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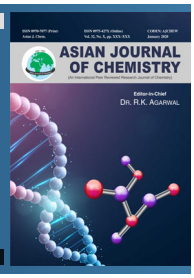

Synthesis of Capsule Film from Water-Soluble Chitosan by Adding Sodium Lauryl Sulfate

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Mixtures comprising water-soluble chitosan (WSC), agar and different concentrations of sodium lauryl sulphate (SLS) were used to synthesize capsule films. The concentration of agar was fixed at 0.02 %, whereas the concentration (v/v) of SLS varied (0, 0.02, 0.04, 0.06 and 0.08 %). Shrimp shell waste was subjected to demineralization, deproteination and deacetylation to obtain chitosan. The chitosan thus obtained was depolymerized to produce water-soluble chitosan (WSC). Fourier-Transform infrared (FTIR) baseline method was used for calculating the degree of deacetylation of chitosan. FTIR spectra of the obtained capsule film exhibited vibrations of its constituent molecules, namely agar, chitosan and SLS. The elasticity of the film matrix increased with SLS concentrations. In swelling tests conducted using water and 0.1 N HCl, the highest swelling values, 123.74 and 235.87 %, respectively were observed in the capsule film containing 0.08 % SLS in the 10th min. The capsule film containing 0.08 % SLS was degraded (broken) in water and 0.1 N HCl in the 10th and 30th min, respectively. The results indicated that a capsule film containing 0.08% SLS was the most eligible film for commercial use.

Keywords: Capsule film, Water-soluble chitosan, Sodium lauryl sulfate, Swelling, Degradation test.

INTRODUCTION

Capsules represent one the oldest forms of drug packaging; capsules were known to and used by ancient Egyptians. Hard and soft capsules are the two types of the capsules currently used. Hard capsules are more commonly used than soft capsules for drug packaging; the estimated annual production of hard capsules is 60 billion units for pharmaceutical purposes [1]. Gelatin is the commonly used material to produce capsules in pharmaceutical manufacturing. Gelatin is a heterogenous mixture polypeptides obtained by hydrolyzing collagen derived from connective tissues of animals. The large-scale use of gelatin manufactured from the raw material pork has caused concern among several people, particularly followers of Islam religion, because of the halal issue involved in the manufacturing of the product [2].

Shrimp shells are an alternative to pork as raw material for capsule production. Chitosan can be obtained from shrimp shells by subjecting the shells to demineralization, deproteination, and deacetylation. The obtained chitosan is a potential alternative to gelatin in the production of drug capsule. The bodies of marine organisms, particularly crustaceans and arthropods, such as shrimp, crab and squid, are rich in chitosan [3]. Chitosan and its derivatives were reported to be suitable for used as raw material in capsule production. Studies have reported the production of capsules composed of chitosan-hyaluronate by using the cast method [4], those composed of chitosan-polyalkileneoxide-maleic acid copolymer by cast method procedure [5], those composed of chitosan from shrimp shells, which is resistant to high moisture [6], and those composed of chitosan-sodium cellulose sulphate capsules by using the cast method [7].

The aforementioned studies showed that the solubility of chitosan capsules was very low in HCl and insoluble in water. The low solubility of biopolymer chitosan is a result of its high molecular weight. Therefore, methods to increase the solubility of chitosan in water are essential. Depolymerization can be used to increase the solubility of chitosan in water. In depolymerization, the length of polymer chain is reduced. Water-soluble chitosan (WSC) can be obtained by depolymerization [8] and can be used as raw material for capsule film synthesis.

In the present study, isolation and synthesis of chitosan from shrimp shells waste was the first step. The obtained chitosan was converted to WSC through depolymerization by using

peroxide acid. The obtained WSC was used as a raw material in capsule film synthesis. Additional material, apart from WSC, is required to ensure proper casting of the capsule film. Agar was the additional material used in the present study. The addition of agar, a gelling agent, strengthens the casted film matrix [9]. Furthermore, a previous study [10] reported the use of a combination of chitosan and sodium lauryl sulphate (SLS) as carrier system for delivering oral insulin. Chitosan and SLS interacted to form a gel that inhibited gastric insulin release. Another study [11] showed that the interaction between chitosan and SLS increased tensile strength, Young′s modulus, and thermal stability of capsule film. Currently, SLS is mostly used in pharmacy as a filler and binder in tablet, pill and capsule production. The molecules of SLS have a hydrophobic portion comprising 12 carbon atoms and a bent sulphate group that bestow amphiphilic properties on the molecule [12].

Based on the aforementioned explanations, in this study, a capsule film was synthesized using WSC as the primary raw material and agar and SLS as additives. The concentration of agar was constant, while that of SLS was varied. The effects SLS addition on the capsule film were determined through FTIR spectroscopy as well as by testing tensile strength, swelling and degradation.

EXPERIMENTAL

The starting materials, shrimp shells waste (collected from Tempurejo traditional market Surabaya) was pulverized in a mill and screened through a 40-mesh sieve, NaOH pellets (Merck, 99.99 %), NaOH powder (SAP chemicals), HCl (Merck, 37 %), aqua demineralization, acetone (Merck, 99.99 %), absolute ethanol (Merck, 99.99 %), ethanol (SAP chemicals, 96 %), H_2O_2 (SAP chemicals, 30 %), acetic acid glacial (Merck, 100 %), sodium lauryl sulfate (Merck, 99,9 %), filter paper (Wattmann) No. 41, universal pH paper (Merck). All chemicals used were of laboratory grade.

Synthesis and characterization water-soluble chitosan: A previously reported method was used for WSC synthesis with some modifications [8]. In brief, 100 g of shrimp shell powder was immersed in 100 mL of 7 % (v/v) HCl at room temperature for 24 h and subsequently filtered. The residual powder was immersed in 1000 mL of 10 % (w/v) NaOH at 60 ºC for 24 h and subsequently filtered. The immersion of the powder in 7% HCl and 10% NaOH was repeated twice. The residual powder (chitin) was washed with 125 mL of 96 % ethanol and dried. Crude chitosan from shrimp and mussel powders was obtained from 30 g of chitin by soaking it in 30 mL of 50% NaOH at 120 ºC for 4 h. The supernatant was filtered and the residue was washed with hot aqua demineralization until a neutral pH was obtained. Then the residue was dried. Next, 5 g of crude chitosan was dissolved in 150 mL of 2 % acetic acid, after it dissolved completely, 5 mL of 30 % H_2O_2 was added. The reaction was allowed to proceed at 40 ºC for 4 h. After the reaction, the neutrality of solution was restored using 10 % NaOH. The residue was removed by filtration, and two volumes of ethanol were added to the filtrate. Crystals of water-soluble chitosan (WSC) were obtained after incubation in a refrigerator overnight and dried in an air oven at 50 ºC.

The obtained chitin, chitosan and WSC were characterized by FTIR spectrophotometer (Shimadzu FTIR-8400S). Deacetylation degree (% DD) of WSC was measured using the FTIR baseline method [13].

Synthesis of capsule film: The obtained of WSC from the incubation process was separated from the filtrate. Next, 0.02 % agar (v/v) was added to WSC and stirred well. Then SLS at various concentrations (0, 0.02, 0.04, 0.06 and 0.08 %) (v/v), was added to aliquots of the mixture. Each mixture was stirred well and cast in petri dishes (size 9 cm × 1.5 cm). Then, each mixture was dried in a vacuum oven at 40 ºC for 17 h.

Characterizations and tests of capsule membrane:

FTIR spectroscopy: Capsule films with (WSC-agar-SLS 0.08 %) and without (WSC-agar) SLS were characterized through FTIR spectroscopy for obtaining information on functional group vibration. The test was performed using wave numbers in the range 4000-500 cm^{-1}.

Tensile strength test: The mechanical properties of the capsule film were determined using stress and strain measurements by using an Autograph Shimadzu type SFL-100 kNAG with rate of 10 mm/min at room temperature. These mechanical properties were calculated using the following equations:

$$\text{Stress } (\sigma) = \frac{F}{A} \quad (1)$$

$$\text{Strain } (\varepsilon) = \frac{\Delta l}{l} \quad (2)$$

where F is the load at failure (force at which the films breaks), A is the initial wide of film, Δl is the increasing of length at failure and l is the initial length of film [14].

Swelling test: Swelling degree test was conducted using a previously reported procedure [15] by drying capsule film. The dry film was immersed in a glass beaker containing 50 mL of aquadest and 50 mL of 0.1 N HCl for 10, 20, 30, and 40 min. The swelling degree calculated using following equation:

$$\text{Swelling degree} = \frac{\text{Wett weight} - \text{Dry weight}}{\text{Dry weight}} \times 100\ \% \quad (3)$$

Degradation test: The dissolution test was conducted by studying the mechanism of film degradation as well as by using a previously reported method [7]. The degradation test in water was conducted by immersing the films in glass beakers containing 50 mL of water at 37-38 ºC for 10, 20, and 30 min, while the degradation test in acid was conducted by immersing the films in 50 mL of 0.1 N HCl at 37-38 ºC for 10, 20 and 30 min. The percentage decrease in film mass was then calculated [16].

RESULTS AND DISCUSSION

Synthesis of water-soluble chitosan (WSC): The chitin obtained from shrimp shells by demineralization and deproteination was subsequently converted to chitosan through deacetylation. Deacetylation involves the removal of the acetyl group (-$COCH_3$) in chitin by using an alkali solution and transformation into hydroxylamine (-NH_2) groups. Chitin exhibits a long crystalline structure with strong hydrogen bonding between nitrogen atoms and carboxylic groups on contiguous chains [16]. The breakage of bonds between the acetyl and amide groups during

transformation into amine groups (-NH_2) occurred in NaOH solution at the high concentration and temperature. In this study, 50 % NaOH solution was used at 120 ºC for 4 h. The reaction that produces chitosan from chitin is an alkaline hydrolysis reaction. Chitin acts as an amide in the presence of alkali NaOH. Initially, an addition reaction occurs, where OH^- the group is taken up by -$NHCOCH_3$ group when elimination of CH_3COO^- group occurs to form an amine group. The resulting structure is called chitosan [17]. After the liberation of acetyl group, the resulting chitosan gains a partial positive charge; consequently, it dissolves in an organic acids such as acetate acid and/or formic acid [18].

According to Du *et al.* [8], chitosan is a high-molecular weight polymer; hence, it has low solubility in water. Reducing the molecular weight of chitosan can increase the solubility of chitosan in water. Reducing the length of the polymer chain of chitosan reduces its molecular weight. In this study, cutting the polymer chain (depolymerization) was performed using H_2O_2 (Fig. 1). Depolymerization is a homogeneous reaction, where intermolecular and intramolecular hydrogen bonding in chitosan is disrupted and the molecules become extended, which cause reactions to occur between all the functional groups of chitosan and H_2O_2. During the treatment, R-NH_2 preferentially reacts with H^+ to produce R-NH_3^+, which reduces [H^+] and causes an increase in pH. In addition, HOO^- is rapidly decomposed to $HO^•$, which indicates that H_2O_2 is continually decomposed. These radicals undergo further reactions rapidly to form water-soluble oxidation products, such as WSC, with a low molecular weight and high solubility in water [4].

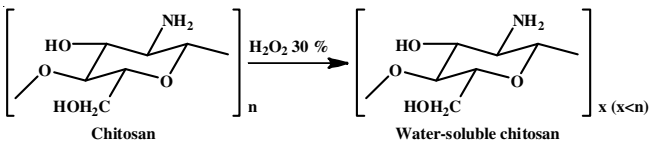

Fig. 1. Depolymerization reaction of chitosan

FTIR analysis of chitin, chitosan and water-soluble chitosan: The FTIR spectra of chitin and chitosan in the present study exhibited absorption patterns that were consistent with those reported in a previous study [19]. In the chitin FTIR spectrum (Fig. 2), an absorption peak was observed at wave number 3443 cm^{-1}, which indicated stretching vibration of O-H and at wavenumbers 3265 and 3107 cm^{-1} indicated a stretching vibration of NH ($NHCOCH_3$). A band at 2960 cm^{-1} indicated stretching vibration of C-H sp^3 and at 1656 cm^{-1} is due to the stretching vibration of C=O ($NHCOCH_3$), while a band 1074 cm^{-1} indicated a stretching vibration of C-O (-C-O-C). In addition to the absorption caused by stretching vibration, some absorption was caused by bending vibrations of NH ($NHCOCH_3$) and CH (-CH_2-) groups, which were observed as peaks at wave numbers 1656 and 1379 cm^{-1}, respectively.

In chitosan FTIR spectrum, the absorption peaks were observed at 3450 cm^{-1}, which indicated stretching vibrations of O-H group, while the bands at 2887 and 1381 cm^{-1} were due to the strecting vibration of C-H sp^3 and C-H sp^2, respectively. The bending vibration of NH (R-NH_2) appeared at 1585 cm^{-1}. and at 1084 cm^{-1}, stretching vibration of C-O (-C-O-C) observed. Unlike the FTIR spectrum of chitin, a spectrum of chitosan does

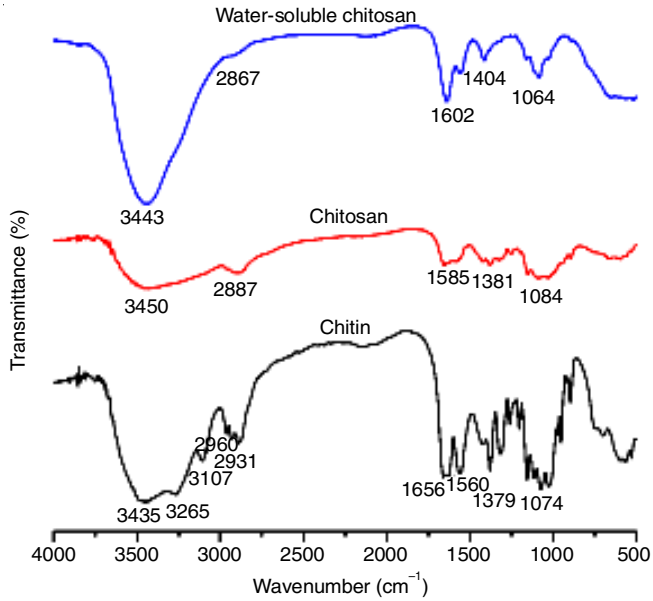

Fig. 2. FTIR spectra of chitin, chitosan and water-soluble chitosan

not show absorptions at 3265, 3107, 2960, 1656 and 1560 cm^{-1}. These differences in the appearance of absorption bands indicated that acetamide group was transformed into the amine group through deacetylation [20]. The FTIR spectra of chitosan and WSC exhibited the same absorption peaks. However, absorption peak shift was observed between chitosan and WSC at 3443, 1602 and 1404 cm^{-1}, while the absorption peaks at 2887 and 1084 cm^{-1} did not change. The absorption shifts occurred because WSC is unstable and can easily absorb moisture from air [21].

Deacetylation degree of chitosan: One of the parameters that influence of the quality of chitosan is deacetylation degree (DD). Deacetylation degree indicates the reduction in the number of acetyl groups in the structure of chitosan. In this study, the determination of DD of chitosan was conducted using the FTIR baseline method as well as a previously reported method [13]. The chitosan FTIR spectrum obtained using the baseline method is shown in Fig. 3.

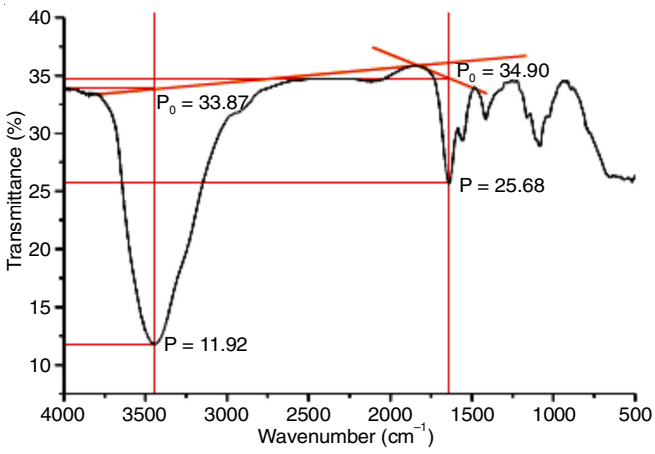

Fig. 3. Chitosan FTIR spectra by baseline method

Calculation:

$$A = \log \frac{P_o}{P} \quad (4)$$

$$A_{1655} = \log\frac{34.90}{25.68} = 0.1332 \quad (5)$$

$$A_{3450} = \log\frac{33.87}{11.92} = 0.4535 \quad (6)$$

$$DD\,(\%) = \left\{1 - \left(\frac{A_{1650}}{A_{3450}} \times \frac{1}{1.33}\right)\right\} \times 100 \quad (7)$$

$$DD\,(\%) = \left\{1 - \left(\frac{0.1332}{0.4535} \times \frac{1}{1.33}\right)\right\} \times 100 \quad (8)$$

$$DD\,(\%) = 77.92 \quad (9)$$

Based on the aforementioned calculation, deacetylation degree of obtained WSC was 77.92 %. The calculation showed that the reaction transforming the acetamide group into a primary amine group in the deacetylation progressed as much as 77.92 %.

Synthesis and characterization of capsule film: Capsule film synthesis was carried out using WSC obtained by depolymerization, as raw material. In this study, 6.5 % (w/v) of WSC was combined with agar and SLS. The motion variable that was observed is the influence of addition of SLS against the characteristic of the formed film. The interactions between WSC and SLS were ionic in nature. These interactions were caused by the difference in the charge of WSC and SLS. WSC is a cationic polymer, while SLS is an anionic surfactant. Amri *et al*. [11] reported that SLS will undergo protonation (in acetate buffer) before it reacts with WSC, thus resulting in the loss of Na^+. The protonated SLS will be bound to O atom in the WSC molecule. The capsule film produced in this study was yellow as shown in Fig. 4. Higher SLS concentrations provide the flexibility to the texture of film.

Generally, FTIR spectra of WSC-agar and WSC-agar-SLS films were similar to the spectrum of WSC (Fig. 5). In WSC-agar film, absorption peaks were observed at 3448, 2920 and 1629 cm^{-1}, which are due to the stretching vibrations of O-H, C-H sp^3 and bending vibrations of NH (R-NH_2), respectively. However, in the spectrum of WSC-agar, intensity attenuation was observed at NH (R-NH_2) and a new absorption peak was observed at 1545 cm^{-1}. The new peak was caused by the protonation of NH_2 to form NH_3^+ when WSC and agar were mixed [22]. In the FTIR spectrum of WSC-agar-SLS, absorption peaks were observed at 3435, 2929 and 1637 cm^{-1}, again attributed to the stretching vibrations of O-H, C-H sp^3 and bending vibrations of NH (R-NH_2), respectively. Moreover, a peak was observed at 1562 cm^{-1}, which indicated the vibration of NH_3^+ group. In addition to the absorption peaks of the aforementioned groups, new vibration peaks of the asymmetric and symmetric -SO_2 group were observed at 1261 and 1076 cm^{-1}, respectively. The absorption peak indicated that a reaction occurred between SLS and WSC [10].

Tensile strength: Tensile strength was conducted for determining the mechanical properties, such as the level of resistance on pulling forcefully of the capsule film. Fig. 6a depicts the changes in the values of stress on capsule film with increasing SLS concentrations. The film with 0.02 % SLS exhibited a low increase in stress, which was approximately 12.75 kN/m^2. Films with SLS concentrations of 0.04, 0.06 and 0.08 % exhibited an increase in the stress values of 15.5, 25.75, and 34.25 kN/m^2, respectively. However, an increase remained lower than the stress value of film without SLS (0 %). High stress values indicated that the films were rigid because the interpolymer chains were tightly associated with each other [9]. Whereas, when SLS was added, the SLS molecules entered the cavities of polymer, which caused the matrix power of films to reduce.

Another mechanical property that was analyzed was strain (Fig. 6b). From the data, a strain increased with an increase in SLS concentration. The highest value of strain was observed in the film with 0.08 % SLS (0.183), whereas the smallest value of strain was observed in the film without SLS (0.027). The magnitudes of strain values indicated that the elasticity of film

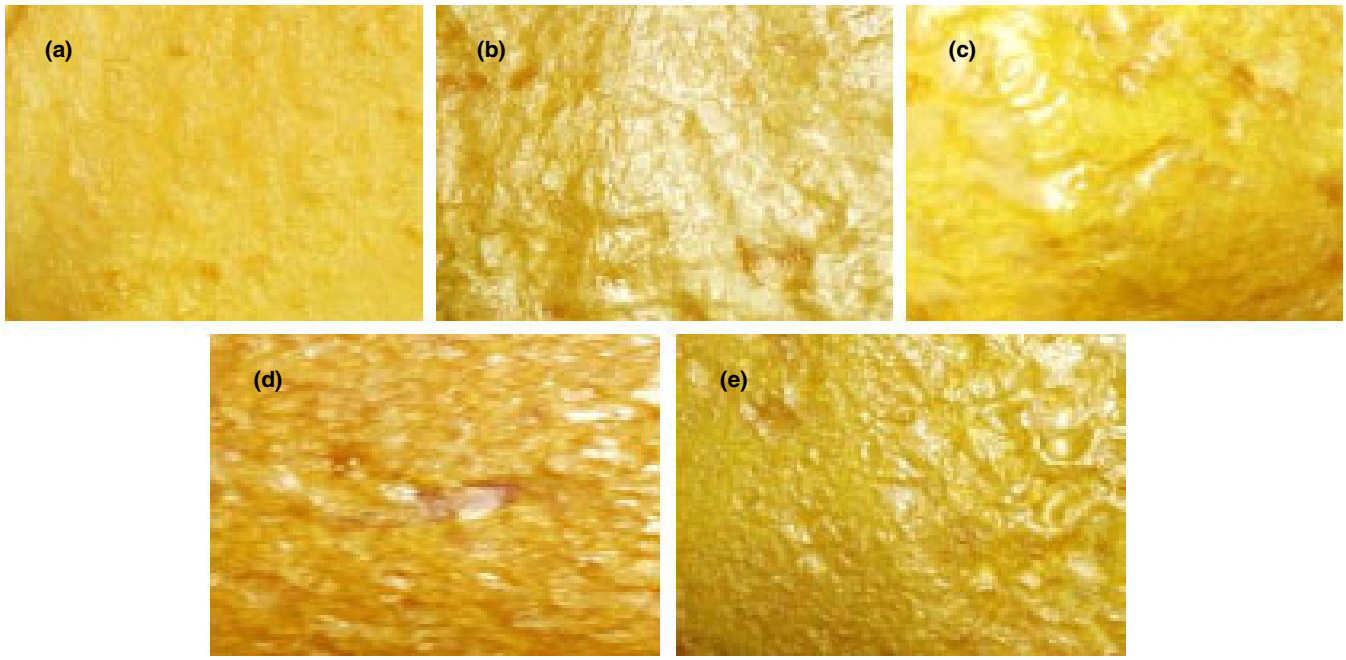

Fig. 4. Surfaces of WSC-Agar with SLS (a) 0 %, (b) 0.02 %, (c) 0.04 %, (d) 0.06 % and (e) 0.08 %

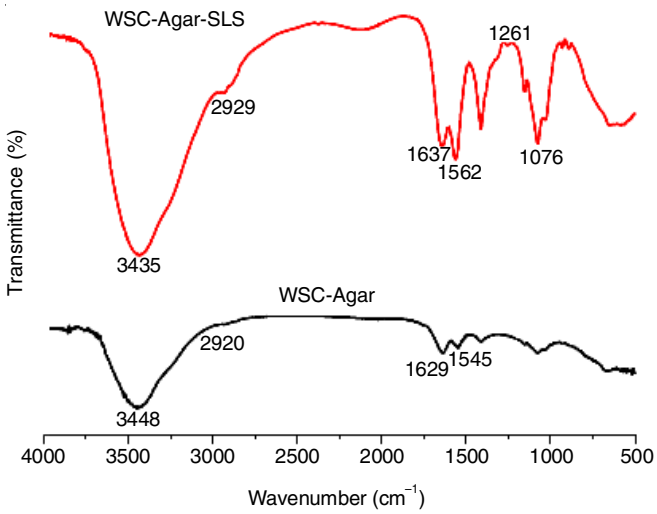

Fig. 5. FTIR spectra of WSC-Agar film and WSC-Agar-SLS film

increased [15]. According to Buana *et al*. [23], an increase in strain value was caused by the plasticization in the matrix film. Plasticization occurred because plasticizers were added into the film mixture, which made the film soft and flexible. And in the present case, SLS acts as plasticizer in the synthesis of capsule film.

Swelling test: Swelling test was conducted to determine the endurance of capsule film to solvents. In this process, solvent molecules entered the film pores and caused swelling of the matrix film. Swelling is affected by material composition, hydrophilicity and hydrophobicity [9]. In this study, swelling test was conducted to determine the effect of added SLS on the endurance of capsule film in water and 0.1 N HCl. The swelling test conducted in two different solvents is shown in Fig. 7.

The swelling test was performed for 40 min with 10 min intervals between weighing. Generally, the film mass increased with an increase in soaking time. The highest degree of swelling in water occurred in a film with 0.08 % SLS. A significant increase in mass occurred in the 20th min. According to a previous study [24], SLS served as a pore-forming agent which can improve the swelling in water. However, the films with 0.02, 0.04 and 0.06 % SLS concentration exhibited lower swelling than the film without SLS. These differences were explained by difference in film thickness during the casting process.

In HCl, a film with 0.08 % SLS was broken in 20 min because swelling occurred to the maximum stage; hence, the bonding between the molecules comprising the film was broken. The films containing 0 and 0.04 % SLS exhibited mass loss in

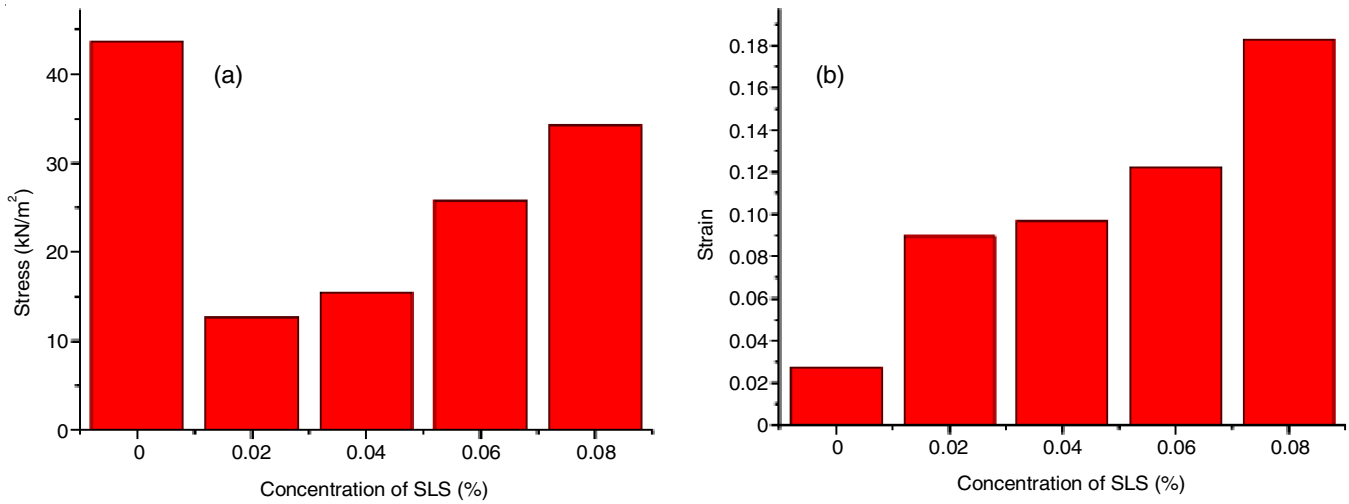

Fig. 6. Tensile strength test (a) stress and (b) strain

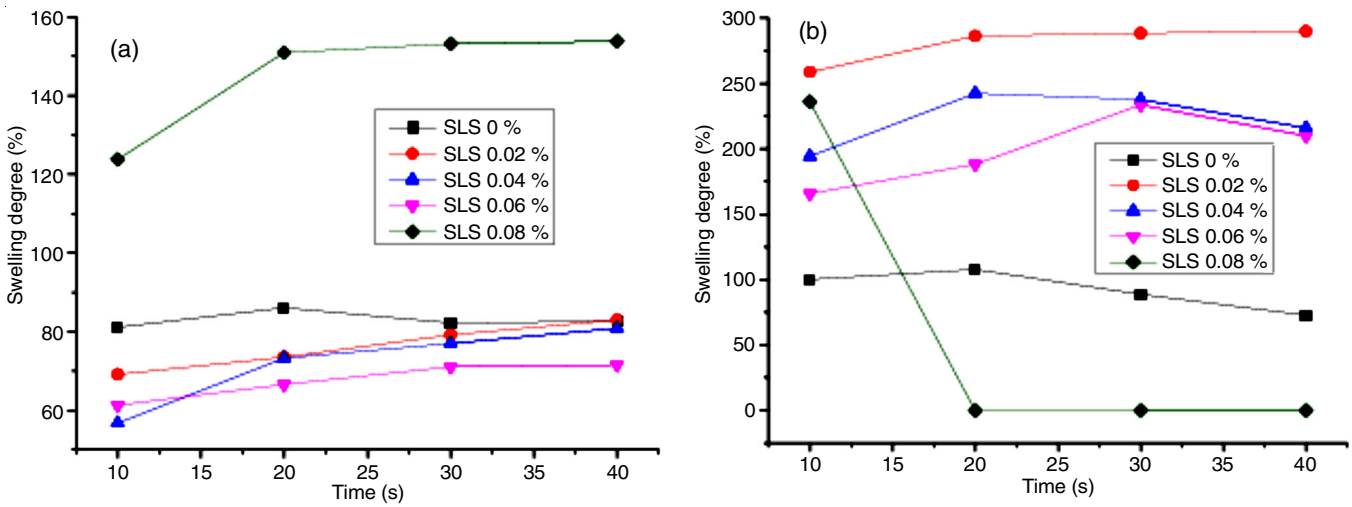

Fig. 7. Swelling test in (a) water and (b) HCl

30 min. Three dissolution zones in the drug release mechanism were reported [25], namely swelling zone, diffusion zone and erosion zone (Fig. 8). Diffusion zone is a state in which the film undergoes maximum swelling because the solvent molecules have diffused into the film matrix. After diffusion process, the film surfaces are eroded gradually because of friction with solvent molecules. This effect was observed in the film with 0 and 0.04 % SLS.

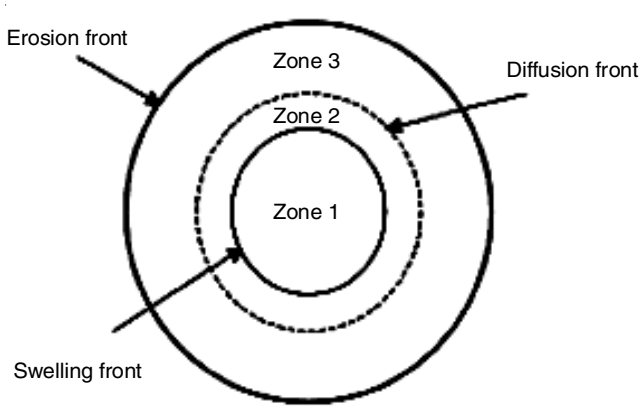

Fig. 8. Schematic illustration of a swellable tablet during radial drug release [Ref. 25]

Degradation test: The degradation test was used to predict the time taken by the capsule film to break and rupture. When the capsule film breaks, the film is assumed to degrade and release the drug. The degradation test was conducted using the weight loss method [7]. In this study, the test was conducted in two solvents at 37-38 ºC. Degradation in water and 0.1 N HCl represented the conditions in the mouth and stomach, respectively. Fig. 9 shows that longer degradation time causes greater film weight loss. The results in water showed that film without SLS (0 %) exhibited the largest weight loss percentage, followed by the film containing 0.02, 0.06, 0.04 and 0.08 % SLS. This trend was observed because the film without SLS was more hydrophilic than the films with SLS. Based on a previous study [25], interaction between polymer and surfactant (chitosan-SLS) can reduce the hydrophilicity of film because SLS contains decyl group ($-CH_3-(CH_2)_9$). However, in the 30th min, a film with 0.08 % SLS broke and ruptured. Hence, drug release occurred in the 30th min.

Generally at pH 1 (0.1 N HCl), the weight loss percentage is higher than that in water because the acid solution destroys materials such as metal, minerals and biopolymers [9]. A film without SLS exhibited the highest weight loss percentage followed by films containing 0.02, 0.06 and 0.04 % SLS. In the 10th min, a film with 0.08 % SLS was broken and ruptured, while the films with 0.04 and 0.06 % SLS did not break and rupture until the 30th min. The results indicated that adding SLS accelerated the degradation because SLS increased the plasticity of the film and acted as a pore-forming agent [24].

Conclusion

Water soluble chitosan (WSC) was used as the main material in the capsule production. Adding the gelling agent agar and plasticizer, SLS increased resistance to strain according to strain test data. The swelling data also showed that film with 0.08 % SLS exhibited the highest swelling degree in water and 0.1 N HCl (153.81 % in 40 min and 235.87 % in 10 min, respectively). The degradation data showed that film with 0.08 % SLS degraded in water and 0.1 N HCl in the 30 and 10 min, respectively. Hence, a capsule film with 0.08 % SLS was the best in this study.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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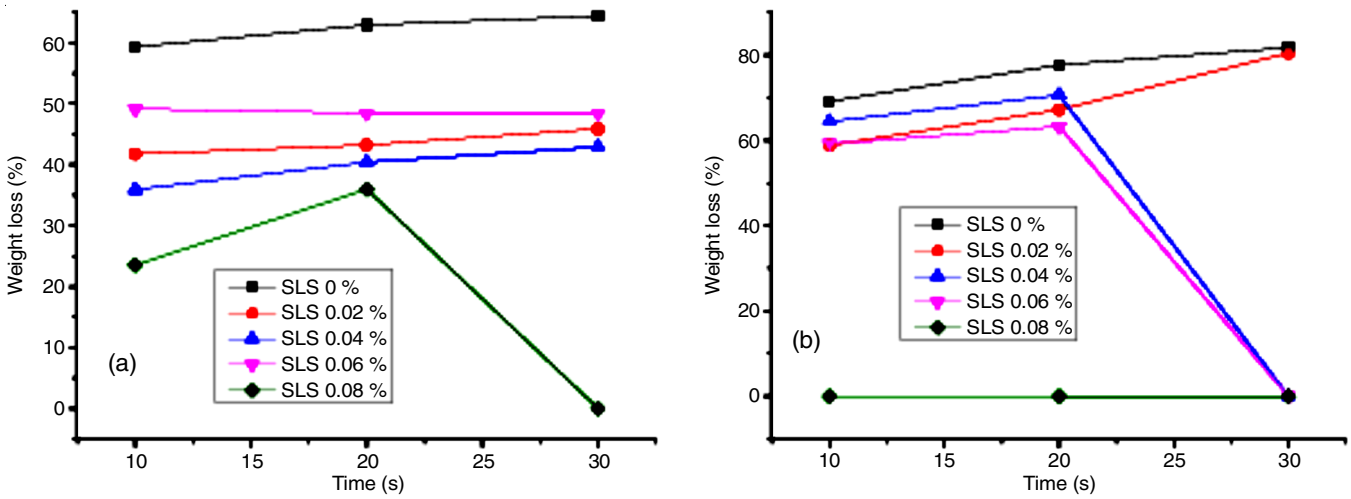

Fig. 9. Degradation test in (a) water and (b) HCl 0.1 N

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