CapsuleDosageFormsContainingNaturalAntioxidant Microcapsules of Cantigi Extract

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.Threemicrocapsuleformulations(F1,F2,andF3)weremadebysolventevaporationmethodusingethyl cellulosecoatingandcharacterizedforcolor,odor,particlesize,shape,recovery,moisturecontent,encapsulation efficiency, drug loading, density, and antioxidant activities. Then, three capsule dosage forms (FI, FII, and FIII) ofmicrocapsules ofthe mostpotentantioxidantactivity, microcrystalline cellulose, and colloidalsilicon dioxide. Theresultsshowedthatthemostpotentmicrocapsuleswere F1,whilethemostpotentcapsuledosageformswere 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-ordermodelkinetics,consistentwitha previous study.Moreover,allcapsule dosage forms have a biphasicslow-release profile for 60 minutes. The conclusion is that this study can prepare hard-gelatin capsule dosage forms containingnaturalantioxidantmicrocapsules ofcantigiextractwithfirst-orderandbiphasicslow-releaseprofiles.

Keywords: CantigiExtract,Capsule DosageForms,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 provideaffordableprices,fewersideeffects,andcurenotonlyoneofthesymptomsordiseasesbutalsoimprove physiological function in the body (Kurek et al., 2022).

Oneoftheplantsthatmaybeasourceofnaturalmedicinesis Cantigi(*Vacciniumvaringiaefolium*(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, antispasmolytic, and antihypertensive. A previous study showed that Cantigi extract has a very potent antioxidant activity (IC_{50}<20 ppm) (Kosasih et al., 2021).

Comment [A1]:
It would be better if in the introduction, the author included a picture or photo of the Cantigi plant.

Comment [A2]: italic

Comment [A3]: italic

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 usingGC-MSmethod,cantigileavescontain33compounds,someofwhichhavepotentialasantioxidants,namely hexamethyl cyclotrisiloxane, 5-(thiopen-2-yl) methyl-2H-tetrazole, hexadecanoic acid methyl ester, 9-octadecenoic acid (Z), beta-mono-olein, 1,2-benzenedicar-boxylic 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,andliverdisease.Theycandestroyareactionchainoffreeradicalformation bydonatingH-atoms,reducingtheconcentrationofreactiveoxygen,reducingfreeradicalsattheinitiationstage, 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 arecoatedwith a coating or encased ina homogeneous or heterogeneous matrix andcreated to give small capsules (Jyothi et al., 2012). It protects micron-sized sensitive substances from the external environmentandprovides controlledrelease.Itmaycontainliquids orsolids withsizes rangingfrom33 nm –20 µm(Abbaspooretal.,2012).Theprincipleofmicroencapsulationistomixacorephase,waterphase,andcoating phase untila stable emulsion forms, thenproceedwith anattaching process of the coating materialto 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 etal., 2021). Therefore, microencapsulating cantigi extract may protect the gastric mucosa while maintaining antioxidant activity caused by unfriendly gastrointestinal conditions. In microcapsule formulations,a coatingaims toprotectthe core substance,whichis non-toxic anddoes notreactwith the extract. Inotherwords,polymers willlayeractive substances (Marieletal.,2022).Coatings formicrocapsules mayuse a combinationofpolymers,suchasethylcellulose,cellulosederivatives,chitosan,alginate,andotherpolymers(Raj et al., 2024;& Singh etal., 2010). In this microcapsule formulation, the coatingpolymer isethyl cellulose. Ethyl celluloseiswater-insolublebutsolubleinvariousorganicsolvents,odorless,colorless,tasteless,andstable.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, solventevaporation,coacervation,andinterfacialpolymerization.Thisstudyusesthesolventevaporationmethod 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. Materialsand 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 PreparationandCharacterizationofCantigi Extract

Cantigiextractionusedakineticmacerationmethodwitharatioof1:10 (drypowder 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 SynthesisandCharacterizationofMicrocapsules

Synthesis of three microcapsule formulations used the below compositions: Cantigi extract (1 g), ethyl cellulose (F1:1,F2:2,andF3:3g),acetone(30mL),liquidparaffin(60mL),tween80(0.78mL),andn-hexane(qs).The ratiosofthecoresubstance(cantigiextract)andthecoating(ethylcellulose)wereF1(1:1),F2(1:2),andF3(1:3). With stirring, dissolved ethyl cellulose in 30 mL of acetone. Cantigi extract was dispersed and stirred for 20 minutes.Inanotherbeaker,60mLofliquidparaffinand0.78mLoftween80weremixedtomakeavehiclephase andcontinuedtostir.Anemulsionwas madebypouringdropbydropthemixtureofcoatingsolutionandcantigi extractdispersiontothevehiclephase,stirredat850rpmandroomtemperaturefor2.50hoursuntilalltheacetone 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; Brleket al., 2021; &Yasin et al., 2021).Characterizationsof microcapsules includeorganoleptic(color,odor,shape),recovery,moisturecontent,entrapmentefficiency,drugloading,particle size distribution, bulk and tapped density (Raj et al., 2024; Hibrah et al., 2022; DitjenFarmalkes, 2022; Song et al., 2022; & Choudhury et al., 2021), and antioxidant activity (Yamauchi et al., 2024).

2.2.3 CapsuleDosageFormsContainingMicrocapsulesofCantigi Extract

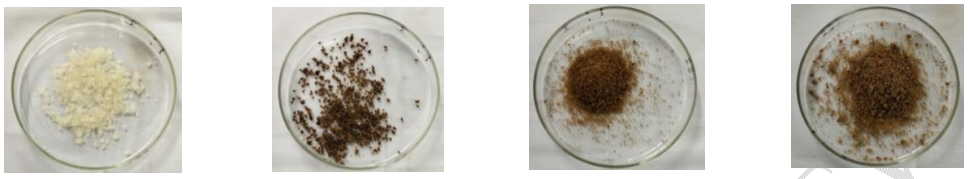
Capsuledosageforms(FI,FII,andFIII)containmicrocapsules(10,20,and30mgeach),colloidalsilicondioxide (2.32,2.24,and2.16mgeach),microcrystallinecellulosePH102(addto300,300,and300each).Thetotalweight percapsuleis300mg.Capsulemasswasmadebymixingallcomponentsandfillinginto#2hard-gelatincapsules. Before filling 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, theresultingcapsuleswereexaminedformassuniformity,disintegrationtime,andreleaseprofile(Šedbarė,2023).

3. Results

Table1:CharacteristicsofspecificandnON-specificparametersofCantigiextract

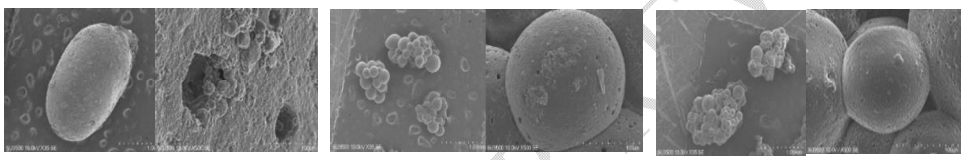
Testparameters	Results
Organoleptic: Color	Darkbrown
Odor	Cantigispecific
Appearance	Thick
pH	4.30±0.01
Solubility: in methanol	Soluble
inethanol 96%	Soluble
inDMSO	Freelysoluble
inpurified water	Soluble
Moisturecontent (%)	8.67±1.56
Antioxidantactivity(IC_{50},ppm)	17.40±1.00ppm(Cantigiextract)

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



(a) (b) (c) (d)

Figure1:FourdifferentphysicalformsofmicrocapsulescontainingCantigiextract. Microcapsules ofF0(a),F1(b),F2(c),andF3(d).



(a) (b) (c)

Figure 2:Shape (morphology)ofmicrocapsulesgeneratedbyanSEM.(a)=F1,(b)=F2,and(c)=F3.

Table2:Characteristics ofMicrocapsules containingCantigi extract

No	Parameters	F1	F2	F3
1	Odor	SpecificCantigi	SpecificCantigi	SpecificCantigi
2	Color	Darkbrown	Lightbrown	Lightbrown
3	Shape	Powder	Powder	Powder
4	Recovery(%)	77.66±0.15	91.74±0.24	87.91±0.01
5	Moisturecontent (%)	3.67±0.34	8.67 ± 0.09	5.10 ±0.10
6	Entrapmentefficiency(%)	73.18±0.33	83.86±0.26	83.84±0.01
7	Drugloading(%)	64.00±0.19	36.31±0.12	28.29±0.00
8	Particlesize (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	Compressibilityindex(%)	4.67±1.16	2.61±0.00	2.27±0.39
12	Antioxidantactivity(IC50,ppm) Week-0 Week-4	 19.3±0.28 22.75±0.52	 27.19±1.12 33.94±0.80	 44.92±0.91 49.38±1.66

Table3:Characteristics ofcapsule masses ofFI,FII,andFIIIcontainingmicrocapsules

No	Parameters	FI	FII	FIII
Capsulemasses				
1	Flowproperty(Directmethod),g/s	2.10±0.26 Cohesive	2.27±0.11 Cohesive	2.12±0.38 Cohesive
2	Flowproperty(Indirectmethod),α°	19.96±1.06 Excellent	18.60±0.29 Excellent	19.44±1.63 Excellent
3	Particlesizedistribution (# 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	Moisturecontent (%)	5.81±0.45	5.73±0.43	5.30±0.14

Table3:Characteristics ofcapsuledosageformsofFI,FII,andFIIIcontaining microcapsules

No	Parameters	FI	FII	FIII
Capsuledosageforms				
1	Cap.weightaverage deviation (mg)	2.32±1.30	3.15±2.12	1.36±0.92
2	Disintegrationtime (min.)	5.38	6.07	7.19
3	Antioxidantactivities (ppm)	79.76±5.58	57.36±1.40	49.29±0.25
4	Extractreleaseofcapsules (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	Releaseprofileofcapsules (5-20% in 60 minutes)	Sustained Notmatch	Sustained Notmatch	Sustained Best fit

Table 4:Analysis ofextractrelease ofFIIIusingmodelkinetics

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

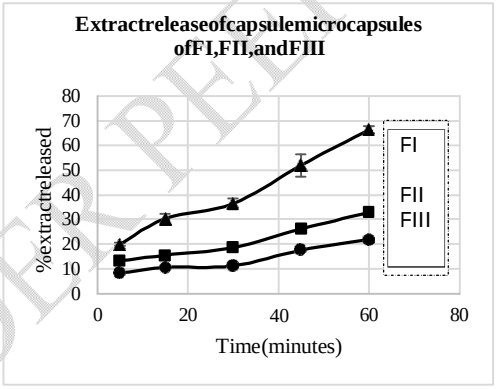


Figure3:Extractreleases inpurifiedwaterofcapsulesFI,FII,andFIII.

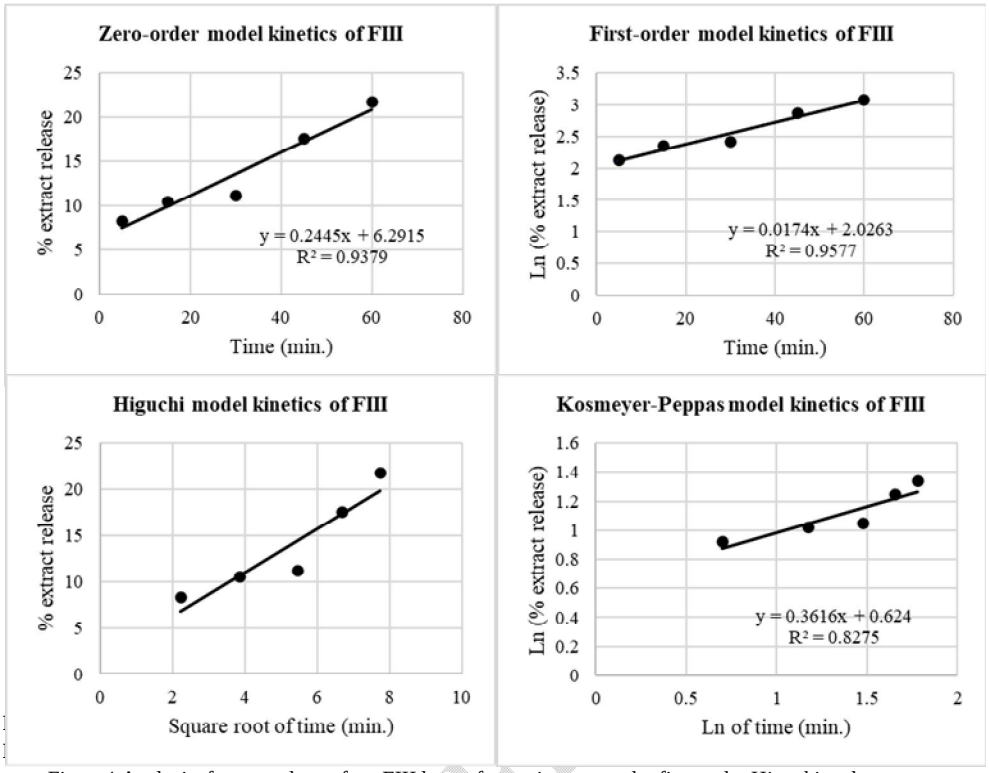


Figure4:AnalysisofextractreleasesfromFIIIdosageformusingzero-order,first-order,Higuchi,and Kosmeyer-Peppas model kinetics

4. Discussion

4.1 Preparationand Characterization ofCantigiExtract

PlantidentificationisattheHerbariumDepokensis(UIDEP),DepartmentofBiology,FacultyofMathematicsand 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 varingiaefolium (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%ofsimpliciapowderpassedthroughthe#18sieve.Thefinenessofsimpliciapowdermayaffectthenumber ofcompoundstoextract(DitjenFarmalkesRI,2017).Preparationextractusingthemacerationmethodof502.346 gramsofdriedsimpliciapowderwith5litersof70%ethanolresultsinathickextractof156.9grams(31.23%and aDER-nativeof3.20).ADER-nativevalueshowstheamountofstartingmaterial(simplicia)usedtomakeaunit ofextract(Monagasetal.,2022).Table1showsthecharacteristicsoftheCantigiextractconsistingoforganoleptic (color, odor, and appearance), pH, solubility in several solvents, moisture content, antioxidant activity, phytochemistry,andheavymetalcontent.Allcharacteristicsarepartsofspecificandnon-specificparametersand extract standardization (DitjenFarmalkes RI, 2017).

TheresultsoftheorganolepticexaminationshowthatthethickextractofCantigileaves was darkbrownincolor withacharacteristiccantigiodor.ThepHoftheCantigiextractis4.3,andtheflavonoidcontentintheextractmay causethislowpHextractedbythe70%ethanolsolvent.Therequirementforthewatercontentoftheextractis ≤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.Bothresultsshowpotentantioxidantactivities.Thiscomparisonmethodistoknowwhetherbothanalyses

of the extract and control are acceptable. The compound group that has a role as natural antioxidants in plants is phenoliccompounds.Basedontheabovephytochemicalscreeningtest,onegroupofnaturalphenoliccompounds isglycosides consistingofflavonoids andtannins.Becauseofitstoxicity,aheavymetalcontentdeterminationis 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 (DitjenFarmalkes RI, 2017).

4.2 Synthesis and CharacterizationofMicrocapsules

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) isaffectedbytheamountofethylcelluloseasthecoatingagent.Themoreethylcelluloseisusedcomparedtothe extract,thebrighterthecoloroftheresultingmicrocapsuleswillbe.While,Figure2showstheshape(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).

Table2shows thecharacteristics ofCantigiextract-loadedmicrocapsulesconsistingoforganoleptic(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 recoveryvaluethatmaybecausedby,duringthemicroencapsulationprocess,theextractisnotcoatedwelldueto thepoorratioofcoatingtoextract.Or,duringthestirringprocess,coatingmaterialstickstothewallsofthebeaker (Sulastri et al., 2019). Table 2 (#5) shows the moisture content of microcapsules. The requirement for moisture content in microcapsules is ≤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 extractin microcapsules. The greater the ethyl cellulose usedintheformulation,thegreaterthecantigiextractcanbeencapsulatedinthemicrocapsules (Kurniawanetal., 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 affectedbythestirringspeedandtheconcentrationofethylcellulose(coating),wherethefasterthestirringspeed, 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 andtapped density of microcapsules.Thecompressibility indexof the microcapsules canbe determined and theflow 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 ≤ 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 antioxidantactivity test usingthe DPPHMethod.TheIC_{50}valueincreases from F1 to F3, meaning the IC50 value is affected by the ratio of the core to the coating. Moreover,there is an increase in the IC_{50}value inweek4foreachformula,althoughtheincreaseis notsignificant,andtheIC_{50}valuesofeachformulaatweek0 and week 4 remain in the very potent category of antioxidant activity (IC_{50}less than 50 ppm).

4.3 CapsuleDosageFormsContainingMicrocapsules ofCantigi 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 ofCantigiextractis basedonthedirectmethodandindirectmethod.Ifviewedfromtheflow 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˚). The flow properties of powder are affected by particle size, particle mass weight, and particle shape. The larger the particlesize,thesmallerthecohesivenessbetweentheparticles,whichcanincreasethepowderflowrate(USP46 -NF41<616>,2023;&USP46-NF41<1174>,2023).Also,aglidanadditioncanimprovethecapsulemass

flow property without a granulation process. Table 3 of #3 shows the particle size distribution of capsule masses of FI, FI, and FIII. The largest particlesize is165 µmin diameter, meaning thatmostcapsulepowderconsists of fineparticlesbecauseitdoesnotgothroughagranulationprocess.Theparticlesizedistributionshowsthat Awet ordrygranulationifcarriedout,mayproducelargerparticles.Also,thefineiscausedbythesizesofmicrocapsules 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 4presents thecharacteristics of capsule dosageforms ofFI, FII, and FIII containing microcapsules. FIII is thebestfitwithaspecificationstatingthattheactiveingredientreleaseiswithin5-20%in60minutes(Kemenkes RI, 2020; & Han et al., 2013). Table 4 of #1 shows the uniformity of capsule weights presented as their capsule deviation.Thedatameetsthestandardofweightvariation.Table4of#2showsthedisintegrationtimesofcapsules meeting the specification of less than 15 minutes. Disintegration time is required for the capsule to break into particles andbecomeavailableinthemolecularformwhenpresentinbodyfluids becausethedrugabsorptionby thebodyisinitsmolecularform.Table4of#4showstheantioxidantactivitiesofcapsuleformulationsdetermined 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 ofmicrocapsules handled by adjusting the dose ofmicrocapsules, and the mostpotentIC50 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 modelkinetics,suchthezero-order,first-order,Higuchi,andKosmeyer-PeppasbycomparingtheR^{2}ofthelinear regression. The first-order model kinetics is the best fit with the R2 of 0.9577. This result is consistent with the previous report (Pinheiro et al., 2007). This result differs from an earlier report using capsulescontaining 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.

Informed Consent Statement/Ethics approval: "**Not applicable**."

Data Availability Statement: "Not applicable."

References

Abbaspoor, S., Ashrafi, A., & Salehi, M. (2018). Synthesis and characterization of ethyl cellulose micro/nanocapsules using solvent evaporation method. *Colloid and Polymer Science*, 296, 1509–1514. https://doi.org/10.1007/s00396-018-4371-2.

Ahangaran,F.(2022).*Chapter18-Microencapsulation:Solventevaporation.*In:Sefat,F.,Farzi,G.,&Mozafari, M., eds. (2022). Principles of Biomaterials Encapsulation Vol. 1.Woodhead Publishing Series in Biomaterials. https://doi.org/10.1016/B978-0-323-85947-9.09993-3

Brlek,I.,Ludaš,A.,&Sutlović,A.(2021).Synthesisandspectrophotometricanalysisofmicrocapsulescontaining immortelle essential oil. *Molecules*, 26(8), 2390. https://doi.org/ 10.3390/molecules26082390. PMCID: PMC8074605. PMID: 33924209.

Choudhury, N., Meghwal, M., Das K. (2021). Review article: Microencapsulation, an overview on concepts, methods, properties, and applications in foods. *Food Frontiers*, 2(4), 426-442. https://doi.org/10.1002/fft2.94.

DitjenFarmalkes RI.(2017). *Farmakope HerbalIndonesiaEdisiII.*KemenkesRI.

DitjenFarmalkes.(2022).*Farmakope HerbalIndonesiaEdisiII:SuplemenI.*KemenkesRI.

Han, X., Wang, L., Sun, Y., Liu, X., Liu, W., Du, Y., Li, L., & Sun, J. (2013). Preparation and evaluation of sustained-release diltiazem hydrochloride pellets. *Asian Journal of Pharmaceutical Sciences*, 8, 244-251.

Hibrah,H.,Ikhsandy,F.,Yahya,A.K.,&Rosalina,R.(2022).Variationoftimeandethanolsolventconcentration of kinetic maceration tannin extraction from aromatic *Areca catechu. JurnalIlmu Teknik Kimia*, 6(1), 9. https://doi.org/ 10.32493/jitk.v6i1.14180

Janczura, M., Sip, S., &Cielecka-Piontek, J. (2022). The development of innovative dosage forms of the fixed-dose combination ofactive pharmaceutical ingredients. *Pharmaceutics*, 14(4), 834. https://doi.org/10.3390/ pharmaceutics14040834. PMID: 35456668; PMCID: PMC9025674.

Jyothi, S.S., Seethadevi, A., Prabha, K.S., Muthuprasanna, P., & Pavitra, P. (2012). Microencapsulation: A Review. *International Journal of Pharmacy and Biological Sciences*, 3, 509-531.

KemenkesRI.(2020).*Diltiazemhydrochlorideextended-releasecapsules.*InKemenkesRI.FarmakopeIndonesia Edisi 6. Kemenkes RI, p. 425.

Kosasih,K.,Sumaryono,W.,Mudhakir,D.,Supriyono,A.,Christian,Y.E.,&Debora,R.(2021).Effectsofgelatin and glutaraldehyde concentrations on characteristics of Cantigi (Vaccinium varingiaefoliumMiq.) extract loaded gelatin nanoparticles as antioxidant. *Journal ofHalal Product and Research*, 4(1), 1-7.

Kosasih,K.,Sumaryono,W.,Supriyono,A.,&Mudhakir,D.(2020).Possiblecytotoxicactivityanalysisofdiethyl ether extract of Vaccinium varingiaefolium (Blume) Miq leaves by GC-MS method. *Journal of Pharmaceutical Science and Research*, 12(6), 840-847.

Kosasih, K., Sumaryono, W., Supriyono, A., &Mudhakir, D. (2022). (Cytotoxic effect of Cantigi [Vaccinium varingiaefolium (Blume) Miq.] extracts on T47D cells. AIP Conference Proceeding, 2563, 050014. https://doi.org/10.1063/5.0103147.

Kosasih, K., Susanty, D., Asianski, I.P.H., &Maryanto, D.I. (2024). Formulation and characterization of antioxidant capsules containing Cantigi extract-loaded nanoparticles synthesized via nanoprecipitation method. *Journal of Natural Product for Degenerative Diseases*, 1(2), 79-85. https://doi.org/10.58511/jnpdd.vli2.6352.

Kurek, M., Benaida-Debbache, N., Garofulić, I.E., Galić, K., Avallone, S., Voilley, A., &Waché, Y. (2022). Antioxidantsandbioactivecompoundsinfood:Criticalreviewofissuesandprospects. *Antioxidants*,11(4), 742. https://doi.org/10.3390/antiox11040742.

Kurniawan,R.,&Rahmat,D.(2017).Mikroenkapsulasicontrolledreleaselansoprazoldengankombinasihydroxy propyl methyl cellulose phthalate dan natrium alginatsecaragelasiionotropik. *Indonesian Journal of Pharmaceutical Sciences*, 14(1), 86-92. https://jifi.farmasi.univpancasila.ac.id/index.php/jifi/ article/view/ 57/44

Mariel, C-O., & Edith, P-A. (2022). The role of microencapsulation in food application. *Molecules*, 27(5), 1499. https://doi.org/10.3390/molecules27051499. PMCID: PMC8912024; PMID: 35268603

Monagas,M.,Brendler,T.,Brinckmann,J.,Dentali,S.,Gafner,S.,Giancaspro,G.,Johnson,H.,Kababick,J.,Ma, C., Oketch-Rabah, H., Pais, P., Sarma, N., & Marles, R. (2022). Understanding plant to extract ratios in botanical extract. *Frontiers in Pharmacology*, 13, 981978. https://doi.org/10.3389/fphar.2022.981978.

Murtaza,G.(2012). Ethylcellulosemicroparticles:areview. *ActaPoloniae Pharmaceutica*,69(1),11-22.PMID: 22574502

Paulo, F., & Santos, L. (2017). Design of experiments for microencapsulation applications: A review. *Materials Sciece Engineering C Materials for Biological Applications*, 1(77), 1327-1340. https://doi.org/10.1016/j.msec.2017.03.219.

Pinheiro,V.A.,Kaneko,T.M.,Velasco,M.V.R.,&Consiglieri,V.O.(2007).Developmentandinvitroevaluation ofextended-releasetheophyllinematrixcapsules.*BrazilianJournalofPharmaceuticalSciences*,43(2),253- 261.

Raj,R.,Nizar,S.,Bhattacharyya,C.,&Savanur,MA.(2024).*Advancesinmicroencapsulationandnanoemulsion techniquesofplantpigments:Improvingstability,bioavailability,andbioactivityforapplicationinthefood industry*. In: Mérillon JM, Ramawat KG, (eds). Plant Specialized Metabolites. Reference Series in Phytochemistry. Springer. https://doi.org/10.1007/978-3-031-30037-0_46-1.

Šedbarė,R.,Janulis,V.,&Ramanauskiene,K..(2023).Formulationandbiopharmaceuticalevaluationofcapsules containing freeze-dried Cranberry fruit powder. *Plants*, 12(6), 1397. https://doi.org/ 10.3390/plants12061397. PMCID: PMC10057423. PMID: 36987086

Singh,M.N.,Hemant,K.S.Y.,Ram,M.,&Shivakumar,H.G.(2010).Microencapsulation:Apromisingtechnique for controlled drug delivery. *Research in Pharmaceutical Sciences*, 5(2), 65–77. PMID:21589795

Song, X-C., Yu, Y-L., Yang, G-Y., Jiang, A-L., Ruan, Y-J., & Fan, S-H. (2022). One-step emulsification for controllable preparation of ethyl cellulose microcapsules and their sustained release performance. *Colloids and Surface B*, 216, 112560. https://doi.org/10.1016/j.colsurfb.2022. 112560

Sulastri, E., Ibrahim, N., & Budiarti, S. (2019). Mikroenkapsulasilikopendaribuahtomatdenganmetodepenguapanpelarut (Microencapsulation of lycopene from tomato fruit by solvent evaporation method). *Galenika Journal of Pharmacy*,5(1), 108-116. https://doi.org/10.22487/j24428744.2019. v5.i1.12406

USP 2023 (United States Pharmacopeia 46 - NF 41):*General Chapter, <921> Water Determination*. webofpharma.com. https://doi.org/10.31003/USPNF_M99710_02_01

USP 2023 (United States Pharmacopeia 46 - NF 41):*General Chapter, <786> Particle Size Distribution Estimation by Analytical Sieving.* webofpharma.com. https://doi.org/10.31003/ USPNF_ M99584_02_01

USP2023(UnitedStatesPharmacopeia46-NF41):*GeneralChapters,<616>BulkDensityandTappedDensity of Powders.* webofpharma.com. https://doi.org/10.31003/USPNF_ M99375_01_01

USP2023(UnitedStatesPharmacopeia46-NF41):*GeneralChapter,<1174>PowderFlow.*webofpharma.com. https://doi.org/10.31003/USPNF_M99885_01_01

Yamauchi, M., Kitamura, Y., Nagano, H., Kawatsu, J., & Gotoh, H. (2024). DPPH measurements and structure-activity relationship studies on the antioxidant capacity of phenols. *Antioxidants*, 13(3), 309. https://doi.org/10.3390/antiox13030309

Yan, C., & Kim, S-R. (2024). Microencapsulation for pharmaceutical applications: A review. *ACS Applied Bio Materials*, 7(2), 692–710. https://doi.org/10.1021/acsabm.3c00776

Yasin, H., Al-Taani, B., & Salem, M.S. (2021). Preparation and characterization of ethylcellulose microspheres for sustained-release of pregabalin. *Research in Pharmaceutical Sciences*, 16(1), 1–15. https://doi. org/10.4103/1735-5362.305184. PMCID: PMC8074809. PMID: 33953770

Yulyana,A.,Winarno, H.,&Kosasih,K. (2016).KarakterisasiekstrakdaunCantigi (*Vacciniumvaringiaefolium* Miq.).*JurnalSainsdanKesehatan*,1(5),276-283. https://doi.org/10.25026/jsk.v1i5.50