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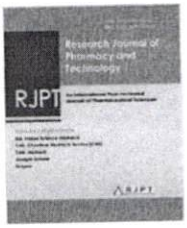

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Preparation and Physical Characterization of Andrographolide-Chitosan-Alginate Microparticles prepared by Ionic Gelation-Freeze Drying

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RESEARCH ARTICLE

Preparation and Physical Characterization of Andrographolide-Chitosan-Alginate Microparticles prepared by Ionic Gelation–Freeze Drying

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ABSTRACT:
This study aimed to determine the effect of alginate concentration on physical characterization (morphology, physical state, and encapsulation efficiency) of andrographolide-chitosan-alginate microparticles prepared by ionic gelation- freeze drying method. Andrographolide-chitosan-alginate microparticles were produced with various amount of alginate by ionic gelation method using tripholyphospate (TPP) as crosslinker and maltodextrin as a lyoprotectant. The physical characteristics were evaluated using Scanning Electron Microscopy (SEM), Fourier Transform Infrared Spectrophotometer (FT-IR), Differential Thermal Analyzer (DTA), Powder X-ray diffractrometer (PXRD), drug content was evaluated using High Pressure Liquid Chromatography (HPLC). The results showed that andrographolide crystallinity changed after encapsulated inside the microparticles supported by changes in IR spectra, and melting point. Furthermore, increased alginate concentration showed rougher surface morphology. The amount of alginate affected the characteristics of the andrographolide-chitosan-alginate microparticles by altering the crystallinity and lowering melting point. The highest encapsulation efficiency shown by microparticles with 0.5% alginate.

KEYWORDS: Microparticles, andrographolide, chitosan, alginates, ionic gelation.

INTRODUCTION:
Andrographolide from *Andrographis paniculata*, known as one of nature's potential ingredients, has promising therapeutic properties such as anti-inflammatory, antidiarrheal, anti-HIV, antimalarial, hepatoprotectant, anticancer, antioxidant, and antihyperglycemia[1–4]. However, andrographolide development is still limited due to several challenging properties, including unstable in gastrointestinal acid and extreme alkaline environment[5,6].

Microparticles are known as object ranged of 1-1000 µm consisted of active pharmaceutical ingredients (API) and microparticle matrixes[7].

Microparticles are widely used as a protection of API from biological environmental conditions and/or performing sustained release profile by encapsulation the API inside the microparticle system[7–11]. Beside its biodegradable and biocompatible nature, combination of chitosan and alginate polymers as a microparticles matrix shows more beneficial effects[7,12]. Alginate polymers are able to prevent drug burst of the chitosan in acid environment, due to chitosan's high solubility in acid[13–15]. Moreover, alginate polymers are able to swell and prevent chitosan precipitation in alkaline environment[13,16,17]. Combination of alginate and chitosan as microparticle matrix is also used into performing controlled drug release[18,19]. Furthermore as a crosslinker, tripholyphospate (TPP) aims to strengthen bonds between chitosan and alginate. Polyelectrolyte complexes were formed between NH_3^+ from chitosan with $HCOO^-$ from the alginate followed by ionic bonds between the NH_3^+ from the chitosan with $H_3PO_{10}^{4-}$ from the TPP[19–21].

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The physical characteristics of microparticles can be affected by several factors. This study aimed to observe the effect of the alginate concentration on the characteristics of the andrographolide-chitosan-alginate microparticles in terms of particle morphology, physical state, and encapsulation efficiency.

MATERIAL AND METHOD:

Chemical and Reagents:

Andrographolide (RD Health Ingredients Co., Ltd.), Chitosan (Biotech. Co. Ltd., Indonesia); Sodium Alginate (Wako Pure Chemical Industry, Japan), Sodium TPP (Nacalai Tesque, Japan), Maltodextrin (Sorini Agro Asia Corporindo, Indonesia), acetic acid p.a, ethanol p.a, Distilled water.

Microparticles Preparation:

Table 1. Andrographolide-chitosan-alginate microparticle formula

No.	Materials	Formula (F)		
		I	II	III
1.	Andrographolide	100 mg	100 mg	100 mg
2.	Chitosan	500 mg	500 mg	500 mg
3.	Alginate	125 mg	250 mg	375 mg
4.	TPP 15% (pH 5)	50 ml	50 ml	50 ml
5.	Maltodextrin 5%	15 ml	15 ml	15 ml

100 mg of Andrographolide were weighed and dissolved in 20 ml of ethanol, followed by adding 50 ml of 1.0% chitosan solution in 1.5% acetic acid while mixed at 500 rpm for 10 minutes using a magnetic stirrer. Alginate solution was prepared in 50 ml distilled water to produce 0.25%, 0.5% and 0.75% alginate solution. Then the alginate solution was added into 15% TPP solution while mixed at 350 rpm for 5 minutes. The chitosan-andrographolide mixture was sprayed onto the alginate-TPP mixture using a spray gun (nozzle 0.6 mm, pressure 2 bars) while mixed at 500 rpm. The stirring continued for 30 minutes at 1000 rpm. The precipitated particles then were separated and mixed with 5% maltodextrin solution followed by freeze drying (Christ Beta 1-8 K) for 48 hours. Dried microparticles in each formula were then evaluated.

Particle Morphology:

Particle morphology was evaluated using Scanning Electron Microscopy (SEM) FEI Inspect S50 (Japan). Samples were placed on a sample holder and coated with palladium gold with a thickness of 10 nm before being analyzed. The morphological observations were carried out at a voltage of 20 kV and a current of 12 mA.

Fourier Transform Infrared (FT-IR):

The sample was prepared by mixing approximately 3 mg of microparticles with 300 mg of KBr powder then pressed using a hydraulic pump pressed until obtained a transparent disc. The disc was irradiated with infrared light using Jasco FT-IR 5300 (USA) with an observing wavelength of 4000-450 cm^{-1}.

Differential Thermal Analysis:

The sample ranging 5-7 mg was placed on a crucible aluminum pan and closed using aluminum lit. The thermal observation was performed at a temperature of 50-250°C with a heating rate of 10 °C/min using Differential Thermal Analyzer FP-65 P-900 Thermal (USA).

X-Ray Diffraction (XRD):

Each microparticle crystallinity was analyzed using powder X-ray diffractometer (PAN analytical) with CuKα radiation. The crystallinity was observed in 2θ range of 5-40º at room temperature, at a voltage of 40 kV and the current of 40 mA.

Drug content and Encapsulation Efficiency:

Drug content of microparticle was measured using high performance liquid chromatography Agilent 1100 Series (Germany) using reversed phase column, Lichrospher column 100 RP-18 4 x 250 mm 5 µm observed at a wavelength of 228 nm. Methanol-phosphate acid pH 3 (50:50) was used as the mobile phase with a flow rate of 0.75 ml/min at 30ºC.

20 mg of microparticles were sonicated and dissolved in 10 ml of ethanol overnight. The solution then filtered using 0.45 µm membrane filter and injected into the column. Samples were replicated triplo. The drug content and encapsulation efficiency was calculated using the formula below:

$$\textbf{Drug content} = \frac{Drug\ amount}{Microparticles\ weight}\ x\ 100\%$$

$$\textbf{Encapsulation efficiency} = \frac{Actual\ drug\ amount}{Theoritical\ drug\ amount}\ x\ 100\%$$

RESULTS AND DISCUSSION:

Morphology observation showed that FI microparticles produced spherical shape with a smooth surface morphology, different results shown by the higher concentration of alginate. Higher concentration of alginate formed coarser surface microparticles, which related to the increased viscosity of the aqueous alginate-chitosan mixture (Figure 1). Furthermore due to the high viscosity, alginate-chitosan mixture and andrographolide-TPP droplets were more difficult to interact and perform crosslink [22]. Lower concentration of alginates indicated smoother surface due to higher crosslinked bond between alginate, chitosan and TPP which provide a compact surface.

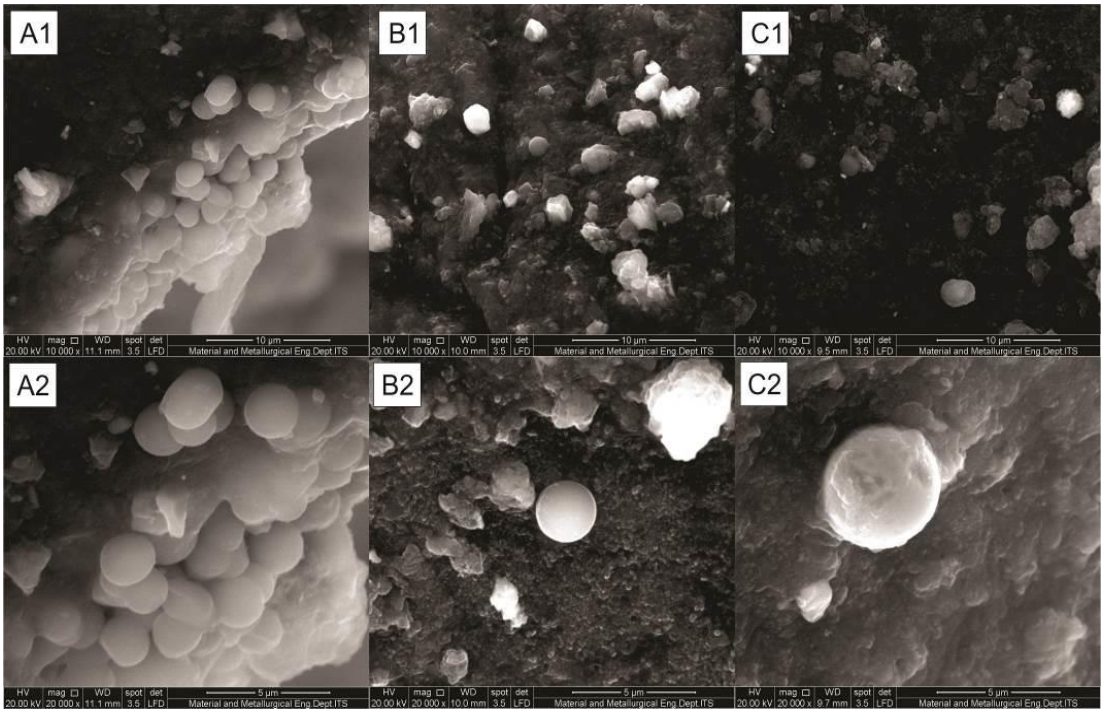

Figure 1. The SEM phtographs of andrographolide-chitosan-alginate microparticles with alginate amounts (A) 0.25%, (B) 0.5%, (C) 0.75% at 10000x (1) and 20000x (2) magnifications.

The formation of chitosan-alginate bonds appeared at wave numbers 3000-3700 cm^{-1} (Figure 2. Red Arrow) which became steeper. Which confirmed that more hydrogen bonds occurred between chitosan and alginate [23]. In addition, the spectrum at wave numbers 1650 cm^{-1} (Figure 2. Blue Arrow) and 820 cm^{-1} (Figure 2. Purple Arrow) which denoted the NH^{3+} of the chitosan and the mannuronate group of alginate became invisible and shifted to 1645 cm^{-1} and 892 cm^{-1}. This indicated the presence of a multi-interaction between chitosan and alginate through hydrogen and electrostatic bonds[22].

Thermal characteristics comparison of andrographolide, chitosan, sodium alginate as well as microparticles with and without andrographolide are shown in Figure 3. Sharp andrographolide peak at 231.6ºC was not visible on the microparticle thermograms. Furthermore, the andrographolide microparticles (Figure 3. E-F) showed lower melting points than pure andrographolide (Figure 3. A). This indicated that the andrographolide has been encapsulated in the system[24]. Various melting point have been shown by F1, F2 and F3 microparticles at 175.1ºC, 161.6ºC, and 168.2ºC, respectively due to the change of crystalline regularity inside the polymer matrix.

Powder X-ray observation showed sharp andrographolide crystalline property at 10º up to 16º. However, the decrease intensity were observed in the andrographolide microparticles diffractogram (Figure 4). Different intensities were caused by changes in the andrographolide crystallinity inside the encapsulated microparticle system. Furthermore, reduced particle sizes and loss of continuity of the atomic plane could also play a significant role [25].

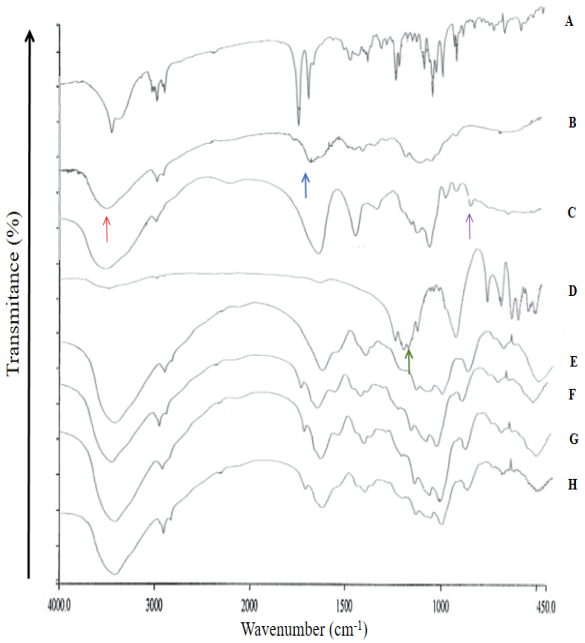

Figure 2. Infrared spectra of (A) Andrographolide, (B) Chitosan, (C) Sodium alginate, (D) Na TPP, (E) microparticles without andrographolide, (F) andrographolide-chitosan-alginate microparticles with alginate amounts of 0.25%, (G) 0.5%, (H) 0.75%

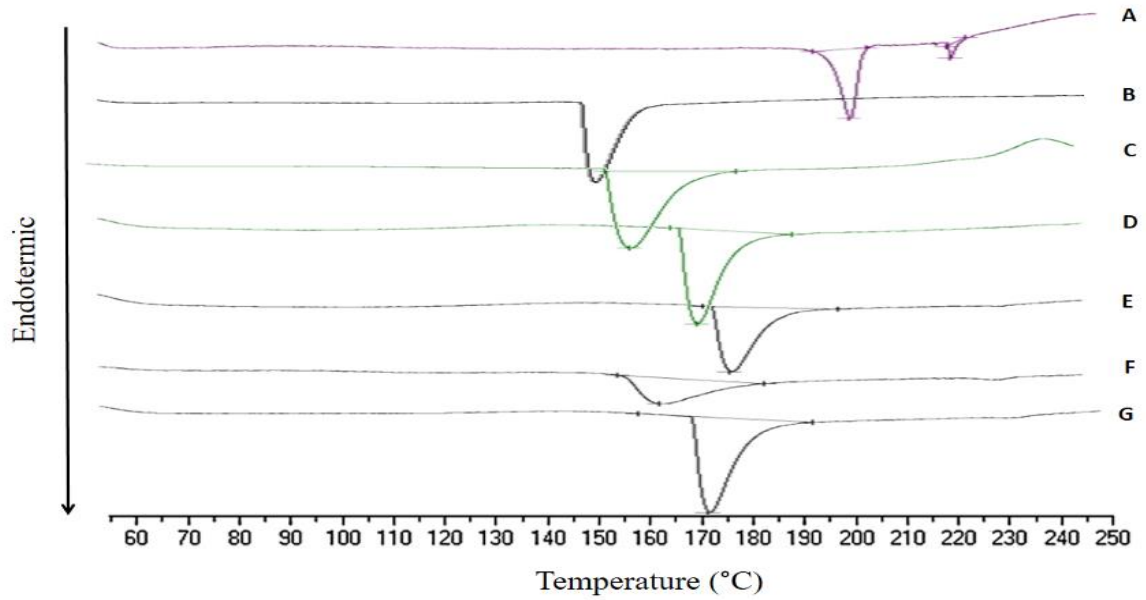

Figure 3. DTA Thermogram of (A) andrographolide, (B) Chitosan, (C) Sodium alginate, (D) Microparticles without andrographolide, andrographolide-chitosan-alginate microparticle with 0.25% (E), 0.5% (F), and (G) 0.75% of alginate.

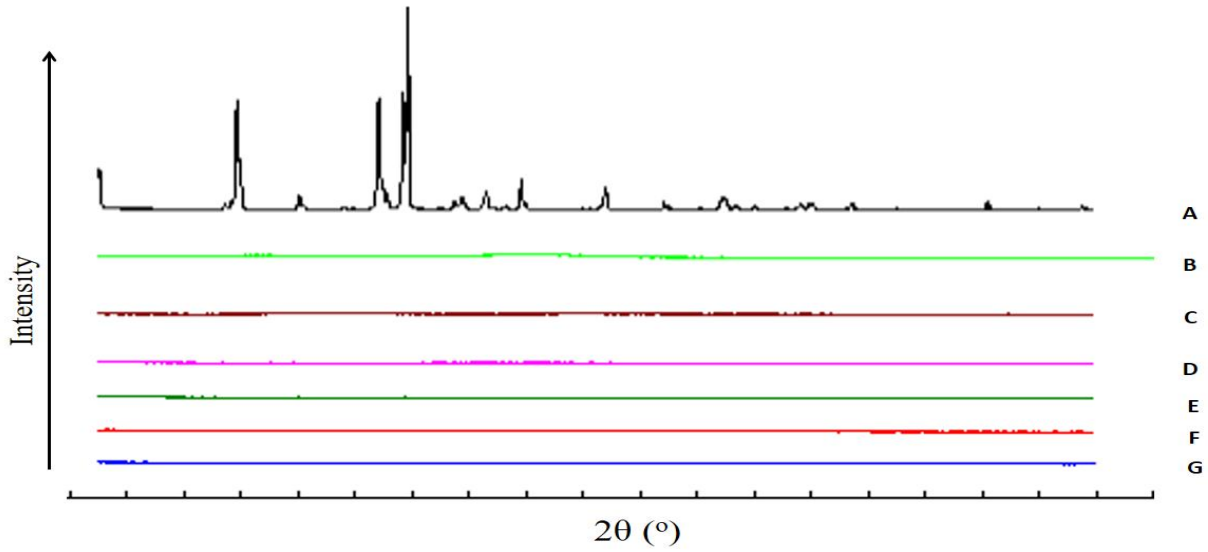

Figure 4. X-Ray Diffractogram of (A) Andrographolide, (B) Chitosan, (C) Sodium alginate, (D) Microparticles without andrographolide, (E) Andrographolide-Chitosan-Alginate Microsphere with with alginate amounts of 0.25%, 0.5% (F), (G) 0.75%.

Table 2. Drug content and Encapsulation efficiency (EE) of andrographolide-chitosan-alginate microparticle with different alginate concentration 0.25% (F1), 0.50% (F2), 0.75% (F3)

Formula	Drug content ± SD (%)	EE ± SD (%)
F I	3.33 ± 0.28	45.86 ± 3.48
F II	3.63 ± 0.14	58.13 ± 2.17
F III	3.09 ± 0.16	53.07 ± 2.80

At 0.5% alginate, encapsulation efficiency of the microparticle increased compared to 0.25% alginate, however the encapsulation decreased at alginate concentration of 0.75% (shown in Table 2). This showed that 0.5% alginate could produce more crosslinking bonds between alginate and chitosan. In result, a more compact network that could encapsulate and prevent andrographolide diffused out from the system during the manufacture. On the other hand, due to the high viscosity, 0.75% alginate inhibited andrographolide to be entrapped into the microparticle system.

CONCLUSION:

The microparticles of andrographolide with combination of chitosan and alginate was easily produced using ionic gelation followed by freeze drying. The amount of alginate affected the characteristics of the

andrographolide-chitosan-alginate microparticles by changing crystallinity, melting point, and particle morphology. The highest encapsulation efficiency was shown by 0.5% alginate.

CONFLICT OF INTEREST:

No conflict of interest

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