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Synthesis of Carboxymethyl Cellulose from Mangrove Nipah (*Nypa fruticans*) as Vitamin C Coating for Drug Delivery System

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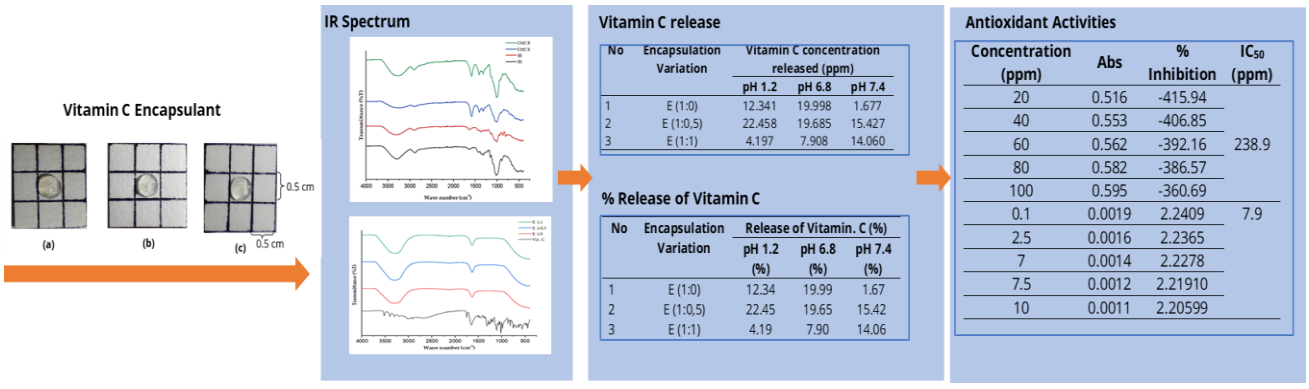
Abstract

Vitamin C is one of the substances needed by the human body. It acts as an antioxidant that effectively overcomes the effects of free radicals that damage cells in the body. However, vitamin C easily oxidizes, so innovation is needed to coat (encapsulate) vitamin C in the form of capsules as a drug delivery system. This research aims to synthesize carboxymethyl cellulose from the skin of Nipah Mangrove (Nypa fruticans) and use it to encapsulate vitamin C. The microencapsulation method was carried out by mixing 3 g of carrageenan-CMC mixture with variations in the ratio of 1:0, 1:0.5, and 1:1 (%b/b). The encapsulated small beads were extruded in 200 mL of 2M KCl-CaCl solution. The microencapsulant was drained and continued with the crosslinking stage using Glutaraldehyde (GA) 1%. In this in vitro oral simulation study, the encapsulation ratio that produced the best treatment with the highest percentage of drug solubility in the intestine was the ratio (1:0.5), followed by (1:1) and the smallest (1:0) with percentage values of 15.42; 14.06; and 1.67 percent, respectively. Our findings in the study successfully synthesized CMC, Encapsulated Vitamin C, and simulated its release.

Keywords: *Carboxy Methyl Cellulose (CMC), Drug Loading, Encapsulation, Vitamin C*

Graphical Abstract



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Introduction

Vitamin C is a bioactive substance, (5R)-[(1S)-1,2-Dihydroxyethyl]-3-4-dihydroxyfuran-2(5H) formula needed by the human body that acts as an antioxidant that effectively overcomes the effects of free radicals that can damage cells in the body [1]. Vitamin C is very important in the body as an antioxidant because it can protect cells from causing cancer [1,2]. Vitamin C is an antioxidant that contains ascorbic acid, which is easily oxidized to dehydroascorbic acid, which can inhibit oxidation reactions. Vitamin C is easily damaged due to the oxidation process with oxygen (O2) in the environment, so it is necessary to do an alternative coating (encapsulation) of vitamin C in the form of capsules as a drug delivery system[3].

Encapsulation is the process of coating a core substance with a coating material in the form of a capsule. The main purpose of microencapsulation is to protect biologically active compounds, such as natural colorants (e.g., anthocyanins), vitamins, and polyphenols, from degradation. In addition, this process enables the controlled release of core substances by delaying their absorption in the gastrointestinal tract and preventing their degradation in the initial digestion process. The use of this encapsulation process allows lowering production costs, eliminating the use of organic solvents, and avoiding high temperatures. Therefore, extrusion methods can be safely used to encapsulate bioactive compounds without thermal degradation[4]. One polymer that can be used for the encapsulation process is cellulose.

Cellulose is a glucose polymer in the form of a linear chain and is connected by β-1,4 glycosidic bonds. The linear structure causes cellulose to be crystalline and insoluble and not easily degraded chemically or mechanically. Cellulose can be obtained from one of the mangroves in the form of nipah fruit (*Nypa fruticans*). Nipah is a plant from the palm tribe (Arecaceae) that grows in mangrove forests[5]. Based on surveys and interviews with residents of coastal Jambi, communities in the East Tanjung Jabung area, it is known that people have not optimally utilized nipah plants. In fact, most people consider that nipah plants disturb other plants. However, Nipah (*Nypa fruticans*) in some areas has been widely used for various purposes, such as for roofing, sources of medicinal materials, fuel and foodstuffs[5]. Nipah has cellulose and hemicellulose content that range from 28.9-45.6% and 21.8-26.4 wt%[6]. The large amount of cellulose content in Nipah fruit makes Nipah fruit potential to be processed into derivative compounds in the form of carboxymethyl cellulose[7].

CMC is a polymer compound modified from cellulose as the main raw material through a carboxymethylation reaction to the -OH group[8] and is able to increase sensitivity to pH, amylase and protease, so in the biomedical field CMC is used as a drug coating[9]. Some factors that affect the quality of CMC include the type of media and alkali concentration. The quality of CMC produced is expressed by several parameters, namely, DS value (Degree of Substitution), viscosity, pH, morphology, functional groups, and purity of CMC[10]. The application of CMC has been developed a hydrogel wound dressing[11]. The addition of CMC in the wound dressing hydrogel using the citric acid crosslinker method of making hydrogel has been successful with the chemical crosslinking method, which shows that adding CMC can reduce the hydrogel gel fraction. In addition, CMC is also used in using hydrogel films in the health sector, which previous studies have done [10]. With the addition of CMC, the level of cross linking will increase and the swelling ratio will decrease

Materials and Methods

Chemical and Equipments

The materials used are nipah fruit, $(NH_4)_2SO_4$ (Merck), NaOH for analysis (Merck), CH_3COOH (Merck), distilled water, KCl (Merck), $CaCl_2$ (Merck), Aluminium Foil, Methyl Chloride (Merck), ethanol 96% absolute (Merck), KCl 2M (Merck), $CaCl_2$ 2M (Merck, Singapore), Glutaraldehid (Merck), Methanol (Merck), 2,2-diphenyl-1-picrylhydrazyl (DPPH) (Merck). The tools used were oven, grinder, analytical balance Kern, hot plate Thermo Scientific, whatmann filter paper, 25 mL and 100 mL measuring cups, 250 mL erlenmeyer, stirrer, buchner funnel, vacuum

pump, drop pipette, soxhlet merk behr Labor-Technik, dry sieving shaker 5E-SSB200, FT-IR spectra were recorded with Bruker Instruments and UV-Vis instruments on a Shimadzu 1700 Model

Hydrolysis and Saccharification

Nipah fruit was collected in East Tanjung Jabung district, Jambi. The skin fiber and nipah fruit flesh were separated. The skin fibers were cut into small pieces, dried for 2 days and oven at 80°C for 4 hours. Crushed and pulverized with a grinding machine and sieved on a shieve shaker with a size of 100 mesh[12].

Cellulose Extraction from Nipah Fruit

There are several stages in extracting cellulose from Nipah Fruit: (1) Dewaxing process, 30 g samples were extracted with 360 mL ethanol-toluene (1:2) at 85°C for 6 hours using the soxhlet method [13]. The residue was dried in an oven at 80°C for 4 hours. The sample was weighed and the yield calculated. (2) Delignification process, the residue was dissolved in 10% NaOH in a ratio of 1:10 between extractive compound-free nipah powder and 10% NaOH. Heated at 85°C for 2 hours, allowed to stand for 24 hours and filtered. The residue was washed with distilled water until the pH was neutral. The cellulose solids were filtered and washed using distilled water and ethanol, then filtered again. Cellulose solids were dried at 80°C for 8 hours. (3) Bleaching process, nipah fruit peel powder free of lignin and hemicellulose was dissolved in 12% NaOCl as much as 250 mL with distilled water added to 500 mL, heated at 60°C for 3 hr while stirring using a hot plate. Separated again and washed with boiling distilled water until the hypochlorite odor disappeared. Cellulose was dried using an oven at 60°C until a constant weight was obtained[14].

$$\% \text{ Yield} = \frac{W1}{W0} \times 100\% \quad \text{.....(1)}$$

W_0 = Sample weight of nipah husk fiber powder
W_1 = Dry weight of nipah husk fiber extract

Synthesis of Carboxymethyl Nipah Cellulose

Synthesis of CMC, 5 g of nipah skin and meat cellulose was added to 100 mL of distilled water and alkalized by adding 40 mL of 30% NaOH solution little by little while stirring at 400 rpm for 2 hours. Carboxymethylation was continued by adding 5 g of CCl_3CO_2Na, heated at 55°C for 5 hours while stirring. CMC was separated and washed with distilled water and neutralized with glacial CH_3COOH until pH 7. Immersion in 100 mL ethanol for 24 hours was carried out. The CMC obtained was dried in an oven at 60°C[14].

Characterization of Carboxymethyl Nipah Cellulose (CMC Nipah)

Characterization was carried out using an FTIR instrument to see the constituent functional groups of CMNC. FTIR analysis was carried out by making CMC pellets and mixing them with KBr. The fiber was crushed together with KBr until homogeneous and became a fine powder. Furthermore, a number of powders were taken and put into a pellet making tool. The pellets that have been formed are inserted into the FTIR. After all spectra were formed, the spectra were analyzed and matched with data from the literature (Sibarani, 2018).

Analysis of Degree Substitution (Ds)

The degree of substitution analysis was calculated with the FT-IR results with the equation 2.

$$\text{Ds} = \frac{\text{Abs OH}}{\text{Abs C=O}} \quad \text{.....(2)}$$

Microencapsulation

Microencapsulation was formed by dissolving 0.1% Tween-80 emulsion in 5 mL of Vitamin C solution. Then stirred with stirring for 3 minutes. Furthermore, the microencapsulation process was carried out by mixing 3 g of carrageenan-CMC mixture with variations in the ratio of 1:0; 1:0.5 and 1:1 (%b/b). The mixture was then heated at 85°C and stirred until the solution was homogeneous. Then, 2 mL of pre-made emulsion solution was added. Encapsulated small bead granules were made in 200 mL KCl-CaCl 2M solution by extrusion technique.

The microencapsulant was then drained and continued with the crosslinking stage using Glutaraldehyde (GA) 1%. The microencapsulant

was drained and subjected to FTIR characterization[15,16].

Microencapsulated Vitamin C was prepared in a 1:1 ratio to CMNC. CMNC was dissolved in 15 mL acetone solvent then Vitamin C was dispersed into the CMNC solution (Solution A). 30 mL of liquid paraffin and 1 mL of Tween-80 (Solution B) were prepared. The mixture of solution A was added drop by drop and emulsified into solution B until it formed an emulsion. The emulsion was stirred with a stirrer at 750 rpm for 30 minutes at room temperature until all the acetone evaporated. Then the microcapsules were separated by centrifugation to separate the filtrate and the residue. The residue obtained was then dried with a frezee-dryer.

Percentage of Encapsulated Product Yield

The percentage yield of the encapsulated product indicates how much microencapsulant is produced from the microencapsulation process, as previously done. Calculate the total weight of the microencapsulated product including the microencapsulated materials (coating materials and emulsifying agents) and the weight of the overall microencapsulated product using the equation 3.

$$\%R = (\frac{W0}{Wt}) \times 100\% \quad \text{..... (3)}$$

%R = percentage of product results ; W_0 = Weight of microencapsulated; W_t = total weight of microencapsulated material

Determination of Standard Solution and Standard Curve

Vitamin C solution was made with a concentration of 100 ppm and re-diluted into standard solution concentrations of 0,4,8,12,16 and 20 ppm. Subsequently analyzed using UV-Vis at a wavelength of 250 nm to make a standard curve of Vitamin C concentration[18].

Loading Capacity

The loading capacity (LC) of the encapsulation is expressed as the mass of Vitamin C entrapped per mass of particles. The loading capacity is calculated by the equation 4.

$$\%LC = \frac{\text{m Vit.C (mg)}}{\text{m particel (mg)}} \times 100\% \quad \text{..... (4)}$$

The mass of Vitamin C contained was determined through UV-Vis spectrophotometer quantitative assay. Vitamin C encapsulant (25 g) was dissolved in 100 mL of 0.1 N HCl. After 30 minutes the solution was centrifuged and the absorbance was calculated at a wavelength of 250 nm. The mass of vitamin C was determined from the standard curve.

In-Vitro Drug Release (DR)

Vitamin C encapsulants were immersed in 15 mL of buffer solution with pH 1.2 (2 hours) then transferred to pH 6.8 (2 hours), then transferred to pH 7.4 (4 hours)[19]. The amount of Vitamin C loaded in this experiment was 0.1g. Then the amount of drug released was measured by UV-Vis in absorbance λ = 250 nm using the formula 5.

$$\%\ DR = \frac{\text{The amount of medicine released}}{\text{0,1 g (100 ppm)}} \times 100 \quad \text{.....(5)}$$

Antioxidant Activity

Antioxidant test, for vitamin C and CMNC encapsulated vitamin C test solution was made by taking 1 mL of each concentration (2.5 ppm, 5 ppm, 7.5 ppm and 10 ppm) and adding 1 mL of 100 mg/L concentration DPPH solution and 2 mL of methanol which was then put into a test tube and incubated for 30 minutes at 370C. Furthermore, the absorbance was measured at a wavelength of 517 nm[20].

Result and Discussion

The stages of cellulose isolation process from Nipah fruit consists of 3 stages. The first is dewaxing, which removes colouring wax substances and impurities in Nipah fruit using polar and nonpolar solvents. The second is delignification, which reduces the lignin content in the fruit. This stage uses an alkaline solvent (NaOH) to dissolve the lignin content in the Nipah fruit so as to facilitate the separation process between lignin and fibre. Third, bleaching, the stage of bleaching to remove lignin and other non-cellulosic compounds with the addition of $NaOCl_2$, aims to degrade and remove substances

that cause brownish colour, which is thought to be lignin.

Characterization of cellulose from nipah peel and fruit was carried out using FTIR instrument which aims to identify the functional groups of each successfully synthesized compound. The following is the FTIR graph of the results of this study.

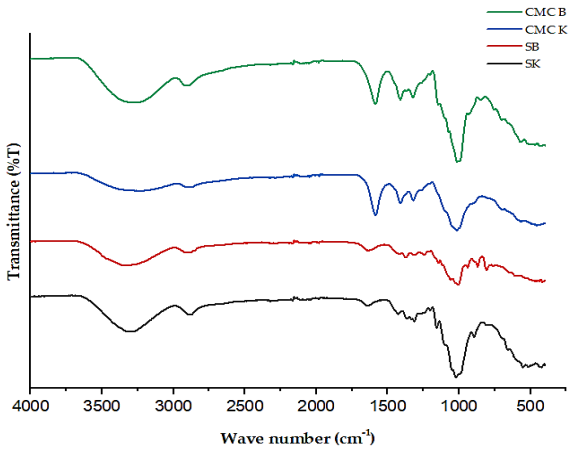

Figure 1. IR Spectrum of Cellulose Skin (SK), Cellulose Fruit (SB), CMC B (CMC Fruit), and CMC K (CMC Skin).

Carboxymethyl Nipah Cellulose

The synthesis of Carboxy Methyl Cellulose (CMC) consists of 2 stages, namely alkalization and carboxymethylation, In the alkalization process, the thing that is done is to mix nipah cellulose powder with 30% Sodium Hydroxide (NaOH) solution which aims to activate the OH group on cellulose. This alkalization process will affect the next stage, namely Carboxymethylation. Carboxymethylation is carried out with the addition of sodium trichloroacetate (CCl_3CO_2Na) which aims to glue the carboxylate group, the addition of sodium trichloroacetate plays an important role in the quality of the carboxymethyl that will be produced. This is because the higher the substitution reaction, the better the CMC that will be produced. The CMC formed is then washed using distilled water and then neutralized with glacial (CH_3COOH). The resulting CMC was then dried to obtain CMC in the form of white powder.

Characterization of cellulose and CMC synthesized from peel and nipah fruit was carried out using FTIR instrument which aims to identify the functional groups of each successfully synthesized compound. The following is the FTIR graph of the results of this study.

Degree of Subtitution

The degree of substitution is the average number of groups per anhydroglucose unit that are substituted (replaced) by other groups. Each anhydroglucose in cellulose has three hydroxyl groups on each anhydroglucose that can be substituted. Where in the CMC synthesis process, the hydroxyl group (-OH) on cellulose is substituted with a carboxymethyl group (carboxyl group, C=O) from the reaction with sodium chloroacetate. The degree of substitution can be calculated based on the absorbance data of CMC samples by comparing the absorbance of hydroxyl groups (-OH) and the absorbance of carbonyl groups (C=O).

Table 1. Degree Substitution of CMC

No	Type	Abs OH	Abs C=O	Ds
1	CMC B	0.062823	0.14638	0,429
2	CMC K	0,169178	0.1756	0,963

CMC quality requirements are regulated by the Indonesian National Standard (SNI), where the degree of substitution of CMC quality I (Grade I) ranges from 0.7-1.2, and CMC quality II (Grade II) ranges from 0.4-0.1. In this study, the degree of substitution of CMC K is 0.963, classified as CMC quality I. Meanwhile, the degree of substitution of CMC B is 0.429, classified as CMC quality II.

Encapsulation

In encapsulation with the extrusion method, carrageenan and CMC are used as coatings. Carrageenan is also one type of polysaccharide as well as CMC. Carrageenan has the properties of developer / chewy, stabilizing agent, gel-based emulsifier, suspension and agent that can increase the viscosity of formulations in the pharmaceutical field including emulsions, tablets and capsules [21]. The mixture of CMC and karegenan will provide better viscosity.

Therefore, an appropriate ratio or formulation combination of the two is required (Figure 2).

The synergism between these two polymer combinations provides a synergy effect that plays an important role in the development of drug formulation technology compared to single polymers. In addition, the microstructure of the gel produced by the polymer combination will be different than that of a single polymer. The more energetic the mechanical properties of the polymer combination, the more stable and long-lasting the drug release from the polymer matrix and the lower the decomposition as a drug encapsulation matrix[22].

The synergism of a polymer combination can be enhanced by adding a cross-linking agent. The agent used as cross-linker is glutaraldehyde. Biodegradable polymers need to be cross-linked to modify their characteristics and make the polymer matrix durable to deliver drugs over a desired period of time. The use of cross-linkers can alter the mechanical strength, swelling properties and degradation rate [23]. Masking and cross-linking will change the diffusion speed of the encapsulated drug molecules to ultimately control the release of the drug.

Microencapsulation using carrageenan-CMC dressing material with variations of 1:0, 1:0.5 and 1;1 (%b/b) can be seen in the figure below, Microencapsulant concentration variation ratio of 1:0 produces bead granules with a denser texture with a more intense color (cloudy). While the 1:1 ratio has a softer texture (prone to breaking) with a brighter color (clear). Microencapsulants that have been made are analyzed by FTIR to see their functional groups.

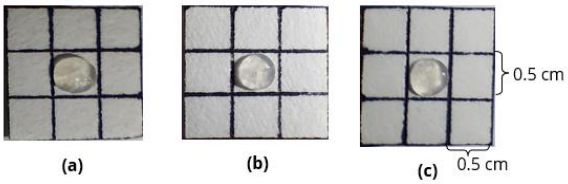

Figure 2. Microencapsulation of Polymer Combination (Carrageenan-CMC) with various concentration ratios or comparisons (%b/b). (a) 1:0. (b) 1:0,5. (c) 1:1.

The FTIR spectrum (Figure 4), it can be seen that there is an absorption peak at a wavelength of 3300-3400 which indicates the presence of -OH groups. Where it can be assumed that the presence of -OH groups detected in the spectrum comes from the -OH groups in kareganan and CMC. Based on the report previous studies the -OH group in the CMC coating is characterized by a band at a wavelength of 3427 nm.

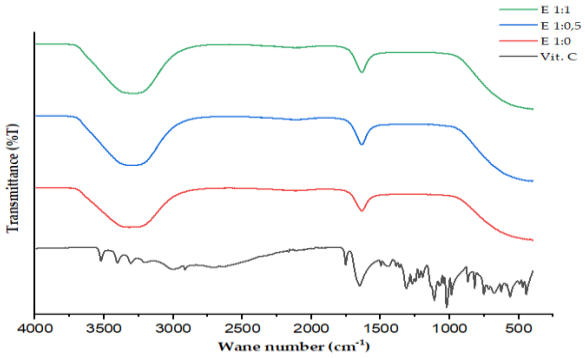

Figure 4. FTIR Characterization: Transmittance vs Wavelength Graphs of Vit. C, E1:0, E1:0.5 and E1:1.

Another absorption peak is at a wavelength of 1630-1635 nm which indicates the presence of a C=O group that has shifted the absorption peak. The absorption peak of the C=O group in the spectrum of pure Vitamin C is at a wavelength of 1752 nm[24]. The C=O group in vitamin C is indicated by an absorption peak at a wavelength of 1762 nm. So that in the encapsulant spectrum, it is suspected that there is a spectrum shift due to the encapsulation process with caregenan-CMC polymer material[25].

Percentage of Encapsulated Product Yield

The percentage yield calculation is used to determine the effectiveness and efficiency in encapsulation. The percentage of encapsulated product yield can be calculated by calculating the total weight of the encapsulated product obtained with the total weight of the material used for encapsulation. Data on the percentage yield of encapsulated products from various comparisons can be seen in Table 2.

Table 2. Data on Percentage of Encapsulation Product Yield

Parameters	(1:0)	(1: 0.5)	(1:1)
Encapsulation product yield (%R)	39.46%	43.79%	30.81%

Based on Table 2, it can be seen that the percentage of encapsulated products is the highest in 1:0.5 encapsulation. This is because the CMC and carrageenan layers in this formulation have good physical structure and high Vitamin C absorption data.

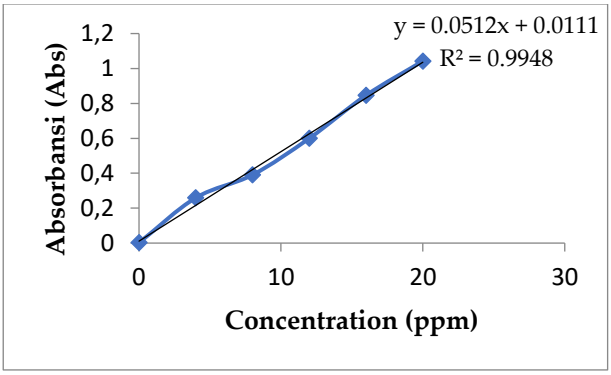

Figure 1. Standard Curve of Vitamin C

Percentage of Loading Capacity (%L_{Cap})

%L_{Cap} shows the ratio between the mass of Vitamin C in the encapsulated product and the mass of the product. CMC's performance in encapsulating Vitamin C provides a positive treatment in the Vitamin C loading process. The combination of carrageenan and CMC polymers creates more hydrogen bonds, allowing for the loading of more Vitamin C compounds. Carrageenan-CMC encapsulated bead can absorb more Vitamin C because the CMC structure has hydrophilic groups so that it can absorb water and swell. However, the higher concentration of CMC will form encapsulant beads that are softer and easily broken. This is due to the amount of water absorbed in CMC. Conversely, this also applies to encapsulants that have a greater concentration of carrageenan. The higher concentration of carrageenan will form denser and less breakable encapsulant beads.
The analysis of the percentage loading capacity of Vitamin C in the encapsulant formed was done through UV-Vis spectrophotometer quantitative test. The results of the data analysis of the percentage loading capacity of Vitamin C are presented in Table 3. Based on the data Table 3, it is known that the largest Vitamin C mass loading is in the 1:0.5 encapsulant formula and the smallest is in the 1:0 encapsulant formula.

Table 3. Vitamin C Loading Capacity

No	Encapsulation Variation	Abs	L_{Cap} (%)
1	E (1:0)	0.363	27.48
2	E (1:0,5)	1.166	90.2
3	E (1:1)	1.158	89.6

In Vitro Drug Release

The stability of the capsules in simulated gastrointestinal fluids. Controlled release of bioactive compounds is important so that the application of encapsulated microcapsules in food products may be viable owing to the avoidance of compound losses during processing. The amount of drug released was measured by UV-Vis at absorbance λ = 250 nm. In-vitro studies of drugs using buffers of pH 1.2, pH 6.8, and pH 7.5 provide important information about the stability, solubility, and activity of drugs under different conditions. Buffers with pH 1.2 are often used to simulate stomach acid conditions. Buffers with pH 6.8 are used to simulate physiological conditions in the human body. This pH environment is mostly as drug solubility and stability in the intestine due to the pH of the intestine usually ranging from 6 to 7. Buffers with a pH of 7.5 are used to simulate the environmental conditions of red blood cells [19]. In this oral simulation in vitro study, it was found that the encapsulation ratio (1:0.5) was the ratio that produced the best treatment. It can be seen from the data obtained that E (1:0.5) gives the highest percentage of drug solubility in the intestine among other comparisons [26].

Table 4. In Vitro Drug Release

No	Encapsulation Variation	Absorbance			Vitamin C released (ppm)			Release of Vitamin C (%)		
		pH 1.2	pH 6.8	pH 7.4	pH 1.2	pH 6.8	pH 7.4	pH 1.2	pH 6.8	pH 7.4
1	E (1:0)	0.643	1.035	0.097	12.341	19.998	1.677	12.34	19.99	1.67
2	E (1:0,5)	1.161	1.019	0.801	22.458	19.685	15.427	22.45	19.65	15.42
3	E (1:1)	0.226	0.416	0.731	4.197	7.908	14.060	4.19	7.90	14.06

Antioxidant Test

Antioxidant testing was carried out using the DPPH (1,1-diphenyl-2-picryl hydrazil) method which will react with antioxidant compounds. Measurement of antioxidant levels with DPPH using a UV-Vis spectrophotometer at a wave number of 517 nm which is the wave number of the DPPH compound. Antioxidants have an important role in the body to protect the body from the effects of free radicals that can cause various diseases. Antioxidants are compounds that inhibit oxidation reactions by binding free radicals by donating electrons (electron donors)[27].

Table 5. Encapsulation IC_{50} value

Concentration (ppm)	Abs	% Inhibition	IC_{50} (ppm)
20	0.516	-415.94	
40	0.553	-406.85	
60	0.562	-392.16	238.9
80	0.582	-386.57	
100	0.595	-360.69	
0.1	0.0019	2.2409	7.9
2.5	0.0016	2.2365	
7	0.0014	2.2278	
7.5	0.0012	2.21910	
10	0.0011	2.20599	

Inhibition Concentration (IC) is a parameter in the measurement of antioxidants. The IC_{50} value is the concentration of sample solution required to reduce DPPH by 50%. The smaller the IC_{50} value, the stronger the antioxidant activity. IC_{50} is the concentration required in the sample to inhibit 50% of DPPH free radicals. The regression value was obtained as y = 13.077x -431.68. The value of x is the value of the concentration required to reduce 50% of DPPH radical activity. The IC_{50} value of encapsulated vitamin C >200 ppm is precisely 238.995 ppm which indicates that encapsulated vitamin C has very weak antioxidant activity (Table 4). When compared with unencapsulated vitamin C from the calculation results obtained regression equation y = 0.0087x + 2.1999 with a regression value of 0.9709. The concentration value against % inhibition is directly proportional. The IC_{50} value of pure Vitamin C is 7.9 ppm, indicating that vitamin C has very strong antioxidant activity.

Conclusion

Our findings in the study successfully synthesized CMC and Encapsulated Vitamin C. In the oral simulation in vitro study, the encapsulation ratio that produced the best treatment with the highest percentage of drug solubility in the intestine was the ratio (1:0.5) followed by (1:1) and the smallest (1:0) with percentage values of 15.42; 14.06; and 1.67 percent, respectively.

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Author Contribution

Conceptualization, I.L.T. and D.D.; Methodology, D.D, V.G.R.M; Software, I.L.T.; Validation, I.L.T, D.D, P.N.S; Formal Analysis, X.X.; Investigation, X.X.; Resources, X.X.; Data Curation, N.A; Writing – Original Draft Preparation, D.D., V.G.R.M, P.N.S, I.L.T.; Writing – Review & Editing, P.N.S, I.L.T.; Visualization, I.L.T

Conflict of Interest

The authors declare no conflict of interest

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