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ASSESSMENT OF SOME CHARACTERISTICS AND PROPERTIES OF α -MANGOSTIN LOADED BY CARRAGEENAN/CHITOSAN PARTICLES

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Abstract. α-mangostin - an active compound extracted from mangosteen fruit peels – has been known with high anti-oxidation, antimicrobial, anti-inflammatory, antiphrastic, antiviral etc. One of disadvantages of α-mangostin is poorly soluble in aqueous solution. Loading α-mangostin by some biopolymers could improve the solubility of α-mangostin in aqueous. Therefore, this paper presents the preparation and characterization of carrageenan/chitosan particles loading α-mangostin - an active compound extracted from mangosteen fruit peels. The carrageenan/chitosan/α-mangostin particles were prepared by ionic gelation method in the presence of sodium tripolyphosphate as a cross-linking agent and potassium chloride as a gel agent. The functional groups in the particles were characterized by infrared spectroscopy. The hydrophobic/hydrophilic characteristic of the particles were assessed through the determination of contact angle of water droplet on the surface of the particles. The drug loading efficacy and solubility of carrageenan/chitosan/α-mangostin particles in buffer/ethanol solutions were also evaluated and discussed. The obtained results suggest that α-mangostin has been loaded by carrageenan/chitosan blend and the content of α-mangostin had a negligible effect on the vibrations of functional groups in the carrageenan/chitosan/α-mangostin particles. As increasing α-mangostin content in the particles, the contact angle of the particles decreased, corresponding to the increase in their hydrophilic ability. The α-mangostin loading efficacy of the particles was quite high, > 90 %. The assessment of the solubility of the particles in ethanol/buffer solutions shows that the solubility of the particles was better than that of α-mangostin.

Keywords: α-mangostin, ionic gelation method, hydrophilic characteristic, carrageenan/chitosan blend.

Classification numbers: 2.7.1, 2.9.4.

1. INTRODUCTION

Mangosteen tree, having the scientific name of *Garciniamangostana* Linn, belongs to the Clusiaceae family, the *Garcinia* genus. Mangosteen fruits are not only favored for their delicious taste, but also their peel has long been used as an heirloom medicine in the treatment of many diseases such as skin infections, colic, dysentery, trauma, etc. [1 - 2]. The peel of mangosteen fruits contains a lot of active compounds such as xanthone compound groups [1, 3 - 4], tanning [5], anthocyanin [6 - 7].

Among xanthone compounds, α-mangostin was one of the first major xanthone isolated from the peel of mangosteen fruit [8]. It has valuable biological activities such as antibacterial, anti-oxidation [9], anti-inflammatory [10], antimicrobial, antifungal, antiphrastic, and antiviral [2, 11], etc. The α-mangostin can be well dissolved in ethanol and methanol. However, the solubility in water and oral bioavailability of α-mangostin is poor (water solubility is $2.03x10^{-4}$ mg/L at 25 °C (est)), limiting its application in treatment [12, 13]. Therefore, to address these disadvantages of α-mangostin, scientists have developed polymeric systems as carriers for α-mangostin to enhance its solubility in water and bioavailability. In 2011, Aisha *et al*. fabricated a solid dispersion of α-mangostin and polyvinylpyrrolidone (PVP) [12]. The solubility of α-mangostin was increased from 0.2 ± 0.2 μg/mL to 2743 ± 11 μg/mL. In another report, the anti-colon cancer ability of α-mangostin was also improved thanks to loading by Eudragit RL100/RS100 polymer nanoparticles [13]. The other polymeric systems carrying α-mangostin have also been successfully studied for their application in pharmaceutical chemistry, for example, the systems based on cellulose [14], poly (ethylene glycol) -poly (l-lactide) [15], cyclodextrin [16], poly (D, L-lactic-co-glycolic acid) [17], chitosan and alginate [18, 19], chitosan and Eudragit S 100 [20]. The nano α-mangostin delivery systems are promising to increase the solubility, selectivity and efficacy of α-mangostin in the treatment of diseases and applications in other fields [21].

Carrageenan and chitosan are natural polymers which have been widely used as carriers for drugs [18 - 19, 22 - 23] due to their non-toxicity, high compatibility, ease of decomposition, good adsorption capacity and biological activity, etc. However, studies on preparation of carrageenan/chitosan particles loading α-mangostin have been still limited. The solubility of α-mangostin was expressed to be improved as loaded by carrageenan and chitosan. Therefore, the purpose of this work is to fabricate carrageenan/chitosan particles loading α-mangostin and to assess some of their characteristics and properties.

2. MATERIALS AND METHODS

2.1. Materials

Chitosan (CS) (powdery, low molecular weight 1.61×10^5 Da, degree of deacetylation > 75 - 85 %), carrageenan (CAR) (powdery, moisture content ≤ 12 %), and sodium tripolyphosphate (STPP) were purchased from Sigma Aldrich (USA). Ethanol (EtOH, 99.7 %), acetic acid (99.5 %), KCl, HCl, NaOH, CH_3COONa, and KH_2PO_4, etc. were analytical chemicals.

2.2. Extraction and isolation of α-mangostin from mangosteen fruit peel

The mangosteen fruit peels were collected in Southern Vietnam since 2019. They were dried under sunlight and stored at -21 ^{o}C until use. The dried peels were crushed to powder with a fineness of 100 % passing through a 1.0 mm sieve. Then, the powder obtained was immersed in 60 % EtOH with a powder : solvent ratio of 1 kg : 20 L. The mixture was put into an ultrasonic tank for 30 minutes. The experiment was repeated 3 times. The extract solution was filtered and the solvent was removed by vacuum evaporation at 40 ^{o}C to obtain the extract. Next, fractional separation with an n-hexane : chloroform system was carried out to obtain α-mangostin-rich extract residue. The α-mangostin was separated from α-mangostin-rich extract residue by column chromatography using a silicagel column with chloroform : methanol (50 : 1, 30 : 1, 20 : 1, 10 : 1, 5 : 1) systems. The α-mangostin extract was continuously cleaned by silicagel column chromatography with n-hexane : dichloromethane (30 : 0, 20 : 1, 10 : 1) systems. Finally, α-mangostin (assigned to GCM1) was obtained as a bright yellow powder with a content higher than 90 % (determined by high-performance liquid chromatography method).

2.3. Preparation of carrageenan/chitosan/α-mangostin particles

The carrageenan/chitosan/α-mangostin particles were prepared with different α-mangostin weights (0, 5, 10, 15, and 20 wt.% as compared to total weight of carrageenan and chitosan) according to the following procedure:

First, a carrageenan solution (solution A) was prepared by adding 0.05 g of carrageenan to 100 mL of distilled water and stirring at 80 ^{o}C for 15 minutes before cooling to 50 ^{o}C. Next, a solution of KCl (0.005 g/5 mL of distilled water) was added into this solution. At the same time, a chitosan solution (solution B) was prepared by dissolving 0.1 g of chitosan in 100 mL of 1 % acetic acid solution. Then, an α-mangostin solution (solution C) was prepared by dissolving different weights of α-mangostin in 20 mL of EtOH. A solution of cross-linking agent (STPP) (solution D) was prepared by dissolving 0.02 g of STPP in 2 mL of distilled water.

Second, solution B was dropped slowly into solution A at a speed of 3 mL/min, then solution C was added to the above mixture. The mixture was ultrasonicated for 5 minutes at a speed of 10000 rpm. Solution D was added to the mixture and ultrasonication was continued for 5 minutes at a speed of 10000 rpm to obtain a homogeneous mixture, which was then cooled for 2 hours and centrifuged at 6000 rpm to remove the solvents. The solid part was freeze-dried using a FreeZone 2.5 device (Labconco, USA). The carrageenan/chitosan/α-mangostin particles were obtained in the form of a powder with a light yellow color. The particles were stored in PE tube at room temperature until use. The abbreviation of carrageenan/chitosan/α-mangostin particles prepared at different α-mangostin weights were CCG0, CCG5, CCG10, CCG15, and CCG20 corresponding to 0, 5, 10, 15, and 20 wt.% of α-mangostin, respectively.

2.4. Characterization of carrageenan/chitosan/α-mangostin particles

Infrared (IR) spectra of the above CCG particles were recorded in the range of wavenumbers from 400 cm^{-1} to 4000 cm^{-1} using a Nicolet iS10 spectrometer (Thermo Scientific, USA) to evaluate functional groups and interactions of components in the CCG particles. The hydrophobic/hydrophilic characteristic of the CCG particles was assessed through contact angle using a Phoenix-150 SEO meter by measuring the angle between the water droplet and the surface of the pellet which was pressed from CCG particles on a press machine. The calibration equation and solubility of the CCG particles were calculated based on the data obtained from ultraviolet-visible (UV-Vis) spectra on a UV-Vis spectrometer (S80 Libra, Biochrom, UK) in the wavelength of 200 nm to 400 nm.

2.5. Assessment of solubility of carrageenan/chitosan/α-mangostin particles in buffer/EtOH solutions

The pH values of the buffer solutions were selected in this study were pH 1.2, pH 4.5, pH 6.8, and pH 7.4, equivalent to the pH values of the lower stomach, upper stomach, intestine and duodenum fluids in the human digestive system, respectively [24].

The calibration equation reflecting the α-mangostin concentration in EtOH was established as follows: 0.01 g of GCM1 was added to 200 mL of EtOH and stirred continuously for 3 hours at 37 ^{o}C with a speed of 400 rpm. Then, the GCM1 solution was diluted with different volumes of EtOH and UV-Vis spectra were recorded at the maximum wavelength of GCM1 in EtOH. The calibration equation was set up using an Excel software based on the data obtained from the UV-Vis spectra.

The assessment of the solubility of α-mangostin and CCG particles in buffer/EtOH solutions at different ratios of buffer solution and EtOH was done by adding 0.005 g of GCM1 or CCG particles to 50 mL of buffer/EtOH solutions. The mixture was stirred continuously for 3 hours at 37 ^{o}C with a speed of 400 rpm. After that, the solution was withdrawn and the UV-Vis spectrum of solution was recorded. The optical densities obtained from the UV-Vis spectrum were used to establish a calibration equation reflecting the solubility of α-mangostin in EtOH to calculate the weight of α-mangostin in solution. The solubility of α-mangostin and CCG particles was calculated according to the following equation:

$$Solubility\ (\%) = \frac{m_a}{m_i} 100 \quad (1)$$

where m_i and m_a represent the initial weight of α-mangostin in the samples and the weight of α-mangostin in solution after 3 hours of testing.

2.6. Assessment of drug loading efficacy of carrageenan/chitosan/α-mangostin particles

The drug loading efficacy of CCG particles was evaluated by determining the weight of free GCM1 in solution after the preparation of CCG particles using UV-Vis spectroscopy. The drug loading efficacy of CCG particles was calculated according to the equation below:

$$Drug\ loading\ efficacy\ (\%) = \frac{m_i - m_f}{m_i} 100 \quad (2)$$

where, m_i and m_f represent the initial weight of α-mangostin in the samples and the weight of free α-mangostin in solution after the preparation of CCG particles.

3. RESULTS AND DISCUSSION

3.1. Infrared spectra of carrageenan/chitosan/α-mangostin particles

The IR spectra of CS, CAR, GCM1 and CCG particles are shown in Figure 1. From the IR spectrum of GCM1, it can be seen that the peaks characterized for vibrations of O-H, C-H, C=C, C-O, C-C groups in molecule of GCM1. The vibrations of O-H, N-H, C-O, C-C groups were appeared in the IR spectrum of chitosan (CS) and the vibrations of O-H, C-O, S=O, C-C groups were indicated in the IR spectrum of carrageenan (CAR) [22, 23]. As observed from Figure 1 and Table 1, the position of characteristic peaks for vibrations of O-H, N-H, C=C, C-N, S=O groups was slightly shifted. This suggested that functional groups of CAR, CS and GCM1

might be interacted together through hydrogen bonding and dipole-dipole interactions [18, 19, 23]. The IR spectra of CCG particles prepared at different GCM1 contents were similar, confirming that the GCM1 content had a negligible effect on the vibrations of functional groups in the CCG particles.

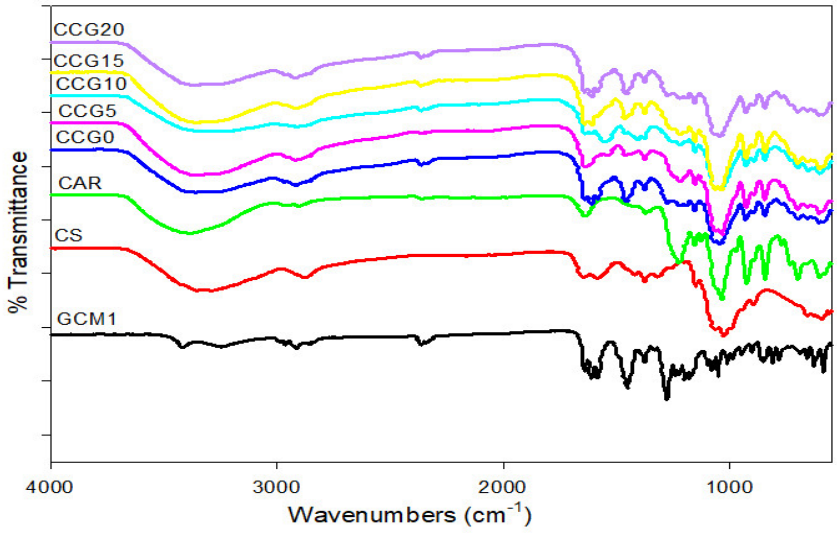

Figure 1. IR spectra of CS, CAR, GCM1 and CCG particles.

Table 1. Some vibrations in the IR spectra of CS, CAR, GCM1 and CCG particles.

Vibrations	CS	CAR	GCM1	CCG0	CCG5	CCG10	CCG15	CCG20
$\nu_{OH, NH}$	3287	3385	3418 3246	3357	3355	3251	3357	3358
ν_{CH}	2874	2960 2906	2962 2912	2912	2919	2906	2913	2913
$\nu_{C=C}$, δ_{OH}	1643	1636	1640 1609	1632	1639	1638	1608	1640 1609
δ_{NH}	1584	-	1581	1537	1550	1544	1580	1582
δ_{CH}	1419 1376	1373	1452 1374	1376	1460 1375	1407	1461 1374	1457 1375
$\nu_{C-N, S=O}$	1205	1223	1238	1216	1217	1218	1218	1221
$\nu_{C-O, C-C}$	1149 1026	1155 1035	1183 1095	1152 1033	1153 1034	1152 1036	1153 1036	1154 1041

3.2. Hydrophobic/hydrophilic characteristics of carrageenan/chitosan/α-mangostin particles

The hydrophobic/hydrophilic characteristics of GCM1 and CCG particles were evaluated through the contact angle values. The shapes of water droplet on the surface of GCM1 or CCG particle pellets are presented in Figure 2. The contact angles of GCM1, CCG5, CCG10, CCG15,

and CCG20 particles were 123.8^o, 93.1^o, 80.7^o, 93.5^o, and 76.22^o, respectively. The contact angle of CCG particles was lower than that of the GCM1, suggesting that the surface of CCG particles became more hydrophilic than that of GCM1 [25]. The increase in the hydrophilic characteristics of the CCG particles may be due to the α-mangostin loading effectiveness of CAR and CS, especially CAR - a hydrophilic polysaccharide.

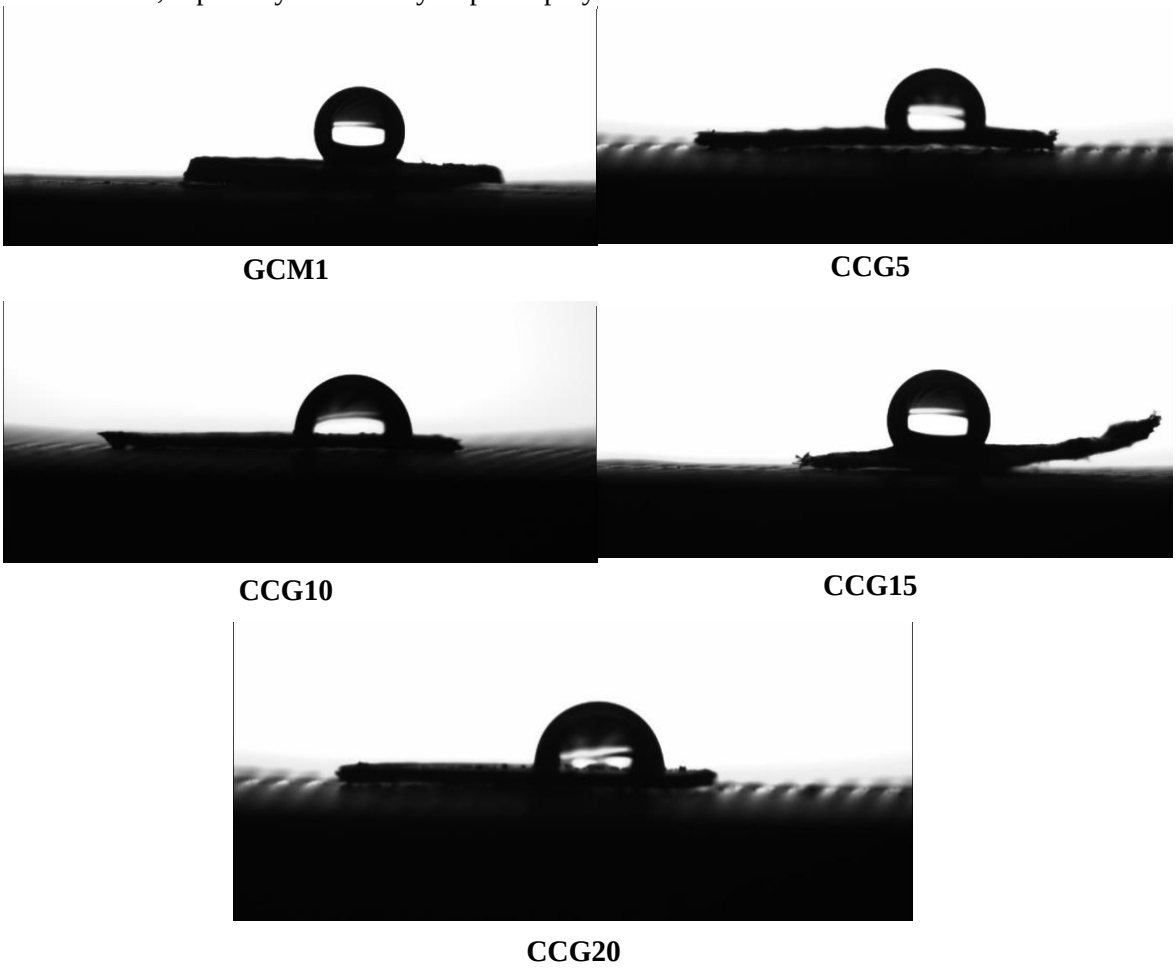

Figure 2. Shape of water droplet on the surface of pellet pressed from GCM1 or CCG particles.

3.3. Calibration equation reflecting the α-mangostin concentration in EtOH

The concentration of GCM1 in EtOH was determined by UV-Vis method. The UV-Vis spectrum of GCM1 solution was scanned from 200 nm to 400 nm because the main absorbance peaks of GCM1 were appeared in this wavelength range. The maximum wavelength of GCM1 in EtOH was 244 nm. The optical density of GCM1 solution was recorded by diluting method. The calibration equation reflecting the α-mangostin concentration in EtOH is shown in Figure 3: $y = 86.234x + 0.0615$, $R^2 = 0.9988$ (x is GCM1 concentration, y is optical density). The value of $R^2 \approx 1$, thus, this equation can be used to determine the GCM1 concentration in the solution.

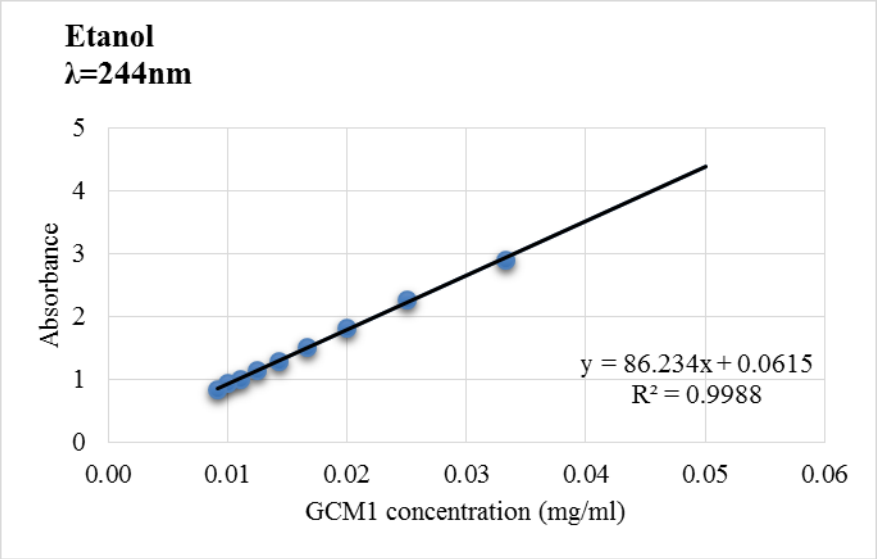

Figure 3. Calibration equation reflecting the α-mangostin concentration in EtOH.

3.4. Drug loading efficacy of carrageenan/chitosan/α-mangostin particles

The α-mangostin loading efficacy of CCG particles was evaluated according to Eq. 2 and is listed in Table 2. From the data in Table 2, all CCG particle samples had a high drug loading efficacy, > 90 %. This shows that carrageenan/chitosan particles were suitable for loading α-mangostine. A high drug loading efficacy also provided a controlled release as reported by Grenha *et al.* [22]. As compared to the mangostin encapsulation efficiency of the chitosan microparticles (95.0 ± 2.1 %) [19], the efficacy of CCG particles is a little lower.

Table 2. Drug loading efficacy of CCG particles.

Sample	Drug loading efficacy (%)
CCG5	92.04 ± 2.22
CCG10	90.04 ± 4.76
CCG15	90.85 ± 5.63
CCG20	90.09 ± 5.78

3.5. Solubility of carrageenan/chitosan/α-mangostin particles in different pH buffer - ethanol solutions

Although α-mangostin can be dissolved in EtOH, it or CCG particles will be taken in the digestive system having different pH values when administered orally. Samprasit *et al.* had evaluated the α-mangostin released from chitosan/alginate nanoparticles in the mixture of buffer solution (pH 1.2, 6.8 and 7.4) and EtOH with a ratio volume of 50/50 [18]. Therefore, in this study, the solubility of GCM1 and CCG particles in solution mixture of buffer solutions (pH 1.2, pH 4.5, pH 6.8 and pH 7.4) and EtOH will be tested. Figure 5 presents the solubility of GCM1 in different buffer/EtOH solution mixtures, indicating that α-mangostin cannot dissolve in buffer

solutions without the presence of EtOH. When increasing EtOH concentration in the mixture, the solubility of α-mangostin was remarkably enhanced. At low concentrations of EtOH, the solubility of α-mangostin in all tested solution mixtures is very poor, below 10 % in solutions containing 20 % of EtOH. When increasing the concentration of EtOH up to 40 %, the solubility of α-mangostin in solutions was improved from 33.7 % to 51.8 %. The solubility of α-mangostin reached 99.1 % when dissolved in –80 % EtOH solution at pH 6.8 and was 17.2 % higher than the solubility of α-mangostin in EtOH solution (100 %). These results suggested that α-mangostin could be better dissolved in a mixture of pH buffer solution and EtOH rather than only in pH buffer solution. This opens up the potential application of α-mangostin in the beverage and food sectors.

It can be also seen from Figure 5 that the solubility of α-mangostin in solution is affected by the pH of the solution. Among the investigated solutions, at high EtOH concentration, the solubility of α-mangostin in EtOH solution with pH 6.8 is the highest, then in EtOH solution with pH 4.5, followed by water - EtOH solution, then EtOH solution with pH 1.2, and finally EtOH solution with pH 7.4. Food is kept the longest in the intestine, so the good solubility of α-mangostin in –EtOH solution at pH 6.8 can enhance the adsorption of α-mangostin in the intestine and make it more efficient to use.

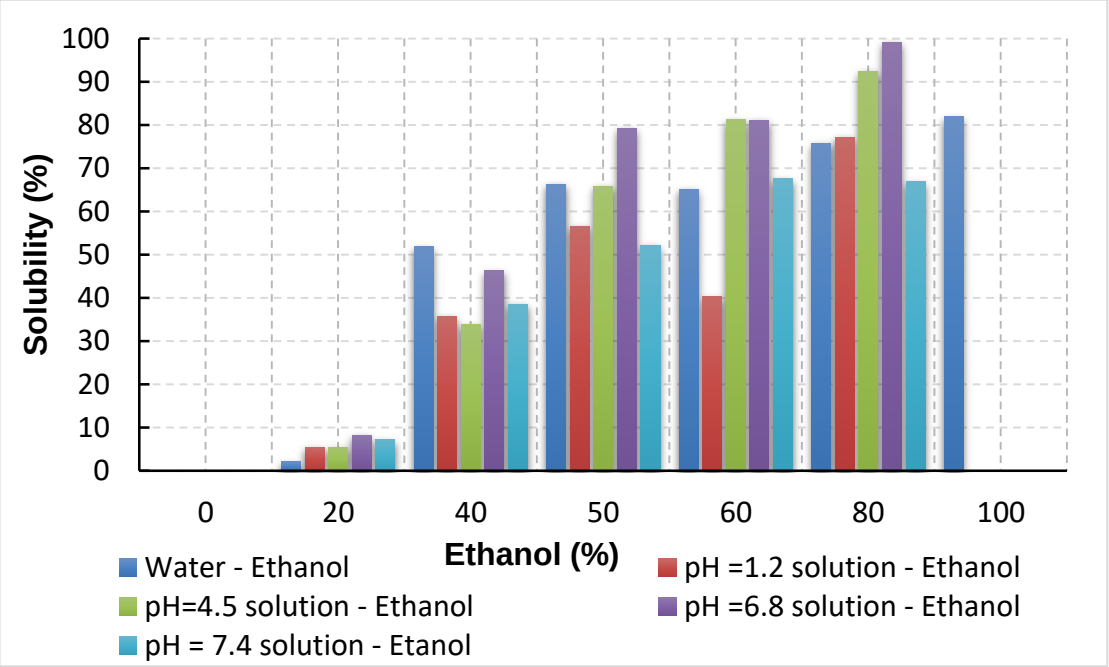

Figure 5. Solubility of GCM1 in different buffer/EtOH solutions.

Figures 6-9 illustrate the solubility of CCG particles in different buffer/EtOH solutions. It is clearly seen that the solubility of most CCG particles was higher than that of GCM1 in all tested solutions. The use of carrageenan and chitosan for loading α-mangostin is necessary to improve the solubility of α-mangostin. The solubility of CCG particles in solutions depends on buffer solution/EtOH ratio, pH of buffer solution and α-mangostin content.

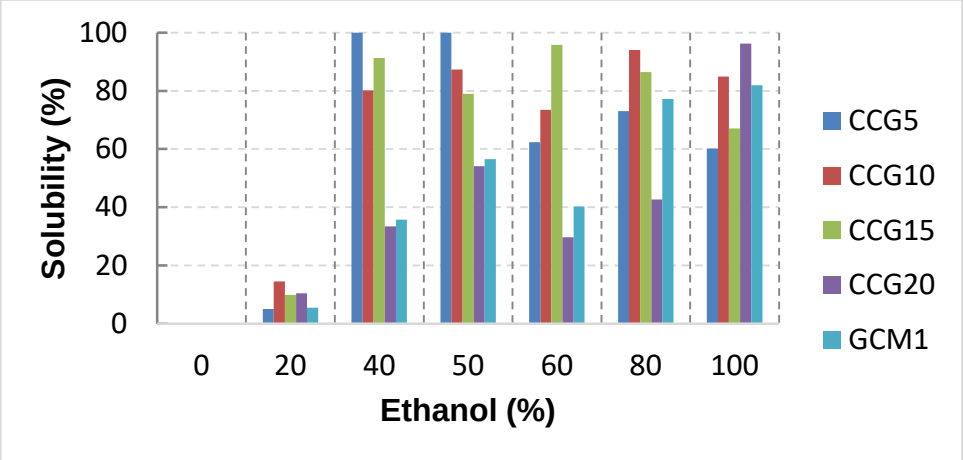

Figure 6. Solubility of GCM1 and CCG particles in EtOH solution mixed with pH 1.2 buffer solution.

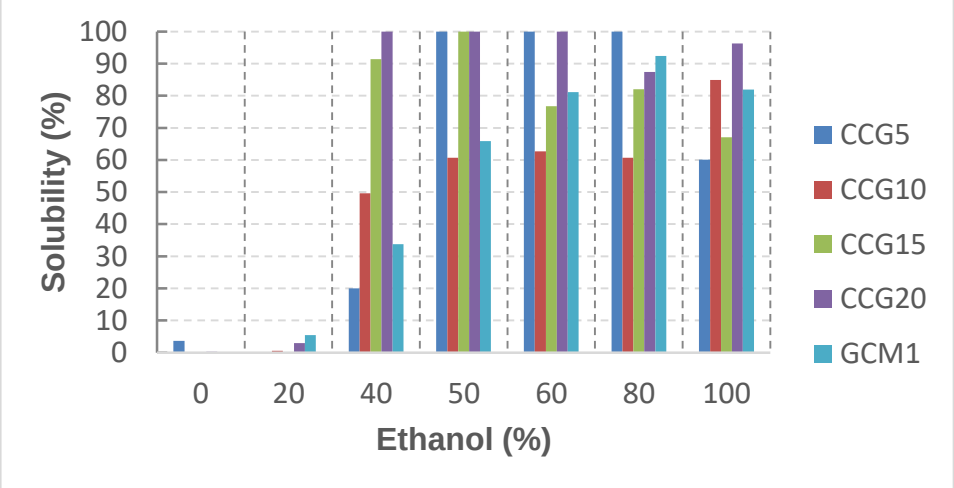

Figure 7. Solubility of GCM1 and CCG particles in EtOH solution mixed with pH 4.5 buffer solution.

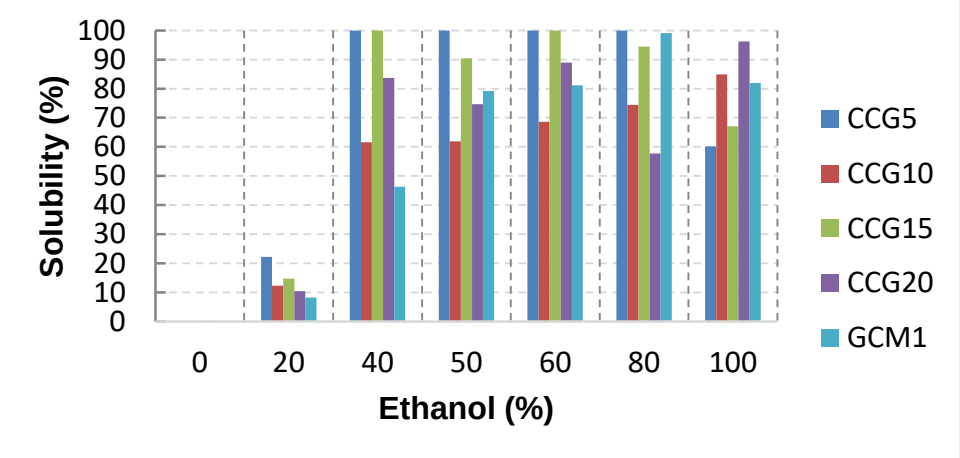

Figure 8. Solubility of GCM1 and CCG particles in EtOH solution mixed with pH 6.8 buffer solution.

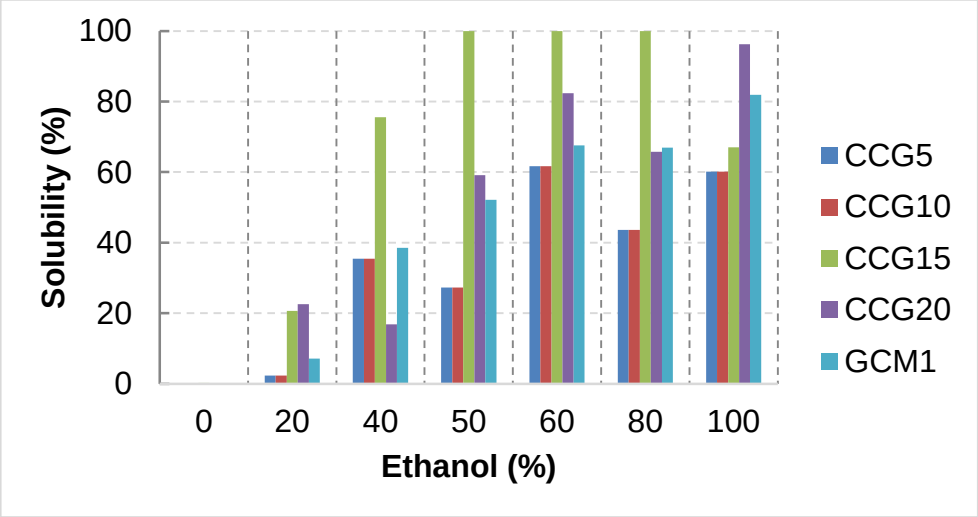

Figure 9. Solubility of GCM1 and CCG particles in EtOH solution mixed with pH 7.4 buffer solution.

When considering the effect of the buffer solution/EtOH ratio on the solubility of CCG particles, some samples of CCG particles could be completely dissolved in solution mixtures containing 40 or 50 % of EtOH, for example, the CCG5 particles in pH 1.2/ethanol (60/40), pH 4.5/EtOH (60/40), pH 6.8/EtOH (60/40) or the CCG15 particles in pH 7.4/EtOH (50/50). Thus, instead of the GCM1 particles dissolved almost completely in pH 6.8/EtOH (20/80), the CCG particles had a much better solubility in the investigated solution mixtures.

Observing the influence of pH of buffer solutions, it is clear that the CCG particles were better dissolved in the solution with pH < 7. This was explained that CS dissolved well in acidic environment [19, 23] while the sulfate groups in CAR could be protonated in that medium [22], leading to enhanced solubility of CCG particles.

The solubility of CCG particles prepared at various GCM1 contents in different solution mixtures did not follow the rule for the content of GCM1 particles. This could be due to the effect of drug loading efficiency on the interactions between drug and polymers, environmental conditions, or other factors which need to be studied in depth. Based on the above obtained results, it could be recognized that the CCG5 particles could be completely dissolved in pH 1.2/EtOH (50/50), pH 4.5/EtOH (50/50), and pH 6.8/EtOH (50/50) while the CCG15 particles could be well dissolved in most solution mixtures containing 50 % of EtOH (78.9-100 %). The CCG10 and CCG20 particles had less solubility in the investigated solutions mixtures containing 50 % of EtOH. Thus, to achieve the best effectiveness in use, the CCG5 particle sample is the most suitable selection.

4. CONCLUSIONS

In this work, carrageenan/chitosan (CAR/CS) particles loading different α-mangostin amounts were successfully prepared by ionic gelation method. Characteristics including IR spectra, hydrophobic/hydrophilic and solubility of α-mangostin and CAR/CS/α-mangostin (CCG) particles were evaluated. The CCG particles contained functional groups of CAR, CS and α-mangostin. As loaded by CAR/CS, the hydrophilic of α-mangostin was increased. The CCG particles had a high drug loading efficiency, from 90.04 to 92.04 %. The solubility of CCG particles in pH buffer/ethanol (EtOH) mixtures was significantly enhanced compared with α-

mangostin alone. In pH 1.2/EtOH (50/50), pH 4.5/EtOH (50/50), and pH 6.8/EtOH (50/50) solutions, CCG5 particles were completely dissolved. These results indicate that CCG particles are suitable for application in beverage and food fields.

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CRediT authorship contribution statement. Nguyen Thi Hien: Methodology, Experiments, Analysis. Nguyen Thi Minh Tu, Hoang Dinh Hoa, Tran Dinh Thang: Supervision. Nguyen Thuy Chinh: Writing, Experiments. Hoang Phuong Thao: Experiments. Thai Hoang: Supervision and Editing.

Declaration of competing interest. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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