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Original Article

Formulation and Characterization of *Eleutherine palmifolia* Extraction in Carriers of Microspheres with Variations in Chitosan Polymer Concentration

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E. palmifolia
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ABSTRACT

This study aims to determine the effect of variations in chitosan concentration as a polymer on the physical characteristics, mucoadhesive properties, and dissolution profiles of mucoadhesive tablets in carrier microspheres. Mucoadhesive tablets are made using the direct felt method. In making mucoadhesive tablets, three different concentrations of *E. palmifolia* extract compared to chitosan are used, including F1 (1:1), F2 (1:2), and F3 (1:3). *Eleutherine palmifolia* (L.) Merr is used as the active ingredient and chitosan is used as a polymer. Evaluation of the physical characteristics of mucoadhesive tablets includes tests for uniformity of content, size, hardness, brittleness, and crushing time. In addition, mucoadhesive properties are also evaluated, including expandability tests, wash-off tests, and dissolution tests. The measurement of content uniformity showed no significant difference from the three formulas with no significant difference ($p > 0.606$). The uniformity test results of size, hardness, brittleness, crushing time, and the wash-off test showed a significant difference by the significant difference in each test sequentially of 0.012, 0.018, 0.028, 0.000, and 0.004. Dissolution tests were carried out with simulated gastric fluid (SGF) pH 1.2 and simulated intestinal fluid (SIF) pH 6.8 dissolution media using a type 2 dissolution tester (paddle), and dissolution level measurements were carried out with UV-Vis spectrophotometer at a maximum wavelength of 340.5 nm. The dissolution values of the three mucoadhesive tablet formulas in simulated gastric fluid (SGF) pH 1.2 media and the median simulated intestinal fluid (SIF) pH 6.8 showed significant differences ($p < 0.000$).

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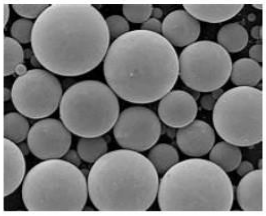
GRAPHICAL ABSTRACT

Eleutherine palmifolia

Drug delivery system with variations in chitosan polymer concentration

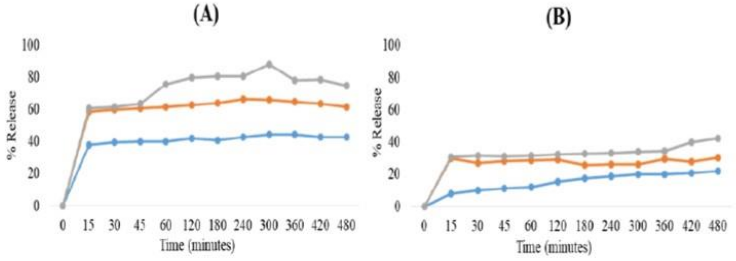


Microspheres

Mucoadhesive tablets are made using the direct felt method

This study aims to determine the effect of variations in chitosan concentration as a polymer on the physical characteristics, mucoadhesive properties, and dissolution profiles of mucoadhesive tablets in carrier microspheres

Evaluation Type	Results ± SD*			Requirements	Results
	F 1	F 2	F 3		
Content Uniformity (%)	97.92 ± 4.48	98.18 ± 3.64	99.77 ± 4.01	The level of the active substance is at least 85% and not more than 115% of the level written on the label.	Fulfill the Requirements
Size Uniformity				The diameter of the tablet is not more than three times the tablet's thickness and not less than 4/3 times the tablet's thickness	Fulfill the Requirements
Thickness (mm)	4.20 ± 0.07	4.30 ± 0.07	4.20 ± 0.08		
Diameter (mm)	12.05 ± 0.01	12.03 ± 0.01	12.04 ± 0.01		
Hardness (Kg)	6.17 ± 1.02	5.90 ± 0.88	5.70 ± 0.76	4-8	Fulfill the Requirements
Friability (%)	0.43 ± 0.05	0.52 ± 0.04	0.56 ± 0.07	< 1	Fulfill the Requirements
Disintegration Time (Minute)	1.54 ± 0.02	0.83 ± 0.33	0.52 ± 0.18	< 30	Fulfill the Requirements



Introduction

Eleutherine palmifolia (L.) Merr (*E. palmifolia*) is one type of plant that has also been proven to have anti-cancer effects. The results of previous studies stated that ethanol extract of *E. palmifolia* exerted cytotoxic effects against HT29 colonic carcinoma with LC_{50} of 3,125 mg/mL [1]. *E. palmifolia* ethyl acetate extract also inhibited the circulation of T47D breast cancer cells and cell apoptosis with IC_{50} of 147.124 µg/mL. In addition, ethanol extract in previous studies was also able to inhibit the growth of HeLa cervical cancer cells with IC50 of 40.36 µg/mL [2].

The ability of *E. palmifolia* plants as a cancer drug indicates that there is a cytotoxic potential of *E. palmifolia* extract against cancer cells due to the presence of secondary metabolite compounds of naphtoquinone derivative compounds such as eleutherinoside A, eleuthoside B, Isoeleutherine, eleutherin and eleutherol [3]. In addition, *E. palmifolia* is also known to contain isoliquirigenin compounds from the flavonoid group, and oxyresveratrol from the phenol group has anti-cancer activity against Hela 2 cervical cancer cells.

One form of *E. palmifolia* development is made in pharmaceutical preparations, namely mucoadhesive tablet preparations with a microspheres carrier system.

Mucoadhesive tablets can bind to mucosal surfaces and cause a longer drug residence time at the absorption site 4. Microspheres are drug delivery systems consisting of polymers and molecularly dispersed drug particles with a diameter of about 1-1000 micrometers [5]. This mucoadhesive tablet with a microsphere carrier can produce a long and constant therapeutic effect. The drug material more easily penetrates the target organ and has a gradual drug-release effect to reduce the frequency of use and improve patient compliance [6]. Polymers are the main component in the manufacture of mucoadhesive tablets with carriers of microspheres. In this study, Chitosan polymer was used. The reason for choosing a Chitosan polymer is because this polymer has good biocompatibility and biodegradability and is non-toxic [7]. Chitosan also has mucoadhesive properties in the gastrointestinal tract to extend the drug's release time [8]. Chitosan concentration significantly influences the value of entrapment efficiency and the mucoadhesive properties of the resulting tablets.

The most optimal concentration of Chitosan polymer in mucoadhesive tablet preparations with carriers of microspheres is a 1:1 ratio of active ingredients and chitosan. This concentration can produce an entrapment efficiency value of 76.74%. However, mucoadhesive properties are best demonstrated by a formula with a ratio of active ingredients and chitosan 1:3 with a mucoadhesive percentage value of 85% [9].

In another study, the optimal concentration of Chitosan polymer was the ratio of active ingredients and Chitosan 1:2 with an entrapment efficiency value of 95% [10]. In addition, other studies show that the ratio of active ingredients and chitosan 1:3 is the optimal ratio, resulting in an entrapment efficiency value of 81.19% [11].

Based on the description above, this study was carried out to make mucoadhesive tablets of *E. palmifolia* extract in a microspheres carrier system with variations in the concentration of active ingredients and polymers, namely F1 (1: 1), F2 (1: 2), and F3 (1: 3), and then evaluated the physical characteristics, mucoadhesive properties, and dissolution tests of each formula to determine the effect of variations in chitosan concentration as a polymer on physical characteristics, mucoadhesive properties and tablet dissolution rate.

Materials and Methods

The ingredients used in this study were *E. palmifolia* extract. The E. palmifolia samples were purchased from vendors in East Kalimantan and identified at the Materia Medica in Batu, East Java, Indonesia, with the accession number 074/342A/102.7/2018. The specimens were then stored in the pharmacognosy Laboratory of the Pharmacy Department, Maulana Malik Ibrahim, State Islamic University of Malang. The other materials used in this suty are as follow: Chitosan (PT. Himedia, Jakarta, Indonesia), acetone (PT. Smart Lab, Bogor, Indonesia), paraffin liquid (PT. Bratachem, Surabaya, Indonesia), span 80 (PT. Bratachem, Surabaya, Indonesia), petroleum ether (PT. Smart Lab, Bogor, Indonesia), Avicel (PT. Bratachem, Surabaya, Indonesia), Mg Stearate (PT. Bratachem, Surabaya, Indonesia), Talk (PT. Bratachem, Surabaya, Indonesia), Aerosil (PT. Bratachem, Surabaya, Indonesia), Media dissolution simulated gastric fluid (SGF), pH 1.2 prepared from HCl P and NaCl pro analysis (Merck, Jakarta, Indonesia), simulated intestinal fluid (SIF), pH 6.8 prepared from KH_2PO_4 (potassium dihydroxide phosphate), NaOH (sodium hydroxide), and pro analysis (Merck, Jakarta, Indonesia).

Microspheres preparation

The delivery system of *E. palmifolia* extract microspheres is made in three formulas with variations in the concentration of Chitosan polymer in each formula. The total number of microspheres made in one formula is 117.669 grams, so the concentration of the active ingredient in each formula is 0.637%, and the concentration of Chitosan profit of each formula is 0.637%, 1.275%, and 1.912%, respectively.

Table 1: Formulation of microspheres extract of *E. palmifolia*-chitosan

Material	Formula Concentration (%)*		
	F1 (1:1)	F2 (1:2)	F3 (1:3)
E. palmifolia extract	0.637	0.637	0.637
Chitosan	0.637	1.275	1.912
Acetone	16.113	16.113	16.113
Liquid Paraffin	64.248	64.248	64.248
Span 80	0.772	0.772	0.772
Petroleum ether	17.591	16.954	16.317

**% (weight/weight)*

Microspheres are made using the solvent evaporation method. The finished microspheres are then calculated for entrapment efficiency and formulated into active ingredients in mucoadhesive tablets. The formula design of microsphere delivery systems is presented in Table 1.

Calculation of entrapment efficiency (EE) and equivalence of microspheres with active ingredients

The percent of EE value determines how much the drug can get trapped in the microsphere system. The percent EE value is also used to calculate microspheres equivalent to 0.05 g of active ingredient. The percent conversion of EE values is carried out using UV-Vis instruments at the maximum wavelengths. To calculate EE microspheres, samples were made with a concentration of 5000 ppm by weighing several microspheres equivalent to 0.05 g of E. palmifolia, and then put into a 10 mL measuring flask and added aquades to the limit mark. After that, the sample is inserted into a centrifuge tube and centrifuged at 2500 rpm for 45 minutes. In this centrifugation process, deposits of E. palmifolia extracts trapped in the microsphere system and supernatants containing E. palmifolia extracts that are not trapped in the microsphere system are produced. The supernatant obtained was then diluted up to 10 times, and the concentration of water-free drugs that were not trapped in the delivery system of microspheres was measured. The EE value is then calculated using $\%\,EE = \frac{Ct - Cf}{Ct} \times 100$. Where, Ct is the amount of used drugs, and Cf is the amount of medicinal material in the water phase. The calculation results of the EE and the equivalence of microspheres with 0.05 g of active ingredient are listed in Table 2.

Formulation of mucoadhesive tablets of E. palmifolia extract with carrier microspheres.

Microspheres of the three formulas above are made in tablet preparations to make felts directly. Formula tablets mucoadhesive are summarized in Table 3.

Table 2: Calculation of entrapment efficiency and equality value with 0.05 g of active ingredient

Formula	% EE ± SD*	The amount of microspheres equivalent to 0.05 g of active ingredient (g)*
Formula 1 (Comparations of Active Ingredients and Chitosan 1:1)	95.707 ± 0.06	0.076
Formula 2 (Comparations of Active Ingredients and Chitosan 1:2)	96.967 ± 0.05	0.129
Formula 3 (Comparations of Active Ingredients and Chitosan 1:3)	98.031 ± 0.07	0.184

**Average of 3 replications (*SD (Standard Deviation) value)*

Table 3: Formulation of mucoadhesive tablets microspheres *E. palmifolia* extract

Bahan	Formula Concentration (%)*		
	F1	F2	F3
Microspheres from Formula 1 (1:1)	0.076 g (10 %)	-	-
Microspheres from Formula 2 (1:2)	-	0.129 g (10 %)	-
Microspheres from Formula 3 (1:3)	-	-	0.184 g (10 %)
Aerocil	1 %	4 %	4%
Mg Stearate	1 %	1 %	1 %
Talcum	5 %	2 %	2 %
Avicel	ad 100 %	Ad 100 %	Ad 100 %

**% (weight/weight)*

Formulation of mucoadhesive tablets

The tablets had a mass of 500 mg. The method used was directly felt. This method was chosen because it does not damage the delivery system of microspheres created [12]. Avicel and Aerosil were sifted using a 40 mesh and mixed until homogeneous. The mixture was then added to mg stearate and glycan talc lubricants, and then stirred until homogeneous. These excipients were subpoenaed with microspheres that had been created. This mixture was then fed into a single-punch tablet printer, and then printed.

Evaluation of physical characteristics of tablets

Test content uniformity

The uniformity test of the content was carried out by selecting no less than 30 tablets. For coated or uncoated tablets, the content of 10 tablets was determined one by one by analysis method using a UV-Vis spectrophotometer at a wavelength of 340.5 nm [13].

Size uniformity test

The Size Uniformity Test was carried out by measuring the thickness and diameter of the tablet using the Erweka hardness tester type 185 [14].

Hardness test

Tablet hardness tests demonstrated the tablet's resistance to mechanical shock during production, packing, and distribution. A total of 10 tablets were randomly taken and measured hardness using the Erweka hardness tester type TBH 125 [14].

Tablet fragility test

Fragility tests were performed on 20 tablets that were randomly taken, weighed the initial weight of the tablets, and then tested with a tool friability tester for 4 minutes at a speed of 25 rpm, after which the final weight of the tablet was weighed, replication was carried out three times [14].

Disintegration test

A total of 6 tablets in each formula were placed in each tube with 900 mL media at a temperature of 37±0.5 °C. Simultaneously with the start of the test equipment, the stopwatch was turned on. It took time to shatter through mesh 10 when the tablet was destroyed [14].

Mucoadhesive physical test

Expandability test

This test is done by inserting each tablet into a centrifugation tube, weighing the tube containing the tablet (Wo), inserting pH 6.8 phosphate as much as 10 mL into this tube, inflating the tablet, and checking the power to expand every 15, 30, 60, 90, and 120 minutes by weighing the weight of the tablet after expanding [12].

Wash off test

Test Wash Off aims to determine the number of mucoadhesive microspheres that can stick to the skin mucosa for 2 hours. This test used the intestinal mucosa of mice. Average percent microspheres: Those still attached are calculated at 30-minute intervals for 2 hours [8].

Dissolution test

The dissolution test uses type 2 dissolution test equipment (paddle type). The test was conducted under two conditions: medium simulated gastric fluid (SGF) pH 1.2 and medium simulated intestinal fluid (SIF) pH 6.8. A dissolution medium of 900 mL is inserted into the dissolution flask, and the paddle stirrer is set at a speed of 50 rpm, with the distance of the paddle stirrer from the base being 2.5 cm. The experimental temperature was maintained in the temperature range of 37 ± 0.5 °C. Samples of 0.5 mL were taken at minutes 15, 30, 45, 60, 90, 120, 180, 240, 300, 360, 420, and 480 14.

The sample taken is replaced with a new dissolution medium in the same amount as the retrieval volume so that the volume of the dissolution medium is fixed. The sample was measured with a UV-Vis spectrophotometer at 340.5 nm.

Results and Discussion

Evaluation of physical characteristics of E.Palmifolia extract mucoadhesive tablets

Evaluation of physical characteristics of mucoadhesive tablets of E. palmifolia extract carried out includes tests for uniformity of content, size, hardness, brittleness, and disintegration. The results of each test can be seen in Table 4.

Content uniformity

The content uniformity test is carried out to determine the degree of uniformity of the active substance in the preparation made [14]. Based on the results obtained from the three formulas, it is known that none of the tablets contains more than 115% or less than 85% of the number of active ingredients used, so it can be concluded that the three formulas meet the requirements for uniformity of content according to the Indonesian Pharmacopoeia edition 3. The uniformity of the active ingredient content in the preparation affects the effect caused by a preparation. If a preparation has a uniform content, it can be ascertained that the effect caused by the preparation is also uniform.

Table 4: Evaluation results in physical characteristics of mucoadhesive tablets of *E.palmifolia* extract

Evaluation Type	Results ± SD*			Requirements	Results
	F 1	F 2	F 3		
Content Uniformity (%)	97.92 ± 4.48	98.18 ± 3.64	99.77 ± 4.01	The level of the active substance is at least 85% and not more than 115% of the level written on the label.	Fulfill the Requirements
Size Uniformity				The diameter of the tablet is not more than three times the tablet's thickness and not less than 4/3 times the tablet's thickness	Fulfill the Requirements
Thickness (mm)	4,20 ± 0.07	4,30 ± 0.07	4,20 ± 0.08		
Diameter (mm)	12.05 ± 0.01	12.03 ± 0.01	12.04 ± 0.01		
Hardness (Kg)	6.17 ± 1.02	5.90 ± 0.88	5.70 ± 0.76	4-8	Fulfill the Requirements
Friability (%)	0.43 ± 0.05	0.52 ± 0.04	0.56 ± 0.07	< 1	Fulfill the Requirements
Disintegration Time (Minute)	1.54 ± 0.02	0.83 ± 0.33	0.52 ± 0.18	< 30	Fulfill the Requirements

**Average of 3 replications (*SD (Standard Deviation) value)*

The data obtained were then analyzed statistically, and it was found that the difference in chitosan concentration in the formula did not significantly affect the uniformity of tablet content, indicated by no significant difference ($p > 0.606$).

Size uniformity

Based on the measurements that have been made, it was obtained that from the ten tablets measured, no tablet diameter is more than three times the thickness of the tablet and not less than 4/3 the thickness of the tablet, so it can be said that the three tablet formulas meet the requirements for uniformity of tablet size, namely the diameter of the tablet is not more than three times the thickness of the tablet and not less than 4/3 times the thickness of the tablet 13. The difference in chitosan concentration in each formula gives a significant difference in the thickness and diameter of the tablet, indicated by significance values of 0.01 and 0.001. Increased chitosan concentration causes the thickness and diameter of the tablet to continue to decrease.

Violence

According to the results of measurements made on ten tablets in each formula, it is known that all three formulas meet the requirements for tablet hardness, which is between 4-8 Kg. The increasing concentration of microspheres in the formula causes the hardness of the tablets to decrease. The decrease in the hardness of the tablet is caused because the active ingredients of the microspheres used have a small particle size (micronized), causing the material to tend to have a sizeable electrostatic force and can increase friction between particles and other materials. This will lead to a decrease in the compactness level of the tablet, which will also decrease its hardness level [15]. The difference in chitosan concentration in each formula gives a significant difference in the hardness of the tablets, indicated by a significant difference ($p < 0.018$).

Friability

The brittleness test aims to determine the resistance of tablets to shocks during the production, packing, and distribution process [14]. The average percent brittleness of mucoadhesive tablets in this study from formulas 1 to 3 was 0.43, 0.52, and 0.56%, respectively, so it can be concluded that the formula meets the requirements of the tablet fragility test that the brittleness of the tablet must be below 1%. The degree of brittleness of tablets is greatly influenced by the degree of hardness of tablets. The greater the hardness value of the tablet, the fragility level of the tablet will also decrease, and vice versa. The smaller the hardness value of the tablet, the more the brittleness level of the tablet will increase [16]. The difference in chitosan concentration in each formula gives a significant difference in the fragility of the tablet, which is indicated by a significant difference ($p < 0.028$).

Disintegration

Based on the research conducted, it was found that every six tablets of each formula had a crushing time of 1.54, 0.83, and 0.52 minutes, so it can be concluded that the three formulas have met the crushing time requirements set in the Indonesian Pharmacopoeia Edition III of 1979, which is ≤ 30 minutes. The results of the crushing time test of mucoadhesive tablets show that the addition of chitosan concentration as a polymer can affect the crushing time of the preparation, where the higher the concentration of chitosan added in the preparation, the faster the crushing time of the preparation.

Adding chitosan to the slow-release tablet formula can help the tablet absorb water to expand and disintegrate [17]. The difference in chitosan concentration in each formula gives a significant difference in the crushing time of the tablet, indicated by a significant difference ($p < 0.000$).

Physical characterization of mucoadhesive tablet E. palmifolia

Table 5: Results of fluffy power test of mucoadhesive tablets of extract *E. palmifolia*

Swelling Index Average (%) at ± Minutes SD*			
15	30	60	120
25.94 ± 2.6	28.14 ± 2.5	30.23 ± 2.3	32.00 ± 2.2
25.49 ± 3.6	26.88 ± 2.5	29.97 ± 4.5	33.96 ± 2.5
22.60 ± 4.5	28.94 ± 6.8	32.30 ± 5.1	35.71 ± 2.6

**Average of 3 replications (*SD (Standard Deviation) value)*

Table 6: Hasil Uji Wash Off tablet mucoadhesive *E. palmifolia*

Formula	Average of Microsphere attached at the minutes to (%) ± SD*				
	0	30	60	90	120
1	100 ± 0	84.52 ± 17.0	80.08 ± 14.8	69.83 ± 11.0	48.74 ± 10.5
2	100 ± 0	90.87 ± 11	87.20 ± 9.87	79.83 ± 13.6	69.09 ± 2.89
3	100 ± 0	94.72 ± 6.0	86.62 ± 7.56	81.66 ± 4.95	79.30 ± 4.83

**Average of 3 replications (*SD (Standard Deviation) value)*

Expandability test

The expanding power test was carried out using a phosphate dapar medium of pH 6.8. This is because tablets are intended as mucoadhesive preparations in the intestine.

The expanding power of the tablet is observed based on the change in weight at a specific time interval of 2 hours. The results of the expanding power test are provided in Table 5.

Based on the study's results, it is known that the increase in the concentration of microspheres is directly proportional to the increase in the expanding power of the tablet. This is because the microspheres used consist of chitosan polymers. Theoretically, in mucoadhesive tablets, the process of development or swelling occurs due to good contact between the polymer and the membrane through wetting. Wetting is the initial process in the adhesion stage on mucoadhesive tablets. During the wetting process, the polymer in the mucoadhesive tablet will absorb mucosal fluid. The absorption of this mucosal fluid will cause the tablet to expand or swell [8]. Chitosan polymer is a cationic polymer that can interact with mucosa through wetting or absorption of mucosal fluid. The process of liquid absorption by chitosan will open the pores of the tablet, causing the tablet to experience a process of expanding or swelling [18].

The higher the content of Chitosan polymer in a tablet, the power or ability to expand it will increase. Statistical tests show that the difference in chitosan concentration used in each formula does not provide a significant difference ($p < 0.188$).

Uji wash off

The wash-off test aims to determine the number of mucoadhesive microspheres that can stick to the skin mucosa for 2 hours. This test used the intestinal mucosa of mice. The average percent of microspheres still attached was calculated at 30-minute intervals for 2 hours. The percent of microspheres still attached is listed in Table 6.

Based on these results, it is known that an increase in chitosan concentration leads to an increase in the ability of microspheres to attach to the mucosa. The ability of microspheres to adhere is influenced by the concentration of chitosan polymers in the formula. Chitosan is a mucoadhesive polymer. Mucoadhesive means the ability to attach to mucosal tissue [12]. Chitosan can bind to mucous tissues through ionic interactions between primary amino groups in chitosan with sialic acid and sulfonic acid in the mucosa. In addition, hydroxyl groups and amino groups in chitosan can interact with mucosa through hydrogen bonds. With more chitosan polymer content in a material, the ability of microspheres to attach to mucosal tissue is increased [18].

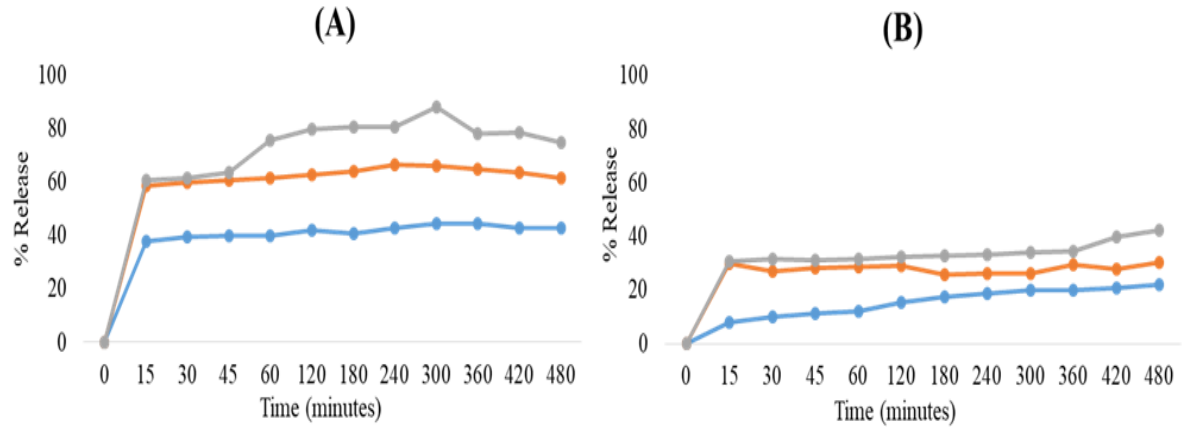


Figure 1: Dissolution profile of average release of 6 tested tablets from each mucoadhesive tablet formula: (a) in simulated gastric fluid (SGF) media ph 1.2 and (b) in simulated intestinal fluid (SIF) media ph 6.8. f1 (mucoadhesive tablets with a ratio of active ingredients and chitosan 1: 1), f2 (mucoadhesive tablets with a ratio of active ingredients and chitosan (1: 2), and f3 (mucoadhesive tablets with a ratio of active ingredients and chitosan 1: 3). The standard used to determine dissolution levels is 1,4-naphthoquinone

Table 7: Result of dissolution efficiency 480 (DE480) tablet mucoadhesive *E. palmifolia* extract

Formula	Average ± SD* DE480 (%)	
	Simulated gastric fluid (SGF) pH 1.2	Simulated Intestinal fluid (SGF) pH 6.8
1	39.98 ± 1.66	17.36 ± 0.44
2	60.20 ± 4.78	27.33 ± 0.58
3	75.19 ± 25.01	33.84 ± 1.87

**Average of 3 replications (*SD (Standard Deviation) value)*

Statistical analysis shows that the difference in chitosan concentration used in each formula provides a significant difference ($p < 0.004$).

Dissolution rate of mucoadhesive tablets of E. palmifolia extract

Test Dissolution uses the type 2 ERVeka Solution Tester tool with the paddle method. Tests were conducted at pH 1.2 and 6.8 with a temperature of 37 °C. Sampling was equalized for each test, and absorption was observed using a UV-Vis spectrophotometer at wavelength 340.5. Dissolution test results are demonstrated in Figure 1.

The dissolution graph shows the discharge profile immediately in the initial minutes and discharges at a lower rate in the following minutes. This can be seen in Figure 1, which shows that the release of the drug increases rapidly until the 15th minute, and then the release rises slowly until the 480th minute. Formula 2 and 3, which are microspheres-carrying systems, experienced a rapid increase in discharge at 15 minutes and then increased slowly until the end of testing 17. The three mucoadhesive tablet formulas gave different release test results. The lowest release was experienced by formula 1; the dissolution profile graph looks the same from minute 15 to minute 45, and at minute 60, there begins to be a difference in the release chart. In this case, formula 3 shows higher levels of released drugs than formula 2. The difference in dissolution profile is due to variations in the chitosan concentration as a polymer added to each formula. In this case, the higher the concentration of chitosan added, the higher the dissolution rate produced. Mucoadhesive tablets made in the form of microspheres delivery systems have a stable dissolution profile. That is, the dissolution rate continues to increase, but the increase is low with each minute of sample measurement. This is because the preparation uses a microsphere delivery system that can control the release of active ingredients from the dosage form [6]. The difference in chitosan concentration in each formula gives a significant

difference in dissolution time, indicated by a significant difference ($p < 0.000$).

In addition to the examination of the release rate profile, the dissolution efficiency (DE) percentage is also calculated to determine the level of active ingredients that can be dissolved during the test time. The results of the calculation of the percentage of DE for 480 are indicated in Table 7.

Based on Table 7, it can be seen that the difference in chitosan concentration in each formula causes differences in extract concentrations of *E. palmifolia*, which dissolved during the test time. The increase in chitosan concentration led to an increase in dissolution for 480 minutes in either SGF or SIF media. The amount of dissolution for 480 minutes in SIF media is higher than in SIF media because the polymer used, chitosan, has properties readily soluble in concentrated acid solvents such as HCl. The highest DE value is found in Formula 3. This is because Formula 3 has a carrier concentration in microspheres. Chitosan is the most common, so the wetting of the particles will be better and cause the drug to dissolve quickly.

Conclusion

Chitosan polymer concentration variations provide significant differences in the physical characteristics and properties of mucoadhesive in particular size uniformity, hardness, brittleness, wash-off disintegration, and dissolution profiles on mucoadhesive tablets of *E. palmifolia* extract in carrier microspheres. This is shown by statistical tests that produce p-values of 0.012, 0.018, 0.028, 0.004, and 0.000, respectively. An increase in Chitosan concentration leads to a decrease in the hardness of the tablet and an increase in brittleness, destruction time, the number of microspheres attached to the mucosa, and the dissolution time of the tablet.

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Disclosure Statement

No potential conflict of interest was reported by the authors.

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Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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