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Preparation and Characterization of Water Soluble Curcuminoid Prepared by Complex Formation with κ-Carrageenan

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***Abstract*—Objectives: The aim of this study was to increased solubility of curcuminoid by inclusion complex formation. Method : Curcuminoid-kappa carrageenan complex formation was perform by kneading method. Then the complex solubility and dissolution rate was evaluated and characterized by Scanning Electron Microscopy (SEM) and Fourier Transform Infrared (FTIR). The results showed that solubility was increased in all formula. Conclusion: Solubility increases more than 41 times after curcuminoid changed into inclusion complex. Dissolution rate increased from 40.91% to 76.67% in the 60 min. SEM dan FTIR showed different intensity of spectrum and particle surfaces, which indicated the formation of inclusion complexes between curcuminoid and kappa-carrageenan. Keywords: Inclusion complex, curcuminoid, kappa carrageenan, Water soluble Curcuminoid.**

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I. INTRODUCTION

A medicinal preparation that is given orally in gastroduodenal have to be involved in the process of the release of physicochemical properties, then the active substance will be dissolved and absorbed. One of the most important physicochemical properties is the solubility of the drug. In general, substances will be absorbed after dissolved in the gastrointestinal fluid where the dissolution rate is the slowest step and a determinant of the speed of drug bioavailability[7].

Curcuminoids are hydrophobic polyphenolic compounds which is found in *Curcuma longa* Linn. In some studies, curcumin has extensive pharmacological activities such as antiinflammatory, antimutagenic, antioxidant, anticancer, antimicrobial and antiparasitic [4,6]. Curcuminoids have poor solubility in water (3.12 mg/L at 25ºC), but are highly soluble in organic solvents such as ethanol and acetic acid [5]. This is a factor that causes low systemic curcuminoid bioavailability [1].

Therefore, it is necessary to improve the solubility of curcuminoids so that they can be absorbed quickly by the human body. This research was conducted to improve the solubility of curcuminoids through the formation of inclusion complexes. One of the methods in the formation of inclusion complexes is the kneading. This method was chosen because it is the simplest method for laboratory scale with low production costs and is able to increase the dissolution rate of the preparation. The complex forming compounds used were carrageenan which has high solubility in water so that it can be effective for the formation of curcumin in solution [8].

II. MATERIAL AND METHOD

A. Procedure

Equipments

The equipments to carry out this study were glassware (Pyrex), micro pipette (Thermo scientific, Finn pipette F3), analytical scales (Hanherr and Sartorius), Ovens (Memmert), desiccators, sieve no. 80 , mortars and stamper, magnetic stirrer (Thermo Scientific), UV-Vis spectrophotometer (Shimadzu UV 1800), Fourier Transform Infra Red (FTIR) (Thermo Scientific Nicolet iS5), Scanning Electron Microscope (SEM) (JSM-6510A, JEOL USA Inc.), and orbital shaker (IKA KS 130 basic).

Materials

The materials used were curcuminoids (isolated by STFI), κ-carrageenan (isolated by STFI), ethanol 96% pro analysis (Merck), aquadest (Merck), toluene (Merck), ethyl acetate (Merck), KH_2PO_4 (Merck), and NaOH (Merck).

Preparation of Curcuminoid-Carrageenan Inclusion Complex

1. Kneading Method

Curcuminoids 150 mg and carrageenan 150 mg were prepared in several molar comparisons (1: 1,1: 2, 2:1). Then, carrageenan were mixed with hot water to form paste-like consistency. The mixtures were dried in the oven at 45°C for 48 hours.

2. Determination of Curcuminoid Contents

Inclusion complex powder 10 mg was dissolved in the solvent, and then diluted to get the concentrations of 10 and 20 ppm. The absorbances were measured at the maximum wavelength of 430 nm by the UV-vis spectrophotometer.

Characterization of Carrageena-Curcuminoid Inclusion Complex.

1. *Solubility Test of Curcuminoid-Carrageenan Inclusion Complex.*

Solubility test of carrageenan curcuminoid complex was carried out using Higuchi and Connors methods.

The standard curcuminoid 10 mg and Carrcuminoid complexes 10 mg were dissolved in 10 ml of aquadest in a separate container and shaken with for 72 hours. The solution obtained was filtered with a membrane filter of 0.20 µm. The filtrate was taken 1 mL, then put in a 10 mL volumetric flask and added by ethanol.

Curcuminoid content was analyzed by UV-vis spectrophotometer at a wavelength of 430 nm. Then the concentration was calculated using the regression equation obtained from the standard curve. The experiment was carried out 3 times.

2. *Dissolution Test of Curcuminod-Carrageenan Inclusion Complex.*

The dissolution test of curcuminoid-carrageenan inclusion complex was carried out using a type 2 USP (paddle type) in 900 ml phosphate buffer pH 6.8. Paddle rotation speed was 75 rpm and medium temperature was 37 ± 0.5 °C. Sampling was carried out at 5, 10, 15, 30, 45 and 60 minutes, as much as 5 ml. Each solution taken was then replaced with phosphate buffer so that the volume remains the same. The absorbance of the test solution was determined by Uv-vis spectrophotometry at a maximum wavelength of 430 nm. Then the parameter value was calculated.

3. *Stability Test of Curcuminoid-Carrageenan Inclusion Complex.*

A number of inclusion complex powders were added to the evaporating plate and then stored in an oven at 40°C to determine the stability of the inclusion complex in high temperature storage for a long time. Samples were stored in an oven for 28 days. Curcuminoid concentration in the inclusion complex was measured every 7 days according to the procedure of determining curcuminoid contents.

4. *Characterization of Curcuminoid-Carrageenan Inclusion Complex.*

a. Spektrofotometer UV-Visible

Spectrophotometer in the formation of the inclusion complex there was a wavelength shift from 430 nm to 432 nm. According to Yang (2013), this happened because the addition of the complexing polymer caused a direct non-covalent interaction between the active substance group and the nonpolar cavity of the complexing agent. The existence of these interactions caused disruption of the electronic energy level of the active substance molecules. The wavelength shift indicated the chromophore group of the active substance was transferred from the water medium to the nonpolar cavity of the complexing agent. The addition of a complexing polymer caused a change in the maximum wavelength to the batochromic.

b. Scanning Electron Microscopy (SEM)

A number of sample powders were glued to a carbon adhesive tape. Then the samples that attached to the carbon tape were given an air pressure. Cylinders were attached to carbon tape that had been sprinkled with samples. Then the sample holder was coated and given air pressure with a vacuum. The voltage was set at 20,000 kV and 30,000 kV, then samples were tested with Scanning Electron Microscopy at magnification of 500, 1,000, 2,000, 5,000 and 10,000 times.

c. Fourier Transform Infra Red (FTIR) Spectroscopy

A number of curcuminoid-carrageenan inclusion complex powders were placed in a sample container. The test was carried out by FTIR spectroscopy with ZNSe ATR method at wavenumbers of 4000 cm-1 to 400 cm-1. The spectrum obtained was compared to the standard spectrum of curcuminoids and carrageenan.

B. Data Analysis

Respondents in this study were divided into two groups, namely the control group and the intervention group. The control group was only observed in the hospital, and the intervention group was observed and intervened in the form of hold relax therapy for 15 minutes and one time a day for three days.

III. RESULTS AND DISCUSSION

Solubility Test for Curcuminoid-Carrageenan Inclusion Complex.

The solubility test showed an increase in curcuminoid solubility of 41 times in aquadest after the formation of the inclusion complex with formula (1:2). This showed the interaction between curcuminoid and carrageenan in which the curcuminoid hydrophobic group was incorporated into the hydrophobic group carrageenan (3,6-anhydro-D-galactose) on the inside, so that the hydrophilic group (hydroxyl and sulfate groups) carrageenan outer molecule facilitated curcuminoid wettability with solvent. According to Ezawa (2016), H atoms on the curcuminoid benzene group would interact with H at the complexing polymer, and then the polymer of the benzene ring in the curcuminoid would interact with the protons in the complexing polymer hole to form an inclusion complex.

TABEL 1: SOLUBILITY TEST FOR CURCUMINOID-CARRAGEENAN INCLUSION COMPLEX

Sample	λ Maximum	Dissolved Curumuminoid Level (µg/ml)	Solubility Increase (times)
Curcuminoid	430 nm	10,5342	-
Inclusion Complex (1:2)	432 nm	435,0722	41,31
Inclusion Complex (1:1)	432 nm	337,0274	32,00
Inclusion Complex (2:1)	432 nm	327,59	31,11

Curcuminoid-Carrageenan Inclusion Complex Dissolution

The dissolution test results showed that the curcuminoid dissolution rate at minute 60 was 40.91%. Whereas the percentage of dissolution of curcuminoid after inclusion complex increased up to 18 times by 76.67% compared to pure curcumin. These results indicate that the inclusion complex has a higher dissolution rate than curcuminoids.

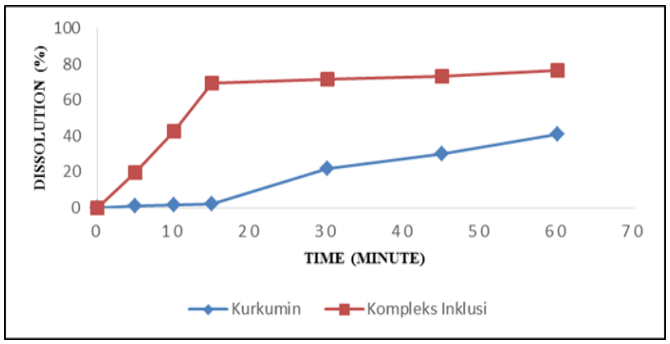

Figure 1. Comparison Chart Dissolution rate Curcuminoid with Inclusion Complexes Curcuminoid-Kappa Carrageenan

Stability Test of Curcuminoid-Carrageenan Inclusion Complex.

The increase in temperature caused a decrease in the stability of the curcuminoid and kappa carrageenan inclusion complexes. This happened due to the nonpolar bond between the guest (curcuminoid) in the hydrophobic host (kappa carrageenan) became weak by the raise of the temperature.

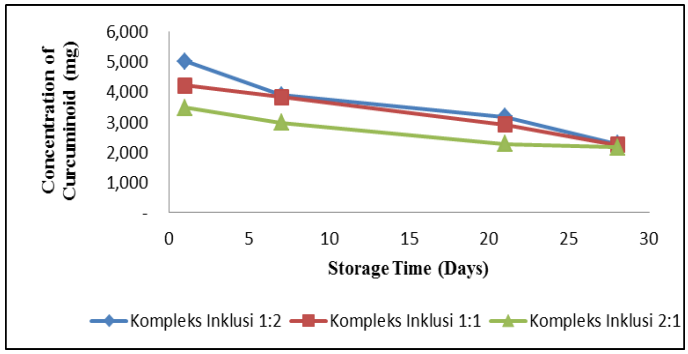

Figure 2. Stability study of Inclusion Complexes

Characteristics Curcuminoid-Carrageenan Inclusion Complex

1. Scanning Electron Microscopy (SEM)

Based on Scanning Electron Microscopy it was known that the inclusion complex resulted in a more amorphous compound. The presence of particle changed (rough surface and agglomeration of particles) shows that the complex has formed in a solid state. This SEM result shows that the curcuminoid was absorbed into the cavity of the complexing material.

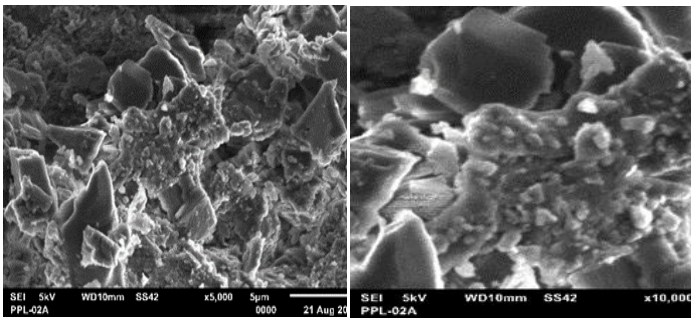

Figure 3. SEM Photograph of Kappa-Karagenan Curcuminoid Inclusion Complex.

2. Fourier Transform Infra Red (FTIR)

Fourier transform Infra-red (FTIR) results showed a reduction in peak intensity in CH group wave numbers at 2360.87 cm-1 and 2341.58 cm-1; spectrum shift at 1627 cm-1, 1600 cm-1.1373 cm- 1, 954 cm-1 and 856 cm-1; and a loss of one peak at 1184 cm-1 in the curcuminoid spectrum. These results show the occurrence of inclusion complexes between complexing compounds and active substances of curcuminoids.

TABLE 2: CURCUMINOID FTIR SPECTRA, KAPPA CARRAGEENAN AND INCLUSION COMPLEXES CURCUMINOID-KAPPA CARRAGEENAN

Type of bond	Wavenumbers (cm^{-1})		
	Curcuminoid	κ-Carrageenan	Inclusion Complex
O-H (Hydroxyl group)	3510	3380	3510
C-H *Strech*	2360	2920	2341
-CO-N *Strech*	1627	-	1627
C=C *Strech* (Aromatic)	1600	-	1600
C=C (Keton)	1508	-	1508
S=O *Strech* (Ester Sulfat)	-	1229	1234
=C-O-C *Asymetric Strech*	1373	-	1373
=C-O-C *Symetric Strech*	1026	1096	1029

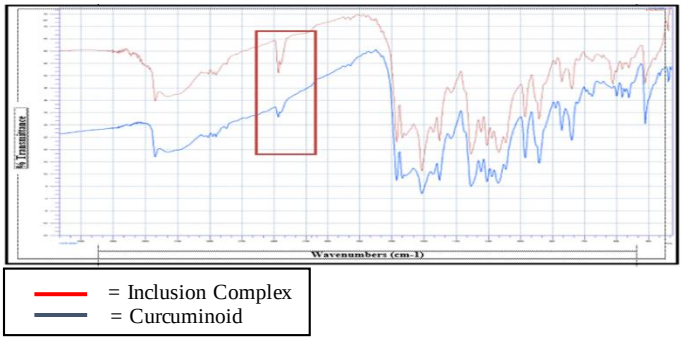

FIGURE 4. RESULTS OF COMBINED FTIR SPECTRA BETWEEN KURKUMINOID WITH INCLUSION COMPLEXES KURKUMINOID-KAPPA-CARRAGEENAN.

IV. CONCLUSION

From this study it can be concluded that kappa-carrageenan was able to form inclusion complexes with curcuminoids at a concentration ratio of 1:1, 1:2, and 2:1. The highest level of curcuminoid-carrageenan complex was obtained in a ratio of 1:2, namely 5,020 mg/20 mg. The complex formation between curcuminoids and kappa carrageenan could improve the solubility of curcuminoids up to 41 times. Moreover, there was an enhancement of dissolution rate from 40.91% to 76.67% in 60 minute. Characterization by Scanning Electron Microscopy (SEM) and Fourier Transform Infra Red (FTIR) methods also showed the formation of complexes between curcuminoids and kappa carrageenan.

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