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Tablet Formulation Containing Chitosan-Alginate Microparticles: Characterization and Release Profile of Xanthones

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Abstract. Mangosteen pericarp extract contains a high amount of xanthones, which are secondary plant metabolites that exhibit high antioxidant activities as well as beneficial pharmacological properties, but low bioavailabilities. In this study, xanthones extracted from the pericarp of soursop fruit were encapsulated in chitosan-alginate microparticles by ionic gelation, and the microparticles were subsequently formulated into antioxidant supplement tablets by direct compression. One of the tablet formulations satisfied the requirements for weight and size uniformity as well as friability, but not hardness. Dissolution test results revealed similar release profiles characterized by a burst release that occurs in the first 60 min of immersion in simulated gastrointestinal fluids and a complete release of xanthones in 120 min. The results obtained herein demonstrated the potential of the tested tablet formulations for the delivery of xanthones into the gastrointestinal tract. If a targeted release to a specific area in the gastrointestinal tract is desirable, the composition of the excipients in the present formulation should be modified.

Keywords: Alginate; Chitosan; Mangosteen; Mangostin; Xanthone

1. Introduction

Food supplements are food products intended to complement a diet with vitamins, minerals, or other substances in concentrated amounts that exert physiological effects (Nicoletti, 2012). Antioxidant compounds present in food supplements reduce the incidence of chronic diseases caused by free radicals in the body, such as cancer, brain dysfunction and heart disease. Although the body can produce antioxidants from cell metabolism, the additional intake of antioxidants is required as the number of free radicals increases.

Meanwhile, the pericarp of mangosteen fruit (*Garcinia mangostana L.*) contains bioactive compounds known as xanthones, which exhibit high antioxidant activities (Jung et al., 2006; Palakawong et al., 2010; Chaovanalikit et al., 2012), and α-mangostin and γ-mangostin are the main derivatives of xanthones (Al-Massarni et al., 2013; Mulia et al., 2015). Figure 1 shows their molecular structures. Mangostins have been reported to exhibit cytotoxic effects, with the ability to induce the apoptosis of cancer cells and to selectively kill cancer cells (Pedraza-Chaverri et al., 2008; Genoux-Bastide et al., 2011).

Owing to its biodegradable, non-toxic and mucoadhesive properties, chitosan is an extensively investigated biopolymer for drug delivery. It has been used in controlled-

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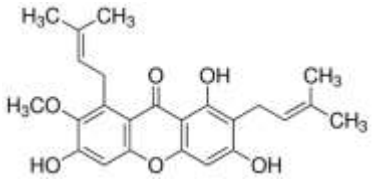
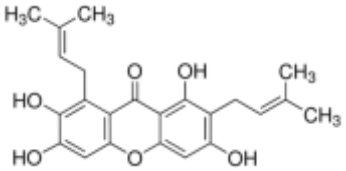
release oral formulations to increase the bioavailability of easily degraded drugs and bioactive compounds such as antibiotics, anticancer agents, proteins, peptides and vaccines (Sinha et al., 2004).



α-mangostin



γ-mangostin

Figure 1 Molecular structures of α-mangostin and γ-mangostin

Alginate is another biodegradable and non-toxic polymer typically used in drug formulations and as a food additive (Tonnesen and Karlsen, 2002). In contrast to chitosan, alginate exhibits stable properties under an acidic pH in the stomach, while it undergoes swelling and dissolution at a more neutral pH in the intestine (Kumar et al., 2005). A tablet is the most commonly used oral formulation for the delivery of drugs into the gastrointestinal tract, comprising active substances and excipients such as diluents, binders, lubricants, crushing agents, coatings, flavoring ingredients and other additives (Ansel et al., 1999). Direct compression is employed to manufacture tablets via the direct compression of a mixture of active substances and dry excipients without prior treatment.

Xanthones, often reported as α-mangostin, have been encapsulated in various chitosan-alginate formulations including powder in a capsule (Peerapattana et al., 2013), microparticles (Krisanti et al., 2017; Mulia et al., 2020), effervescent tablets (Widowati et al., 2013), dispersion in a microgel (Ahmad et al., 2012), tablets (Tamat et al., 2014), hydrogel films (Wathoni et al., 2019) and freeze-dried matrices (Mulia et al., 2019). Recently, the optimization of chitosan-alginate microparticles by using the Box–Behnken experimental design confirmed that alginate is a suitable biopolymer to complement chitosan for the delivery of mangostin to the colon area (Mulia et al., 2020). For further investigation, tablet formulations of microparticles as an antioxidant supplement were prepared and tested. In this study, physicochemical characteristics of tablet formulations of xanthone-loaded chitosan-alginate microparticles (including dissolution, hardness and friability tests), as well as the release profile of xanthones in simulated gastrointestinal fluids, were investigated.

2. Methods

2.1. Chemicals

Mangosteen pericarp was purchased from Solo, Central Java, and it was identified as *G. mangostana L.* by the Herbarium Bogoriense, Research Center for Biotechnology-Indonesian Institute of Science. Standard α-mangostin (98%) was purchased from Aktin Chemicals, China. Chitosan (medical grade; degree of acetylation = 93.6%; viscosity of 23.3 cps) was obtained from Biotech Surindo, Indonesia. Food-grade sodium tripolyphosphate was obtained from Brataco Chemical, Indonesia. Calcium chloride, alginate, KH_2PO_4, HCl, KCl, NaOH, sodium carboxymethyl cellulose (NaCMC), mannitol, lactose, talc and magnesium stearate were purchased from Merck, Indonesia. α-Amylase and β-glucosidase were purchased from Sigma, Singapore.

2.2. Preparation of Mangosteen Extract in the Ethyl Acetate Fraction

Mangostin was obtained from the mangosteen pericarp extract by solvent extraction based on a reported previously procedure (Jung et al., 2006). Mangosteen pericarp was washed and drained under sunlight for 5 days, ground to a powder, macerated for 7 days in 96% ethanol (mangosteen powder to ethanol ratio of 1:3 w/v), and stirred periodically. Then, the mixture was filtered, and ethanol was evaporated using a rotary evaporator (EYEELA N-1000) to obtain a viscous ethanolic extract. Next, the ethanolic extract was subjected to fractionation using a mixture of water and ethyl acetate in a 1:1 ratio (v/v). The ethyl acetate fraction was separated, concentrated and dried to obtain the mangostin extract.

2.3. Qualitative and Quantitative Analysis of Mangostin and Xanthone

A liquid chromatography–mass spectrometer (LCMS) was employed for the qualitative analysis of xanthones present in the mangosteen extracts. Mass spectra were recorded in the negative-ion mode with a collision energy range of 4–75 V for 22 min. The presence as well as amount of α-mangostin in the ethyl acetate fraction were determined by a Shimadzu high-performance liquid chromatography (HPLC) apparatus equipped with a reverse-phase C18 column (240 mm × 4.6 mm, 5 µm) and operated at a temperature of 30 °C. The mobile phase comprised 95% acetonitrile and 5% buffer (0.1% H_3PO_4), the flow rate was 1 mL/min, and the UV detector was set at a wavelength of 244 nm (Aisha et al., 2012a). The retention time of α-mangostin in the ethyl acetate fraction was matched to that of standard α-mangostin.

UV spectrophotometry at an absorption wavelength of 316 nm (Spectroquant® Pharo 300 Merck) with α-mangostin as the marker compound was employed to analyse the amount of total xanthones in the ethyl acetate fraction and in the chitosan-alginate microparticles, as well as in the simulated gastrointestinal fluids (Aisha et al., 2013). The standard calibration curve was prepared from the absorbance data of α-mangostin standard solutions (4–20 mg/L); therefore, the amount of xanthones is reported as the α-mangostin equivalent.

2.4. Microparticle Preparation

Chitosan-alginate microparticles were prepared by ionic gelation with tripolyphosphate (TPP) as the crosslinking agent (Yu et al., 2009). First, 0.1 g of the mangostin extract was dissolved in a small amount of ethanol before being added into 50-mL of an acetic acid solution (2.5% v/v) containing 1 g of chitosan. Second, the mixture was mixed using a four-blade impeller (IKA Labortechnik) at 1000 rpm for 15 min until a homogeneous solution was obtained. Then, the mangostin-chitosan solution was dropped into 100 mL of a 1% (w/v) TPP solution using a syringe and stirred at an impeller speed of 600 rpm for 10 min. Then, the solution was kept inside a covered glass beaker at room temperature for 30 min. Next, the formed beads of mangostin-loaded TPP-linked chitosan were separated, washed with water and dried using a vacuum filter. The dry beads were ground using a mortar and sieved to obtain particles with a size of less than 100 µm. The chitosan-mangostin-TPP particles were encapsulated with alginate by the addition of the particles into the alginate solution (0.25 g of alginate in 12.5 mL of water). Mixing was performed by setting the impeller to 1000 rpm for 15 min until a homogeneous suspension was formed. The chitosan-alginate suspension was slowly dropped into the $CaCl_2$ solution (6% w/v) and kept for 30 min at room temperature. Then, the formed beads were washed with water, separated using a vacuum filter and dried using a freeze dryer (EYELA FDU-1200; –49°C; 12 Pa). Dry particles were ground using a mortar and sieved to form particles with a size of less than 100 µm, followed by storage in a clear vial for further use.

2.5. Determination of Encapsulation Efficiency and Loading of Xanthones

Encapsulation efficiency and loading were calculated by the quantification of xanthones present in the supernatant during particle preparation by the following formulas:

$$\text{Encapsulation efficiency (\%)} = \frac{\text{mass of xanthones in microspheres}}{\text{mass of drug used}} \times 100 \quad (1)$$

$$\text{Loading (\%)} = \frac{\text{mass of xanthones in microspheres}}{\text{total mass of microspheres}} \times 100 \quad (2)$$

2.6. SEM Analysis

Scanning electron microscopy (SEM) was employed to observe the morphology of the microparticles. Table 1 summarizes the composition of microparticles used for SEM analysis.

Table 1 Microparticle composition

Composition			Microparticle
Extract (g)	Chitosan (g)	Alginate (g)	
0.1	1	0.25	A
0.2	1	0.25	B
0.4	1	0.25	C

2.7. Tablet Preparation

For the manufacture of supplement tablets, active and excipient substances were mixed according to the composition for formulas D1 and D3 as shown in Table 2. The two tablets comprised different percentages for NaCMC, mannitol and lactose, while the percentages for Mg stearate and talc were the same. The weight of each tablet was maintained constant at 500 mg. The tablets were prepared by direct compression, which involved the direct mixing of excipient ingredients with microparticles and printing using a tablet printing machine.

Table 2 Tablet composition

Ingredients (mg)	Composition			
	D1 (mg)	%	D3 (mg)	%
Chitosan-alginate microparticles	200	40	200	40
NaCMC	10	2	50	10
Mannitol	230	46	150	30
Lactose	35	7	75	15
Mg stearate	2.5	1	2.5	1
Talc	22.5	5	22.5	5
Total	500	100	500	100

2.8. in vitro Xanthone Release

The release profile of xanthones from chitosan-alginate microparticles was obtained using simulated gastrointestinal fluids: simulated gastric fluid (SGF) with a pH of 1.2 (buffer 0.2 M KCl and 0.2 M HCl in a ratio of 1:1.7), simulated intestinal fluid (SIF) with a pH of 7.4 (buffer 0.1 M KH_2PO_4 and 0.1 M NaOH in a ratio of 1:0.782) and simulated colonic fluid (SCF)

with a pH of 6.8 (buffer 0.1 M KH_2PO_4 and 0.1 M NaOH in a ratio of 1:0.448). To investigate the in vitro release, 100 mg of particles was immersed in 50 mL of simulated fluid at an incubation temperature of 37°C. The cumulative release of xanthones was monitored by sampling 4 mL of the simulated gastrointestinal fluids every 30 min for 120 min (SGF) or every 60 min for 240 min (SIF and SCF). The concentration of xanthone as the α-mangostin equivalent was determined by UV spectrophotometry. The profile release was obtained by plotting the percentage of the cumulative release of xanthones as a function of time.

2.9. Physical Characteristic Test

A series of tests were performed to determine the physical characteristics of the tablets. Test parameters for the physical appearance of a tablet included shape, colour, surface shape and taste. Size uniformity was determined by the diameter and thickness measurement of each tablet using a caliper: The diameter could not be more than three times and not less than 1⅓ of the thickness of the tablet. Weight uniformity was determined by weighing each sample and calculating the average weight: No more than two tablets could exhibit deviation from the permissible values. Tablet hardness was determined using the Erweka hardness tester. The tablet was placed perpendicular to the instrument, and the pressure at which the tablet breaks was recorded. Generally, the hardness of tablets ranges from 4 to 10 kPa depending on their diameter and thickness. Friability was determined by using the Erweka friability tester, and tablets were declared eligible if the weight loss was no greater than 1% (Lachman et al., 1986). Three tablets were cleaned to remove dust, and the total weight was determined; the tablets were subsequently inserted into the device, which was operated at 25 rpm for 4 min. The tablets were cleaned again to remove dust and weighed again. Friability was calculated as the percentage of the tablet weight loss.

2.10. Dissolution Test

The dissolution test was conducted by using a paddle-type dissolution apparatus at a rotation speed of 50 rpm. Each tablet was placed in 500 mL of simulated gastrointestinal fluid (SGF, SIF, or SCF) maintained at a temperature of 37±0.5°C. The three simulated gastrointestinal fluids were used as the dissolution medium: SGF with a pH of 1.2 (buffer 0.2 M KCl and 0.2 M HCl in a ratio of 1:1.7), SIF with a pH of 7.4 (buffer 0.1 M KH_2PO_4 and 0.1 M NaOH in a ratio of 1:0.782) and SCF with a pH of 6.8 (buffer 0.1 M KH_2PO_4 and 0.1 M NaOH in a ratio of 1:0.448).

The xanthones released from each tablet were monitored by taking samples of SGF (4 mL every 30 min for 120 min) and of SIF or SCF (4 mL every 60 min for 240 min). The total volume of the release media was maintained constant by the addition of 4 mL of fresh simulated gastrointestinal fluid after each sampling. The concentration of xanthone as the α-mangostin equivalent was determined by the absorption measurement of samples by using a UV–Vis spectrophotometer set at a wavelength of 316 nm. The percentage of the cumulative release of xanthones as a function of time was calculated and reported as release profiles.

3. Results and Discussion

3.1. Analysis of Xanthone Extract by LCMS, HPLC and UV–Vis Spectrometry

The final yield of the obtained extract was 6.1% (w). Table 3 summarizes the list of xanthones in the ethyl acetate extract as determined by LCMS, in addition to their compositions in relative percentage, which are calculated on the basis of the peak area of each component. Eight derivatives of xanthones were identified from the extract of mangosteen pericarp: α-Mangostin was the most abundant component.

Table 3 Extract composition

Compound	Composition (%)		
	LCMS	HPLC	UV-Vis
Garcinone C	3.6		
α-Mangostin	52.7	73.1	
Garcinone D	5.5		
1-Isomangostin hydrate	5.5		
γ-Mangostin	3.8		
8-Deoxygartanin	4.6		
Garcinone E	5.1		
Dulciol A	5.1		
Total xanthones (α-mangostin equiv.)			81.6

HPLC and UV–Vis spectrophotometry were employed for the quantification of α-mangostin and total xanthones (as α-mangostin equivalent), respectively. From HPLC analysis, the peak observed at a retention time of 5.6 min corresponded to the absorption of α-mangostin in the sample. From the UV–Vis spectra, the absorbance measured at 316 nm corresponded to all of the xanthones with similar chromophores and not that of α-mangostin alone. Therefore, UV–Vis spectrometry yields a higher percentage for the total xanthones compared to the percentage of α-mangostin from HPLC analysis.

3.2. Encapsulation Efficiency and Loading Capacity

The encapsulation efficiency and loading capacity of the xanthone-loaded chitosan-alginate microparticles were 99.9% and 6.2%, respectively. Xanthones are highly non-polar compounds with extremely low solubilities in water, ~0.2 μg/mL for α-mangostin (Aisha et al., 2012b). Generally, this low water solubility enhances the encapsulation efficiency of α-mangostin or xanthones.

3.3. Scanning Electron Microscopy

Based on the visual assessment of SEM images with 100× magnification, the diameter of the microparticles was not greater than 220 μm. Figure 2 shows the morphology of the chitosan-alginate microparticles loaded with various amounts of the xanthone extract. Compared with those of the loaded microparticles, the unloaded microparticles exhibited a more coarse and porous exterior. The surface with a high extract loading was also smooth. In this case, NH^{3+} branches in chitosan split and bind to mangostin and TPP. At a high loading, a high number of bonds are formed between the bioactive compounds and chitosan, leading to dense and smooth microparticles. As shown in Table 1, the formula of microparticle A was utilized to prepared microparticles in the tablet formulation.

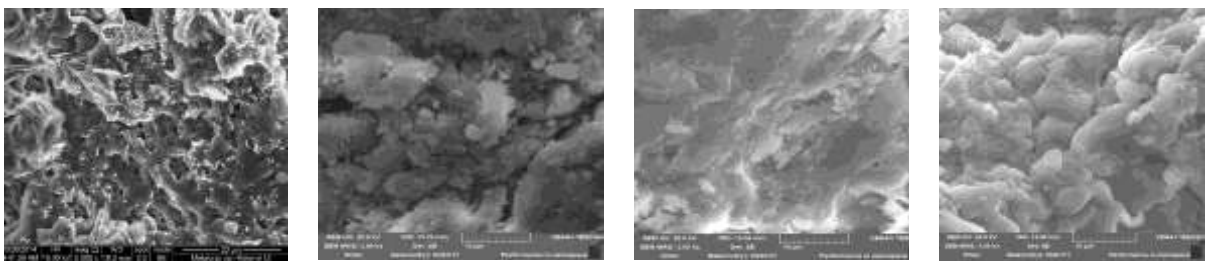


Figure 2 SEM morphology of microparticles with various loadings of xanthone (5000× magnification)

3.4. Physical Characteristic Test

Two tablet formulas were tested: D1 and D3. The shape and colour of both tablets were circular and brown, respectively; both tablets smelled like medicine, with a rough surface texture. The chitosan-alginate microparticles rendered brown colour to the tablet. Table 4 summarizes the results obtained from the physical characteristic test.

Table 4. Characteristics of tablet formulation

Formula	Diameter (cm)	Thickness (cm)	Diameter/ Thickness	Friability (%)	Weight/tablet (mg)	Deviation (%)	Hardness (kPa)
D1	1.11 ± 0.00	0.43 ± 0.005	2.56 ± 0.03	1.429	506.47 ± 0.58	0.09 ± 0.07	1.83 ± 0.2
D3	1.11 ± 0.00	0.43 ± 0.004	2.58 ± 0.025	0.907	507.37 ± 1.84	0.25 ± 0.25	2.07 ± 0.064

Tablets D1 and D3 satisfied the requirements of size and weight uniformity; however, the tablets did not satisfy the requirements for hardness in the range of 4–10 kPa. Only tablet D3 satisfied the friability requirement, which was less than 1% (Lachman et al., 1986). This result was related to the considerably higher concentration of the binder (NaCMC) in tablet D3, which was five times as much as that in tablet D1, making it more resistant to shocks.

3.5. Tablet Dissolution Test and Release Profile of Xanthones

Figures 3a, 3b and 3c shows the results obtained from the tablet dissolution test in SGF with a pH of 1.2, in SIF with a pH of 7.4 and in SCF with a pH of 6.8, respectively. Burst release or the abrupt release of mangostin from the tablet in these simulated gastrointestinal fluids was clearly observed in the first 60 min, with a cumulative release of greater than 70%, followed by the complete release of xanthones in 120 min. Similar bursts and release profiles revealed that the components of the excipients facilitate more rapid degradation of the chitosan-alginate microparticles regardless of the pH of the release medium in contrast to the recently reported pH-dependent release profiles of xanthones from chitosan-alginate microparticles (Mulia et al., 2020) or the zero-order release of α-mangostin from the chitosan-alginate hydrogel film (Wathoni et al., 2019).

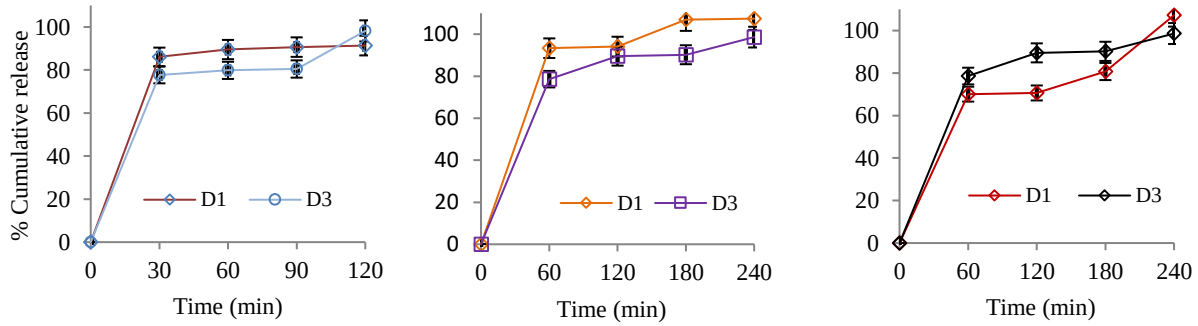


Figure 3 Release profile of xanthones in simulated gastrointestinal fluids

The observed burst releases could be explained by the fact that mannitol and lactose rapidly dissolve in water, leading to the swelling and disintegration of the tablets. Furthermore, previous studies have reported increased release rates of atenolol from HPMC matrices (Lotfipour et al., 2004), chlorhexidine digluconate from vaginal inserts (Abruzzo et al., 2013) and verapamil hydrochloride from chitosan-alginate tablets (Sah and Juyal, 2012) in the presence of NaCMC, mannitol and lactose as excipients, respectively. Despite the observed burst releases, the tablet formulation of chitosan-alginate microparticles demonstrates the potential for the delivery of xanthones to the

gastrointestinal tract. If release to a targeted area in the digestive tract is desirable, the excipient composition of the tablet should be modified.

4. Conclusions

Xanthone-loaded chitosan-alginate microparticles in a tablet formulation were evaluated in terms of their physicochemical characteristics and release profiles in simulated gastrointestinal fluids. The two tablet formulations satisfied the requirements for weight and size uniformity, but not for hardness; only one formula satisfied the friability requirement. The dissolution test using three simulated gastrointestinal fluids revealed similar pH-independent cumulative release profiles of mangostin. All simulated gastrointestinal fluids exhibited burst releases in the first 60 min of the immersion time. The results obtained herein demonstrated the potential of the tested tablet formulations for the delivery of xanthones into the gastrointestinal tract. To achieve the release to a targeted area in the digestive tract, the excipient composition of the tablet should be modified.

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