

SYNTHESIS AND CHARACTERIZATION OF PECTIN-CARBOXIMETYL CHITOSAN (CMC) MEMBRANE AS DRUG DELIVERY MATRIX FOR CURCUMIN

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ABSTRACT

Pectin and chitosan are biomaterials with unique properties, such as biocompatibility, biodegradability, mechanical properties, and the capacity for controlled release of drugs. All these characteristics make the material an important candidate for pharmaceutical applications, including drug delivery materials. This study aims to synthesize and characterize a pectin-based membrane modified with carboxymethyl chitosan (CMC) intended for drug delivery carriers for curcumin. The membrane was prepared by the solvent-casting method by dissolving powdered pectin and CMC with 1:1 ratio in 2% acetic acid solution and stirring until a homogeneous solution was obtained. The solution was thoroughly printed in polypropylene tubes and then dried at 50°C for 24 h. The pectin-CMC membrane was characterized by FTIR to determine functional groups, XRD to calculate the degree of crystallinity, and SEM to investigate surface morphology. The curcumin loading capacity was subsequently tested by contacting curcumin onto the membrane at predetermined time intervals. The concentration of curcumin was determined using a UV-Vis spectrophotometer at λ 426 nm. Results showed that the pectin-CMC membrane was a thin, clear, and homogeneous film. The FTIR characterization showed absorption of peaks at wavenumber 3441.01 cm^{-1} of OH group, wave number 1604.77 cm^{-1} of carbonyl group, and wavenumber 1512.19 cm^{-1} of an ammonium group. The XRD data suggested the amorphous structural formation of the membrane. The SEM characterization demonstrated that the membrane surface was uneven and porous. The optimum contact time of the curcumin loading on the pectin membrane was 60 min with a loading capacity of 28%.

Keywords: Pectin, Carboxymethyl Chitosan, Curcumin, Drug Delivery

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INTRODUCTION

The development of controlled drug delivery remains a research focus that aims to maximize the drug delivery process. This is driven by three main reasons, which are creating an effective therapy system (effectiveness), reducing the detrimental effects of the system (safe), so that the system can be well received by patients (acceptability).¹ Currently, various natural materials are used in new drug delivery systems. Pectin and chitosan are natural polymers that have properties of biocompatibility, biodegradability, relatively cheap, non-toxicity, low allergenicity. Thus, they are widely chosen as excipients in drug formulation or carriers for drug delivery systems.²⁻³

Pectin is a polymer of D-galacturonic acid which is linked by 1,4 glycosidic bonds to form polygalacturonic acid. The carboxyl group is partially esterified with methanol and part of the secondary alcohol group is acetylated. Pectin is a biopolymer that is abundantly found in the middle lamellae of the wall of higher plants. In this case, pectin functions as an adhesive, texture-forming, and cell membrane.⁴ Pectin can increase viscosity and stabilize the emulsion system so that it is used as a thickening and gelling agent. In the food industry, pectin is used as a gelling agent, thickener, product stabilizer, and also as packaging material for edible films. In the pharmaceutical field, pectin is used for anti-diarrhea, lowering blood cholesterol levels, anti-anemia, drug admixtures, and heavy metal biosorbent.⁵ Various studies have shown that pectin is used for drug delivery systems because of its gelling characteristics.⁶ As a drug delivery

material, pectin is used as a membrane-forming or drug coating agent.⁵ As a bioactive agent carrier, pectin has the advantages of non-toxic properties, low production costs, and high availability. This allows pectin to be used as a drug delivery agent by oral, nasal, rectal, and vaginal.

Chitosan is a biopolymer derived from the outer skin of crustaceae class animals, such as shrimp and crabs. The chitosan membrane has major limitations concerning its stability under acid, so it is modified by grafting the active amine or hydroxyl group to form carboxymethyl chitosan (CMC).⁷ CMC is one of the chitosan derivatives obtained through the etherification (carboxymethylation) process of chitosan with monochloroacetic acid.⁸ Synthesis of CMC was carried out by reacting chitosan with monochloroacetic acid under alkaline conditions.⁹ The carboxymethyl group of monochloroacetic acid replaces the hydroxyl group and the amine group. In principle, the reaction to form CMC is an acid-base reaction.¹⁰ This modification is very useful in its application as an adsorbent because it can multiply the active functional groups thus increasing the adsorption power. This modification can occur due to the presence of a carboxymethyl group attached to the active site of chitosan. The nature of CMC is water-soluble, biodegradable, biocompatible, and non-toxic.¹¹ CMC can increase chitosan in terms of its physical and chemical capabilities, has a high viscosity and gelling ability and can improve mechanical properties as a drug delivery material.¹²

Curcuminoids are low molecular weight polyphenols found in the rhizome of turmeric (*Curcuma longa*) and used for various medical purposes.¹³ Curcumin is the most abundant and active curcuminoids, besides demethoxycurcumin and bisdemethoxycurcumin, which give the pigment its yellow color.¹⁴ Curcumin exhibits various pharmacological activities, including antioxidant, anti-inflammatory, anti-cancer, anti-bacterial, anti-neoplastic.^{14,15} However, its application as a drug is partly limited by its poor water solubility and low oral bioavailability.¹⁶ In order to increase the effectiveness of drug absorption according to the target in the body that allows the drug to enter the body, a drug delivery system is needed. This drug delivery system can be modified to increase the therapeutic index by reducing drug toxicity or by increasing drug efficacy.¹⁷ In vitro drug release also depends on several key parameters, i.e. pH, polarity, and the presence of enzymes in the medium of dissolution.¹⁸

Pectin and CMC are attractive alternatives as curcumin delivery matrix. As carriers they have good stability, so the drug can be properly absorbed by the body and achieve the desired target. This study aims to examine the possibility of pectin-CMC membrane as a drug delivery system for curcumin.

EXPERIMENTAL

Material

Pectin (local product), carboxymethyl chitosan (local product), curcumin (local product), acetic acid, hydrochloric acid, ethanol (Merck).

Synthesis of Pectin-CMC Membrane

0.5 g of powdered pectin and 2.8 g of powdered CMC were separately dissolved in 25 ml of 2% acetic acid, then stirred for 1 h using a magnetic stirrer until homogeneous. Both solutions were then mixed and stirred with a magnetic stirrer until homogeneous. The solution was thoroughly printed in polypropylene tubes and then dried with oven drying at 50°C for 24 h.

Analysis of Loading Capacity

The amount of drug loading in the membrane was calculated from the reduction in the concentration of the initial drug solution to the solution concentration remaining drug after the process of drug entry into the membrane. Drug loading efficiency is calculated as the ratio between concentrations of the final drug with the initial concentration of the drug. 25 mL of 100 ppm curcumin was contacted onto 50 mg of pectin-CMC membrane for 2 h. At predetermined times of 5, 10, 15, 30, 45, 60, and 120 min, curcumin samples were taken and the concentration was measured. The concentration of the curcumin was measured by measuring the absorbance of the solution with a UV-Vis spectrophotometer (Shimadzu UV3150 UV-Vis Spectrophotometer) at wavelength 426 nm.

Characterization of Pectin-CMC Membrane

Membrane characterization was carried out by instruments as follow:

FTIR characterization to identify functional groups of the pectin-CMC membranes that have been formed. Samples were analyzed using the FTIR (Shimadzu FT-IR 8201PC Spectrometer) carried out by FMIPA UGM.

SEM characterization to investigate the surface morphology of the synthesized pectin-CMC membrane. SEM characterization was carried out by LIPI Bandung.

XRD is a non-destructive technique for analyzing the structure of crystalline or semi-crystalline characteristics of materials. XRD characterization was carried out by LIPI Bandung.

RESULTS AND DISCUSSION

Synthesis of Pectin-CMC Membrane

In this study, the synthesis of pectin-CMC membranes was carried out by dissolving 0.5 g of pectin powder in 25 ml of 2% acetic acid and 2.8 g of CMC powder in 25 mL of 2% acetic acid then stirring using a magnetic stirrer for 1 h without heating until homogeneous. Both the pectin gel and CMC gel were mixed and stirred the mixture using a magnetic stirrer until homogeneous. The gel was printed into a PVC container then dried using an oven for 24 h with a temperature of 50 °C. Oven drying aims for evaporation and removal of solvents, like acetic acid, so that the pectin membrane formed was solvent-free. The results of the membrane can be seen in Fig.-1.

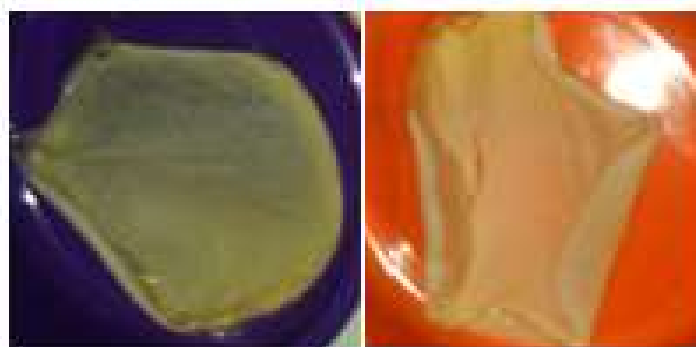


Fig.-1: The Physical Appearance of formed Pectin-CMC Membrane

The resulting pectin-CMC membrane has a pale yellow color with a smoother texture than pure CMC. The pectin-CMC membrane was insoluble in water. In comparison, with a similar process, the pure pectin membrane has a clear color and a smoother surface, while the surface of the pure CMC membrane was coarser and yellowish in color. Pure pectin membranes were more difficult to dissolve in water.¹⁶

Evaluation of Loading Capacity

The loading capacity test aims to determine the efficiency of the drug that can be loaded into the membrane. Measurements were done indirectly, by measuring the concentration of the drug remaining in the solution. The mass of drug-loaded into the membrane is determined by carefully calculating the difference between the initial drug concentration and the drug concentration remaining in the liquid. Drug loading efficiency is calculated as the ratio between the masses of loaded curcumin with the initial mass. The initial curcumin mass was 2,5 mg, loaded into 50 mg of the membrane. The profile of the loading capacity test is presented in Fig.-2.

As seen in Fig.-2, the loaded curcumin onto the membrane shows an increasing trend in the first 60 minutes, and after that point, the graph tends to decrease. The loaded curcumin after 5 min reached 17%, and then gradually increases and reached a percentage of the encapsulation efficiency of 28% within 60 min. It indicates that the curcumin loaded into the pectin-CMC membrane has been saturated.

In the pectin-CMC membrane, a wider empty space between the molecules gives an opportunity for curcumin to enter (loading) into the membrane. The higher amount of drugs can enter the membrane, the greater the efficiency of drug loading on the membrane

FTIR Test

Pectin-CMC membrane was prepared by cutting it into pieces and powder. The FTIR data is presented in Fig.-3.

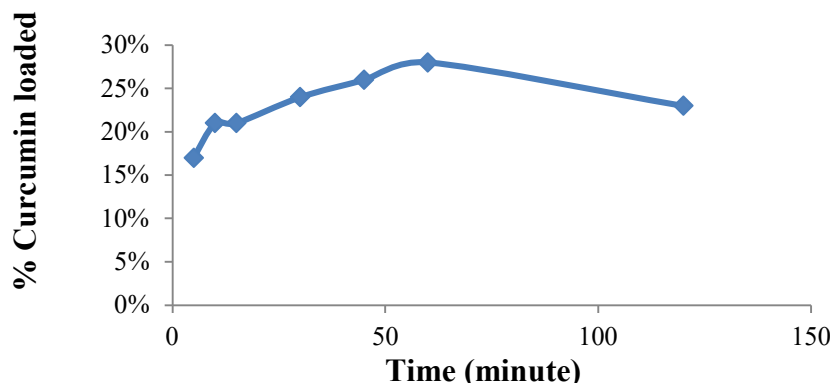


Fig.-2: The Profile of Loading Capacity of Curcumin onto the Pectin-CMC Membrane

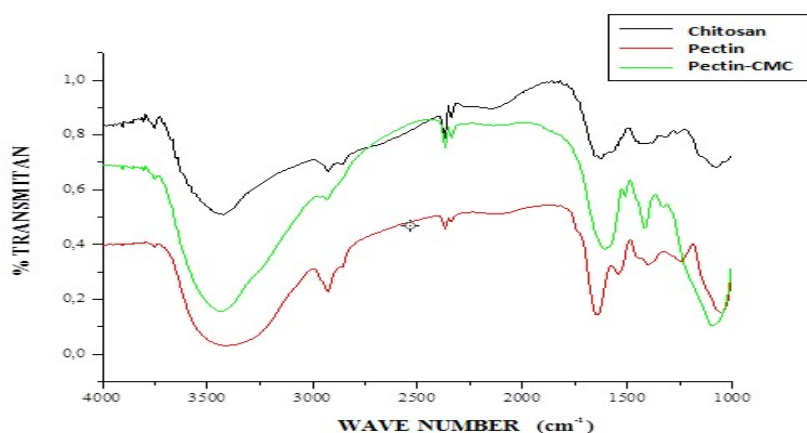


Fig.-3: FTIR of Pectin, Chitosan and Pectin-CMC membranes

Based on the IR spectra interpretation, there was a wave number at the peak of the hydroxyl group (OH) at 3448.72 cm^{-1} and the carbonyl at wave number 1604.77 cm^{-1} ¹⁹. On the chitosan membrane, a wave number appears at 3425.58 cm^{-1} which is a hydroxyl group, a wave number also appears at 1627.92 cm^{-1} which is a carbonyl group and at a wavenumber at 1519.91 cm^{-1} is an amine group.²⁰ Meanwhile, on the pectin-CMC membrane, a wavenumber of 3441.01 cm^{-1} appears which indicates group vibrations (-OH). The peak of 1604.77 cm^{-1} showed the vibration of the range of carbonyl groups (-COOH), at the peak of 1512.19 cm^{-1} was the vibration of the range of amine groups. The peak of the wave 1095.57 cm^{-1} was a range vibration (-C-O).

XRD Test

XRD was a non-destructive technique for analyzing the structure of crystalline or semi-crystalline materials. SEM data is presented in Fig.-4.

In Fig.-4(B), the diffractogram showed that the pectin membrane has the highest peak intensity with an angle of 2θ at 20° to 30° , indicating the structure was semi-crystalline. In Fig.-4(C), the chitosan membrane has the highest peak intensity with an angle of 2θ at 10° to 20° indicating that the structure of this compound is also semi-crystalline spectra. Furthermore, the pectin-CMC membrane can be seen from the highest peak intensity with an angle of 2θ at 10° to 20° was decreased. This is consistent with the results of the thermogram on CMC with an angle of 2θ at 10° to 20° indicating an amorphous structure. This was due to the occurrence of bonds caused by hydrogen bonds.²¹

SEM Test

SEM characterization aims to investigate the surface morphology of the membrane. SEM data is presented in Fig.-5.

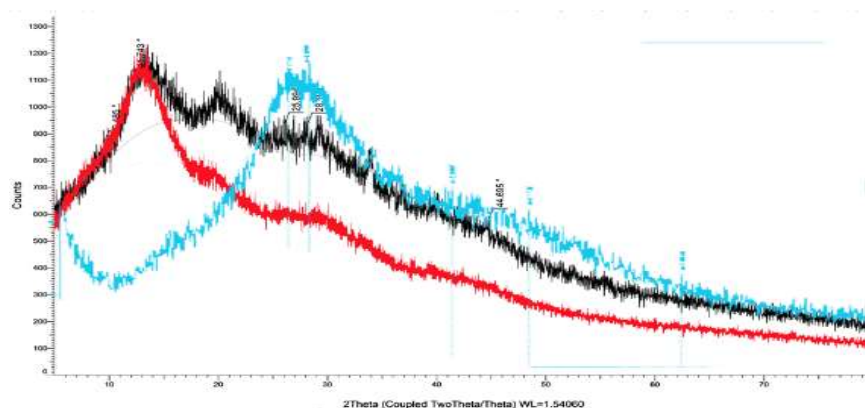


Fig.-4: SEM Characterization of (A) Pectin Powder (B) Pectin (C) Chitosan (D) Pectin-CMC

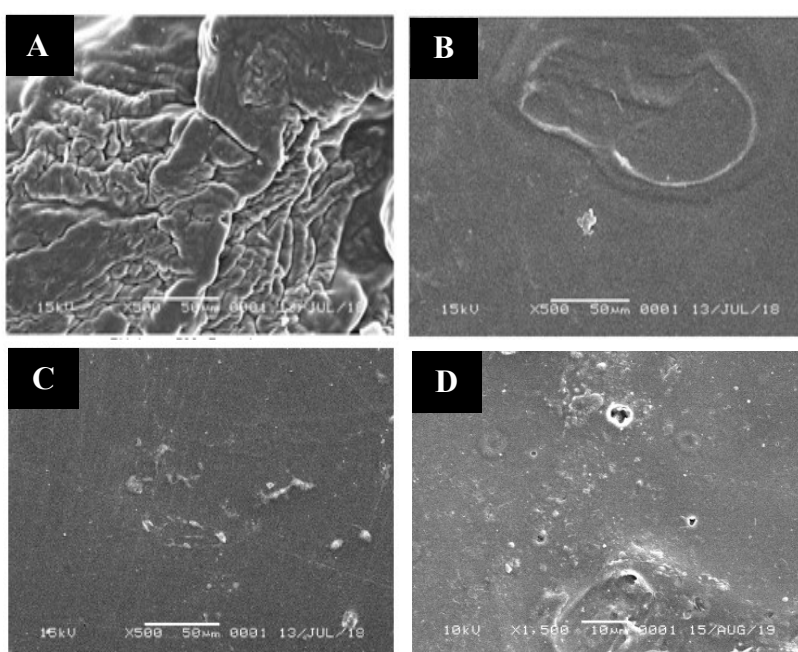


Fig.-5: SEM Characterization of (A) Pectin Powder (B) Pectin (C) Chitosan (D) Pectin-CMC

In Fig.-5(A), the pectin powder showed a rough and unstable surface. In Fig.-5(B), the SEM data showed that the pectin membrane surface has a smooth surface indicating a stable polyelectrolyte compound was formed. In Fig.-5(C) the SEM results of the chitosan membrane show similar characteristics to those of pectin. Furthermore, as shown in Fig.-5(D) the pectin-CMC membrane showed a smooth and porous surface, because of stable polyelectrolyte formation. The presence of pores on the curcumin-encapsulated chitosan pectin membrane is intended to make it easier for the drug to be digested in the body. When the drug dissolves in the body, the active drug substance will release through the pores of the drug matrix that is formed.²²

CONCLUSION

The pectin-CMC membrane was successfully synthesized based on the results of FTIR, XRD, and SEM characterization. Based on the interpretation of the IR spectra, there is a peak of 3441.01 cm^{-1} from hydroxyl ($-\text{OH}$), a peak of 1604.77 cm^{-1} from carboxyl groups ($-\text{COOH}$), a peak of 1512.19 cm^{-1} from amine groups, and the peak of 1095.57 cm^{-1} from ($-\text{C-O}$). XRD characterization showed that the pectin membrane was amorphous. The membrane showed a fine porous morphology based on the SEM results. Furthermore, the result revealed that curcumin can be loaded into the membrane with an encapsulation efficiency of 28% and an optimum time of 60 min.

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