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Research Article

Characterization, Disintegration, and Dissolution Analyses of Carrageenan-Based Hard-Shell Capsules Cross-Linked with Maltodextrin as a Potential Alternative Drug Delivery System

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Hard-shell capsules commonly consist of gelatin which is not a universal material considering it is extracted from animal parts. Moreover, the mad cow disease triggered the scrutinization of the use of gelatin in pharmaceutical products. Hence, an alternative to conventional hard-shell capsules is needed. Carrageenan- (CRG-) based hard-shell capsules were successfully prepared by cross-linking CRG with maltodextrin (MD) and plasticizing with sorbitol (SOR). These CRG-MD/SOR hard-shell capsules were produced as an alternative to conventional hard-shell capsules in the oral drug delivery system (DDS). The physical properties of CRG-MD/SOR capsules were characterized using the degree of swelling, FTIR, and SEM analyses. The disintegration and dissolution profile release of paracetamol from CRG-MD/SOR hard-shell capsules was performed in an aqueous medium with three different pH levels. The degree of swelling of CRG-MD/SOR was $529.23 \pm 128.10\%$. The main peaks in the FTIR spectrum of CRG-MD/SOR were at 1248, 930, 847, and 805 cm^{-1} for ester sulfate groups, 3,6-anhydrogalactose, galactose-4-sulfate, and 3,6-anhydrogalactose-2-sulfate, respectively. The SEM analysis exhibited minuscule pores on the surface of CRG and CRG-MD/SOR at 5000 times of magnification. The CRG-MD/SOR capsules required 18.47 ± 0.11 min on average to disintegrate. The CRG-MD/SOR dissolution was better in a weakly acidic medium (pH 4.5) than in a strongly acidic (pH 1.2) and neutral (pH 6.8) media. Based on the aforementioned results, CRG-MD/SOR capsules are the potential candidate to replace conventional hard-shell capsules.

1. Introduction

A capsule is a common dosage form used in our daily life [1]. It is produced from gelatin and the capsules themselves are readily found in a soft- or hard-shell form. One of the advantages of hard-shell capsules is that they can deliver both solid and liquid medicines [2]. This indicates that the presence of hard-shell capsules is important as a drug delivery system (DDS). However, conventional capsules that commonly consist of gelatin are produced from animal parts such as skins or bones, which means they cannot be a universal ingredient to be consumed by all humans, e.g., vegetarians and Moslems who cannot use them [3]. Moreover, because gelatin is an animal-derived ingredient, mad cow disease triggered the scrutinization of the use of gelatin in pharmaceutical products [4]. Hence, another nature-based source for hard-shell capsules is needed as an alternative to gelatin.

Some alternative capsules have been developed, e.g., alginate capsules, which could not form hard-shell capsules [5], carrageenan capsules, which have slow disintegration time [6], and hypromellose capsules, which are sensitive to temperature change [7]. These examples show that recent

plant-based hard-shell capsules have disadvantages that still need to be resolved This paper reports on the development of new material for hard-shell capsules prepared from CRG cross-linked with MD and plasticized with SOR in order to create rigid yet flexible capsules that have an optimum disintegration rate.

Eucheuma spinosum contains a heavy polysaccharide known as CRG, which is comprised of various units of disaccharide galactoses [8]. Commercial CRG production is performed by extracting the seaweeds of *Eucheuma cottonii* in basic solvents at high temperatures. The six types of CRG (μ, κ, ν, ι, λ, and θ) that are thus produced can be used for daily purposes, such as gelling agents and natural sweeteners [9]. Among these six types of CRG, only κ-CRG exhibits the potential as a source for hard-shell capsules because of its gel-forming ability [10, 11]. However, CRG will undergo syneresis when it is dried from gel to film, causing it to become brittle [12]. Therefore, a cross-linker is needed to reduce the brittleness by strengthening the polymer's networks and thus improving CRG's gel-forming ability.

MD is prepared by heating amylose in acidic and humid conditions. This polysaccharide is usually comprised of less than 20 units of dextrose [13]. The high molecular weight of MD results in its high viscosity, in low osmotic pressure, and in a low sweetness. BeMiller [13] reported that MD is used commonly as a food additive in baby foods, bread, cereals, canned fruits, jelly, margarine, and syrups. MD is in widespread use because it is nontoxic even when consumed in excessive quantities and is inexpensive. Previous studies have shown that the gelling ability of κ-CRG can be improved by cross-linking CRG with MD [14–16]. Hence, we opined that MD is able to modify CRG's structure to reduce the brittleness of the capsules.

Based on the aforementioned information, CRG-based hard-shell capsules were successfully prepared by cross-linking CRG with MD and plasticizing with SOR. The capsules were characterized using SEM, FTIR, and degree of swelling analyses. Disintegration and dissolution analyses were also conducted to determine the release kinetics profile of the paracetamol as the drug model from the capsules.

2. Materials and Methods

2.1. Material. Food-grade κ-CRG powder was purchased from Kappa Carrageenan Nusantara, Inc., Pasuruan, Indonesia. Food grade MD and SOR were purchased from Brataco Chemica, Inc., Surabaya, Indonesia. PA-grade concentrated HCl (36.5%), citric acid, trisodium citrate dihydrate, KH_2PO_4, and K_2HPO_4 were purchased from Sigma-Aldrich.

2.2. Capsule Preparation. CRG and MD were measured in a precise ratio of mass (6 : 1 *w*/*w*) to obtain a mixture, mixed with 100 mL of deionized water and then with 1.5% *v*/*v* of SOR added. This heterogeneous mixture was heated for 5 hours until it formed a homogenous mixture. The bars used to print the capsules (defined as "pin bar" from this point) were dipped into this mixture and dried for 3 hours at room temperature. Finally, dried capsules were collected from pin bars and cut neatly to produce a good shape of hard-shell capsules.

2.3. Degree of Swelling Analysis. A degree of swelling analysis was performed in six replicates. All the capsule samples were floated onto 100 mL distilled water for 20 min at 37 ± 0.5°C. The samples were dried in an oven at 50°C for 3 hours and then weighed to determine the degree of swelling using equation (1), as follows [17, 18]:

$$\mathrm{DS} = \frac{m - m_0}{m_0} \times 100\%. \quad (1)$$

DS is the degree of swelling, m_0 is the initial mass, and m is the dried sample mass after 30 min.

2.4. FTIR Analysis. FTIR analysis was conducted using FTIR Shimadzu IRTracer-100 Spectrometer to obtain information about the functional groups of the samples. A 2 mg solid sample of CRG-MD/SOR hard-shell capsule and a 200 mg KBr were accurately mixed to form a homogenous mixture and printed into a transparent pellet for further analysis. The FTIR analysis was conducted for CRG and MD powders and CRG-MD/SOR capsules.

2.5. SEM Analysis. The morphology of the surface and pores of the samples was characterized using SEM type JEOL JSM-8360LA. The morphological differences between CRG and CRG-MD/SOR capsules were observed using a cross section of samples. Film samples were cut into a cube with dimension 3 × 3 × 2 mm. Following this, the films were placed on a specimen holder. DoTile was smeared around the samples in order to prevent vacancy spaces between the holder and samples. Afterwards, the samples were inserted into a fine coat so that the analysis could be conducted.

2.6. Disintegration. Following United States Pharmacopeia (USP) no. 701, a disintegration test was performed using the Veego Disintegration Test Apparatus Model VTD-AVP that consisted of eight open-ended transparent tubes. Eight samples of the CRG-MD/SOR capsules were placed in the tubes and then immersed in a 600 mL aqueous medium at 37 ± 0.5°C. Then, the apparatus was turned on to continuously move the tubes upside down until all the capsules were disintegrated. The capsules were filled with active carbon for ease of observation. The time (in minute) needed for the active carbon to initially diffuse from the capsules into the medium was recorded as the disintegration time of the capsules.

2.7. Dissolution Test Analysis Using Paracetamol. The dissolution test was adopted from USP-711 and was conducted to study the porosity of capsules and their relation with the drug release rate. Next, six capsule replicates were dispersed in three different pH levels of 1.2 (HCl), 4.5 (citrate buffer), and 6.8 (phosphate buffer) representing the pH of the gastrointestinal tract and the intestine in the human body. The dissolution test was performed within 3 hours at 37 ± 0.5°C for each capsule using the basket method at 100 rpm.

2.8. Statistical Analysis. Student's t test was used to assess the difference value obtained from disintegration and dissolution test. The difference will be considered significant if the p value is less than 0.05 ($p < 0.05$).

3. Results and Discussion

3.1. Physical Properties of Prepared CRG-MD/SOR Hard-Shell Capsules. Ridgway [19] states that gelatin capsules similar to our prepared capsules (type 0) must have a length, body diameter, cap diameter, average mass, and thickness of 17.90–28.90 mm, 7.290 ± 0.100 mm, 7.600 ± 0.100 mm, 0.096 g, and 0.194–0.214 mm, respectively. The physical properties of the CRG-MD/SOR hard-shell capsules are shown in Table 1. The length, diameter, mass, and thickness of the capsule were obtained by measuring eight samples with a digital micrometer. Although the same machine might be used to produce CRG-MD/SOR hard-shell and gelatin capsules, the CRG-MD/SOR hard-shell capsules had different properties, particularly their average diameter, mass, and thickness. These differences may have resulted from the differences in the raw materials of gelatin and CRG-MD/SOR in the printing process.

The CRG-MD/SOR capsules are the first hard-shell capsules made from fabricated materials. These data can therefore serve as a reference in further developments. The different starting materials of conventional gelatin capsules and CRG-MD/SOR hard-shell capsules can produce capsules with different chemical properties. This difference can be utilized for drugs that are suitable for CRG-MD/SOR hard-shell capsules specifications.

3.2. FTIR Analysis. Figure 1 represents the FTIR spectra of CRG powder and CRG-MD/SOR. Both CRG powder and CRG-MD/SOR spectra exhibited main peaks at 1248, 930, 847, and 805 cm^{-1} for ester sulfate groups, 3,6-anhydrogalactose, galactose-4-sulfate, and 3,6-anhydrogalactose-2-sulfate, respectively [20].

Figure 2 shows the proposed schematic structure of the CRG-MD/SOR capsule. Since sulfate groups are what make CRG a negatively charged polymer [9], it is possible that if these groups are the most reactive ones, they are to form a cross-link. The presence of MD and SOR significantly changed the peak at 1248 cm^{-1}, which for CRG-MD/SOR was not as sharp as that for CRG powder. This may support our statement that the cross-linking between CRG and MD was formed at the ester sulfate group. Conversely, SOR expanded the space between the cells in the cross-linked CRG-MD network [21]. The –OH band in CRG-MD/SOR spectra was narrower than that of CRG. This might indicate that more –OH groups bind more water and thus increase the rate of dissolution. In order to support our argument, it was reported that the addition of a more water-soluble polymer for capsule formulation reduces the disintegration time [4].

Pure CRG gel is a brittle material, and the addition of SOR increases its material elasticity [22]. This statement is supported by Balqis et al. [23] who studied the effect of SOR on the tensile strength and elongation percentage of CRG film. They found that the higher the concentration of SOR, the less the brittleness of CRG film would be.

Table 1: Dimension and mass of CRG-MD/SOR (carrageenan-maltodextrin/sorbitol) hard-shell capsules.

Length	22.56 ± 0.69 mm
Body diameter	7.18 ± 0.12 mm
Cap diameter	7.37 ± 0.13 mm
Thickness	0.14 ± 0.02 mm
Mass	0.12 ± 0.01 g

3.3. Morphological Analysis. Ma et al. [24] prepared gelatin films from rabbit and swine skins to analyze both mechanics and structural properties. Based on SEM, there was a patterned matrix on the surface of both films, with no significant difference between the two. These patterns show that gelatin has good structural integrity. In addition, there were no visible pores observed at 10,000 times of magnification, indicating that the pores of gelatin films were extremely small. Figure 3 shows the results of the SEM analysis of the surfaces of CRG and CRG-MD/SOR. Both CRG and CRG-MD/SOR exhibited invisible pores even at 5000 times of magnification. In addition, no cracks were observed. Król et al. [25] analyzed that at the scale of 1 : 200 nm, there were still no pores observed on the surface of gelatin film but the pores were observed on the surface of the CRG film. Therefore, we can conclude that the pores of CRG are bigger than that of gelatin.

The presence of extremely small pores confirms the observed high degree of swelling of CRG-MD/SOR. These small pores could indicate that the drugs would be released slowly from the capsules. Garcia et al. [26] reported that material with plasticizer resulted in a less compact matrix compared with the unplasticized material. Thus, the presence of SOR would help to optimize the rate of disintegration by widening the spaces between networks of cross-links. Shahi et al. [27] used SOR to form pores in the development of a diltiazem hydrochloride tablet. It was stated that the increase of SOR could increase the formation of the pores in the tablet.

Figure 3 also shows that the surface of both films is not smooth due to the presence of aggregates on the surface, indicated by white spots. These aggregates were invisible to the naked eyes due to the relatively small size. A hole was also present in the figure, and with the help of a software (ImageJ), it is estimated that the diameter of the hole was 1.82 μm. The presence of holes could affect the release kinetics of drugs. Repetitions are therefore needed in the disintegration and dissolution test in order to obtain statistical data to be precisely analyzed.

3.4. Degree of Swelling Analysis. Six CRG-MD/SOR capsules floated in 100 mL aqueous medium for 20 min at 37 ± 0.5°C resulting in a maximum degree of swelling of 529.23 ± 128.10%. Pudjiastuti et al. [6] found that the average degree of swelling of gelatin capsules was 145.5%. The calculation

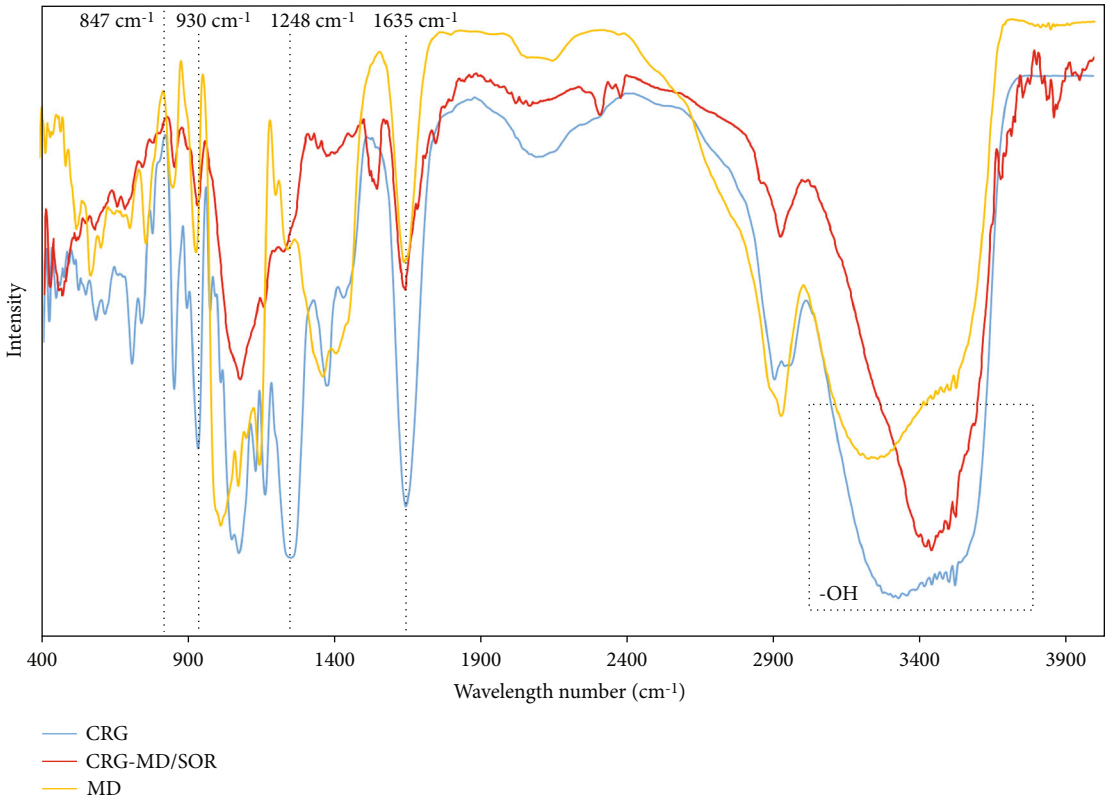

Figure 1: FTIR spectra of CRG (carrageenan) powder, MD (maltodextrin) powder, and CRG-MD/SOR (carrageenan-maltodextrin/sorbitol) capsule.

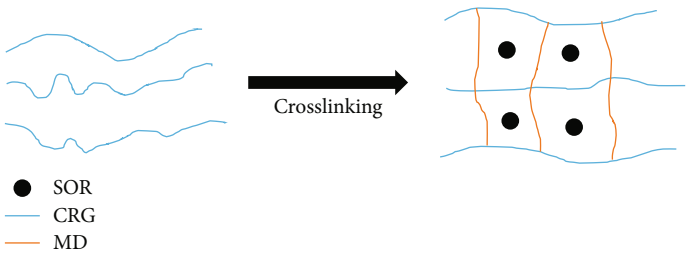

Figure 2: Schematic reaction mechanism process of CRG (carrageenan), MD (maltodextrin), and SOR (sorbitol).

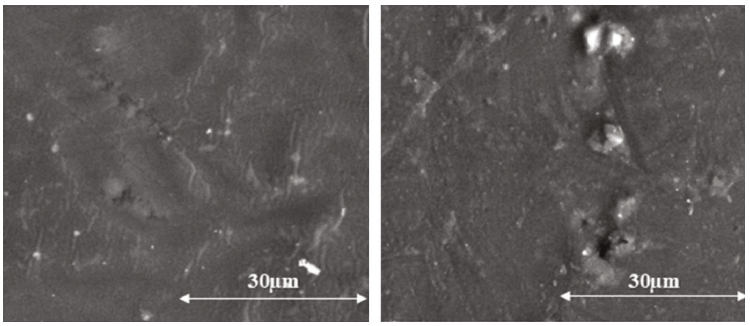

Figure 3: SEM surface morphologies of CRG (carrageenan) hard-shell capsules (a) and CRG-MD/SOR (carrageenan-maltodextrin/sorbitol) hard-shell capsules (b) at 5000 times of magnification.

shows that the degree of swelling of CRG-MD/SOR capsules was up to 3.6 times higher than that of gelatin capsules. Thus, CRG-MD/SOR has the capability to contain more water than gelatin capsules, making it difficult to dissolve under normal conditions.

CRG is comprised of long linear chains of D-galactose and β-3,6-anhydrogalactose. With ester sulfate as a side branch, these groups support the formation of helices that cause the formation of gel [28]. Therefore, a possible reason for the high degree of swelling of CRG-MD/SOR capsules is the gel-forming ability of CRG. Although the size of the pores of CRG was bigger than gelatin, this high swelling degree will help the material to withstand disintegration and dissolution longer than gelatin.

3.5. Disintegration and Dissolution of Paracetamol from CRG-MD/SOR Hard-Shell Capsules. The CRG-MD/SOR capsules required 18.47 ± 0.19 min with significant statistical variance (p value = 0.00 using t test at $p < 0.05$) to disintegrate CRG-MD/SOR hard-shell capsules, demonstrating a longer disintegration time than conventional capsules [29], which was 7.17 ± 0.03 min. t test analysis resulted in a p value of 0.00, which indicated that there was a significant difference between both types of the capsule. The results were obtained from eight capsules that were tested using a disintegration tester by repeatedly soaking the capsules in 600 mL aqueous medium at 37 ± 0.5°C. Active carbon powder was used to observe the time when the capsules leaked due to disintegration, causing it to be released from the capsules.

Paracetamol had different dissolution profiles in different acidities, as shown in Figure 4. In 10 min, the drug was dissolved for $8.47 \pm 3.14\%$, $5.18 \pm 2.96\%$, and $1.48 \pm 0.52\%$ at pH 1.2, 4.5, and 6.8, respectively. t test analysis indicated that there was no significant difference at this time of sampling. Significant difference occurred at 20 min, where paracetamol was dissolved for $31.00 \pm 9.19\%$, $69.39 \pm 26.19\%$, and $3.57 \pm 1.14\%$ at pH 1.2, 4.5, and 6.8, respectively. t test analysis also indicated that the p value between the results at pH 1.2 and 4.5 was 0.007, which was less than 0.05. Thus, it was proven that there was a significant difference between the dissolution at pH 1.2 and 4.5 at 20 min. In other words, paracetamol is more rapidly dissolved at pH 4.5 than at pH 1.2 and 6.8. It is therefore easier to dissolve CRG-MD/SOR in a weakly acidic medium than in strongly acidic or neutral media. A citrate buffer can decrease the intramolecular hydrogen bond in the secondary structure of CRG [28] because citrate contains hydrogen bond donors and acceptors. This decreased the intramolecular hydrogen bond and increased the solubility of CRG-MD/SOR in citrate buffer. This was not the case for pH 1.2 and 6.8 because the HCl and phosphate buffer were not able to form hydrogen bonds. Paracetamol containing three hydrogen bond groups can be a factor leading to the fast dissolution at pH 4.5 because the citrate buffer could have interacted with hydrogen bonds in paracetamol.

Glube et al. [30] compared the dissolution rates of gelatin with HPMC capsules and found that more than 80% of the gelatin capsules dissolved in 20 min at pH 4.5, whereas less than 20% of the HPMC capsules dissolved in the same amount of time. In comparison, approximately 70% of the CRG-MD/SOR capsules dissolved in 20 min at pH 4.5, showing similar dissolution behavior to that of gelatin capsules. Further research is required to study the potential of CRG-MD/SOR as hard-shell capsules.

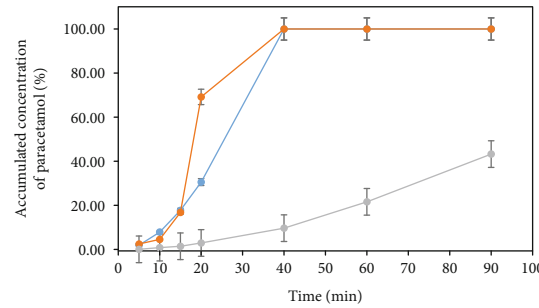

Figure 4: Dissolution profile of paracetamol released from CRG-MD/SOR capsules at pH levels of 1.2 (blue), 4.5 (orange), and 6.8 (gray).

4. Conclusions

Carrageenan-based hard-shell capsules were successfully prepared as the alternative to conventional hard-shell capsules by cross-linking CRG with MD and plasticizing it with SOR. Cross-linking reaction was indicated using FTIR and its surface morphology at 5000 times of magnification showing no pores, indicating that the material has very small pores. The degree of swelling of CRG-MD/SOR capsules was 3.6 times higher than that of conventional capsules under conditions of rapid dissolution in a weakly acidic medium. This indicates the ability of the material to withstand disintegration better than conventional capsules. These types of capsules can therefore be considered as an alternative to conventional hard-shell capsules in an oral drug delivery system.

Data Availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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