords:** *Ethosome, Physical Stability, Flavonoids, Adsorption Efficiency, Penetration.*

## I. INTRODUCTION

Tekelan (*C. odorata* L.) is an Asteraceae/Compositae family plant. Secondary metabolites contained in this plant that have antioxidant properties are flavonoids (Hamid et al., (2010). Researcher Vijayaraghavan et al. (2017) stated that the content of phytochemical compounds in *C. odorata* L., including flavonoids including quercetin, synceretin, sakuranetin, padmatin, kaempferol, salvagenin and phenolic acids. Nurwahidah (2021) stated that based on the results of isolation on the leaves of *C. odorata* L., quercetin is the most distributed compound that is most widely distributed in plants (60-75%).

The penetration pathway of quercetin compounds across the stratum corneum is through the transcellular pathway, where this pathway passes through proteins in cells and passes through lipid-rich areas (Casagrande et al., (2007). passes through proteins in cells and areas rich in lipids (Casagrande et al., (2007)). Quercetin compound has low bioavailability due to limited absorption and rapid elimination. Quercetin is categorized in class 2 based on the Biopharmaceutical Classification System (BCS) because it has a low water solubility and high permeability (Syofyan et al., (2018)).

To overcome the problems found in quercetin compounds, when applied topically, an ethosomal preparation was formulated. ethosome preparation that focuses on the penetration process through the skin so that the quercetin compound can achieve its therapeutic effect. The ethosome formulation is more effective because topical administration increases the drug's permeation through the skin. Topical administration does not contain toxic compounds in the formulation, the ethosome composition is safe, and the components are approved for pharmaceutical and cosmetic use; delivery of inhibitory molecules (such as protein peptide molecules) is possible, is a simple method for drug delivery compared to iontophoresis and other combined methods, ethosomal systems are passive-non-invasive and easy to market, improve patient adherence to the patient adherence to ethosomes when administered in semi-solid form (gel or cream), is a drug delivery system that can be widely applied to the field of drug delivery. Drug delivery systems can be widely applied to the pharmaceutical medical cosmetic fields (Jaiswal et al., (2016)).

## II. RESEARCH METHODS

### 2.1 Preparation of Ethanol Extract of Tekelan Leaf (*C. odorata* L.)

2000 g tekelan leaf powder was extracted using 96% ethanol solvent (to filter out most of the secondary metabolites contained in the powder) as much as 20,000 mL. Most of the secondary metabolites contained in the simplisia powder) are as much as 20,000 mL. Soaked for the first 6 hours while occasionally stirring, then allowed to stand for 18 hours. They were separating maceration with filtering. The process was repeated twice with the same type of solvent, and the solvent volume was half the amount in the first extract. Volume of solvent in the first extract. Collected all the macerates, then evaporated with rotavapor until a thick extract was obtained and calculated the yield obtained, namely the percentage of weight (b/b) between the yield and the weight of the simplisia powder used, with the weight of the simplisia powder used by weighing (Indonesian Herbal Pharmacopoeia Edition II (2017).

## 2.2 Formulation of Ethosomes

Ethosomal Base	
R/ Lecitin soya 1 g	Ethanol 10 mL
Propyleneglicol 1 mL	
Distilled water ad 100 ml	(Zamzam et al., (2019))

Variations in the composition of the ethosom formula

Composition	Formula I	Formula II	Formula III	Formula IV
Extract	-	0.5g	1g	1.5g
Lecitin soya	3g	3g	3g	3g
Ethanol	10 mL	10 mL	20 mL	30 mL
Propyleneglicol	1 mL	1 mL	1 mL	1 mL
Distilled ad	100 mL	100 mL	100 mL	100 mL

### Preparation of Tekelan Leaf Extract Ethosomes

Ethosomes were prepared using the hot method. Lecithin was dispersed in water by heating at 40°C until a colloidal solution was formed (mixture 1). Ethanol and propyleneglycol were heated to 40°C, and tekelan extract was dissolved (mixture 2). Mixtures 1 and 2 were stirred at 40°C using a magnetic stirrer at 700 rpm for 30 minutes. The suspension was cooled at room temperature and stored in a refrigerator.

## 2.2 Ethosome Preparation Characteristics

### 2.2.1 Organoleptic Observation

Organoleptical observations included the colour and odour of the ethosomes. Observations were made visually (Hapsari et al., (2012)).

### 2.2.2 Particle Size and Zeta Potential Observations

A particle size analyzer carried out particle size and zeta potential measurements. Analyzer, the sample was inserted into the cuvette after 100x dilution. stability of ethosomal preparations was evaluated organoleptically in the form of colour changes and the formation of particulates dispersed into the carrier liquid. In the carrier liquid.

### 2.2.3 TEM (*Transmission Electron Microscopy*)

TEM was conducted at the Chemistry Laboratory of Gadjah Mada University. TEM was performed to analyze the morphology of the inside of the ethosome particles. Ethosome samples of tekelan leaf extract were diluted with a dilution of 20x and 50x. The sample was dripped on a Formvar-coated cumprum grid as much as one drop and dried at room temperature. one drop and dried at room temperature. After drying, it was analyzed by TEM. The sample was put into a container and analyzed at 25°C (Nugroho et al., 2019).

### 2.3 Measurement of pH

The pH test was conducted to determine the pH value of the ethosomal preparation. The pH value was measured using a pH meter at a temperature of  $25^{\circ}\text{C}\pm 2$ . The method of measuring pH is that the pH meter electrode is washed with distilled water and then dried with a tissue. Then, the pH meter is standardized with a pH 6.0 buffering solution. Then, the electrode is rinsed again with distilled water and dried. The number shown by the pH meter (constant number) is recorded in the pH observation table and replicated three times (Listiyana, 2015).

### 2.4 Room Temperature Storage Stability ( $25\pm 0.5^{\circ}\text{C}$ )

The preparation was stored at room temperature ( $25\pm 0.5^{\circ}\text{C}$ ) for 12 weeks, then subjected to observations were made for 12 weeks. Observations were made in the form of organoleptic observations (colour change, odour, phase separation and clarity). In addition, particle measurement of each formulation (Wilhelmina, 2011).

### 2.5 Data Analysis

PSA (Particle Size Analyzer) observed size determination and zeta potential. 295.90 Stability test to see the stability of the ethosome formula in stora e. The data obtained were then analyzed descriptively and presented as tables and figures.

## III. RESULTS AND DISCUSSIONS

### 3.1 Tekelan Leaf Extract Result

The yield of ethanol extract of tekelan leaves obtained from the maceration process can be seen in **Table 1** below.

**Table 1** Percentage of Tekelan Leaf Extract Yields

Powered weight (g)	Weight of The Extract (g)	Yields (%)
2000	295.90	14.795

The fine tekelan leaf powder was extracted using the maceration method. This method is suitable for withdrawing chemical compounds soluble in liquid and active substances not resistant to high temperatures. The maceration bottle is dark to maximize the maceration process and protect the active compounds in tekelan leaf powder. The solvent used is 96% ethanol to extract the active substances contained in tekelan leaves.

### 3.2 Chemical Compound Identification Results of Tekelan Leaf

Identifying chemical compounds in tekelan leaves aims to prove the presence or absence of compounds such as alkaloids, flavonoids, tannins, steroids and saponins. The identification results can be seen in Table 2 below.

**Table 2 Chemical Compound Identification Results of Tekelan Leaf**

<b>Chemical Compound Identification Results</b>			
<b>Compound</b>	<b>Powder</b>	<b>Extract</b>	
Alkaloids	+		+
Flavonoids	+		+
Tannin	+		+
Saponin	+		+
Steroid/Triterpenoide	+		+
Glikocides	+	+	

The identification results obtained in the ethanol extract of tekelan leaves contained alkaloid, flavonoid, tannin, saponin, glycoside and steroid/triterpenoid compounds. These results are to the research of Andika et al. (2020), which states that ethanol extract of tekelan leaves has secondary metabolites such as alkaloids, saponins, flavonoids, phenols and tannins.

### 3.3 Ethosome Characterization Results

Ethosome characteristics of ethanol extract of tekelan leaves (*C. odorata* L.) observed in this formulation are organoleptic (odour, colour, consistency), pH, particle morphology, and particle size. These are organoleptical (odour, colour, consistency), pH, particle size morphology, and particle size.

#### 3.3.1 Organoleptical Observation

In this study, liposome formulations were made with four types of formulations. F1 (no extract and ethanol 10 mL), F2 (0.5 g extract and 10 mL ethanol), F3 (1 g extract and 20 mL ethanol) and F4 (1.5 g extract and 30 mL ethanol). The four formulations were observed for particle size, vesicle morphology, zeta potential and TEM (*Transmission Electron Microscopy*).

The resulting ethosomes are yellow-brown suspension and odourless. Ethosomes ethanol extract of tekelan leaves (*C. odorata* L.) can be seen in Figure 1.



**Figure 1** Etosomes of Tekelan (*C. odorata* L.) Leaf Ethanol Extract and Etosomes Without Extract

The formula consists of the active ingredients of tekelan leaves and cholesterol as a stabilizer and reduces ethosome leakage; lecithin functions as an emollient and emulsifying agent. Ethanol functions as an enhancer that can increase the ability of drugs to penetrate, make vesicles elastic and stretch the structure of the skin layer and antimicrobial (Romero and Morilla, 201). Distilled water is a solvent, and propylene glycol is a penetration enhancer or wetting agent (Jain, 2001).

#### 3.3.2 Particle and Zeta Potential Measurement Results

Particle measurement results of ethosomes of ethanol extract of tekelan leaves using PSA (Particle Size Analysis). Measurement was performed on four formulations, namely F1 (without extract), F2 (extract with 10 mL ethanol), F3 (extract with 20 mL ethanol) and F4 (extract with 30 mL ethanol). Each formula has a composition of ethanol extract of tekelan leaves, soy lecithin, propylene glycol, ethanol and water.

The results of particle size measurements can be seen in Table 3.

**Table 3 Results of Particle Size and Zeta Potential of Ethosomes**

Formula	Particle Size (nm±SD)	Potential Zeta (mV±SD)
I	273.87±13.78	+27.0±1,0
II	256.93±22.30	+28.0±1,0
III	240.57±29.52	+32.67±0,58
IV	161.2±32.0	+34.33±0,58

Description:

Formula I = without extract with total ethanol 10 mL Formula II = 0.5 g extract with the amount of ethanol 10 mL Formula III = 1 g extract with total ethanol 20 mL

Formula IV = 1.5 g extract with total ethanol of 30 mL

The smallest particle size was found in formula IV ( $161.2 \pm 32.0$  n ). While the largest particle size was found in formula I ( $273.87 \pm 13.78$  n ). Particle size measurement determines the size of the vesicles formed and their penetration ability into the SKN. Vesicles form and determine their penetration ability into the SKN. The vesicle size or diameter of the ethosomal vesicles will meet the requirements of being nanovesicles. Meet the requirements to be nano vesicles if they are in the range of 10-1000 m. The size of the vesicles produced depends on the variation of the constituent components, the method of preparation, the technique of using tools such as sonicators, and the size of the vesicles. (Ramadon and Mun'im, 2016).

Formula IV has more ethanol (30 mL) than the other formulas. This affects the size of the particles produced. The more ethanol contained in a formula, the smaller the vesicle size. Vice versa (Akib, et al., (2014)).

Based on the statistical data of the one-way ANOVA method, the significance value of particle size is 0.003 ( $p < 0.0$  ). This shows a significant difference in each formula based on particle size. Moreover, when with the Tukey HSD test, two groups were obtained. The first group obtained a significance value 1.000 ( $p > 0.0$  ). This shows that Formula IV is single in terms of particle size. At the same time, the second group obtained a significance value of 0.427 ( $p > 0.00$  ). This indicates no significant difference in particle size between formulas I, II, and III.

Zeta potential is a parameter that shows the level of stability of ethosomes during storage. Vesicles are qualified if the zeta potential value exceeds +25 mV or -25 V. The more. The more positive or negative the charge of a vesicle, the less likely it is to aggregate (Fitrya et al., (2021) ). The zeta potential value obtained in this study lies between  $\pm 27.0 \pm 1.0$  mV to  $\pm 34.33 \pm 0.58$  mV.

Based on the statistical data of one-way ANOVA method, the significance value of zeta potential is 0.000 ( $p < 0.00$  ). This shows a significant difference between each formula regarding zeta potential. When continued with the Tukey HSD test, two groups were obtained. Namely, the first group obtained a significance value of 0.480 ( $p > 0.0$  ). The formula I and II are similar in determining zeta potential. The second group obtained a significance value 0.134 ( $p > 0.0$  ). This shows that formulas III and IV are similar regarding potential zeta determination.

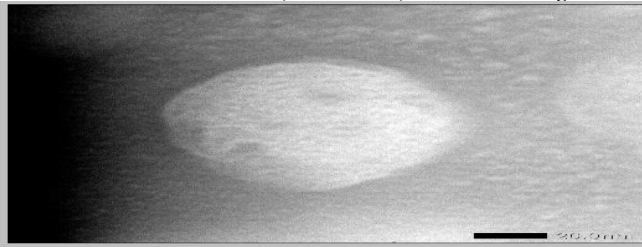
A good zeta potential value indicates that the strength of the particles to repel each other is stronger, resulting in a stable dispersion preparation. Meanwhile, a poor zeta potential value indicates that the strength of the particles to repel each other is getting weaker so that the particles experience a tendency to aggregate and cause the dispersion of the preparation to be less stable (Prasatiowati et al., (2018)).

### 3.4 Morphology Observation of Ethosomes

The morphology of the ethosomes of ethanol extract of tekelan (*C. odorata* L.) leaves was observed by Transmission Electron Microscopy (T.E.). TEM instrument was chosen because this instrument is best used to show the morphology of nanometer-scale liquid preparations (Fatmawaty et al., 201 ). The working principle of TEM is that electrons are fired and fired through the object of the specimen by focusing the electrons by the condenser lens. Then the electrons will Then the electrons will hit

the fluorescent screen, where the screen will emit light if subjected to electrons (Julianto et al., (2017)).

TEM morphology testing only took one formula, considered the best formula for particle size and distribution. The size is found in formulation-4 with the amount of extract 1.5 g and the most ethanol (30 mL). The TEM results observed were TEM before and after purification. TEM observation results of ethosomes of ethanol extract of tekelan leaves (*C. odorata* L.) can be seen in **Figure 2** below.



**Figure 2** TEM results of ethosomes of ethanol extract of tekelan leaves (*C. odorata* L.) formulation-4.

**Figure 2** shows the observation of a closed spherical shape. The results of this observation are in accordance with the observations of Limsuwang (2012), namely, the morphology of ethosomes is a closed spherical shape.

### 3.5 Results of pH Measurement of Ethosomes

pH measurement is carried out to determine the pH of the preparation. pH can affect the availability of drugs in molecular form. Drugs in molecular form can penetrate easily. The results of the ethosome pH measurement were seen for 12 weeks. These results can be seen in Table 4.

**Table 4** Results of pH Measurement of Ethosomes of Ethanol Extract of Tekelan Leaf for 12 Weeks

Formula	pH awal	2nd Week	4th Week	6th Week	8th Week	10ndWeek	12ndWeek
I	6.33 ± 0.06	6.30 ± 0.00	6.30 ± 0.00	6.23 ± 0.06	6.23 ± 0.06	6.20 ± 0.10	6.20 ± 0.17
II	5.21 ± 0.15	5.20 ± 0.00	5.17 ± 0.06	5.13 ± 0.06	5.03 ± 0.01	5.03 ± 0.01	5.03 ± 0.01
III	4.43 ± 0.12	4.43 ± 0.06	4.43 ± 0.06	4.43 ± 0.12	4.27 ± 0.06	4.27 ± 0.06	4.27 ± 0.06
IV	4.23 ± 0.12	4.23 ± 0.12	4.23 ± 0.06	4.13 ± 0.06	4.10 ± 0.10	4.10 ± 0.00	4.10 ± 0.00

Description:

I = No extract with 10 mL ethanol

II = 0.5 g tekelan leaf ethanol extract and 10 mL ethanol

III = Ethanol extract of tekelan leaves 1 g and ethanol 20 mL  
IV = 1.5 g tekelan leaf ethanol extract and 30 mL ethanol

Normal skin pH is at 4.5-6.5. This study is in accordance with the preparation specifications set at 4.5-6.5, where the skin can adapt to preparations at pH 4.5-6.5 (Ali et al., (2013)). From all formulas, it can be seen that the pH after

adding the extract decreases. This is because the pH of the extract is acidic (4.1). After storage for 12 weeks, the pH of all preparations decreased slightly but still met the pH requirements of the skin.

### 3.6 Observation of Particle Size in Room Temperature (25±0.5°C)

The results of measuring ethosome particles of ethanol extract of tekelan leaves using PSA (Particle Size Analyze). Measurements were made on four formulas, namely F1 (no extract with 10 mL ethanol), F2 (0.5 g tekelan leaf ethanol extract with 10 mL ethanol), F3 (1 g tekelan leaf ethanol extract with 20 mL ethanol) and F4 (1.5 g tekelan leaf ethanol extract with 30 mL ethanol). Each formulation has a composition of tekelan leaf ethanol extract, cholesterol, lecithin soy, propylenglycol and ethanol. The results of particle size readings can be seen in **Table 5**.

**Table 5** Particle Size Observation Results at Room Temperature Storage (25±0.2°C)

Formula	Before Storage		After Storage	
	Particle Size (nm±SD)	Potential Zeta (mV±SD)	Particle Size (nm±SD)	Potential Zeta (mV±SD)
I	273.87±13.78	+37.0±1.00	273.03±0.21	+36.67±0.57
II	256.93±22.30	+38.0±1.00	256.33±0.90	+37.67±0.58
III	240.57±29.52	+32.67±0.58	240.30±29.52	+32.33±0.58
IV	161.2±32.0	+34.33±0.58	161.13±0.70	+33.67±1.53

Description:

I = No extract with 10 mL ethanol

II = 0.5 g tekelan leaf ethanol extract and 10 mL ethanol

III = Ethanol extract of tekelan leaves 1 g and ethanol 20 mL  
 IV = 1.5 g tekelan leaf ethanol extract and 30 mL ethanol

**Table 5** shows that in formula I of the ethosome base, the particle size is smaller than 400nm and will more easily penetrate through the skin layer (Barry et al., (2007)). There was no change in particle size in storage at room temperature. It can be concluded that the ethosome preparation is stable at room temperature storage.

Limsuwang (2012) states that the size of ethosomes ranges from tens of nanometers to micro size, which is influenced by the composition of the formula. After obtaining the nano size of formula I, followed by particle measurement with the addition of 0.5 g extract (ethanol 10 mL), 1g (ethanol 20 mL) and 1.5 g (ethanol 30 mL). The smallest particle size found in formula IV is 161.13 ± 0.70 nm and has the largest zeta potential of +33.67 ± 1.3. Ethosomes with the smallest particle size had the largest amount of ethanol, 30 mL. This is because ethanol lowers surface tension and provides a level of steric stabilization. Ethanol reduces the density of the stratum corneum in the skin, making the vesicles softer so that permeation more easily reaches the circulatory system (Pirvu et al., (2010)). Increasing ethanol concentration in the ethosome formula causes a reduction in vesicle size, which allows the drug to be absorbed at a higher rate. The vesicles are more tenuous, and the solubility of the active substance is higher so that the active ingredient will be more easily absorbed in the lipid bilayer and core ethosomes (Maurya et al., (2011)).

Ethanol concentration is inversely proportional to vesicle size. High ethanol concentration causes the vesicle size to be smaller. The higher the ethanol concentration, the thinner the vesicle membrane. Ethanol in high concentrations can stretch the structure of the vesicles. It can change the characteristics of the vesicle surface due to modification of the surface charge of each vesicle that does not combine, which causes the vesicle size to be smaller (Rasheed et al., (2007)).



The zeta potential is a technique for determining the surface charge capable of attracting a thin layer of ions with opposite charges to the surface of the nanoparticles. The magnitude of a particle's zeta potential can be used to predict its stability. A nanoparticle zeta potential value more significant than +30 mV or smaller than -30 mV indicates a degree of stability. Particles in suspension with a zeta potential value greater than  $\pm 30$  mV will repel each other, so there is no tendency to flocculate (Ratnasari and Anwar, 2011). There was a decrease in zeta potential in all formulas, but the decrease in zeta did not experience a significant decrease and was still in the range of  $\pm 30$  mV. Significant and still in the range of  $\pm 30$  mV.

Statistically, the One-way ANOVA method obtained a significance value in testing particle size  $p < 0.05$  (0.003) and in testing zeta potential  $p < 0.05$  (0.000). This shows that in testing particle size and zeta potential.

#### IV. CONCLUSIONS

Tekelan plant has a low solubility when made into a specific preparation. For this reason, ethosome formulation was carried out to stabilize the solubility of the formula. Based on the formula obtained, formula-4 has the best particle size, zeta potential, pH and stability. Formula-4 contains 1.5 g tekelan leaf extract in 30 mL ethanol.

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