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Optimization of Starch— κ -Carrageenan Film as Drug Delivery System Using Response Surface Method

Khairun Nisah ¹, Afrilia Fahrina ², Diva Rayyan Rizki ³ and Kana Puspita ^{4,*}

¹ Department of Chemistry, Faculty of Sciences and Technology, Universitas Ar-Raniry, Banda Aceh 23111, Indonesia; khairun.nisah@ar-raniry.ac.id (K.N.)

² Research Center for Marine and Land Bioindustry, National Research and Innovation Agency (BRIN), North Lombok 83756, Indonesia; afrilliafahrina26@gmail.com (A.F.)

³ Medical Research Unit, School of Medicine, Universitas Syiah Kuala, Banda Aceh, 23111, Indonesia; divarayriz@gmail.com (D.R.R.)

⁴ Department of Chemistry Education, Faculty of Teacher Training and Education, Banda Aceh 23111, Indonesia; kanapuspita@usk.ac.id (K.P.)

* Correspondence: kanapuspita@usk.ac.id

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Abstract

Development of drug delivery systems (DDS) has been widely carried out using safe biopolymers - starch and κ -carrageenan. However, for optimal use, the foregoing polymers still suffers from mechanical weakness. Combining both polymers could enhance the properties of each of the polymer. This research aimed of improving the applicability of starch and κ -carrageenan as DDS by means of polyelectrolyte complexation to form a polymer film. The composition ratio of starch: κ -carrageenan was optimized using response surface method (RSM) on Design Expert 11.0 based on water swelling, tensile strength, and disintegration time of the film. Fourier transform infrared spectrometry was performed on the prepared starch— κ -carrageenan film and suggested the successful film preparation. The bulk characteristics of the film are dependent on the starch or κ -carrageenan composition ratio, where starch has been associated with higher thickness, while κ -carrageenan — rigidity. From the RSM, the optimized composition was revealed to be 2.95 and 2.84 g for starch and κ -carrageenan, respectively, in a 60 mL aqueous solvent. The predicted optimum properties of the film were 160.21%, 3.26 MPa, and 17.47 min for swelling degree, tensile strength, and disintegration time, respectively. Taken altogether, the characteristics of starch or κ -carrageenan individually could be modified by polymeric combination, where they could be optimized by means of RSM.



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1. Introduction

Starch and κ -carrageenan have been widely used in the field of biomedicine because of their abundance, non-toxicity, and biocompatible [1]. In addition, starch can be digested in human body, making it a good drug delivery system (DDS) [1]. However, starch alone has major drawbacks of being mechanically weak and easily dissolvable in water. Moreover, starch could attract free

water molecules from the air and subsequently reduced the material's durability. To overcome, polymer combination has been evidenced to improve the native properties of starch [2, 3]. Even among our research group, we have employed the same strategy and successfully improved the physical and chemical properties of cellulose [4–6], chitosan [7–9], and pectin [10, 11].

In this study, the polymer blend consists of starch and κ-carrageenan. Similar to starch that is abundant in plants, plenty number of κ-carrageenan is produced by edible seaweed. This biopolymer has been commonly used as a stabilizer and thickener in food industries. Its application as DDS has been well recognized among researchers owing to its possession of sulfate ester functional group that has a strong affinity with drugs. Moreover, this functional group is responsible for the gelling property and dissolubility of κ-carrageenan which are significant parameters in DDS. However, the functional group is also responsible for the adverse health effects of being cytotoxic (note that κ-carrageenan is generally safe but in some of its forms, cytotoxicity may be increased, especially due to the sulfate group), anti-coagulant, and pro-inflammatory [12]. Since the functional group is negatively charged, it could form a polyelectrolyte complex with cationic starch when dissolved in water [13, 14]. The combination could enhance the mechanical strength as well as reduce the toxicity of κ-carrageenan [13, 15]. Hence, combining the two polymers in this present study is also meant to improve κ-carrageenan beneficial properties as DDS.

2. Materials and Methods

2.1 Materials

Biopolymers used in this study, starch and κ-carrageenan, are purchased from the local store in food grade quality (Banda Aceh, Indonesia). Other chemicals included sodium tripolyphosphate and glycerol which were purchased from Merck (Selangor, Malaysia) in analytical grade quality. All materials used in this research without any further purification.

2.2 Preparation of starch—κ-carrageenan films

Inversion method was used to construct the film with starch:κ-carrageenan ratios of 1:1, 1:2, 2:1, 2:3, and 3:2 w/w. Both polymers in powder form were dissolved in 60 mL distilled water, followed by the addition of sodium tripolyphosphate (2%) and glycerol (96%) and stirred for 2 h (80 °C; 120 rpm). Casting solution was then poured onto acrylic molds and left-cold for 24 h at room temperature before ready for use.

2.3 Characterization

Identification of functional group was carried out by Fourier transform infrared (FT-IR) spectrometry on FT-IR Cary 630 Anti Agilent (Penang, Malaysia). Prior to FT-IR analysis, the sample was oven-dried at 40 °C overnight and crushed into powder. Swelling degree was measured using distilled water and performed at room temperature. Time to disintegrate was based on

disintegration test protocol using distilled water (at room temperature). Tensile strength value was obtained from Universal Testing Machine HT8503 (Hung Ta Instrument Co., Ltd, Taichung, Taiwan) following ASTM D638-TYPE IV. All measurements were carried out in triplicate.

2.4 Optimization using response surface method

The composition of the polymeric film was optimized based on water swelling (Y1), tensile strength (Y2), and disintegration time (Y3). Y1 and Y2 act as maximizing functions, while Y3 – minimizing function. Independent variables were starch composition (X1) and κ-carrageenan (X2) with a constrain limit of 0—3. The parameters were input into Design Expert 11.0 to run the response surface method (RSM) with central composite design (CCD) approach.

2.5 Statistical analysis






Data from the CCD model was calculated for their average, median, and standard deviation (Std dev). Statistical significance was based on ANOVA. R-square was used to determine the data agreement in the model. All statistical data were generated from Design Expert 11.0.

3. Results and Discussions

3.1 Characteristics

Bulk characteristics and visual appearances of the films have been presented in Table 1. Addition of starch appear to give more thickness and roughness to the film, while addition of κ-carrageenan – more rigidity. Therefore,

Table 1. Bulk characteristics and visual appearances of starch—κ-carrageenan film.

| Bulk characteristics | Visualization | Starch: κ-carrageenan ratio (w/w) |
|--|---|-----------------------------------|
| Very thin, elastic, smooth, and homogenous |  | 1:1 |
| Smooth, homogenous, thin, and elastic |  | 2:1 |
| A little rough, thin, less homogenous, and elastic |  | 1:2 |
| Homogenous, strong, thick, rough, and rigid |  | 3:2 |
| Not homogenous, thick, strong, rough, and very rigid |  | 2:3 |

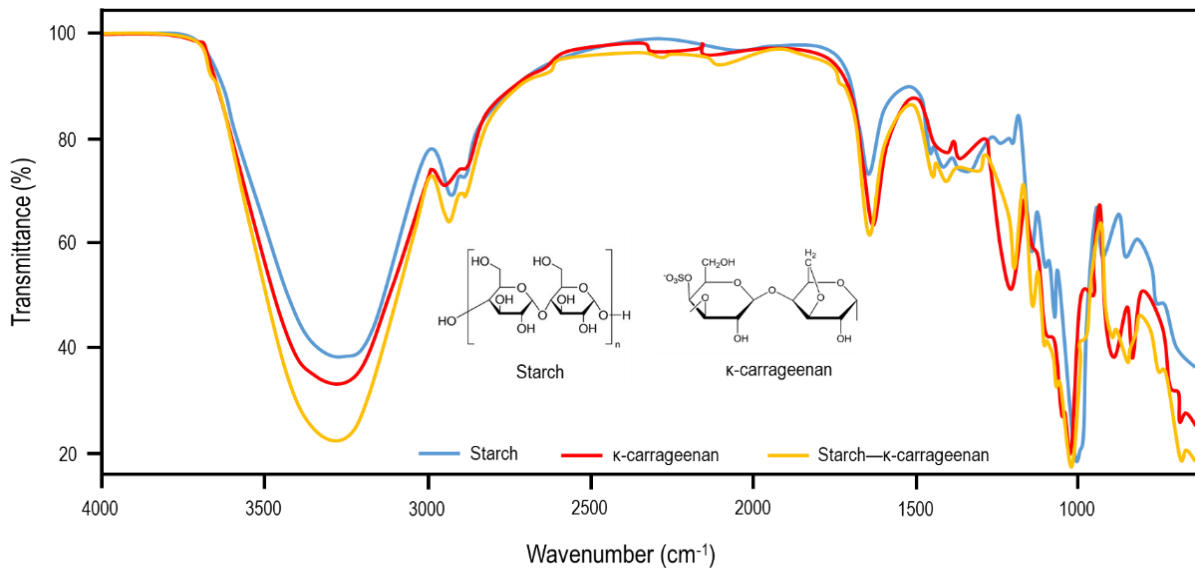


Figure 1. FT-IR spectra of starch, κ-carrageenan, and starch—κ-carrageenan film.

by varying composition, we can control the bulk characteristics of the film.

The functional groups characteristics of the tested polymers could be observed through FT-IR spectral profile presented in Figure 1. Both polymers are polysaccharides and show identical FT-IR spectral profiles. A narrow band at around 1000 cm⁻¹ is typical for carbohydrates which are originated from the carbonyl vibration. The distinctive FT-IR characteristic which can be observed only in κ-carrageenan is a spectral peak at 1212 cm⁻¹ which is assigned as S=O vibration. Its presence in starch—κ-carrageenan suggests the success of the polymer preparation.

Quantitative properties of the starch—κ-carrageenan film with different composition ratio have been presented in Table 2. The greatest water swelling was observed in composition where starch had dominant composition. Meanwhile, the highest mechanical strength was obtained from a sample consisting of 3:2 starch:κ-carrageenan. Sample with the highest durability against disintegration test is assigned to that with a ratio of 1:2 (starch:κ-carrageenan).

3.2 CCD-based optimization results

All response variables were matched with the first order model, second order model, and square models. For Y1 and Y2, the most representative model was the quadratic model. Meanwhile, for Y3, the best model is the linear one. The regression (R²) shows that Y1 and Y2 have the acceptable fitness to the model (R²=0.963 and 0.993, respectively), while the contrary result was

Table 2. Swelling degree, tensile strength, and disintegration time of starch—κ-carrageenan film.

| Ratio | Water swelling (%) | Tensile strength (MPa) | Disintegration time (min) |
|-------|--------------------|------------------------|---------------------------|
| 1 : 1 | 72.0 | 0.33 | 5.8 |
| 1 : 2 | 102 | 0.36 | 17.34 |
| 2 : 1 | 113.7 | 0.70 | 10.11 |
| 2 : 3 | 85.9 | 1.61 | 13.7 |
| 3 : 2 | 158.1 | 2.90 | 12.16 |

obtained for Y3 (R²=0.719). Based on ANOVA, all response variables are statistically significant (p<0.005), hence their applicability as variable in the model. Based on the model, we obtained the following mathematical relationship:

$$Y1 = - 26.78 X1^2 - 46.52 X2^2 + 50.71 X1X2 + 77.60 X1 + 44.63 X2 - 8.18 \tag{1}$$

$$Y2 = 0.2546 X1^2 - 0.0911 X2^2 + 0.3216 X1X2 - 0.4192 X1 + 0.00971 X2 + 0.0484 \tag{2}$$

$$Y3 = 1.92X1 + 4.61 X2 - 1.29 \tag{3}$$

Positive values of factors from the polynomial or linear equations above indicate the response synergism, whilst the negative sign represents antagonism. Results from the response surface post analysis with confidence of 95% confirm the optimum composition for starch (X1) and κ-carrageenan (X2) which are 2.95 and 2.84 g, respectively. If the compositions were used to prepare the starch—κ-carrageenan hybrid film, the predicted composition would be as presented in Table 3. From the predicted averages or medians, water swelling, tensile strength, and disintegration time appeared to reach 160.21%, 3.26 MPa, and 17.47 min, respectively. For

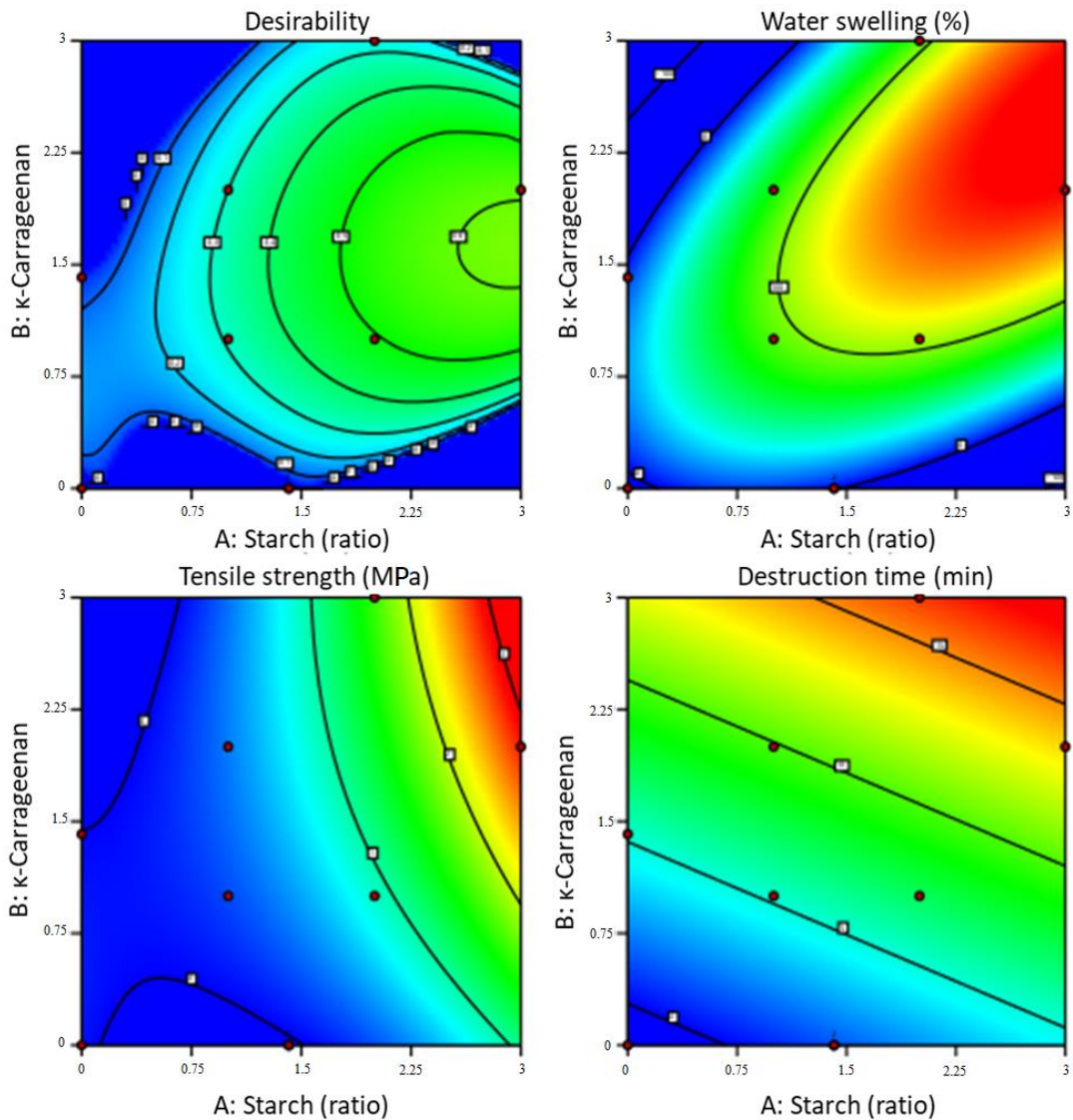


Figure 3. Desirability and optimization results for response variables water swelling (Y1), tensile strength (Y2), and disintegration time (Y3). Increasing intensity from blue to red indicate the optimized ratio.

better presentation, the desirability and optimization results have been presented in Figure 3. It shows that the optimization could provide improved properties of either starch or κ-carrageenan in the film. These overall findings are in line with previously reported studies [13, 14]. Nonetheless, as the limitation of this study, a validation has not been performed on the actual value.

Table 3. Predicted values of swelling degree, tensile strength, and disintegration time of the starch—κ-carrageenan film,

| Response | Average | Median | Std dev |
|---------------------------|---------|---------|----------|
| Water swelling (%) | 160.206 | 160.206 | 19.0677 |
| Tensile strength (MPa) | 3.25599 | 3.25599 | 0.134657 |
| Disintegration time (min) | 17.4665 | 17.4665 | 4.23702 |

4. Conclusions

Polymer combination could enhance the properties of starch and κ-carrageenan as DDS. Optimization using RSM revealed that starch:κ-carrageenan ratio of 2.95:2.84 w/w as the optimum composition with predicted median swelling degree, tensile strength, and disintegration time of 160.21%, 3.26 MPa, and 17.47 min, respectively. Further investigation is required, especially for the validation.

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