ASEAN Engineering Journal

Full Paper

OPTIMIZING ANTIOXIDANT POTENTIAL THROUGH MICROENCAPSULATION OF KAFFIR LIME LEAVES EXTRACT (*CITRUS HYSTRIX DC*) WITH MALTODEXTRIN AND GELATIN

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Article history
Received
17 January 2024
Received in revised form
26 March 2024
Accepted
27 March 2024
Published online
31 August 2024

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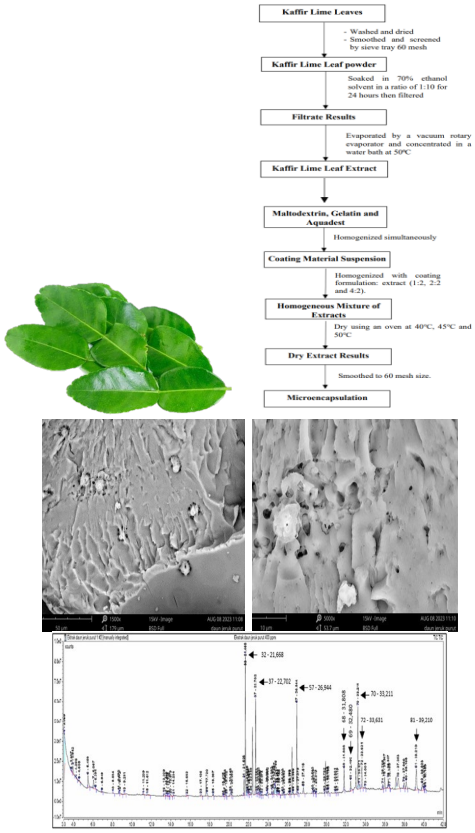
Graphical abstract



Abstract

Kaffir lime leaves *(Citrus hystrix DC)* are a natural antioxidant compound that can ward off free radicals due to the presence of flavonoid compounds. The flavonoids in this plant were extracted by extraction using a maceration method using 70% ethanol solvent with a soaking time of 24 hours. The ratio used between samples and solvent is 1:10. The microencapsulation process uses a drying method using an oven with maltodextrin coating combined with gelatin in the ratio (coating: kaffir lime leaf extract = 1: 2, 2: 2 and 4: 2) and dried using an oven at temperatures of 40℃, 45℃ and 50℃. Encapsulants with a variant ratio (coating: extract = 4:2) with a gelatin weight of 3 grams at a drying temperature of 50℃ showed the best results, namely 69.079%. Based on GC-MS testing, microencapsulated kaffir lime leaf extract contains compounds terpenoid, phenolic and fatty acid compounds. Antioxidant activity was tested using DPPH analysis and obtained an IC50 result of 48.5694 µg/ml. The morphological characteristics of the microencapsulation were tested using Scanning Electron Microscopy (SEM) analysis. The microencapsulation dissolution test showed that all samples disintegrated within 12 minutes. Overall, it can be concluded that microencapsulation made from maltodextrin and gelatin can encapsulate antioxidants in kaffir lime leaf extract well and dissolve easily at room temperature.

Keywords: antioxidant, kaffir lime leaf extract, maltodextrin, microencapsulation, gelatin

1.0 INTRODUCTION

Natural antioxidants are in the form of flavonoid compounds, which are a group of polyphenolic compounds originating from plants such as tea, fruit, and vegetables [1]. One plant that contains antioxidant compounds is found in kaffir lime leaves (*Citrus hystrix DC.*). Orange leaf extract (*Citrus hystrix DC.*) contains chemical compounds such as alkaloids, phenols, terpenoids, and flavonoids amounting to (0.687%) which have antioxidant activity [2;33]. In the extraction of kaffir lime leaves, the method used in this research is the maceration method. The maceration method

was chosen in this research because maceration is the simplest method for extracting the desired active compound [3].

After getting a thick extract from kaffir lime leaves, the next step is the microencapsulation process. Microencapsulation protects active ingredients in gasses, liquids, and solids using coating or wrapping materials, usually used in the food and beverage, pharmaceutical, textile, and cosmetics industries [4]. Microencapsulation is a technique to protect the core material from liquid form into a solid form so that it is easy to handle and can protect the core material from color loss [5]. The analysis of microencapsulation shape and size was conducted using Scanning Electron Microscopy. Capsules are categorized by particle size >5000 µm (macro), 1.0-5000 µm (micro), and <1.0 µm (nano) [34]. Making microcapsules or microencapsulation uses certain coating materials [6]. Maltodextrin stands out as a viable option for microencapsulation packaging due to its neutral taste and odor, water solubility, low viscosity even at high concentrations, film-forming ability, and effective protection against the oxidation of the core material [7]. Maltodextrin is used because it is easily soluble in water.

However, maltodextrin is weak in forming emulsions, so it needs to be combined with other encapsulants or emulsifiers [8]. Therefore, the next material used is gelatin because it has the ability to form a good emulsion so with the combination of gelatin and maltodextrin encapsulants, microcapsules of good quality and high stability will be produced [9]. However, coatings also have weaknesses because the emulsion is less stable, so it is necessary to increase the entrapment ability by using gelatin as a good emulsifier. Adding gelatin to maltodextrin will produce better emulsion stability than combining maltodextrin and starch [10]. This research aims to determine the compound content, antioxidant content, release speed, and morphological structure of kaffir lime leaf extract microcapsules.

2.0 METHODOLOGY

2.1 Raw Material

The materials used in this research include materials for extraction and microencapsulation. Materials for extraction require kaffir lime leaves, and 70% ethanol solvent was purchased from Indrasari chemical store, Semarang City, Central Java. The materials for microencapsulation use thick kaffir lime leaf extract, maltodextrin food grade (Lihua), beef gelatin (Hays), and distilled water. Kaffir lime leaves were obtained from the market in Semarang City. The equipment used in this research includes a blender (Panasonic), rotary evaporator (KNF RC 600), water bath (Memmert), homogenizer (IKA Eurostar 40), and oven (Memmert).

2.2 Kaffir Lime Leaf Extraction

Kaffir lime leaves are washed with water until clean and dried in hot sunlight until the water content is gone for about 2 days. Then, it is smoothed using a blender and filtered using a 60-mesh sieve tray. The extraction process is carried out using the maceration method. The solvent is 70% ethanol in a ratio of 1:10. Maceration was carried out for 24 hours with stirring twice for 2 minutes. The maceration results are filtered using a cloth filter to separate the filtrate and dregs. The filtered filtrate was then concentrated using a vacuum rotary evaporator at a temperature of 50˚C at 80 rpm for 35 minutes.

The extract produced by the vacuum rotary evaporator process is a liquid extract that still contains residual solvent. The remaining solvent is removed using a water bath at 50°C until a thick extract of kaffir lime leaves is obtained. The preparation of a thick extract of kaffir lime leaves is shown in Figure 1.

2.3 Microencapsulation Process Using Oven Drying Method

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The process of microencapsulating the thick extract of kaffir lime leaves into microcapsules consists of several stages, namely measuring the ingredients, homogenizing, and drying process. First, the ingredients were weighed according to the formulation (maltodextrin: kaffir lime leaf extract = 1: 2, 2: 2, and 4: 2). Maltodextrin, gelatin, and distilled water were homogenized at 3000 rpm for 15 minutes. Then, put the kaffir lime leaf extract into it and homogenize again at a stirring speed of 3000 rpm for 10 minutes. After that, the homogeneous mixture of extracts is poured into a baking dish and placed in the oven at a temperature of 40°C, 45°C, and 50°C. Next, the results are removed from the oven, ground using a blender, and sieved using a 60-mesh sieve. The process of kaffir lime leaf extract microcapsules is shown in Figure 2.

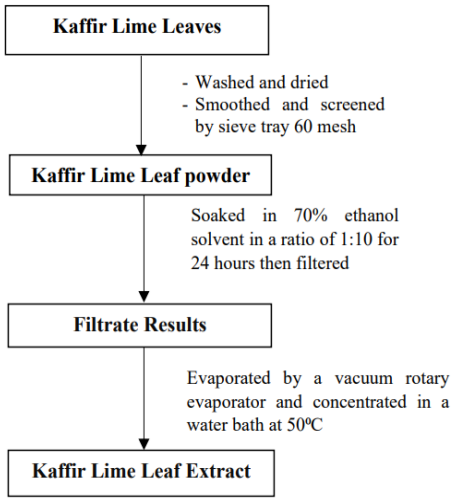

Figure 1 Process of Making Thick Kaffir Lime Leaf Extract

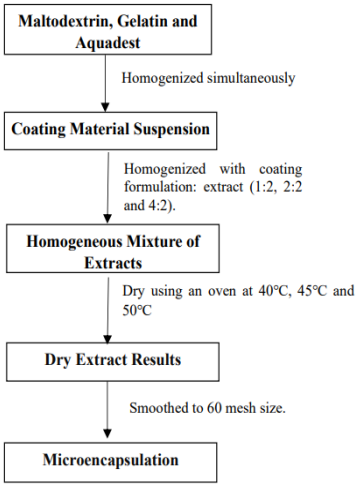

Figure 2 Process of Kaffir Lime Leaf Extract Microcapsules

2.4 Analysis of Data

2.4.1 DPPH Test

The DPPH method is an in vitro method often chosen for testing antioxidant activity because it is simple, easy, fast, sensitive, and requires a small sample. The DPPH method provides information on the reactivity of the sample tested with a stable radical [38]. Data analysis in this study was carried out after testing the antioxidant activity of the microencapsulation of kaffir lime leaf extract. The kaffir lime leaf extract was then tested for antioxidant activity using the DPPH method. The operating time of DPPH using a wavelength of 517 nm, and the maximum wavelength is measured in the range of 400-600 nm, measured from a DPPH concentration of 10 ppm, then the extracted sample is tested for antioxidant activity by making the sample concentration 10, 30, 50, 70 and 100 ppm. Then 0.5 ml DPPH solution was added, and the operating time and maximum wavelength obtained were read. Antioxidant activity is expressed in % inhibition, which is calculated using the formula from research [33].

$$\%\ Inhibition = \frac{Control\ Absorbance - Sample\ Absorbance}{Control\ Absorbance} \times 100\% \text{.....(1)}$$

IC50 is the concentration required to reduce DPPH by 50%. IC50 is obtained using a linear regression equation. From the equation y = a + bx, the IC50 value is calculated using the formula: 50 = a + bx, which is obtained as the IC50 value. IC50 is the concentration required to reduce DPPH by 50%. The IC50 was calculated through linear regression from equation 2 and generated the IC50 value through equation 3.

$$y = a + bxy \text{ ..... (2)}$$
$$50 = ax + bx \text{ ..... (3)}$$

2.4.2 GC-MS Test

Gas Chromatography Mass Spectrometry (GC-MS) is a gas chromatography technique used with mass spectrometry. Gas chromatography looks for compounds that easily evaporate under high vacuum and low-pressure conditions when heated [39]. Meanwhile, mass spectrometry is used to determine molecular weight and molecular formula and produce charged molecules [40]. GC-MS (Gas Chromatography-Mass Spectrometry) technique identifies various compounds in test samples by adopting liquid gas chromatography and mass spectrometry methods. GC-MS analysis is useful for revealing information related to the components of compounds that are volatile, non-ionic, and have high thermal stability, as well as for assessing their molecular weight, which tends to be low.

2.4.3 SEM Test

Scanning Electron Microscopy (SEM) is an electron microscope variant designed to generate high-resolution images of a sample's surface. The SEM operates by directing an electron beam onto the object's surface and capturing images through the detection of backscattered electrons that are emitted from the surface of the specimen [12]. Advances in the use of Scanning Electron Microscopy (SEM) make it possible to scan large areas and collect large amounts of data to obtain sample characteristics, including counting objects and collecting statistics on these objects, one of which is obtaining size morphology images to determine size distribution [13]. Scanning Electron Microscopy (SEM) testing makes it possible to obtain morphological and concentration images of a mixture of materials [14].

2.4.4 Dissolution Test

The dissolution test is a study of the effect of the ethanol solvent ratio of kaffir lime leaf extract on the dissolution ability of kaffir lime leaf extract in mesoporous silica nanoparticles or release [11]. The disintegration time test was carried out using a medium that had been adapted to the condition of the human body, namely at a temperature of 37°C. These temperature provisions are specified in the USP or Pharmacopoeia, and if not stated otherwise, the dissolution medium uses distilled water at a temperature of 37°C. Disintegration time using 9 tablets in 800 ml distilled water medium at a temperature of 37°C with the requirement that the disintegration time for uncoated tablets be no more than 15 minutes.

3.0 RESULTS AND DISCUSSION

3.1 Analysis of Antioxidant Activity of Microencapsulated Kaffir Lime Leaf Extract

In Table 1, the obtained results for the slope and intercept were 0.0072 and 0.1503, respectively, for the highest percentage of free radical inhibition (DPPH), which was 81.25%. The result of the antioxidant activity testing was the IC50 value, representing the extract concentration capable of capturing 50% of free radicals compared to the standard curve of vitamin C via linear regression equation [15]. In this research, testing was carried out using UV-Vis spectrophotometry equipment at a wavelength of 517 nm. The test was carried out 7 times, and a standard error value of 0.075 was obtained.

Table 1 Testing of DPPH Microencapsulation of Kaffir Lime Leaf Extract

Concentration(ppm)	Absorbance	Blank Correct	% Inhibition
control	0.817	0.688	0.00%
0	0.129	0	100.00%
10	0.661	0.532	22.67%
30	0.625	0.496	27.91%
50	0.401	0.272	60.47%
70	0.344	0.215	68.75%
90	0.252	0.123	82.12%
100	0.258	0.129	81.25%

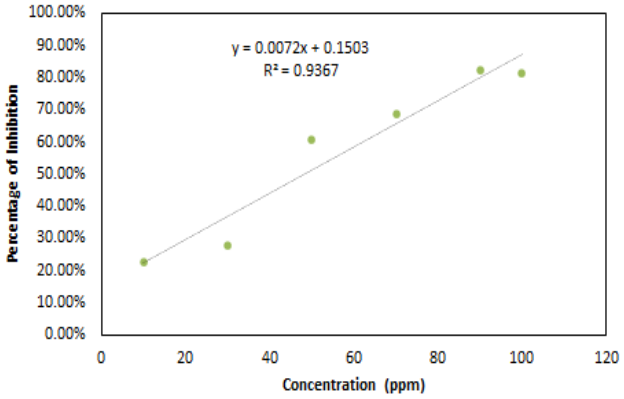

Figure 3. Effect of Inhibition Percentage on Concentration (ppm)

The effect of inhibition percentage on concentration (ppm) shown in Figure 3. The IC50 value of the microencapsulated kaffir lime leaf extract obtained was 48.5694 µg/ml, indicating a very strong antioxidant activity of the microencapsulated kaffir lime leaf extract.

Table 2. Classification of Antioxidant Activity [16]

Antioxidant Activity Levels	IC50
Very Strong	< 50 µg/ml
Strong	50 - 100 µg/ml
Medium	101 - 150 µg/ml
Weak	> 150 µg/ml

The classification of antioxidant activity microcapsules is shown in Table 2. This result aligns with and is higher than the findings in [7] regarding antioxidant activity testing of ethanolic kaffir lime leaf extract, which had an IC50 value of 187.36 ppm and was classified as moderate. This also demonstrates that the microencapsulation treatment of kaffir lime leaf extract significantly functions in preserving the antioxidant compounds present in the kaffir lime leaf extract.

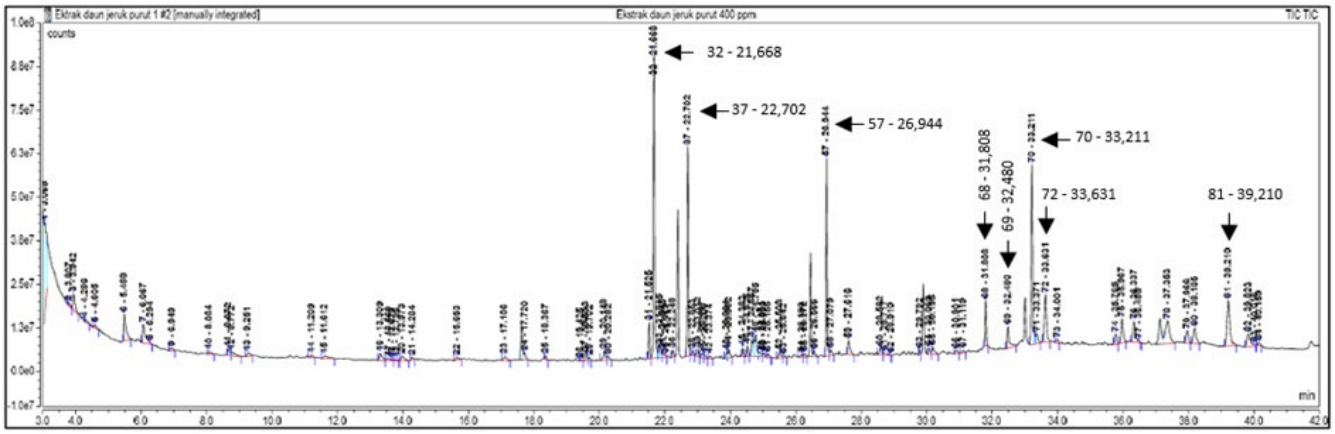

Figure 4 GCMS Analysis of Kaffir Lime Leaf Extract at 400 ppm

Based on the analysis using Gas Chromatography-Mass Spectrophotometry (GCMS), it shows that the kaffir lime leaf extract produced contains several components. The GCMS used is GC Thermo Scientientific Trace 1310 and MS Thermo Scientientific ISQ 7000. In this test, a standard error value of 0.075 was obtained. From Figure 4 and Table 3, it can be seen that the standard error of data is 1.583, and the main component of kaffir lime leaf extract is in the form of terpenoid, phenolic and fatty acid. The terpenoid compounds are Cyclododecane (13.89%) and phenolic compounds consisting of 2,4-Di-tert-butylphenol (8.56%) 1-Heptatriacotanol (3.51%) and Estra-1,3,5(10)-trien-17ß-ol (1.50%). In addition, the fatty acid groups are Hexadecanoic acid, ethyl ester (9.70%), Dodecyl acrylate (7.86%), Heptadecanoic acid, 15-methyl-, ethyl ester (4.61%), and Hexadecanoic acid, methyl ester (1.85%). A hexadecanoic fatty acid is classified as a substance that has antibacterial properties, works by damaging the structure of cell walls and membranes synergistically with a variety of active compounds, increasing the effectiveness of antibacterial activity [22]. This is in line with the research done by [23,24], who said that fatty acid groups such as hexadecanoic acid, ethyl ester, dodecyl acrylate, and hexadecanoic acid, methyl ester in kaffir lime leaf extract have a function to prevent bacterial growth.

Table 3 Components Contained in Kaffir Lime Leaf Extract

Retention Time	% Area	Component
21.668	13.89	Cyclododecane
22.702	8.56	2,4-Di-tert-butylphenol
26.944	7.86	Dodecyl acrylate
31.808	1.85	Hexadecanoic acid, methyl ester
32.480	1.50	Estra-1,3,5(10)-trien-17ß-ol
33.211	9.70	Hexadecanoic acid, ethyl ester
33.631	3.51	1-Heptatriacotanol
39.210	4.61	Heptadecanoic acid, 15-methyl-, ethyl ester

These phenolic groups, fatty acids, and terpenoids can act as antioxidants and antimicrobial compounds [25]. This shows that the compound structure of kaffir lime leaf extract affects the antioxidant activity that can reduce the level of free radical reactivity. His research [26] revealed that phenolic compounds are 2,4-Di-tert-butylphenol and are antioxidants by donating hydrogen atoms or transferring electrons to DPPH free radicals. Research [27] also revealed that Heptadecanoic acid, 15-methyl-, ethyl ester, and Estra-1,3,5(10)-trien-17ß-ol are phenolic compounds that have antioxidant properties and have anti-osteoporosis activity [28]. The compound 1-Heptatriacotanol is one of the phenolic compounds that have benefits as a substance that is antimicrobial, anticonvulsant, antidepressant, anti-inflammatory, analgesic, antiplatelet, antimalarial, anticancer, antifungal, antituberculosis, antiviral and cardioprotective [29].

The antibacterial mode of action of terpenoid compounds involves membrane destruction with the involvement of lipophilic components. This damages transmembrane proteins, known as porins, in the outer layer of the bacterial cell membrane. As a result, the permeability of the cell wall is disrupted, and the intake of nutrients into the cell is reduced, leading to bacterial cell death [30]. From the results of the study [31], it was revealed that terpenoids can cause cell death by causing damage and irregularities in the integrity and function of the cell membrane. Some terpenoids, such as cyclododecane, have the ability to inhibit microbial growth, and terpenoid compounds also have antioxidant properties [32].

3.2 Effect of Coating Material Ratio on Microencapsulation Results of Kaffir Lime Leaf Extract

Maltodextrin and gelatin were used as coating materials for microencapsulation of kaffir lime leaf extract. As a coating material, maltodextrin is not sweet, white, odorless, has high solubility, has good stability to oxygen and is safe for consumption by the body [48]. However, maltodextrin has weak emulsion capacity and stability so it needs to be combined with gelatin. Gelatin has the characteristics of solubility, emulsification properties, air binding capacity, and good foaming properties, so the combination of maltodextrin and gelatin can produce a coating that has stability and emulsifier characteristics that can dissolve well in the body [19]. The results of microencapsulation of kaffir lime leaf extract with variable temperatures (40°C, 45°C, 50°C) and coating material: extract ratios (1:2, 2:2, 4:2) are shown in Table 4. From Table 4, we can get a standard error value of 1.839.

In this research, analysis was also carried out to determine the effect of microencapsulation yield on the ratio of coating material and extract (MD: Extract).

Yield is the ratio between the microcapsules obtained after drying and the amount of microcapsule-forming material [21]. According to research conducted by [20], microencapsulation yield can be calculated using the formula:

$$Yield(\%) = \frac{Microcapsule\ Weight\ (gram)}{Microcapsule\ Forming\ Material\ (gram)} \times 100\% \quad .....(4)$$

From Figure 5, it can be seen that the standard error value is 2.941. The analysis results show that the microencapsulation yield will increase along with the increase in the maltodextrin ratio formulation used. A ratio formulation (MD: Extract) of 4:2 can increase the yield value because the resulting emulsion is more stable, producing more powdered microcapsules when drying.

This is in line with research [24], which states that the results of yield calculations show that formulations with a coating ingredient concentration of 3% have a higher value than formulations with a coating ingredient concentration of 2%. Based on research [25], it is stated that formulations with a lower amount of coating compared to extracts generally produce lower yields. This is because the lower the coating concentration added, the less capacity the encapsulate can encapsulate the entire extract.

Table 4 Results of Microencapsulation of Kaffir Lime Leaf Extract

Temperature	Ratio (coating agent: extract)	Encapsulant Weight (gram)	Yield (%b/b)
40°C	1:2	4.724	26.242
40°C	2:2	10.230	48.714
40°C	4:2	17.520	64.889
45°C	1:2	4.857	26.981
45°C	2:2	11.018	52.465
45°C	4:2	18.544	68.682
50°C	1:2	8.510	47.278
50°C	2:2	14.433	68.731
50°C	4:2	18.651	69.079

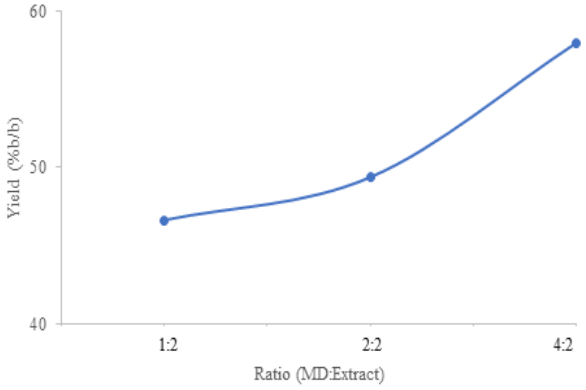

Figure 5. Effect of Coating Material Ratio on Microencapsulation Results of Kaffir Lime Leaf Extract

3.3 Microcapsule Morphology Analysis Using Scanning Electron Microscope (SEM)

The analysis of microencapsulation shape and size was conducted using Scanning Electron Microscopy. Capsules are categorized by particle size >5000 µm (macro), 1.0-5000 µm (micro), and <1.0 µm (nano) [34]. Microencapsules can be formed in various models, such as spherical, rectangular, or irregular. The SEM morphology

results show that the diameter of this product at 1500x magnification is 50 µm, and at 5000x magnification, it has a diameter of 10 µm; this shows that this product is not a nano-encapsulated product but is microencapsulated. The shape and morphology of the microencapsulation extracted with a ratio of 4:2 and a temperature of 50°C can be seen in Figure 6.

Some factors that affect the shape and morphology of microcapsules are stirring speed and viscosity. The faster the emulsion is stirred, the smaller the shape [35]. Microencapsulated particles are slab-like crystals and irregular in shape. Bubbles that appear are caused by excessive oven temperature. When the walls of the encapsulated particles are unable to withstand the pressure inside, the walls will break and form wrinkled particles. The presence of wrinkles on the surface of microencapsulated kaffir lime leaf extract is thought to result from the heat released from the core. This phenomenon is crucial in preserving the antioxidant content during the microencapsulation process. As the drying temperature rises and water evaporation occurs rapidly, the outer layer of the encapsulated particles solidifies, leading to the formation of wrinkles [36]. The microencapsulation of kaffir lime leaf extract has a wrinkled and tight morphology, indicating that the addition of gelatin can close the surface so as to prevent the degradation of antioxidant compounds. This is in line with research conducted by [37], which states that the desired microencapsulation morphology is a morphology that is tighter, wrinkled, and has minimal gaps because it allows fewer compounds or extracts to diffuse and degrade.

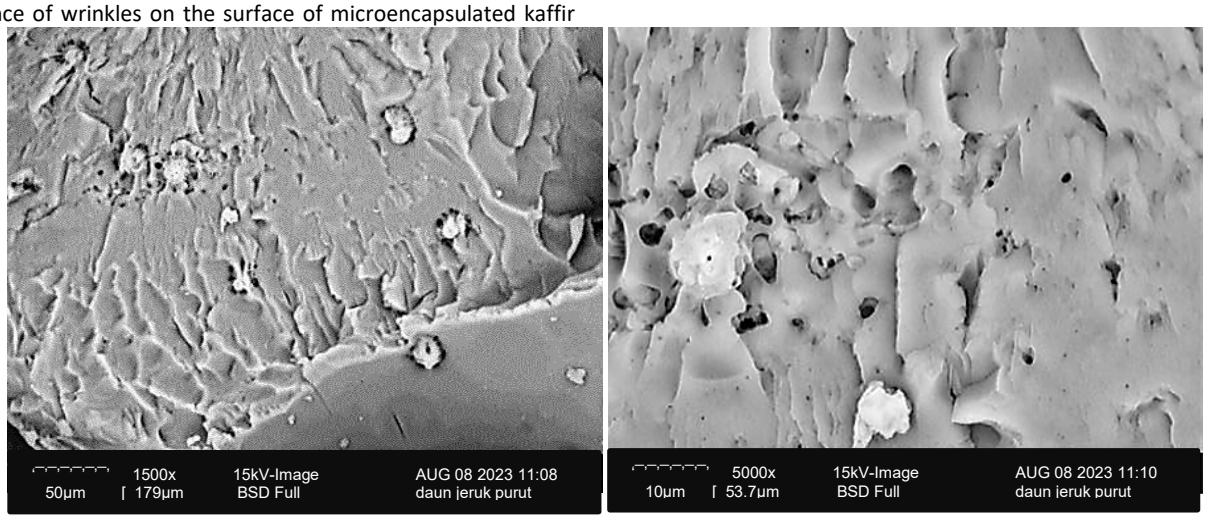

Figure 6. SEM Micrograph of Microencapsulation of Kaffir Lime Leaf Extract with different magnification, (a) 1500x, (b) 5000x

3.4 Analysis of Microencapsulation Dissolution Test of Kaffir Lime Leaves

Disintegration time is a parameter to evaluate the time required for a tablet to disintegrate in body fluids or in other words to determine the speed at which the drug dissolves in body fluids. The disintegration time test was carried out using a medium that had been adapted to the condition of the human body, namely at a temperature of 37°C. These temperature provisions are specified in the USP or Pharmacopoeia, and if not stated otherwise, the dissolution medium uses distilled water at a temperature of 37°C. The disintegration time using 9 formulas with a microencapsulation weight of 900 mg in each 800 ml distilled water medium at 37°C resulted in all disintegrating at the 12th minute. This value meets the requirements. Namely, the disintegration time for tablets is no more than 15 minutes. Fast disintegration time can accelerate the therapeutic effect. The disintegration time test results can influence the drug's dissolution time [17]. This is in accordance with research that has been carried out [18], which states that drugs will dissolve quickly if the drug has the characteristics of breaking down more quickly.

4.0 CONCLUSION

Based on research that has been carried out, the most optimal results of microencapsulation of kaffir lime leaf extract were obtained at a ratio variant of 4:2 at a temperature of 50°C with an encapsulant yield of 69,079%. This composition results in high yields and good drying rates. Maltodextrin is an auxiliary agent in accelerating drying, while gelatin has the effect of forming a good emulsion. The antioxidant activity of microencapsulated kaffir lime leaf extract showed that the IC50 value obtained was 48.5694 µg/ml, which indicated that the antioxidant activity of microencapsulated kaffir lime leaf extract was very strong. The disintegration time using 9 tablets in 800 ml distilled water medium at a temperature of 37°C resulted in all disintegrating in the 12th minute. This value meets the requirements. Namely, the disintegration time for uncoated tablets is no more than 15 minutes. The morphological characteristics of the microencapsulated kaffir lime leaf extract at 1500x and 5000x magnification show that the encapsulant sample has a structural appearance that is relatively smooth and mostly does not have cavities. Microencapsulation of kaffir lime leaf extract made from maltodextrin and gelatin has been proven to be able to maintain the antioxidant activity of the extract well.

Acknowledgment

Thank you to the Faculty of Engineering, Universitas Negeri Semarang, which has funded this research according to the DIPA Research Funding Cooperation Agreement under contract number: 51.17.4/UN37/PPK.05/2023.

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