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Potency of (Poly) Acrylic/Carboxymethyl Starch-Chitosan Biohydrogel for Curcumin Oral Delivery Matrix

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ABSTRACT
Biohydrogel has gathered great interest in the pharmaceuticals field. This natural polymers were biodegradable, non-toxic, biocompatible, and its specific ability to response environment change can be considered for the controlled released matric of bioactive compound. In this study, the biohydrogel was synthesized by graft-copolymerization of acrylic acid onto carboxymethyl starch (CMS) and chitosan. The objective of this research was to determine the effect of CMS-chitosan ratio on the biohydrogel characteristic. The acrylic acid was grafted on to the backbone (3:1) using cerric ammonium nitrate as the inisiator.A standarded curcumin was applied to test the binding potency of matrix. A higher CMS ratio in the polymer mixture (4:1) revealed the highest swelling power (16.9 w/w) and percentage of curcumin absorption (17.34%). All samples have pH-responsive swelling properties, with the swelling trend was observed in the order of distilled water >HCl solution > phosphate buffer solution. FTIR spectra and SEM micrographs has confirmed the graft-copolymerization of PAA/CMSCs biohydrogel by describing the appearance of peak around 1600 cm-1and the morphology of granular structure, respectively. The graft-copolymerization of acrylic acid onto the two anionic natural polymer by cerric ammonium nitrate as the initiator has resulted a pH-dependent swelling biohydrogel, and it has the ability to deliver curcumin in stomach-targeted system.

***Keywords**: acrylic acid; biohydrogel; carboxymethyl starch; chitosan; curcumin*

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INTRODUCTION

Biohydrogel, synthesized from natural polymer, has been employed for a wide range of biomedical applications. The abundant polysaccharides like starch, cellulose, chitosan, alginat, pectin, carragenan, and guar gum have been extensively used to control drug release due to their high biocompatibility, low toxicity, and biodegradability (Mehr & Kabiri, 2008; Tokarev & Minko, 2010; Qiu & Park, 2012). Some previous researches studied polysaccharides-based hydrogel for drug or bioactive compound carrier such as 5-amino salisylic acid, diclofenac sodium and curcumin (Zhang *et al.*, 2016; Saboktakin *et al.,* 2010; Wang *et al.,* 2009). Furthermore, the three-dimensional structure of biohydrogel made of polymeric chains has provided excellent shape stability during swelling (Tripathi & Misra, 2012), and the swollen state of biohydrogel has a much higher mass fraction of water than the polymer mass fraction (Ahmed, 2015). The such structure of biohydrogel can be obtained by different techniques like copolymerization, interpolymer complexes, and semi-interpenetrating polymerization (Bhatia *et al.*, 2013).

Chemical graft copolymerization involved the initiators to generate active sites on backbone, andit provided the most effective method to improve the biohydrogel characteristics. Cerric salts (Ce(IV)), such as the cerric nitrate and cerric sulphate, has been used as free radical initiators in starch-based graft coploymerization by transferring single electron on the reducing agent (Jyothi & Carvalho, 2013; Athawale & Rathi, 1999). Copolymerization and crosslinking of natural polymers with other monomers, such as methacrylic acid and acrylic acid produced a high swelling power biohydrogel in neutral pH and tend to alkaline (El-Hag & Al-Arifi, 2009; Lazim *et al.,* 2013). The graft copolymer based on polysaccharides was synthesized by generating free radical sites on the primary backbone chain and allowing these free radical sites to act as micro-initiators for acrylic and vinyl monomers (Pal & Das, 2013).

Native starch has limited application in pharmaceutical field. Its physicochemical properties such as insolubility in cold water, high viscocity and hydrophilic were not suitable for deliver matrix (Jaspret *et al.,* 2007; Sangseethong *et al.,* 2015*)* . Modification of starch could

improve its characteristics to meet industrial requirements. Carboxymethyl starch (CMS) is a modified starch in which its anhydrous glucose unit (AGU) was etherified with carboxymethyl groups (Nattapulwat *et al.,* 2008). However, the use of CMS as a single hydrogel matrix has limitations, especially in the stability of forming a stable, three-dimensional network. Mixing CMS with chitosan was expected increasing the compatibility of biohydrogels and resulting the pH-dependent swelling biohydrogel for colon-targeted system (Grabovac *et al.*, 2005). Chitosan, a liniear hydrophilic polysaccharide, composed of glucosamine and *N*-acetyl glucosamine (Roja *et al.,* 2005), and the large quantities of amino groups on its chain resulted a pH-sensitives swelling in low pH condition (George & Abraham, 2006). However, it is necessary to examine the exact concentration ratio of the natural polymer combination as the main matrix of biohydrogel.

Curcumin, the major bioactive agent in turmeric (*Curcuma lunga*), has various pharmaceutical activities. Extensive researches have revealed that the health benefits of curcumin were including anti-oxidative, anti-inflammatory, anti-proliferative, anti-microbial, anti-parasitic, anti-mutagenic, and anti-tumor activities (Kunnumakkara *et al*., 2008; Wilken *et al.,* 2011). Unfortunately, the curcumin has low chemical stability, besides the lack of water solubility and rapidly metabolized in the gastrointestinal tract (GIT), which caused poor oral bioavailabilty (Letchford *et al*, 2008; Anand *et al.,* 2010). Polysaccharide-based hydrogel can be designed to facilitate the curcumin in colon-targeted delivery system and improve its characteristics.

METHODS

Materials

Native sago starch was procured from local starch industries in Bogor, and chitosan (degree of deacetylation 93.8 %w/w) was provided by Department of Marine Products, Bogor Agricultural University. Sodium monochloroacetate (SMCA), sodium hydroxide, isopropanol, chloride acid, acrylic acid, cerric ammonium nitrate (CAN) and curcumin were all analytical grade chemical.

Preparation of Carboxymethyl Starch (CMS)

Synthesis of CMS was developed according to previous research with slight modification (Sangseethong *et al*., 2005). Dried sago starch was dissolved in isopropanol (1:4 w/v) in a 250 mL three-necked round-bottom flask. While the slurry was vigorously stirred at 250 rpm, sodium hydroxide in different concentration (Table 1) was added and heated to 40°C. After stirring for 20-30 min, SMCA (1.5 mol/mol of AGU) was added to the mixture. The reaction was carried out for 3 h and then neutralized by chloride acid (1N). Crude product was purified by 85% ethanol (v/v) until the filtrate gave negative response to silver nitrate solution (the filtrate did not show a turbidity when the nitrate solution was added into it). The pure CMS was then dried in an oven at 50°C. The degree of substitution values (DS) of CMS was determined according to ISO method 11216 (International Organization for Standardization, 1998), while its swelling power and solubility was analyzed according to Ref (Li & Yeh, 2001). The formation of carboxymethyl functional group was confirmed by fourier transform infrared spectroscopy (FTIR), and the morphology structure was observed by scanning electron microscope (SEM) .

Synthesis of Poly(Acrylic Acid)(PAA)/CMS-Chitosan Biohydrogel

The PAA/CMS-chitosan biohydrogel was synthesized by graft copolymerization with cerric ammonium nitrate (CAN) as an initiator. The monomer solution consisted of 50 mL monomer (aqueous acrylic acid 30%v/v) and 4g of sodium hydroxide (NaOH). The polymer mixture (CMS-chitosan) in a different type CMS and ratio(Table 1) was dissolved in the monomer solution and then the total volume was adjusted to 100 mL by adding distilled water. The mixing was continuously stirred (250 rpm) at room temperature after which 0.005 M of CAN (diluted in 1 M of HNO_3) was added to the homogenous mixture. The reaction was conducted for one hour, then the product was neutralized with 2.5 N of NaOH solution and precipitated by ethanol for 24 h. The crude product was filtered and oven-dried at 70° C, then purified by immersing and re-washing with methanol for several times to dilute the excess of acrylic acid and oven dried.

Table 1. Formula of Polyacrylic/CMS-chitosan Biohydrogel

Sample	NaOH Concentration (mol/mol AGU)	Ratio of Polymer (g/g)		Ratio of Polymer and Polyacrylic Acid (g/mL)
		CMS	Chitosan	
PAA/CMSaCs1	1.8	4	1	1:10
PAA/CMSaCs2	1.8	3	2	1:10
PAA/CMSbCs1	1.9	4	1	1:10
PAA/CMSbCs2	1.9	3	2	1:10

Swelling Power Measurement

Swelling power and solubility of biohydrogel was studied in three different solvent at room temperature by using gravimetric method. For this purpose, 50 mg of sample (*Wo*) was immersed in distilled water, 0.1 N HCl (pH 1.2) and 0.02 M phosphate buffer solution (pH 7.4) respectively for 24 h. After the immersion time was vanished, the swollen biohydrogel was separated by filtration, and its weight was measured (*Ws*).The swelling power (g water/g biohydrogel) biohydrogel were calculated by the equation:

$$SwellingPower = \frac{Ws - Wo}{Ws}$$

Curcumin Absorption Measurement

Briefly, the standard curcumin solution (4 g) was solubilized in absolute ethanol (450 mL), and then 25 mL of the stock solution was diluted in 250 mL of absolute ethanol. The swollen biohydrogel ethanol was immersed in the diluted curcumin solution for about 30 minutes at ±30°C. Finally, the absorbance of solution at λ = 422 nm was recorded by a UV spectrophotometer. The percent absorption of curcumin by biohydrogel was calculated by the equation:

$$Percent\ absorption = \frac{Ct - Co}{Co}\ x\ 100$$

where *Co* is the initial concentration of curcumin solution (mg/ml), and *Ct*is the concentration of curcumin after immersing (mg/ml), while the equation of curcumin standart curve was *y=0.1495x-0.0167* (R^2 = 0.996). The certain functional group of curcumin absorption by biohydrogel was detected by fourier transform infrared spectroscopy (FTIR), and the morphology structure was observed by scanning electron microscope (SEM) .

FTIR Spectroscopic Analysis

The certain of functional group describing the graft co-polymer formation was detected by fourier transform infrared spectroscopy (FTIR). The samples had been mounted on studs, sputter-coated with gold. In addition, the functional group formation during carboxymethylation was confirmed by using FTIR spectra (Tensor 37, Buker). For each sample, 32 scans were taken at 4000 to 400 cm^{-1}.

Morphological Analysis (SEM)

The morphology structure was observed by scanning electron microscope (SEM). All the samples were grinded and examined with EVO MA 10 scanning electron microscope (Carl Zeiss, SMT AG, Oberkochen, Germany) in various magnifications.

RESULTS AND DISCUSSION

Characteristic of Carboxymethyl Starch (CMS)

Modification of starch in the form of CMS results in significant properties differences compared to natural starch.In this study, CMS was obtained by reaction of sago starch and sodium monochloroacetate (SMCA) in the presence of sodium hydroxide with isopropanol as the organic solvent. CMS, an anionic starch, produced from the etherification of its anhydrous glucose unit (AGU) with the carboxymethyl group[28] according to Williamson ether synthesis. Substitution hydroxyl group (-OH) of starch with alkali (NaOH)), and then continued with etherification were able to increase the swelling power properties and solubility at ±30°C (Table 2). The granula surface of CMS was also much more porous than native sago strach (Fig. 4), it is due to the strong alkaline condition during the carboxymethylation (Lawal *et al*., 2008). Furthermore, the DS value (approximately 0.54-0.55) categorized to medium value (Spychaj *et al*., 2013), and it met the criteria of biomedical grade (0.5-0.9).

Swelling Power of PAA/CMS-Cs Biohydrogel

Graft copolymerization of acrylic acid onto CMS-chitosan was carried using cerric ammonium nitrate initiator. The –OH group present on the backbone polymer acts as the active sites for the graft copolymerization of PAA onto the CMS-chitosan. The swelling studies of PAA/CMSCs biohydrogel were performed in different solvents (Figure. 1). It can be seen that the maximum swelling was obtained in water for all the samples (10.6-16.9 w/w). The higher ratio of CMS has increased the swelling capacity of biohydrogel, and the highest swelling valuewas found in PAA/CMSaCs1 (CMS : chitosan = 4:1). The porous granula structure of CMS (Fig. 4) was suggested improve the biohydrogel network to absorb the water.

Table 2. Characteristic of Carboxymethyl Starch (CMS) in Different NaOH Concentration

Parameters	Native Starch	CMSa	CMSb
DS value	-	0.54	0.55
Swelling power	9.30	12.73	12.80
Water solubility (%)	20.00	60.00	62.67

CMSa = 1.8 mol/mol AGU of NaOH, CMSb = 1.9 mol/mol AGU of NaOH

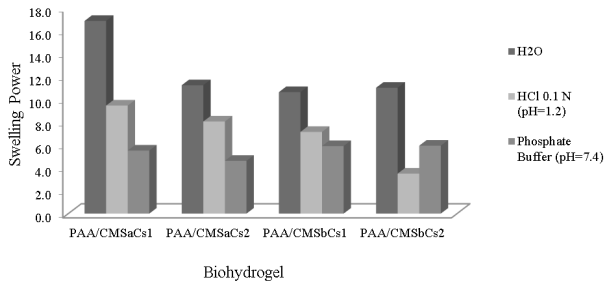

Figure 1. Swelling Power of PAA/CMS-Chitosan (Cs) Biohydrogel After 24 H Immersing in Three Different Solvents : Distilled Water (H2O), 0.1 N Hcl (Ph 1.2), and 0.02 M Phosphate Buffer (Ph 7.4)

All the samples were also swellable in acidic and base condition, however their swelling power were slight lower in both environment rather than in water. Presumably, CMS greatly influenced the biohydrogel swelling power than chitosan. The previous study reported the CMS sensitively respond to pH, and its microgels showed shrinkage at low pH due to protonation of the carboxilyc groups (Zhang *et al*., 2015). The carboxilyc group formation in sago CMS has confirmed by FTIR spectra (Fig. 3). Furthermore, the biohydrogel PAA/CMSCs were more swollen in acidic condition than basic condition, and it was contributed by the chitosan characterization that was easy dissolved at low pH and insoluble at higher pH range. The protonation of amine groups of chitosan under low pH condition leads to chain repulsion, and this property was suitable for stomach-targeted drug delivery (Yao *et al*., 1994).

Curcumin Absorption Study of PAA/CMS-Cs Biohydrogel

The performance test of biohydrogel in curcumin absorption was completely done by using the high concentration of curcumin for initial condition in order to rapidly observed the concentration change. This study showed that the curcumin were succesfully loaded in all of PAA/CMS-Cs biohydrogels within 30 minutes of immersion. Visually, the colour gradation of curcumin, dark orange to light orange, representing the concentration reduction was clearly detected (Fig. 2).

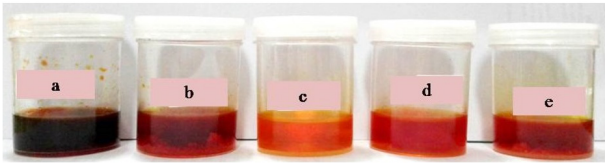

Figure 2. Images of Different Curcumin-Loaded Biohydrogel After Curcumin Absorption in 30 Minutes: (A) Curcumin Solution,(B) Curcumin-Loaded PAA/CMSaCs1 Biohydrogel (C), Curcumin-Loaded PAA/CMSaCs2 Biohydrogel, (D) Curcumin-Loaded PAA/CMSbCs1 Biohydrogel, and (E) Curcumin-Loaded PAA/CMSbCs2

PAA/CMSaCs1 that has a maximum swelling capacity (Fig. 1), subtantially absorbed the curcumin in a high percentage (17.34% w/w). It is similar to previous studies, alginate-based hydrogel beads has succesfully encapsulated about 16% of curcumin (w/w), while chitosan-alginat mixture improved the curcumin encapsulation to 24-35% (w/w) (Zhang *et al.*, 2016; Herdini *et al*., 2010). In addition, the higher ratio of CMS resulted approximately 3-4 times higher of loaded-curcumin than lower ratio of chitosan (Table 3). It was assumed that the higher CMS ratio increased the absorption capacity of biohydrogel in swollen state, since the absorption study was carried out by using water-swollen biohydrogel and CMS was good swelling in water.

FTIR Spectra Analysis of PAA/CMS-Cs Biohydrogel

FTIR spectroscopic identified some specific functional groups of the polymer and monomer involved in the graft copolymerization of PAA/CMS-Cs biohydrogel (Fig. 3). In this study, one of the samples (PAA/CMSbCs1) was selected to be observed for FTIR spectra and microscopic analysis according to its swelling power and curcumin absorption ability. All the spectra showed the functional group at peaksof 1650.10 cm^{-1} indicating carboxymethylation of sago starch (CMS) as the backbone. This result was similar to carboxymethylation of potato starch and Indian Palo starch (1580-1600, 1410 and 1318cm^{-1}), those bands represented C=O and C=O streching (Das *et al*., 2015). However, the same peak found in PAA/CMSbCs1 biohydrogel (1628.94 cm^{-1}) and curcumin-loaded PAA/CMSbCs1(1627.91 cm^{-1})was sharper than in CMS. It is prooved that polyacrylic was succesful grafted-copolymerized onto the CMS, since the spectra absorption bands at 1730-1650 cm^{-1} was either characterized as C=O stretch of carboxyl group comingfrom CMS and polyacrylic acid (Abdel-Halim & Al-Deyab, 2014). Moreover, the –NH-peaks in the amide groups of chitosan were also located at 1650 cm^{-1} and 1550 cm^{-1} (Lee *et al*., 1999). Noticeably, the increased peak at 1627.91 cm^{-1} of biohydrogel has indicated the polyacrylic grafting onto chitosan as the copolymer.

Microscopic Analysis of PAA/CMS-Cs Biohydrogel

Microscopic studies was carried to examine the surface morphology of biohydrogel, and also provide evidences for the occurrence of chemical modifications.SEM microgrphs described a different granula morphology of biohydrogel (Fig. 4b) comparing to CMS (Fig. 4b) as the main backbone and the biohydrogel loaded-curcumin (Fig. 4c-d).

Sago-based CMS has a porous surface (diametre range 4.133µm-22.33µm) because of chemical modification by alkalization process in which the Na^+ ion released, and this processed has broken down the hydrogen bond

Table 3. Curcumin Absorption in PAA/CMS-chitosan (Cs) Biohydrogel after 30 Minutes Immersion

Curcumin Absorption	PAA/CMSaCs1	PAA/CMSaCs2	PAA/CMSbCs1	PAA/CMSbCs2
Curcumin concentration (mg/ml)	1455.88	368.30	1100.57	359.64
Percentage of loaded-curcumin	17.34	4.39	13.11	4.28

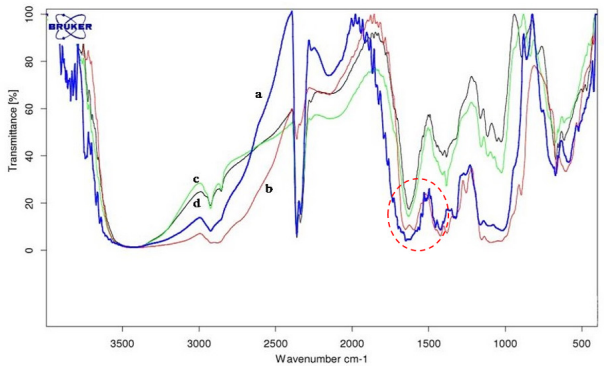

Figure 3. FTIR Spectra: (a) CMS, (b)Chitosan (Cs), (c)PAA/CMSbCs1Biohydrogel, and (d)Curcumin-loaded PAA/CMSbCs1Biohydrogel

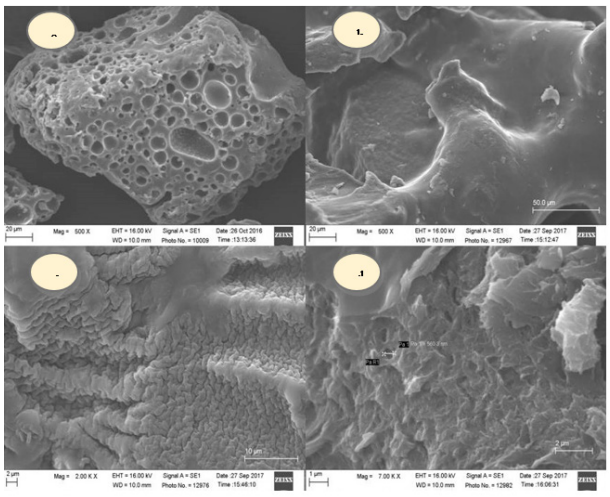

Figure 4. Scanning Electron Micrograph : (a) CMS, (b)PAA/CMSbCs1Biohydrogel, (c-d)Curcumin-loaded PAA/CMSbCs1Biohydrogel (Fig. a-c were taken in 2000x of magnification, Fig. d was taken in 7000x of magnification).

and disrupted the structure (Sangseethong *et al*., 2005). Contrary, the graft copolymerization of acrylic acid onto CMS-chitosan resulted a less smooth granula of biohydrogel than its initial main matrix (CMS). This result was similar to hydrogel from acrylic acid-attapulgit-alginat and acrylic acid-pectin that was spherical in shape with a smooth surface (Wang *et al.*, 2009; Lazim *et al*., 2013). In case of loaded-curcumin biohydrogel, it can be seen that the curcumin was orderly stacked up in the biohydrogel surface and covered it. More detail, in higher magnification of observation (7000x), the porous surface of biohydrogel was also found in uncovered surface with pores size was approximately 560.3 nm. It is presumably, the curcumin has not entrappped optimally in the hydrogel pores due to the larger size of curcumin than hydrogel pores, and this could be noted from low absorption curcumin data in Table 3 (4-17% (w/w) of curcumin absorption).

CONCLUSION

Biohydrogel was succesfully synthesized by graft-copolymerization of poly(acrylic acid) (PAA) ontoCMS-chitosan (CMC-Cs) mixture as the backbone and cerric ammonium nitrate as the chemical initiator. A higher CMS ratio in the polymer mixture (4:1) revealed the highest swelling power (16.9 w/w) and percentage of curcumin absorption (17.34%w/w). All the samples have the pH-responsive swelling properties, with the swelling trend was observed in the order of distilled water > HCl solution > phospathe buffer solution. FTIR spectra and SEM micrographs has confirmed the graft-copolymerization of PAA/CMSCs biohydrogel by describing the appearance of peak around 1600 cm^{-1} and the morphology of granula structure, respectively.

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