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RESEARCH

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Drug release kinetics of capsule shells from seaweed carrageenan extract (*Eucheuma cottonii*) and potato starch as a gelling agent

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Abstract

Background Capsules are created to put a drug or active pharmaceutical ingredient in an elegant, odorless, tasteless, easy-to-swallow and to-fill shell commonly produced from gelatin. Therefore, carrageenan is one of the other natural ingredients that can replace gelatin. This study aims to make capsule shells from carrageenan seaweed (*Eucheuma cottonii*) with variations in carrageenan composition and temperature using potato starch as a gelling agent with the addition of PEG as a plasticizer and to determine the kinetics model of the drug release system from the capsules that have been made.

Results In the research there are two variations namely composition and temperature. The capsule shell dissolution test results were calculated using kinetic models of order 0, order 1, Higuchi, and Korsmeyer-Peppas. The result on zero order is that at the C composition and temperature 55 ºC variations obtained the reaction rate constant (k) are 1.05 and 1.27 min respectively. While in first order obtained the reaction rate constant of 4.59×10^{-2} and 2.06×10^{-2} min^{-1} respectively at variations in capsule D composition and temperature of 60ºC. In the Higuchi model, the correlation coefficient for composition variation is better than temperature variation of 0.92. In the Korsmeyyer-Peppas model, the value of reaction rate constant (k) at composition C and temperature of 55 ºC variations are 1.41×10^{-2} and 9.49×10^{-3} min^{-n}.

Conclusions The Korsmeyyer–Peppas kinetic model is suitable for illustrating the drug release kinetics of capsule shells from seaweed carrageenan extract (*Eucheuma cottonii*) and potato starch as a gelling agent.

Keywords Capsule shells, Kinetic reaction, Potato starch, Seaweed carrageenan

Background

Capsules are dosage forms that have been used for a long time in pharmacies. Basically, capsules are created to put a drug or active pharmaceutical ingredient (API) in an elegant, odorless, tasteless, easy-to-swallow and to-fill shell. Currently, there are two types of capsules, namely, hard gelatin capsules and soft gelatin capsules, usually called soft shells. Hard gelatin capsules are commonly used for dry fillings such as powders, liquids, and semisolids. Meanwhile, the soft shell is specifically applied for liquid and semisolid filling materials (Qiu et al. 2017). The advantages of capsules are easy

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to swallow, easy to adjust drug dosages and to combine with other drugs depending on patient needs, and they are also suitable for drugs with low compressibility, slow dissolution, and bitter taste (Poeloengasih et al. 2017). Therefore, as a drug delivery system (DDS), hard shell capsules are essential. Traditional capsules are generally derived from gelatin produced from animal parts (bones or skin), which means that not all humans can consume these capsules, such as vegetarians and Muslims (Rabadiya and Rabadiya 2013; Fauzi et al. 2020). Therefore, within the last several decades, herbal polysaccharides have attracted greater interest and have drastically advanced as medicinal pill substances to provide high-dose paperwork for drugs. Numerous herbal polysaccharides, including starch and cellulose derivatives, have been investigated for their potential to update gelatin (Poeloengasih et al. 2017). Thus, other natural ingredients for hard shell tablets are expected to be an opportunity to replace gelatin (Fauzi et al. 2020). There are several options for capsules that have been developed, namely, alginate capsules not applied to make hard shell capsules, carrageenan capsules with a slow disintegration time, and capsules sensitive to temperature changes, namely, hypromellose capsules (Fauzi et al. 2020). Carrageenan is also a carbohydrate polymer that has the capacity to renew plastics in its application in the pharmaceutical industry due to its easy processing and abundance (Hamdan et al. 2020).

Carrageenan is a natural sulfate polysaccharide that is soluble in water (Farhan and Hani 2017). Carrageenan is commonly used as a gelling agent in some products (frozen foods, jellies, and yogurt) (Noor 2018). In general, there are three types of carrageenan: kappa, iota, and lambda carrageenan (Hamdan et al. 2020). Kappa-type carrageenan is obtained from red seaweed extract mainly from two different species, namely, *Eucheuma cottonii* and Kappaphycus alvarezii extracts (Jiao et al. 2011). Due to its excellent gelling ability, kappa carrageenan is commonly used as a gelling agent in hard capsule production (Adam et al. 2020). Carrageenan is obtained by the seaweed extraction process using alkaline solvents at high temperatures. The type of alkali used as a solvent in the extraction process will affect carrageenan formation (Hasizah et al. 2021). Generally, alkaline solvents that can be used are NaOH, $Ca(OH)_2$, and KOH. Alkali has two functions: to help the extraction of polysaccharides to be more complete and to accelerate the chain breaking of the 6-sulfate monomer units into 3,6-anhydro-D-galactose, hence increasing gel strength and product reactivity to protein. The use of KOH has the advantage of increasing the yield and quality of the resulting carrageenan, so the alkaline solution used to extract seaweed is potassium hydroxide (KOH) (Diharmi et al. 2017).

Starch draws greater interest as a gelatin replacer candidate due to its ideal aggregate; moreover, it is inexpensive, abundant, and has film-forming properties. The starch film has a good ability as an oxygen barrier. Due to its dense hydrogen bond network structure, starch has good mechanical strength. Starch films are highly dependent on the amylose or amylopectin ratio. A strong film is produced when the amylose content is high, whereas it will produce a film with poor mechanical properties if there is more amylopectin. However, due to the hydrolytic properties of starch, starch films generally have poor moisture barrier properties. As a result, to prevent this, other natural polymers whose interactions are compatible with starch can be added (Poeloengasih et al. 2017).

Based on the aforementioned background, this study aims to make capsule shells from carrageenan seaweed (*Eucheuma cottonii*) with variations in carrageenan composition and temperature using potato starch as a gelling agent with the addition of PEG as a plasticizer and to determine the kinetics model of the drug release system from the capsules that have been made.

Methods

Materials

The research materials were aquadest, PEG 400 (Merck), HCl 37% (Merck), KCl (Merck), KOH (Merck), potato starch 100%, carrot powder (as natural dye), carrageenan powder (*Eucheuma cottonii*), TiO_2 (Merck), and sucrose.

Instrument

The research instruments were zero-dimensional capsule molds such as the frame and hard shell capsule head components; beaker glass; Erlenmeyer; funnel; Genesys 10S UV–VIS Spectrophotometer; glass rod; hot plate; IKA Labortechnik Dissolution Tester; MJK0040 Vanguard Disintegration Tester MDL LIJ-2; magnetic stirrer; mesh filter; Ohaus analytical balance; oven; porcelain cup; rubber bulb pipette; spatula; thermometer; volumetric flask; volumetric pipette; and watch glass.

Method

Here are the methods conducted in this research: Thirty grams of dried *Eucheuma cottonii* seaweed were soaked in 500 mL of distilled water for ± 24 h. *Eucheuma cottonii* was extracted with 0.8N KOH solvent (in 1000 mL distilled water) at 85 °C for 1 h. The ratio of dry *Eucheuma cottonii* seaweed to solvent was 1:30 (g/mL). The solvent volume was kept constant by adding hot solvent all the time. After 1 h, the extraction was stopped by separating the filtrate from the seaweed dregs. This filtrate was accommodated in a beaker and allowed to stand until the filtrate reached room temperature 30 °C. Afterward, 1N

Table 1 Composition variations of hard capsule formulations

Compositions	Formula			
	A	B	C	D
Carrageenan (%w/v)	4	6	8	10
Potato starch (%w/v)	4	3	2	1
PEG (%v/v)	2	3	4	5

Table 2 Temperature variations in the hard capsule from formula C

Capsule from formula C	
Variations	**Temperature (°C)**
A	40
B	50
C	55
D	60

KCl was poured into the filtrate at a ratio of 1:1 to the volume of the filtrate, with continuous stirring until hydrocolloid fibers (carrageenan fibers) were formed. After the fiber was allowed to stand for approximately 24 h, it was filtered and cleaned using water until the pH was neutral. Wet carrageenan was dried in an oven at 120 °C until the weight was constant. Carrageenan sheets dried and constantly weighed were cut into small pieces and crushed to form a coarse powder.

A total of 100 mL of distilled water was heated and then mixed with TiO_2 and natural dye (carrot powder) as much as 1 g each. After homogenization, carrageenan (4, 6, 8, 10) % w/v and potato starch (4, 3, 2, 1) % w/v were mixed in a beaker glass. The solution was stirred until completely mixed, and PEG 400 (2, 3, 4, 5) %v/v was added and stirred again until homogeneous. The mold for the capsule cover was dipped in 2.5 cm and for the body part of capsule mold was dipped in 3 cm. Then, the capsule dough and its molds were dried in an oven at 45 °C for 5 h. 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 h. The variations in the composition and temperature formulation of each capsule shell are shown in Tables 1 and 2.

A dissolution test was carried out to determine the porosity of the drug and its relationship with the speed of drug release. Then, the pills were dispersed in a pH range of 1.2 (HCl), representing the pH of the digestive tract and intestines in the human body. The dissolution test was carried out within 1 h at 37 °C ± 0.5 °C in 900 mL for each capsule using the basket technique at a speed of 100 rpm (Fauzi et al. 2020). The capsule preparation filled with paracetamol was put into a dissolution flask adjusted for stirring speed and temperature. A 5 mL sample was taken from the paracetamol release test solution at time intervals of 5, 10, 15, 30, 35, 40, 45, 50, 55, and 60 min. The sample was placed in the middle between the surface of the dissolution medium and the top of the paddle no less than 1 cm from the container wall. The solution was kept until the volume of the dissolution medium was constant, and the number of samples taken was replaced with the dissolution medium with 5 mL used at the same temperature.

The drug concentration absorption was measured using a spectrophotometer.

UV–VIS at a maximum wavelength of 288 (200–400 nm) (Gloria 2018).

Results and discussion

Results

The capsule shell dissolution test results were calculated using kinetic models of order 0, order 1, Higuchi, and Korsmeyer-Peppas.

Zero order

Figure 1 illustrates the relationship between time (min) and cumulative % in the composition variations. On the other hand, Figure 2 gives information about the connection between time (min) and cumulative % in the temperature variations.

Based on Fig. 1, it is known that the highest % cumulative value is in formula E with a % cumulative value of 80.09 and a dissolution time of 60 min. Based on research conducted by Kar and Kar (2020), the highest % cumulative paracetamol release value is in the F-A variation at 90 min. According to a previous study (Goscianska et al. 2021), the kinetic release of paracetamol in gastric fluid with wrinkled mesoporous carbon was confirmed to be zero-order simulated for 24 h.

Based on Fig. 2, it is known that the highest % cumulative value is in temperature C with a % cumulative value of 87.79 and a dissolution time of 60 min. According to Gupta et al. (2010), the value of k on the order of zero is 12 h using a mixture of polyethylene glycol 400 and diethyl phthalate as a plasticizer. According to research (Prescott 1980), the half-life of paracetamol release following a zero-order kinetic model is 1.5–2.5 h. Meanwhile, the half-life of the release aspirin is 15 min (Elhasan 2017).

According to Dash et al. (2010), drug dissolution from the dosage form ideally follows a zero-order kinetic

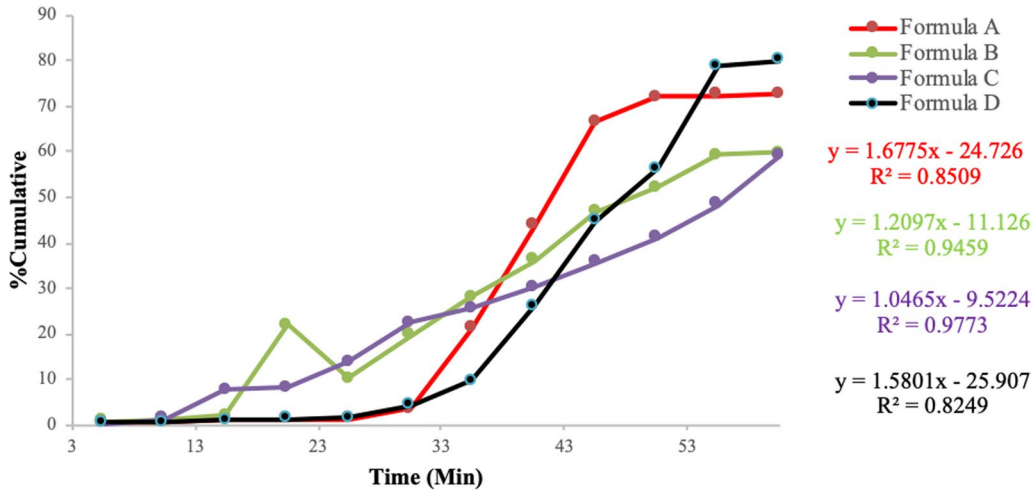

Fig. 1 Zero-order kinetics for composition variations

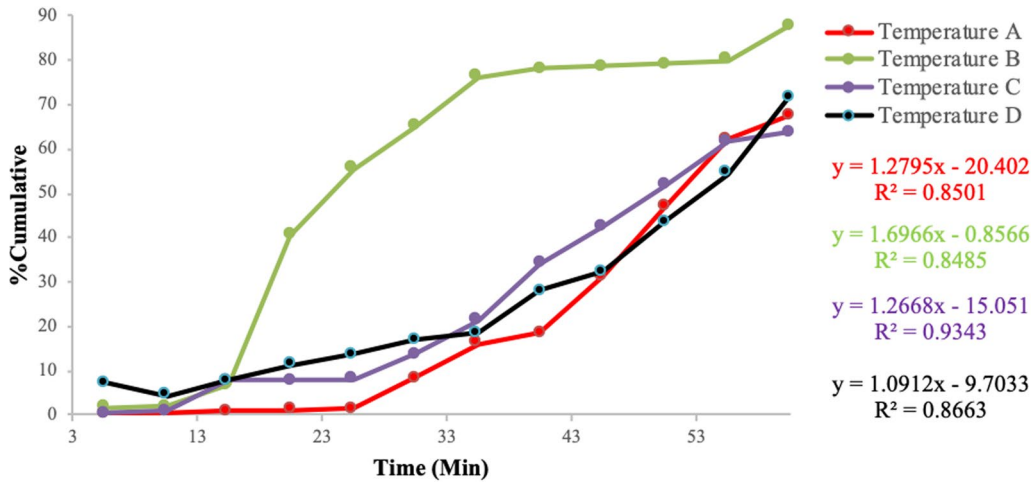

Fig. 2 Zero-order kinetics for temperature variations

model, i.e. Drug release is constant from beginning to end. Drug release following a zero-order kinetic model occurs through an erosional mechanism and describes a concentration-independent drug release rate system. From Eq. (1), it can be seen that the zero-order kinetic model is known.

$$Q_t = Q_0 + k_0 t \quad (1)$$

where Q_t = amount of accumulated concentration, Q_0 = initial concentration, k_0 = zero-order reaction constant, and t = time. In this model, drug release data are described as the cumulative amount of drugs released against the effect of time. This model serves for the delivery of transdermal, ophthalmic, and poorly soluble drugs. In addition, this mode is ideal for slow and delayed delivery of drugs such as antibiotics, antidepressants, blood pressure regulators, analgesics, and anticancer drugs (Son et al. 2017).

First order

Figure 3 shows the relationship between time (min^{-1}) and log % cumulative in the composition variations, while Fig. 4 describes the correlation between time (min^{-1}) and log % cumulative in the temperature variations.

Figure 3 shows that the largest log % cumulative value is in formula E with a value of 1.90 at a dissolution time of 60 min. Otherwise, according to the reults of the study (Li et al. 2012), it is known that the half-life of ibuprofen release is 1.75 min.

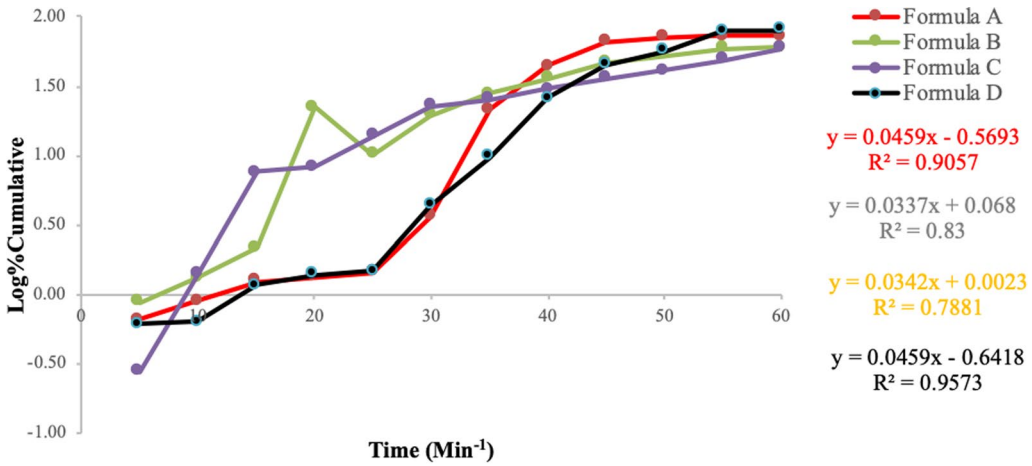

Fig. 3 First-order kinetics for composition variations

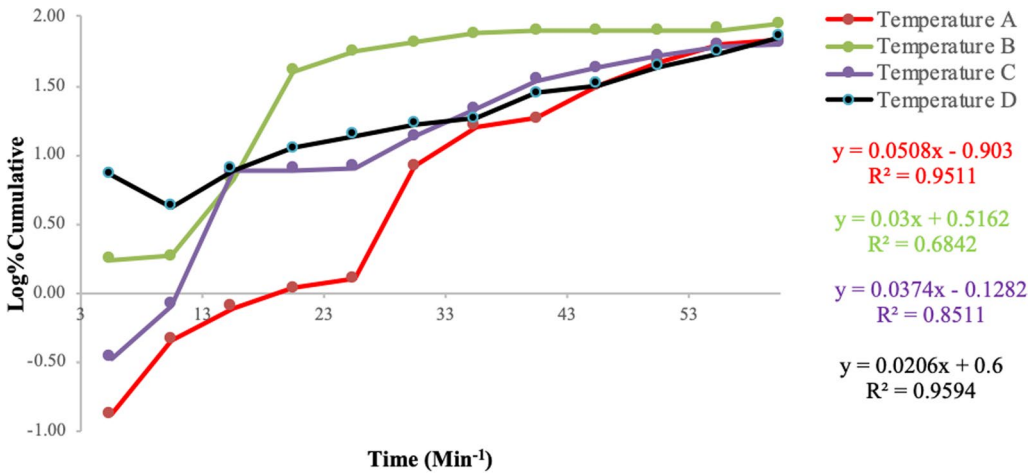

Fig. 4 First-order kinetics for temperature variations

Figure 4 shows that the largest log % cumulative value is at temperature C with a value of 1.94 at a dissolution time of 60 min. According to Gibb and Anderson (2008), the half-life of ibuprofen release is 4.5 min. For aspirin, it is known that the half-life of decay is 0.35 h (Voelker and Hammer 2012).

The first-order reaction kinetics model is a system in which the rate of drug release depends on the concentration. The following equation is the equation of the first-order kinetic model:

$$\log C = \log C_o - \frac{kt}{2.303} \quad (2)$$

where the initial drug concentration is C_0, the first-order rate constant is K, and time is (t). Released data are expressed as the cumulative log percentage of drug remaining in time and a straight line with a slope of $K/2.303$ (Son et al. 2017).

Higuchi

Figure 5 depicts the relationship between the square root of time ($min^{1/2}$) and cumulative % in the composition variations. In addition, Fig. 6 provides information about the correlation between the square root of time ($min^{1/2}$) and cumulative % in the temperature variations.

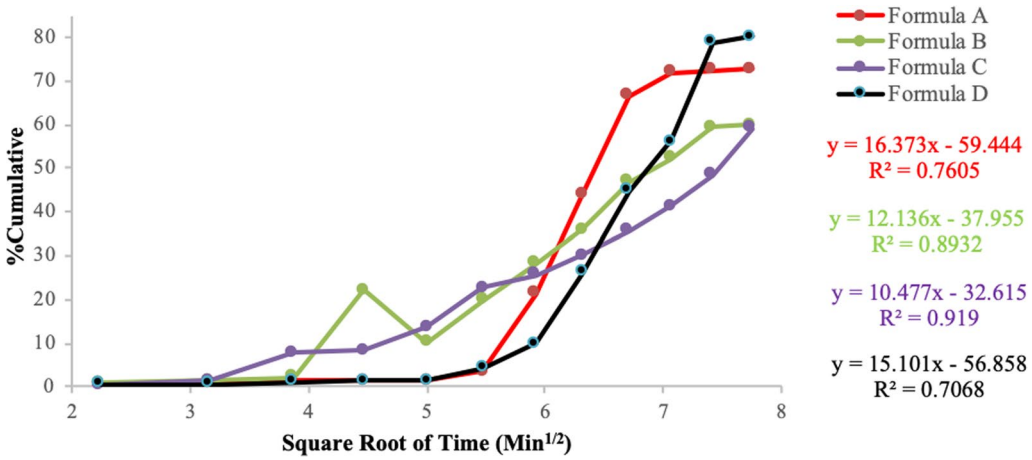

Fig. 5 Higuchi kinetics for composition variations

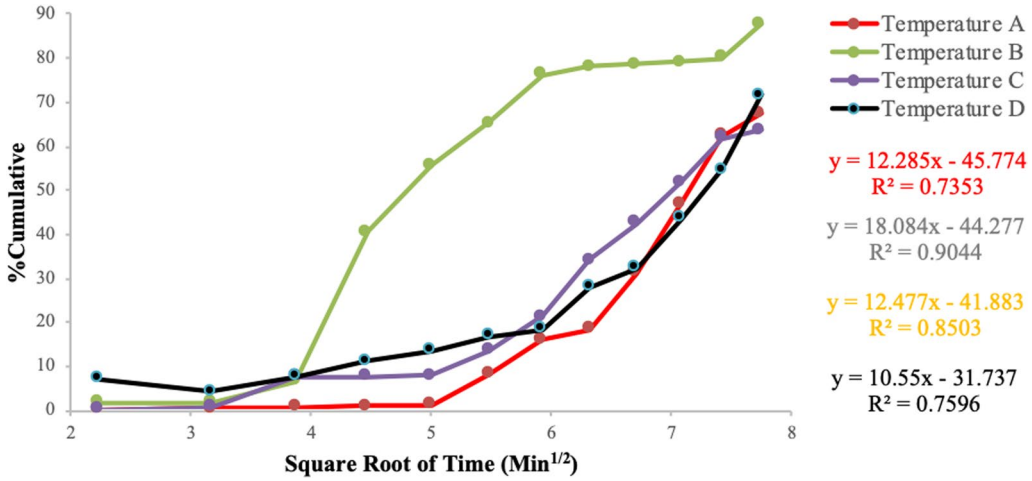

Fig. 6 Higuchi kinetics for temperature variations

Based on Fig. 5, it is known that the highest % cumulative value is in formula *E* with a value of 80.09 at the square root of time 7.75 min.

Based on Fig. 6, it is known that the highest % cumulative value is in temperature C with a value of 87.79 at the square root of time 7.75 min. Meanwhile, according to the study (Meirelles and Raffin 2017), the release of rhodamine B using the Higuchi model was 80% for 8 h.

The following is the equation of Higuchi's kinetic model:

$$ft = Q_t = [D(2C - C_s)C_t]^{1/2} \quad (3)$$

where the amount of drug released in a unit area at a certain time (t) is Q_t, the initial drug concentration is C, the drug solubility is C_s, and the diffusion constant is D. The model is simplified to

$$ft = K_H t^{1/2} \quad (4)$$

where K_H = Higuchi dissolution constant. Thus, this model can be used to describe drug release as a diffusion process based on Fick's law (depending on the square root of time) (Son et al. 2017).

Korsmeyer-Peppas

Figure 7 illustrates the relationship between log time (log min) and log % cumulative in the composition variations. On the other hand, Fig. 8 describes the relationship

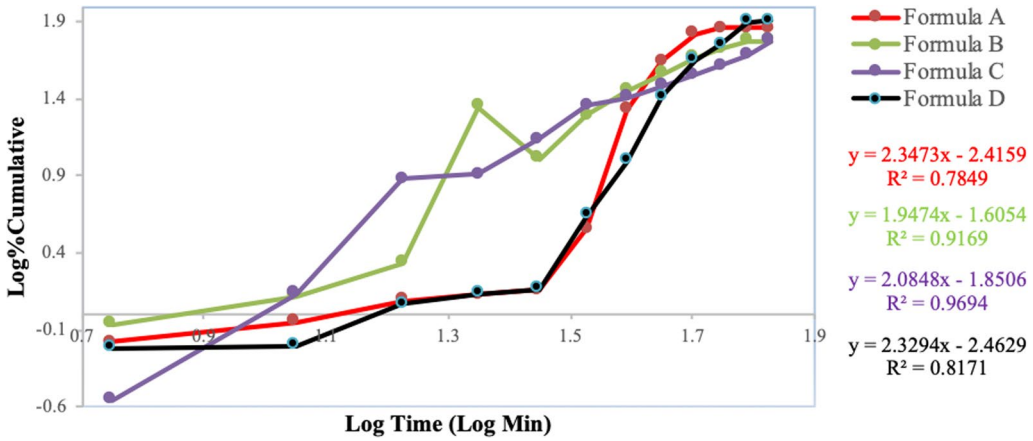

Fig. 7 Korsmeyer-Peppas kinetics for composition variations

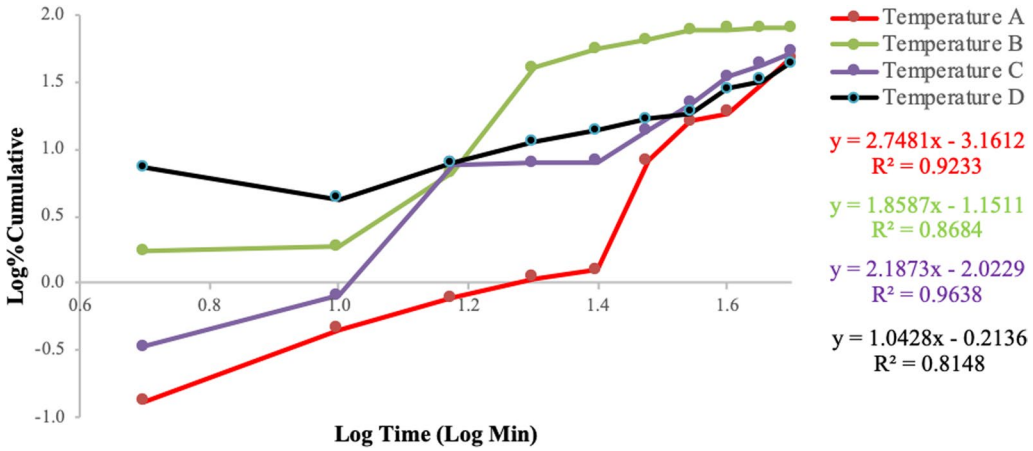

Fig. 8 Korsmeyer-Keppas kinetics for temperature variations

between log time (log min) and log % cumulative in the temperature variations.

From Fig. 7, it is known that the highest log% cumulative value is in formula E with a value of 1.9 at 1.78 min log time. Meanwhile, Fig. 8 shows that the highest log% cumulative value is in temperature C with a value of 1.94 at 1.78 min log time.

According to Son et al. (2017), the Korsmeyer-Peppas equation model can be seen in Eq. (5):

$$\frac{Mt}{M\infty} = K_t^{\eta} \tag{5}$$

where $\frac{Mt}{M\infty}$ is the fraction of drug released at time t, k is the release rate constant, and η is the release index. The value of η can predict the drug release mechanism. The value of $\eta \geq 0.45$ means the model fits Fickian diffusion, while $0.45 < \eta < 0.89$ fits non-Fickian transport, $\eta = 0.89$ means Case II transport, and $\eta > 0.89$ means Super Case II transport.

Table 3 Correlation coefficient (R^2) in four models in the composition variations

Formula	Model				Selected model
	0 order	1 order	Higuchi	Korsmeyer-Peppas	
A	0.85	0.91	0.76	0.78	1 order
B	0.95	0.83	0.89	0.92	0 order
C	0.98	0.79	0.92	0.97	0 order
D	0.82	0.96	0.71	0.82	1 order

Table 4 Correlation coefficient (R^2) in four models in the temperature variations

Temperature	Model				Selected model
	0 order	1 order	Higuchi	Korsmeyer-Peppas	
A	0.85	0.95	0.73	0.92	1 order
B	0.85	0.68	0.90	0.87	Higuchi
C	0.93	0.85	0.85	0.96	Korsmeyer Peppas
D	0.87	0.95	0.76	0.81	1 order

Table 5 Kinetic constant (k) value for composition variations

Formula	Model			
	0 Order (min)	1 Order (min^{-1})	Higuchi ($min^{1/2}$)	Korsmeyer-Peppas (min^{-1})
A	1.68	4.59×10^{-2}	16.37	3.84×10^{-3}
B	1.21	3.37×10^{-2}	12.14	2.48×10^{-2}
C	1.05	3.42×10^{-2}	10.48	1.41×10^{-2}
D	1.58	4.59×10^{-2}	15.10	3.44×10^{-3}

Discussion

Furthermore, the release kinetics model was chosen to determine the mechanism of drug release from the capsule dosage form. The selection is based on the value of the correlation coefficient (R^2), which is close to 1, where the value of each R^2 can be seen in Tables 3 and 4.

Table 3 describes four models, namely, zero order, first order, Higuchi, and Korsmeyer-Peppas, in the variation composition. Based on Table 3, the best correlation coefficient (R^2) in the D formula using the Korsmeyer-Peppas model is 0.97. Table 4 displays four models, namely, the zero-order, first-order, Higuchi, and Korsmeyer-Peppas models, for the temperature variations. From Table 4, the Korsmeyer-Peppas model is the best model in the D temperature variation with a correlation coefficient (R^2) of 0.96.

Meanwhile, the value of the release kinetic constant was obtained from the linear regression equation of each model. The release kinetic constants (k) for each model can be seen in Tables 5 and 6.

From Table 5, the suitable kinetic constant (k) in the D composition.variation using Korsmeyer Peppas is $1.41\times10^{-2}\ min^{-1}$.

Table 6 shows that the D temperature variation Korsmeyer Peppas model becomes an appropriate kinetic constant (k) with a k value of $9.49\times10^{-3}\ min^{-1}$. According to the results of the study (Wójcik-Pastuszka et al. 2019), drug release following the zero-order kinetic model obtained a constant with a value of 3.63×10^{5} to $7.49\times10^{5}/mg.min^{-1}$. Research conducted by Biswas et al. (2015) using composition variations, the results obtained are the value of the drug release kinetics model following the Higuchi model with a constant value between 5.66—11.57. Meanwhile, according to Imani and Kusumaningrum (2019), it is known that the Higuchi constant is 3.13×10^{-5} $minutes^{1/2}$. For research on drug release kinetics following the Korsmeyer-Peppas kinetic model by Çulcu et al. (2021), it is known that the constant value is 8.29 using dexketoprofen (DEX) from propylene glycol (PG) and the poloxamer gel system as raw materials. For the raw materials using aceclofenac (Syedabidali and Omair 2019), the constants were 1.226 to 1.442, and according to Wahab et al. (2011), the constant values were between 1.041 and 9.041. In addition, using a different membrane, (Cojocaru et al. 2015) obtained a constant of 0.9798. This was also investigated by Imani Moqadam et al. (2015) using Tween 80 raw material, and a constant of 0.599 was obtained.

Conclusion

Based on the research that has been conducted, it can be concluded that carrageenan has the potential to be a substitute for gelatin in the manufacture of hard shell capsules. In the variation of the composition, the best formula is found in formula C with the kinetic model

Table 6 Kinetic constant (k) value for temperature variations

Temperature	Model			
	0 Order (min)	1 Order (min^{-1})	Higuchi ($min^{1/2}$)	Krosmeyer-Peppas (min^{-n})
A	1.28	5.08×10^{-2}	12.29	6.89×10^{-4}
B	1.69	3.00×10^{-2}	18.08	7.06×10^{-2}
C	1.27	3.74×10^{-2}	12.48	9.49×10^{-3}
D	1.09	2.06×10^{-2}	10.55	6.12×10^{-1}

selected being Korsmeyer-Peppas, and the k value is 1.41×10^{-2} min^{-1}. For temperature variations, the best temperature is obtained at temperature C with a k value of 9.49×10^{-3} min^{-1} and selected from the Korsmeyer-Peppas kinetic model.

Abbreviations

API	Active pharmaceutical ingredient
DDS	Drug delivery system
PEG	Polyethylene glycol
Temperature A	Temperature of 40ºC
Temperature B	Temperature of 50ºC
Temperature C	Temperature of 55ºC
Temperature D	Temperature of 60ºC

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Author contributions
The paper was written and proof read by EE and RF. SN supervised procedure of dissolution test. Kinetic analyzed data using Microsoft Excel was done by MM and HH. PRS, EE and AUR made paper based on template and made revisions. All authors have read and approved the final manuscript.

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Availability of data and materials
The data generated or analyzed during this study are included in this publication.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent of publication
Not applicable.

Competing interests
The authors have no competing interest.

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