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Capsule Dosage Forms Containing Natural Antioxidant Microcapsules of Cantigi Extract

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Abstract

Microencapsulation technology in product development of the food, beverage, and health sectors may provide innovative products with better stability, functionality, and prolonged releases. This study aims to formulate capsule dosage forms containing natural antioxidant microcapsules of Cantigi extract and analyze slow-release profiles. Three microcapsule formulations (F1, F2, and F3) were made by solvent evaporation method using ethyl cellulose coating and characterized for color, odor, particle size, shape, recovery, moisture content, encapsulation efficiency, drug loading, density, and antioxidant activities. Then, three capsule dosage forms (FI, FII, and FIII) of microcapsules of the most potent antioxidant activity, microcrystalline cellulose, and colloidal silicon dioxide. The results showed that the most potent microcapsules were F1, while the most potent capsule dosage forms were FIII. FIII provides the slowest release compared with FI and FII. By analyzing the kinetics of FIII using zero-order, first-order, Higuchi, and Kosmeyer-Peppas models, the release profile of FIII is the best fit with the first-order model kinetics, consistent with a previous study. Moreover, all capsule dosage forms have a biphasic slow-release profile for 60 minutes. The conclusion is that this study can prepare hard-gelatin capsule dosage forms containing natural antioxidant microcapsules of cantigi extract with first-order and biphasic slow-release profiles.

Keywords: Cantigi Extract, Capsule Dosage Forms, Microencapsulations, Release Profiles

1. Introduction

The uses of natural ingredients in medicinal preparations worldwide have increased over time as many drug manufacturers are starting to switch to producing drugs using natural ingredients. The advantages of use may provide affordable prices, fewer side effects, and cure not only one of the symptoms or diseases but also improve physiological function in the body (Kurek et al., 2022).

One of the plants that may be a source of natural medicines is Cantigi (*Vaccinium varingiaefolium* (Blume) Miq.) from the Ericaceae family growing well near volcanic craters. Cantigi is part of the same genus of *Vaccinium* as Bilbery (*Vaccinium mystillus*), which has been well-known worldwide. The empirical uses of Cantigi are anti-inflammatory, antispasmodic, and antihypertensive. A previous study showed that Cantigi extract has a very potent antioxidant activity ($IC_{50} < 20$ ppm) (Kosasih et al., 2021).

Cantigi leaves contain flavonoids, steroids, tannins, triterpenoids, saponins, and steroids (Kosasih et al., 2022). They have two kinds of color; the young are red, and the old are green. Generally, plants having red or purple colors contain anthocyanin compounds, which are potent antioxidants (Kosasih et al., 2021). Previous research using GC-MS method, cantigi leaves contain 33 compounds, some of which have potential as antioxidants, namely hexamethyl cyclotrisiloxane, 5-(thiopen-2-yl) methyl-2H-tetrazole, hexadecanoic acid methyl ester, 9-octadecenoic acid (Z), beta-mono-olein, 1,2-benzenedicarboxylic acid, mono(2-ethylhexyl) ester, and friedelin (Kosasih et al., 2020).

Antioxidants may neutralize free radicals and protect the body from degenerative diseases such as cancer, heart disease, arthritis, cataracts, diabetes, and liver disease. They can destroy a reaction chain of free radical formation by donating H-atoms, reducing the concentration of reactive oxygen, reducing free radicals at the initiation stage, and chelating transition metal catalysts (Yamauchi et al., 2024).

Microencapsulation is a process of enclosing micron-sized particles in a polymeric shell, or by which the small particles or droplets are coated with a coating or encased in a homogeneous or heterogeneous matrix and created to give small capsules (Jyothi et al., 2012). It protects micron-sized sensitive substances from the external environment and provides controlled release. It may contain liquids or solids with sizes ranging from 33 nm – 20 µm (Abbaspoor et al., 2012). The principle of microencapsulation is to mix a core phase, water phase, and coating phase until a stable emulsion forms, then proceed with an attaching process of the coating material to the surface of the core substance and the particle reduction process (Yan et al., 2024). Several advantages of microcapsule formulations include masking the bitter taste of drugs, regulating the drug release site, improving drug release properties, reducing undesirable drug reactions and side effects, extending shelf-life, enabling drug delivery at specific locations, and enabling controlled and sustainable medicinal compounds (Paulo et al., 2017). According to previous research, ethanol extract from cantigi leaves has a pH of 2.87 (acid), so it has the potential to irritate the stomach (Kosasih et al., 2021). Therefore, microencapsulating cantigi extract may protect the gastric mucosa while maintaining antioxidant activity caused by unfriendly gastrointestinal conditions. In microcapsule formulations, a coating aims to protect the core substance, which is non-toxic and does not react with the extract. In other words, polymers will layer active substances (Mariel et al., 2022). Coatings for microcapsules may use a combination of polymers, such as ethyl cellulose, cellulose derivatives, chitosan, alginate, and other polymers (Raj et al., 2024; & Singh et al., 2010). In this microcapsule formulation, the coating polymer is ethyl cellulose. Ethyl cellulose is water-insoluble but soluble in various organic solvents, odorless, colorless, tasteless, and stable. Some reasons for choosing ethyl cellulose are: Non-toxic, biocompatible, safe for consumption, maintains the stability of the core ingredient (active substance) well, and masks the unpleasant taste of medicinal ingredients (Murtaza, 2012). There are several microencapsulation methods, including spray-drying, spray-congealing, freeze-drying, solvent evaporation, coacervation, and interfacial polymerization. This study uses the solvent evaporation method by which the active substance is suspended in a polymer solution containing an anhydrous organic solvent and then evaporated (Ahangaran, 2022).

After microencapsulation, microcapsules are mixed with other excipients and filled into gelatin capsules. The advantages of Capsule formulations include maintaining the stability of the microcapsules that function as antioxidants, covering unpleasant tastes and odors, and making them easier to consume as an oral preparation because of their small size and smoother surface (Janczura, 2022). The DPPH method is the most common antioxidant testing, where antioxidant activity is analyzed using the DPPH (1,1-diphenyl-2-picrylhydrazyl) reagent. The advantage of this method is that it is simple, easy, fast, inexpensive, and sensitive for samples with small concentrations (Kosasih et al., 2020).

Based on the previous information, this study aims to formulate capsule dosage forms containing natural antioxidant microcapsules of cantigi extract and analyze their release profiles.

2. Materials and Methods

2.1 Materials

The Cantigi leaves are from the White Crater, Mount Patuha in Bandung, Indonesia, identified at the Herbarium Depokensis (UIDEP), Department of Biology, Faculty of Mathematics and Natural Sciences, University of Indonesia. Other materials used are analytical or pharmaceutical grade.

2.2 Methods

2.2.1 Preparation and Characterization of Cantigi Extract

Cantigi extraction used a kinetic maceration method with a ratio of 1:10 (dry powder simplicia: 70% ethanol) for 6 hours. The concentration of the extract used a rotary evaporator at 45°C, and the characterization of the thick extract obtained includes organoleptic (color, odor, appearance), pH, solubility, moisture content, antioxidant activity, phytochemistry, and heavy metal content (Yulyana et al., 2016; & Hibrah et al., 2022).

2.2.2 Synthesis and Characterization of Microcapsules

Synthesis of three microcapsule formulations used the below compositions: Cantigi extract (1 g), ethyl cellulose (F1: 1, F2: 2, and F3: 3 g), acetone (30 mL), liquid paraffin (60 mL), tween 80 (0.78 mL), and n-hexane (qs). The ratios of the core substance (cantigi extract) and the coating (ethyl cellulose) were F1 (1:1), F2 (1:2), and F3 (1:3). With stirring, dissolved ethyl cellulose in 30 mL of acetone. Cantigi extract was dispersed and stirred for 20 minutes. In another beaker, 60 mL of liquid paraffin and 0.78 mL of tween 80 were mixed to make a vehicle phase and continued to stir. An emulsion was made by pouring drop by drop the mixture of coating solution and cantigi extract dispersion to the vehicle phase, stirred at 850 rpm and room temperature for 2.50 hours until all the acetone evaporated. After microcapsules formed, filtered, washed three times with n-hexane, and dried in an oven for 2 hours at 40-50°C (Song et al., 2022; Brlek et al., 2021; & Yasin et al., 2021). Characterizations of microcapsules include organoleptic (color, odor, shape), recovery, moisture content, entrapment efficiency, drug loading, particle size distribution, bulk and tapped density (Raj et al., 2024; Hibrah et al., 2022; Ditjen Farmalkes, 2022; Song et al., 2022; & Choudhury et al., 2021), and antioxidant activity (Yamauchi et al., 2024).

2.2.3 Capsule Dosage Forms Containing Microcapsules of Cantigi Extract

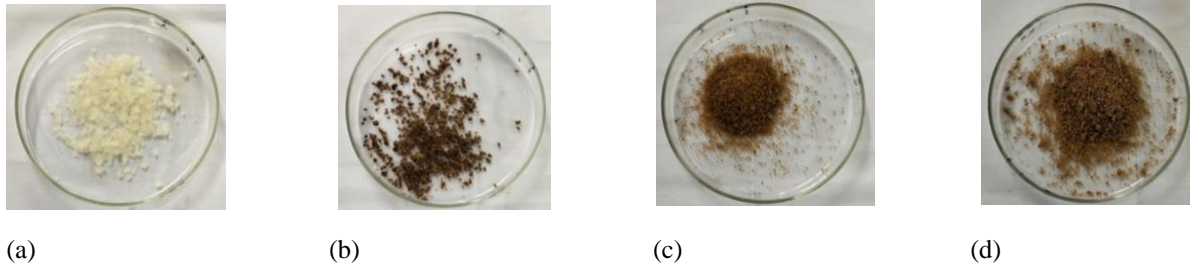
Capsule dosage forms (FI, FII, and FIII) contain microcapsules (10, 20, and 30 mg each), colloidal silicon dioxide (2.32, 2.24, and 2.16 mg each), microcrystalline cellulose PH 102 (add to 300, 300, and 300 each). The total weight per capsule is 300 mg. Capsule mass was made by mixing all components and filling into #2 hard-gelatin capsules. Before filling into hard gelatin capsules, the capsule mass was characterized for moisture content (USP <921>, 2023), particle distribution (USP <786>, 2023), bulk density (USP <616>, 2023), tapping density (USP <616>, 2023), Carr's index, Hausner ratio, and flowability (USP <1174>, 2023). After filling into hard gelatin capsules, the resulting capsules were examined for mass uniformity, disintegration time, and release profile (Šedbarè, 2023).

3. Results

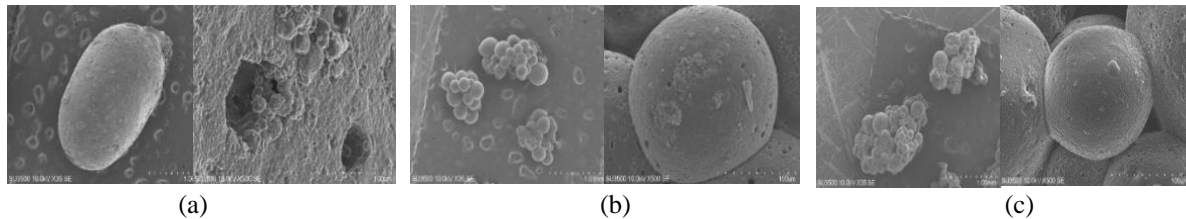
Table 1: Characteristics of specific and non-specific parameters of Cantigi extract

Test parameters	Results
Organoleptic: Color	Dark brown
Odor	Cantigi specific
Appearance	Thick
pH	4.30±0.01
Solubility: in methanol	Soluble
in ethanol 96%	Soluble
in DMSO	Freely soluble
in purified water	Soluble
Moisture content (%)	8.67±1.56
Antioxidant activity (IC ₅₀ , ppm)	17.40±1.00 ppm (Cantigi extract)

		2.75±0.040 ppm (Vitamin C, control)
Phytochemistry:		Alkaloids: + Saponins: + Tannins: + Phenolics: + Flavonoids: + Steroids: - Triterpenoids: + Glycosides: +
Heavy metal content:	Pb	Undetectable
	Cd	Undetectable



(a) (b) (c) (d)
Figure 1: Four different physical forms of microcapsules containing Cantigi extract. Microcapsules of F0 (a), F1 (b), F2 (c), and F3 (d).



(a) (b) (c)
Figure 2: Shape (morphology) of microcapsules generated by an SEM. (a) = F1, (b) = F2, and (c) = F3.

Table 2: Characteristics of Microcapsules containing Cantigi extract

No	Parameters	F1	F2	F3
1	Odor	Specific Cantigi	Specific Cantigi	Specific Cantigi
2	Color	Dark brown	Light brown	Light brown
3	Shape	Powder	Powder	Powder
4	Recovery (%)	77.66±0.15	91.74±0.24	87.91±0.01
5	Moisture content (%)	3.67±0.34	8.67 ± 0.09	5.10 ±0.10
6	Entrapment efficiency (%)	73.18±0.33	83.86±0.26	83.84±0.01
7	Drug loading (%)	64.00±0.19	36.31±0.12	28.29±0.00
8	Particle size (µm)	0.1067	0.2614	0.2455
9	Bulk density (g/mL)	0.31±0.00	0.24±0.00	0.24±0.00
10	Tapped density (g/mL)	33±0.00	0.25±0.00	0.25±0.00
11	Compressibility index (%)	4.67±1.16	2.61±0.00	2.27±0.39
12	Antioxidant activity (IC50, ppm)			
	Week-0	19.3±0.28	27.19±1.12	44.92±0.91
	Week-4	22.75±0.52	33.94±0.80	49.38±1.66

Table 3: Characteristics of capsule masses of FI, FII, and FIII containing microcapsules

No	Parameters	FI	FII	FIII
Capsule masses				
1	Flow property (Direct method), g/s	2.10±0.26 Cohesive	2.27±0.11 Cohesive	2.12±0.38 Cohesive
2	Flow property (Indirect method), α°	19.96±1.06 Excellent	18.60±0.29 Excellent	19.44±1.63 Excellent
3	Particle size distribution (# Mesh; % weight)	20; 0 20/40; 1,14 40/60; 1,50	20; 0 20/40; 0 40/60; 0.8	20; 0.33 20/40; 1.06 40/60; 2.85

		60/80; 5,68 80/100; 41,73 100/120; 40,92 120; 9,02	60/80; 7.2 80/100; 33.6 100/120; 37.6 120; 20.8	60/80; 14.66 80/100; 35.48 100/120; 30.39 120; 15.23
4	Moisture content (%)	5.81±0.45	5.73±0.43	5.30±0.14

Table 3: Characteristics of capsule dosage forms of FI, FII, and FIII containing microcapsules

No	Parameters	FI	FII	FIII
Capsule dosage forms				
1	Cap. weight average deviation (mg)	2.32±1.30	3.15±2.12	1.36±0.92
2	Disintegration time (min.)	5.38	6.07	7.19
3	Antioxidant activities (ppm)	79.76±5.58	57.36±1.40	49.29±0.25
4	Extract release of capsules (Time (min): % release)	5: 19.89±0.62 15: 30.31±1.84 30: 36.30±2.09 45: 51.94±4.53 60: 66.36±1.39	5: 13.21±0.15 15: 15.48±0.62 30: 18.58±0.28 45: 26.15±0.93 60: 32.77±1.18	5: 8.31±0.67 15: 10.54±0.18 30: 11.16±0.56 45: 17.56±0.56 60: 21.98±0.16
5	Release profile of capsules (5-20% in 60 minutes)	Sustained Not match	Sustained Not match	Sustained Best fit

Table 4: Analysis of extract release of FIII using model kinetics

No	Model kinetics	Regression equation	R ²	Conclusion
1	Zero-order	y = 0.2445x + 6.2915	0.9379	-
2	First-order	y = 0.0076x + 0.8800	0.9577	Best fit
3	Higuchi	y = 2.366x + 1.5476	0.8642	-
4	Kosmeyer-Peppas	y = 0.3616 + 0.6240	0.8275	-

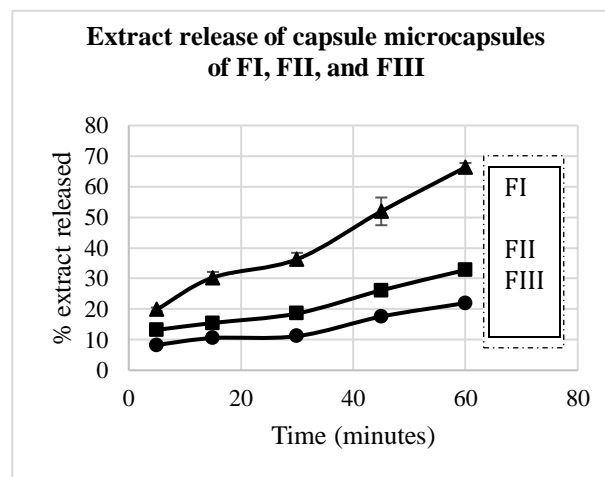


Figure 3: Extract releases in purified water of capsules FI, FII, and FIII.

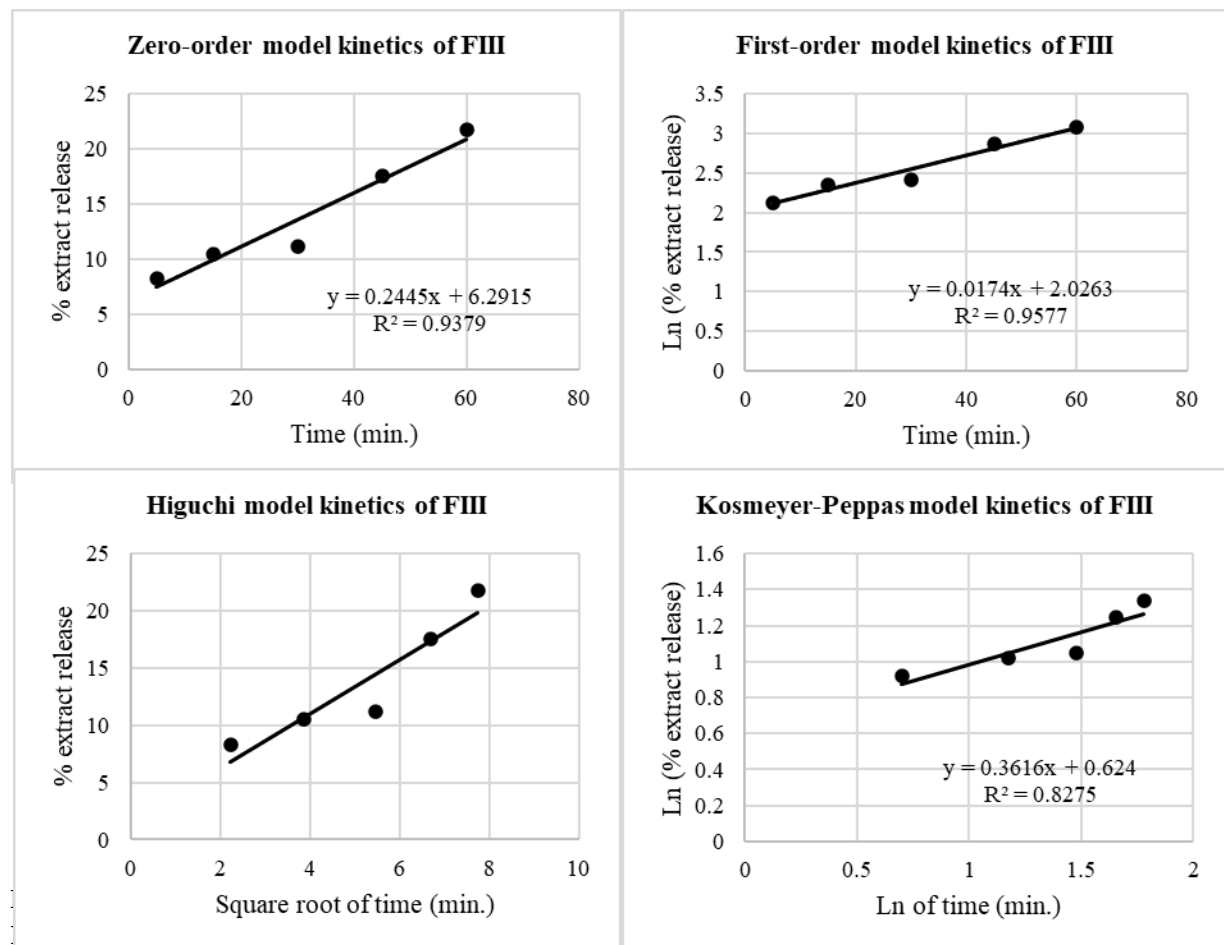


Figure 4: Analysis of extract releases from FIII dosage form using zero-order, first-order, Higuchi, and Kosmeyer-Peppas model kinetics

4. Discussion

4.1 Preparation and Characterization of Cantigi Extract

Plant identification is at the Herbarium Depokensis (UIDEP), Department of Biology, Faculty of Mathematics and Natural Sciences, University of Indonesia, and receives a letter of No. 115/UN2.F3.11/PDP.02.00/2023 stating that the leaves used are from the species *Vaccinium varingaefolium* (Blume) Miq. of the Ericaceae family. The degree of fineness of simplicia powder showed that 100% of simplicia powder passed through the #4 sieve, and 24.35% of simplicia powder passed through the #18 sieve. The fineness of simplicia powder may affect the number of compounds to extract (Ditjen Farmalkes RI, 2017). Preparation extract using the maceration method of 502.346 grams of dried simplicia powder with 5 liters of 70% ethanol results in a thick extract of 156.9 grams (31.23% and a DER-native of 3.20). A DER-native value shows the amount of starting material (simplicia) used to make a unit of extract (Monagas et al., 2022). Table 1 shows the characteristics of the Cantigi extract consisting of organoleptic (color, odor, and appearance), pH, solubility in several solvents, moisture content, antioxidant activity, phytochemistry, and heavy metal content. All characteristics are parts of specific and non-specific parameters and extract standardization (Ditjen Farmalkes RI, 2017).

The results of the organoleptic examination show that the thick extract of Cantigi leaves was dark brown in color with a characteristic cantigi odor. The pH of the Cantigi extract is 4.3, and the flavonoid content in the extract may cause this low pH extracted by the 70% ethanol solvent. The requirement for the water content of the extract is $\leq 10\%$, but the average water content of the extract is 8.67%. Water content above 10% may cause microbial contamination. The antioxidant activity tests use the Cantigi extract and vitamin C (as a control) and the DPPH method. Both results show potent antioxidant activities. This comparison method is to know whether both analyses

of the extract and control are acceptable. The compound group that has a role as natural antioxidants in plants is phenolic compounds. Based on the above phytochemical screening test, one group of natural phenolic compounds is glycosides consisting of flavonoids and tannins. Because of its toxicity, a heavy metal content determination is a requirement. Lead (Pb) and cadmium (Cd) are heavy metals and if they contaminate an extract, there is a high risk of chronic poisoning and weakness. The analysis results show no heavy metal content detected (Ditjen Farmalkes RI, 2017).

4.2 Synthesis and Characterization of Microcapsules

Figure 1 shows four different physical forms of microcapsules consisting of the Blank Formula (F0), Formula 1 (F1), Formula 2 (F2), and Formula 3 (F3). The color of the resulting microcapsules (Figure 1 and Tabel 2 of #2) is affected by the amount of ethyl cellulose as the coating agent. The more ethyl cellulose is used compared to the extract, the brighter the color of the resulting microcapsules will be. While, Figure 2 shows the shape (morphology) of microcapsules generated by an SEM. The greater the ratio of ethyl cellulose to extract, the more the core can be coated and become a better round shape, but this results in the microcapsule particles sticking to each other (Monagas et al., 2022).

Table 2 shows the characteristics of Cantigi extract-loaded microcapsules consisting of organoleptic (odor, color, and shape), recovery, moisture content, entrapment efficiency, drug loading, particle size, drug loading, bulk density, tapped density, compressibility index, and antioxidant activity. Table 2 (#4) shows the relatively low recovery value that may be caused by, during the microencapsulation process, the extract is not coated well due to the poor ratio of coating to extract. Or, during the stirring process, coating material sticks to the walls of the beaker (Sulastri et al., 2019). Table 2 (#5) shows the moisture content of microcapsules. The requirement for moisture content in microcapsules is $\leq 10\%$. The moisture content values of the three microcapsule formulas meet the specification (Monagas et al., 2022). Higher moisture content may cause microbial contamination. Table 2 (#6) shows the encapsulation or entrapment efficiency of the extract in microcapsules. The greater the ethyl cellulose used in the formulation, the greater the cantigi extract can be encapsulated in the microcapsules (Kurniawan et al., 2017). Table 2 (#7) shows the drug loading of Cantigi extract in microcapsules. The smaller the drug loading value, the smaller the amount of ethyl cellulose used. The more the coating is used, the less the extract can be loaded. Table 2 (#8) shows the average of microcapsule particle sizes. The particle size of microcapsules can be affected by the stirring speed and the concentration of ethyl cellulose (coating), where the faster the stirring speed, the smaller the microcapsules formed, and the more ethyl cellulose used, the larger the particle size will be. In addition, a thing that can affect particle size is that the greater the coating ratio in each formula, the larger the particle size will be (Kurniawan et al., 2017) [31]. Table 2 (#9, #10, and #11) shows the bulk and tapped density of microcapsules. The compressibility index of the microcapsules can be determined and the flow characteristics of the powder according to the Carr compressibility index (CI) can be identified using bulk and tapped density data. If the Ci of powder has a percentage value $\leq 10\%$, the powder has excellent flow characteristics. The CI values of the three formulas show excellent flow characteristics. Table 2 (#12) shows the results of the microcapsule antioxidant activity test using the DPPH Method. The IC_{50} value increases from F1 to F3, meaning the IC_{50} value is affected by the ratio of the core to the coating. Moreover, there is an increase in the IC_{50} value in week 4 for each formula, although the increase is not significant, and the IC_{50} values of each formula at week 0 and week 4 remain in the very potent category of antioxidant activity (IC_{50} less than 50 ppm).

4.3 Capsule Dosage Forms Containing Microcapsules of Cantigi Extract

Table 3 shows the characteristics of capsule masses that meet the requirements of flow properties, particle size distribution, and moisture content. Tables 3 of #1 and # 2 show the flow property of capsule mass containing microcapsules of Cantigi extract is based on the direct method and indirect method. If viewed from the flow time alone, the powder flow velocity of the three formulations falls into the cohesive category (1.6-4.0 g/s), but when viewed from the angle of repose value, the powder flow properties are within the excellent category ($<25^\circ$). The flow properties of powder are affected by particle size, particle mass weight, and particle shape. The larger the particle size, the smaller the cohesiveness between the particles, which can increase the powder flow rate (USP 46 - NF 41 <616>, 2023; & USP 46 - NF 41 <1174>, 2023). Also, a glidan addition can improve the capsule mass

flow property without a granulation process. Table 3 of #3 shows the particle size distribution of capsule masses of FI, FII, and FIII. The largest particle size is 165 μm in diameter, meaning that most capsule powder consists of fine particles because it does not go through a granulation process. The particle size distribution shows that A wet or dry granulation if carried out, may produce larger particles. Also, the fine is caused by the sizes of microcapsules having small particle sizes of 0.11-0.26 μm . The particle size distribution of capsule mass is carried out using a mesh-screening method. Table 3 of #4 shows the moisture contents of capsule masses of FI, FII, and FIII. All moisture contents meet specification (<10%). The higher moisture contents may promote microbial growth.

Table 4 presents the characteristics of capsule dosage forms of FI, FII, and FIII containing microcapsules. FIII is the best fit with a specification stating that the active ingredient release is within 5-20% in 60 minutes (Kemenkes RI, 2020; & Han et al., 2013). Table 4 of #1 shows the uniformity of capsule weights presented as their capsule deviation. The data meets the standard of weight variation. Table 4 of #2 shows the disintegration times of capsules meeting the specification of less than 15 minutes. Disintegration time is required for the capsule to break into particles and become available in the molecular form when present in body fluids because the drug absorption by the body is in its molecular form. Table 4 of #4 shows the antioxidant activities of capsule formulations determined using the DPPH method. The capsule antioxidant activity test determines whether the excipient addition would affect the antioxidant activity of microcapsules containing Cantigi extract. The addition of excipients does affect the IC50 value of microcapsules handled by adjusting the dose of microcapsules, and the most potent IC50 value is FIII capsules with a 30 g microcapsule dose of cantigi extract.

Figure 3 shows the extract releases in purified water of capsules FI, FII, and FIII, with the FIII being the best fit with a standard of 5-20% release in 60 minutes (Kemenkes RI, 2020). The release profiles provide a biphasic model. Meanwhile, Table 5 and Figure 4 provide the analysis results of the extract releases of FIII using several model kinetics, such the zero-order, first-order, Higuchi, and Kosmeyer-Peppas by comparing the R^2 of the linear regression. The first-order model kinetics is the best fit with the R^2 of 0.9577. This result is consistent with the previous report (Pinheiro et al., 2007). This result differs from an earlier report using capsules containing gelatin nanoparticles of Cantigi extract. The best fit is the zero-order model kinetics (Kosasih et al., 2024).

5. Conclusions

In conclusion, this study can prepare hard-gelatin capsule dosage forms containing natural antioxidant microcapsules of cantigi extract with first-order and biphasic slow-release profiles.

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