https://doi.org/10.48047/AFJBS.6.12.2024.3758-3770

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

Characteristic of Capsule Shell From Eucheuma Cottonii and Corn Starch as Gelling Agent

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Article History
Volume 6, Issue 12, 2024
Received: 02 Jun 2024
Accepted: 25 Jun 2024
doi:
10.48047/AFJBS.6.12.2024.3758-3770

Abstract— An amount of 30 g Eucheuma cottonii seaweed was dried and soaked in 500 mL of distilled water for ± 24 hours. Samples was extracted with 0.8 N KOH solvent at the temperature of 85°C for 1 hour. The ratio of dry Eucheuma cottonii seaweed to solvent was 1:30 (g/mL). Amount of 1N KCl was poured into the filtrate with a ratio of 1:1 to the volume of the filtrate, with continuous stirring until hydrocolloid fibers (carrageenan fibers) were formed. The fiber turned into filtered and washed with water until the pH was neutral. Wet carrageenan was dried off in an oven at 120°. A total of 100 mL of distilled water was heated, as much as 1 g of added TiO_2 and 1 g of natural dye (matcha). The variation of mass of carrageenan (1: 3: 5: 7: 9) % b/v and corn starch (1: 2 : 3 : 4 and 5)% b/v, and then polyethylene glycol was added (1:2:3:4:5) % v/v then it was stirred until homogeneous. The capsule dough and its molds were dried off in an oven at the temperature of 45°C for five hours. Of the various variations carried out, the best composition variation is formula A. The reaction kinetics obtained in formula C variation followed the first-order kinetics model with a k value of 0.0296 min-1 for temperature variations, while the best is temperature C because it had test specifications that met the required requirements. The reaction kinetics obtained at temperature C followed a first-order model with a K value of 0.0364 min^{-1}.

Keywords—*Eucheuma cottonii*; extraction, capsule shell, drug release kinetics

I.INTRODUCTION

Capsules are popular for various medical transport system. Since being produced as a container to mask flavor and aroma of medicines, capsules are accepted by purchasers and doctors due to their flexibility. Capsules have many benefits because they are smooth to swallow, flexible to dispense doses and mixtures of drugs according to the patient's specifications and suitable for drugs with shallow compressibility, gradual dissolution and sour taste [1, 2]. A capsule is not a usual place utilized in our everyday life. It is constructed from gelatin and the capsules are in a hard shape or soft shape. Benefits of hard-shell capsules is that they will provide stable and liquid medicines [3, 4]. The presence of hard-shell capsules could be very crucial as a drug transport system. Nevertheless, ancient capsules that include gelatin is made from animal components such as bones or skins, which suggests they cannot be used by all humans, e.g., vegetarians and Muslims [3, 5]. Furthermore, due to the fact gelatin is from animal, cow ailment caused the scrutinization of using gelatin in medicine products. For more than a century, gelatin has been followed because the primary fabric for medicine capsule due to unimaginable feature that embrace gelling, picture establish and its solubility. Nevertheless, non-secular and ethnic

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issues aside, Bovine Spongiform Encephalopathy (BSE or mad cow disease) episode among side the Nineties and also the character of gelatin capsule are known as severe weakness of gelatin capsule. Consequently, research and improvement of herb-derived cloth with all specific helpful homes rather like gelatin had been held. Among the past decades, flavored polysaccharides has been drastically advanced as meditative capsule substances to supply higher and stronger dose for drugs. Various flavored polysaccharides including starch and polysaccharide subsidiary product have indicated their possibilities to improve gelatin. Hence, other nature-based total supplies for hard-shell capsules are wanted as an opportunity for gelatin [3, 6]. Some alternative drugs have progressed, such as alginate drugs which couldn't form hard-shell capsules, carrageenan drugs that have gradual disintegration time, and hypromellose drugs which can be sensitive to temperature change [3]. Besides the improvement of bio composite from herbal carbohydrate polymers, the interest is significantly growing specifically in pharmaceutical and food packaging software. This is to restore the current petroleum-based fabricated polymers aiming to dispose garbage and pollute water globally. Carrageen an is one of the carbohydrate polymers with the capacity to update the plastic in pharmaceutical software program application because of its travers ability and abundance. Carrageenan is a herbal and water soluble sulfate polysaccharide [7, 8]. The release of the drug from the pills prolonged because the polymer percentage increased. This is because of reduced penetration of the solvent molecules within side the presence of hydrophobic polymer, main to decreased diffusion of the drug from matrix system [9]. Capsules have the funds for a tasteless, odorless enclosure handy for management of kind of medicaments, that are in any other case hard to administer [10]. A drug must be brought most effective while it's miles wanted and in which it's miles to be absorbed with inside the minimal required dose [11].

Commercial tough shell capsules are usually made from gelatin wherein it is produced with the resource of the usage of hydrolysis of collagen from buffalo, cow, and pork. On the opportunity hand, carrageenan is a sulfated polysaccharide, in general hard to find from *Eucheuma* genus of red seaweed of *Rhodophyceae* class[12–14]. *Eucheuma spinosum* consists of a heavy polysaccharide referred to as carrageenan, that's produced from numerous gadgets of disaccharide galactoses [3, 15]. Commercial carrageenan production is finished through way of manner of bring out the seaweeds of *Eucheuma cottonii* in easy solvents at immoderate temperatures. The kind of carrageenan (μ, κ, ν, ι, λ, and θ) which may be consequently produced can be used for each day objective, which encompass gelling sellers and native flavored [3, 16]. Among those six kind of carrageenan, simplest κ-carrageenan famous the capacity as a supply for hard-shell capsules due to its gelling agent ability. Kappa carrageenan is regulary applied in food and pharmaceutical application as it may form a powerful, fragile aggregate or gels. Bio composite film from carrageenan cannot shape a excessive mechanical energy and without problems torn bio composite [17]. However, Carrageenan will undergo syneresis even as it's miles dried from gel to film, causing it to grow to be fragile [3, 18].

Fig 1. *Eucheuma cottonii* as raw material of capsule shell

Carrageenan is employed as a gelling agent in products, as well as yogurt, frozen foods and jelly [19]. Commonly, carrageenan has been produced in six kind sorts based mostly on their specification [20]. Among the six polymers, κ-carrageenan is the maximum manufactured because of its excessive gelling capacity due to the C_4 configuration at the 3,6-anhydro-D-galactopyranosyl which paperwork a helical

structure [21]. A sizeable variety of –OH organizations that shape many hydrogen bonds support the helical structure [22, 23]. κ- carrageenan is extracted from red seaweed particularly approach from one-of-a-kind species which might be *Kappaphycus alvarezii* and *Eucheuma cottonii* extract [24]. κ-carrageenan has one sulfate class consistent with disaccharide replicated unit with 20% of ester-sulfate content material and a mean relative molecular mass above a hundred kDa [25]. Due to its awesome ability from gelling agent, κ-carrageenan is usually used because the gelling agent within side the tough capsule manufacture [26]. Carrageenan is obtained by the extraction process. Seaweed was extracted with alkali at high temperature. The use of alkali as the solvent used in the extraction have effect against carrageenan formed [27]. Many alkalis can be obtained by adding an alkaline solution, for example a solution of NaOH, $Ca(OH)_2$, and KOH. The use of alkali has functions, specifically to assist the extraction of polysaccharides to be greater ideal and boost up the termination of a sequence of 6-sulfate devices of monomer to 3.6-anhidro-D-galactose in order that it is able to growth the gel power and reactivity of the product towards the protein. The use of KOH has its benefits towards the impact of the growth of yield and best of carrageenan produced then from a number of the alkaline solution used to extract seaweed used potassium hydroxide (KOH) [28].

Starch draws greater hobby as gelatin replacer candidate due to great aggregate amongst price, availability and film-forming residences and availability [2, 29]. Starch films have first rate oxygen barrier houses and accurate mechanical electricity due to their tightly packed, ordered hydrogen-bonded network structure. Mechanical houses of starch films are surprisingly relying on amylose/amylopectin ratio [2, 30]. Excessive amylose content material manufactures sturdy films, while separate shape of amylopectin typically ends in films with bad mechanical residences. Nevertheless, starch movies typically have bad moisture barrier residences because of the hydrophilic nature of starch. A powerful approach to conquer this trouble is via way of means of combining starch with different herbal polymers that are owning well matched interplay with starch [2].

The purpose in designing sustained shipping structures is to lessen the frequency of the dosing or to growth effectiveness of the drug through localization on the site of action, decreasing the dose required or supplying uniform drug shipping [31]. Carrageenan's have powerful synergism with starches and different biopolymers because of their wonderful bodily practical properties. Carrageenan's also are implemented in non-meals industries inclusive of pharmaceutical and cosmetic, printing and fabric formulation, wine fining and beer, puppy meals, domestic products. Starch/carrageenan device is mixed in which gelling homes are the number one importance [32]. This study aims to manufacturing capsule shell from seaweed carrageenan (*Eucheuma cottonii*) in the variation of composition carrageenan and temperature using corn starch as gelling agent with additional PEG as plasticizer.

II. MATERIALS AND METHODS

Materials

Red seaweed (*Eucheuma cottonii*) came from Surabaya, East Java, Indonesia, aquadest, poly ethylene glycol 400 (Merck), HCl 37% (Merck), KCl (Merck), KOH (Merck), corn starch 100%, natural dye (Matcha), TiO_2 (Merck), and sucrose.

Instrument

Special equipment for capsule education that turned into used is the dimensions zero dipping pens such as the frame and head components of hard-shell capsule, porcelain cup, glass funnel, Disintegration Tester (Vanguard Pharmaceutical Machinery), Dissolution Tester (IKA Labortechnik), Spectrophotometric UV-VIS (Genesys 10S UV-VIS), erlenmeyer, watch glass, beaker glass, weighing filter, hot plate, volumetric flask, magnetic stirrer, analytical balance, oven, glass rod, spatula, pippete bulb, volumetric pippete, and thermometer.

Methods

Amount of 30 g [33] *Eucheuma cottonii* seaweed was dried and soaked in 500 mL [34] of distilled water for ±24 hours. *Eucheuma cottonii* was extracted with 0.8 N KOH (Pottasium hydroxide) solvent (in 1,000 mL distilled water) at temperature of 85°C for 1 hour. The ratio of dry *Eucheuma cottonii* seaweed to solvent was 1:30 (g/mL) [35]. The solvent volume was kept constant by adding hot solvent all the

time. After 1 hour, the extraction was stopped by separating the filtrate from the seaweed dregs. This filtrate was accommodated in a beaker glass and allowed to stand until the filtrate reaches room temperature (30ºC). After that, 1N KCl was poured into the filtrate with a ratio of 1:1 to the volume of the filtrate, with continuous stirring until hydrocolloid fibers (carrageenan fibers) were formed. After being allowed to stand for about 24 hours, the fiber became filtered and then washed with water until the pH was neutral. Wet carrageenan was dry off in an oven at 120°C till the mass was constant. Carrageenan sheets were dried and weighted constant. They were reduced into small pieces and soft crushed to form a coarse powder.

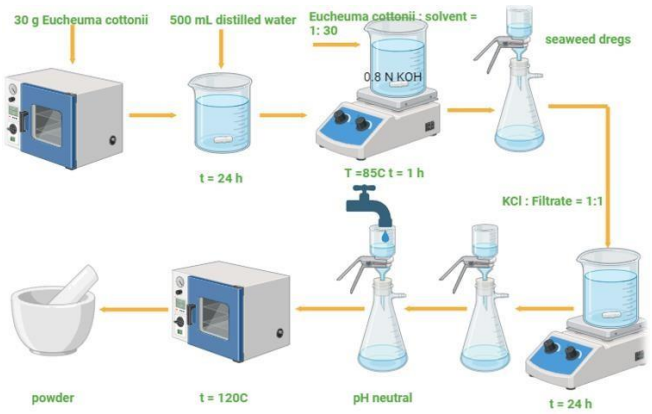

Fig 2. The making carrageenan steps

Amount total of 100 mL of distilled water was heated, as much as 1 g of added TiO_2 (Titanium dioxide) [36], 2.5 g of sucrose, and 1 g of inputted natural dye inputted (matcha). Aqueous were mixed became after being homogeneous. As much as of carrageenan in the variation of mass (1: 3: 5: 7: and 9 g) and corn starch in the variation of mass (1: 2 : 3 : 4 and 5 g). The solution was stirred until completely mixed, then added polyethylene glycol (1:2:3:4: and 5 mL) then stirred again until homogeneous. The mold for the capsule cover was dipped as deep as 2.5 cm and for the capsule mold the body part was dipped as deep as 3 cm [3]. Then the capsule dough and its molds were dried in an oven at temperature of 45°C for five hours [36]. Furthermore, the best capsule shell formulation was selected. The same steps were repeated for the best capsule shell formulation and the capsule shell was dried at various temperatures (35, 40, 50, 55, and 60°C) for 5 hours [36]. The flow diagram of the process can be seen in the Fig 3.

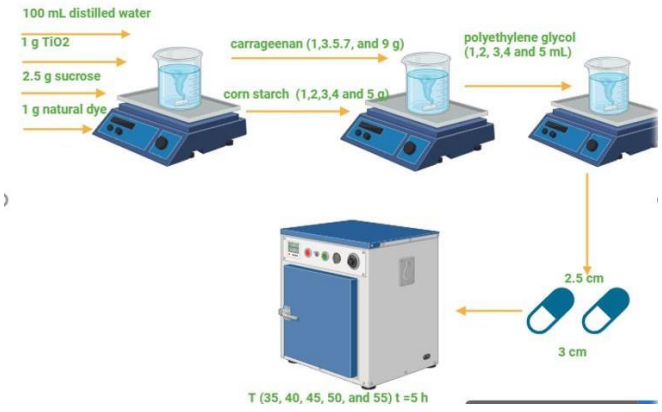

Fig 3. The making capsule shell steps

The formulation of each capsule shell seen from the ratio of carrageenan, corn starch and polyethylene glycol in various compositions and temperatures are shown in Table 1 and Table 2.

Table 1. Formulation hard shell capsule composition variations

Variations	Ratio carrageenan	Corn starch	Polyethylene glycol
Formula A	1	3	1
Formula B	3	4	2
Formula C	5	3	3
Formula D	7	2	4
Formula E	9	1	5

Table 2. Formulation hard shell capsule composition variations

Variation	Capsule Formula C Temperature
Temperature A	35ºC
Temperature B	40ºC
Temperature C	50ºC
Temperature D	55ºC
Temperature E	60ºC

III. RESULTS AND DISCUSSION

3.1 Product Analysis

(a) Hard Capsule Weight Analysis

The result of hard capsule analyze can be seen in Fig 4.

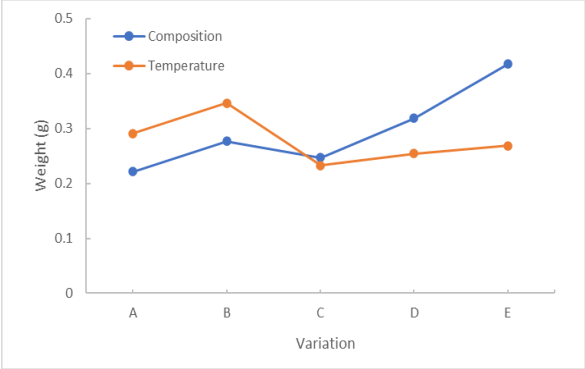

Fig 4. Hard capsule weight results

From the evaluation results in Fig 4, it can be seen that the addition of capsule shell weight growth along with the increase in the concentration of kappa carrageenan and was also associated with an increase in capsule shell thickness. The results of the highest weight and thickness measurements are in formula E for composition variations and temperature B for temperature variations, this is due to the higher viscosity of kappa carrageenan so that during the shell molding process, the film solution with a higher concentration of kappa carrageenan produces a shell with a thicker thickness.

Meanwhile, the weight of the capsule shell become weighed the use of an analytical balance. The objective of capsule shell mass check is to determine the capsule shell's thickness. The thicker the capsule shell, the more its mass increases. This is because carrageenan will increase the total dissolved solids in the capsule making solution so that it can growth the mass of the capsule after the drying process. In addition, the thickness of the capsule is affected by the process of dyeing and turning the mold

after dyeing. Irregular rotation of the mold can produce an uneven thickness of the capsule shell, in addition, the manual manufacturing process can also produce different thicknesses.

The factors that influence result of capsule shells analysis are weight of carrageenan, PEG, drying temperature, and drying time. The use of a little carrageenan can make the product has a thinner thickness. Addition of PEG as a plasticizer can increase permeability and flexibility of gas, water vapor and growth resistance mainly if saved at low temperatures [36, 37]. The drying temperature and drying time very influential on the final product because if it is too dry, the product will be difficult to remove from the mold. And for a thick capsule shells solution, the product that will be produced is dryer.

(b) Water Content Analysis

The result of the analyze water content can be seen in Fig 5.

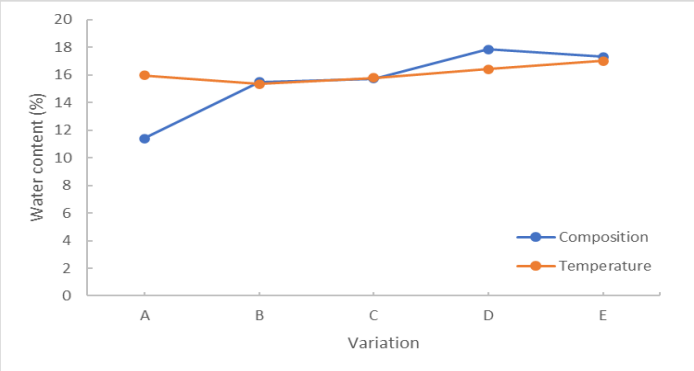

Fig 5. Water content hard capsule results

Water content testing needs to be carried out to determine the amount of water contained in raw materials related to the quality of these raw materials. Hard capsule shells generally have a water content of 12%-15% [38]. From the results of the study, it can be concluded that the moisture content of the capsule shells in formulas A, B, and C for variations in composition and temperatures of A, B, and C for temperature variations meets the water content standards of commercial capsule shells. High water content can potentially be overgrown with fungus and mold. The higher the concentration of carrageenan, the higher the water content, and the higher the temperature the lower the water content. However, the moisture content test can also be affected by the thickness of the capsule shell.

The low water content indicates that the capsules have the potential to be better in terms of storage and are good for use in containers of moisture sensitive medicinal ingredients. The high or low water content of a raw material is calculated by the nature and ability of the material to attract water as well as the drying process and the composition of the raw material itself [28], and storage of capsules in an environment that has high humidity can absorb water and result in capsules become softer. Under overly dry storage conditions with low humidity, the capsules will release water into the environment and the capsules become brittle.

(c) Hygroscopic Hard Capsule Analysis

The result of the hygroscopic hard capsule analyze can be seen in Fig 6.

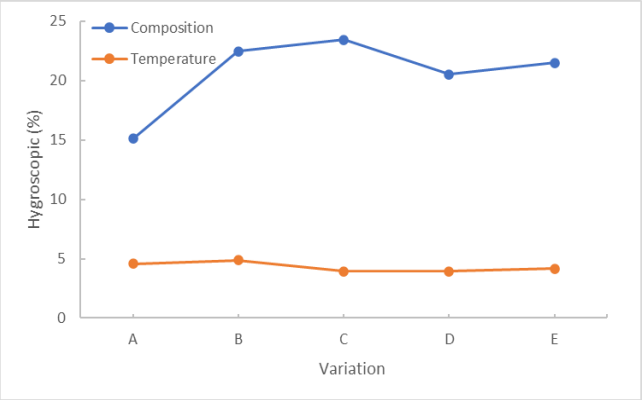

Fig 6. Hard capsule hygroscopic results

Fig 6 illustrates relationship between composition and temperature to percentage of hygroscopic. In the variation of temperature, the percentage of hygroscopic are relatively stable at 4%. While in the composition variation the percentage of hygroscopic increase slowly from 14% to 22%. Based on Figure 4, the result of hygroscopic analysis in the variation of compositions are 15.1-23.5%. On the other hand, in the temperature variations are 3.9-4.9%. From the variation in composition, all formulations showed very hygroscopic properties, while for temperature variations showed hygroscopic properties. From the results obtained, the higher the concentration of carrageenan, the resulting capsule shell has high hygroscopic properties. Meanwhile, the higher the temperature, the hygroscopic nature of the capsule shell decreases. From the results of this evaluation, it can be seen that the appropriate storage conditions in an effort to maintain the capsule shell in this study were containers that were tightly closed and given drying material (silica gel), conditions that were not too dried and packed made of aluminum-foil in strips.

(d) Swelling Degree Analysis

The result of the analyze degree of swelling hard capsule can be seen in Fig 7.

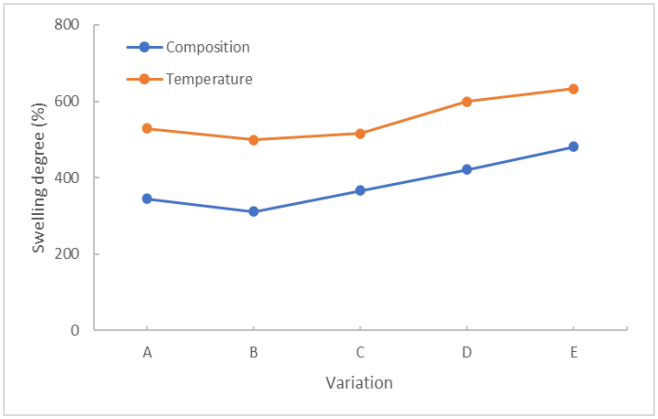

Fig 7. The degree of swelling in the hard capsule

Fig 7 shows the relationship between composition and temperature to swelling degree. In the temperature variations the swelling degree increase slowly at 550% in temperature of 35ºC to 600% in the temperature of 65ºC. Swelling is defined as a kinetic technique in which mass delivery and mechanical deformation are ruled through the interaction between the solvent and the polymer network [39]. In swelling degree analysis, a capsule is soaked in a hundred mL of the medium at 37°C ± 0.5°C.

The sample mass is measured using the hydrolysis method where the chemical bond amongst the particles of the samples is degraded, and afterwards the particles are surrounded by the solvent particles [3]. Alternatively, dissolution is defined as a device in which the solute at the molecular level dispersed in a solvent.

When a hydrophilic polymer comes into touch with water, the water penetrates the polymer through a selected machine. Water penetration causes swelling to the polymer, and some of the polymer debris will then decrease in size (chemical degradation) that will affect the polymer's overall dissolution in the long term. Dissolution Kinetics is the time it takes for specific polymer particles to dissolve in water. Kinetic Release refers to the system of a drug dissolving from a polymer [40].

This evaluation should provide an amazing indication of whether or not seaweed-based prescription drugs have a higher strength to dissolute in water compared to other different types. To date, there isn't any preferred SD aside the manufacturing of prescription drug that we are aware of. The observation by [3] indicates that the highest *swelling degree* is from κ-carrageenan-based prescription drugs (529.23% ± 128.10%).

The results for the degree of swelling of the variation formulas conform the requirements, while for temperature variations D and E exceed the requirements. From the results of the experiments carried out, higher the concentration of carrageenan and plasticizer, so higher the degree of swelling produced. Thus, the hard capsule has the ability to contain more water than capsules commercial, making it difficult to dissolve under normal conditions.

Carrageenan is constructed from lengthy linear chains of D-galactose and β-3,6-anhydrogalactose. With ester sulfate as a aspect branch, those classification assist the structure of helices that reason the structure of gel [21]. Therefore, a likely purpose for the excessive degree of swelling of capsules is the gelling agent capacity of carrageenan. Even if the scale of the pores of carrageenan became larger than gelatin, this excessive swelling degree will assist the fabric to resist disintegration and dissolution longer than gelatin and capsule commercial.

(e) Disintegration Tester Analysis

The result of the disintegration tester hard capsule analyze can be seen in Fig 8.

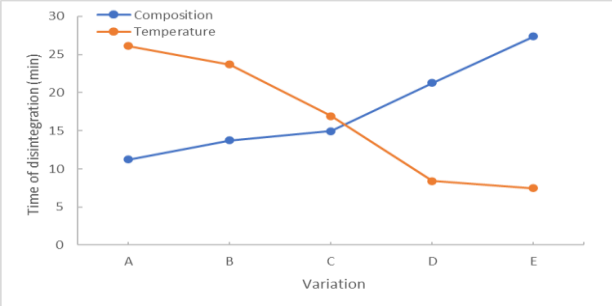

Fig 8. Hard capsule disintegration test results

The capsule shells serve as a packaging for drugs in the form of powder. The capsule shells which is easily damaged or easily penetrated by water can cause drug that inside of capsule shells dissolved, so that the bitter taste will be tastes. Disintegration time is the time required for the capsule to disintegrate in a suitable medium. A good disintegration time is 15 minutes or less. The disintegration time of the resulting capsules is still within the disintegration time set by the Pharmacopoeia, which is less than 30 minutes. The results of the capsule shell disintegration time in this study still met the capsule shell disintegration time requirement of the USP (2010), which was <30 minutes (United States Pharmacopoeia Convention, 2010). However, the disintegration time in the variations of Formula D and E are based on specification of Pharmacopoeia and PT. Kapsulindo as a producer of shell capsule in Indonesia, but in the variations of temperature A, B, and C are below a very much different comparison with the disintegration time of the commercial carrageenan capsule shell have been producing by PT. Kapsulindo Nusantara, Bogor, Indonesia which is less than 15 minutes**.** This is because the molecular

weight of carrageenan is greater than the degree. Carrageenan with a large molecular weight has a low solubility. The capsule shells serve as a packaging for drugs in the form of powder. The capsule shells which is easily damaged or easily penetrated by water can cause drug that inside of capsule shells dissolved, so that the bitter taste will be tastes shells. And also the effect of PEG used [36]. Like the function of PEG, which is as a plasticizer so with adding PEG in the manufacture of capsule shells will affect the disintegration time.

3.2 Dissolution Tester Analysis

Fig 9 and Fig 10 present the information about relationship between capsule formulas and temperatures to dissolution test.

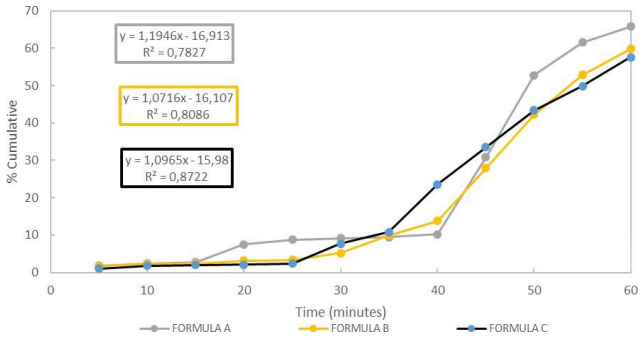

Fig 9. Dissolution test for composition variations

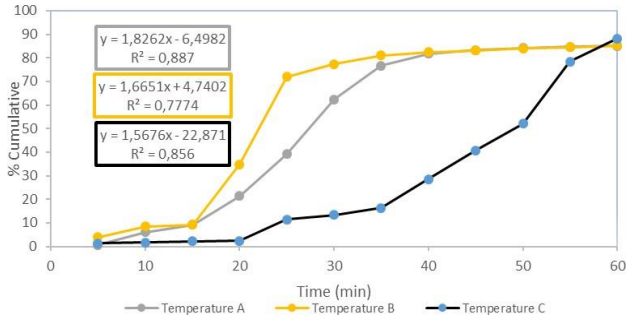

Fig 10. Dissolution test for temperature variations

The dissolution test aims to determine the rate of solubility of the active substance from the drug preparation in the body for absorption. Parameters in dissolution depend on the measurement of the speed of opening and dissolution of the active substance from the preparation.

The dissolution test was carried out using a drug in the form of paracetamol at pH 1.2. It adjusts the pH in the stomach, duodenum, and small intestine by conducting experiments on variations in composition and temperature which gained different results of dissolution, because the crack was different at each variation of time. The highest dissolution percentage is 65% in the formula A variation because it has started to dissociate at the 15 minute and the final result of dissolution was at the 60 minutes. Meanwhile, for temperature C is the best in temperature variations because it has started to crack at the 15 minute and the final percent dissolution was 88%.

These results can be influenced by several factors, such as the degree of swelling factor. The capsule shells serve as a packaging for drugs in the form of powder. The capsule shells which are easily damaged or easily penetrated by water can cause drug inside the capsule shells to dissolve, hence the bitter taste will taste like shells, and also the effect of PEG used [41]. Likewise, the function of PEG as a plasticizer with the added PEG in the manufacture of capsule shells will affect the disintegration time.

3.3 Drug Release Kinetics Data Analysis

Fig 11 gives information about the relationship between time in a minute to log cumulative in the variation of compositions in the first-order kinetics. The correlation between time to log % cumulative get regression linear equation. Capsule A to capsule C got coefficient correlation (R^2) between 0.9433 to 0.9665. The value of coefficient drug release of capsule A is suitable for explaining kinetic drug release using first order.

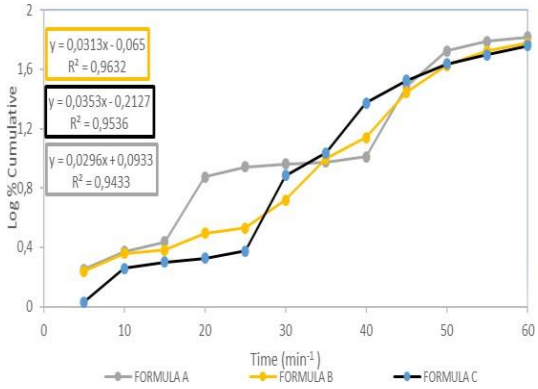

Fig 11. Release kinetic of seaweed carrageenan capsule shell according to first order kinetics from composition variations

Fig 12 illustrates the relationship between temperature to log % cumulative in the variation of temperatures in the first-order kinetics. The value of coefficient correlation was between 0.6993-0.9614. The temperature C can illustrate kinetic drug release using first order because the coefficient drug release equal to 1.

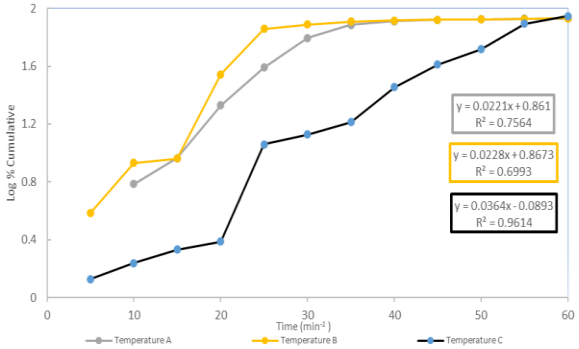

Fig 12. Release kinetic of seaweed carrageenan capsule shell according to first order kinetics from temperature variations

Table 3. The correlation coefficient value and first-order rate constant

Formulas	Composition Variations			Temperature Variations		
	R^2	k_1 (min^{-1})	$t^{1/2}$ (min)	R^2	k_1 (min^{-1})	$t^{1/2}$ (min)
A	0.943	$2.96x10^{-2}$	23.412	0.756	$2.21x10^{-2}$	22.82
B	0.963	$3.13x10^{-2}$	32.535	0.699	$2.28x10^{-2}$	30.985
C	0.967	$3.53x10^{-2}$	19.632	0.961	$3.64x10^{-2}$	19.038

Based on Table 3, the value of constant rate of first order kinetics in the variation compositions was between $2.96x10^{-2}$ to $3.53x10^{-2}$/min and that in the temperature variations was $2.21x10^{-2}$ to $3.64x10^{-2}$/min. In the composition variations, the value of half-time first order release was between 19.632 to 32.535 min. On the other hand, that in the temperature variations was between 19.038 to 30.395 min. The research about half time first-order release rate of paracetamol conducted by (Cummings et al., 1967) was 1.6-2.8 hours. Meanwhile, some of the research about first-order rate constant on the drug

conducted by [43] and [44] revealed the value of half-time release ibuprofen which was 1.75 and 4.5 minutes respectively. Based on the research done by [45], the value of half-time release aspirin was 0.35 hour. The first-order drug release mechanics describes the speed of drug release counting on the concentration. The speed of release at any given time was proportional to the concentration of the drug remaining within the preparation at that time. The upper the concentration of the active substance, the bigger the quantity of drug released.

IV. CONCLUSION

Carrageenan-primarily based totally hard-shell capsules had been correctly organized because the opportunity to traditional hard-shell capsules through variant carrageenan and corn starch with extra PEG for plasticizer. From the various variations carried out, the best composition variation is formula C because it has the specifications of the test that has been carried out according to the required requirements.

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