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Diffusion coefficient determination to evaluate the release of red ginger oleoresin from the chitosan microcapsules

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Abstract

This study aimed to determine the amount of red ginger oleoresin released from the chitosan microcapsules cross-linked with the sodium tripolyphosphate (TPP) and to determine its diffusivity coefficient based on the effect of the chitosan concentration, TPP solution concentration, and pH level. The red ginger oleoresin microcapsules were prepared using the emulsion cross-linking method. The preparation of the microcapsule was initiated by mixing the red ginger oleoresin with the chitosan solution, which was then stirred to form the first emulsion. Afterward, it was added to the oil and stirred again to form the second emulsion. The TPP solution dripped slowly. After the process was complete, it was continued with the addition of acetic acid to adjust the pH level. The formed microcapsules were washed and dried, and the release of the red ginger oleoresin was analyzed in a phosphate buffer medium. This research has been successfully carried out at various affecting factors such as the concentration of chitosan and TPP, and pH level. An increase in the concentration of chitosan and TPP solutions decreased the amount of red ginger oleoresin released from the microcapsules. In a variation of pH level, an increase in pH level from 4 to 5 decreased the cumulative release of red ginger oleoresin, but an increase in pH level from 5 to 6 increased the cumulative release value. The highest and the lowest cumulative release values were 65.06 ±1.54% and 48.82±2.1%, respectively. The values of diffusion coefficients were from 3.49×10^{-10} to $4.86\times10^{-10}\ \frac{\text{cm}^2}{\text{sec}}$.

Keywords: Cumulative release, Diffusion, Emulsion cross-linking, Equilibrium constant

1. Introduction

Ginger contains essential oils and oleoresin with varying values depending on the geography and climate where it grows [1]. Commonly, the essential oils and oleoresin in ginger are about 1-4% and 4-7.5% of the ginger's overall composition, respectively [2,3]. The oleoresin has more active components than the essential oil because the former contains volatile and nonvolatile compounds [4]. The main components contained in the oleoresin are gingerol [4,5] and shogaol which is formed from dehydration of gingerol during heating and storage [6,7].

Red ginger is a variety of ginger that contains higher flavonoid and phenol contents than white ginger (*Zingiber officinale Roscoe*) [8]. Like ginger in general, the main components of red ginger oleoresin are shogaol and gingerol [5,6]. Bioactivity from the red ginger oleoresin can function as an antioxidant, anti-inflammatory, anticancer, and antimicrobial [2,8-12]. However, the oleoresin in red ginger is sensitive to environmental conditions such as light, heat, and oxygen [13,14]. Shogaol in the red ginger oleoresin is also susceptible to changes in acidic pH and heat treatment, which may lead to degradation [15]. The red ginger also has a pungent aroma and sharp flavor, so it is difficult to consume directly. One alternative that can be done to protect the red

ginger oleoresin from environmental influences and reduce the sharp flavor is encapsulation. Some encapsulation methods have been developed such as coacervation, in situ polymerization, cross-link emulsion, interface polymerization, spray drying, freeze-drying, extrusion, and fluidized bed [16].

This study used the emulsion cross-linking technique. This method involves a polymer (biopolymer) containing the core material in emulsion droplets, which is then added with a cross-linking agent to cross-link with the chitosan functional group to result in microcapsules [17,18]. The emulsion cross-linking method is a simple and versatile method for both liquid and solid materials and is capable of producing microparticles and nanoparticles [18,19]. The microcapsule wall material that was used to coat the oleoresin in this study was chitosan since it is non-toxic and safe for consumption. Chitosan is also biocompatible and biodegradable, so it can be widely used as a microcapsule wall material [20]. For a cross-linking agent, glutaraldehyde saturated toluene (GST) can be selected. There are concerns about the use of glutaraldehyde due to its toxic nature. Campos, et al. [21], however, reported that GST did not cause cell damage because it was minimized by the occurrence of cross-linking between aldehydes and amines. One of the alternative cross-linking agents that is safer than GST is TPP. The interaction between TPP and chitosan in the emulsion cross-linking technique is an ionic interaction in which the amine groups are protonated in the chitosan with negative ions from TPP [22]. The encapsulation process of the red ginger oleoresin using the emulsion crosslinking method with TPP and chitosan as a crosslinking agent and wall material has been successfully conducted by Jayanudin, et al. [23]. The focus of the study of Jayanudin, et al. [23] was the analysis of the controlled release of red ginger oleoresin from microcapsules.

Controlled release is designed to control the drug release over time, to help the drug in passing the physiological barriers, protect the drug from premature elimination, and deliver the drug to the desired place while minimizing the release of the drug elsewhere in the body [24]. Compared to the conventional systems, the controlled release system provides more benefits such as maximum drug efficacy, minimal side effects, and reduced drug accumulation with chronic doses and drug level fluctuations [25]. Many controlled drug release implementations have been developed, such as in the manufacture of antibiotics (Dicloxacillin sodium and amoxicillin trihydrate) [26], Ibuprofen [27], and Indomethacin [28].

The cumulative release depends on the density of the microcapsule wall. The more rigid the microcapsule wall, the lower the cumulative release will be. Changes in the concentration of chitosan and TPP affect the stiffness of the microcapsule wall, as well as changes in pH which also affect the density of the microcapsule wall [23]. These three factors will affect the diffusion coefficient because the red ginger oleoresin diffusion rate changes with the changes in the chitosan concentration, TPP concentration, and pH level. Analysis of the released red ginger oleoresin was carried out based on its diffusivity coefficient. The mathematical model used to determine the diffusivity coefficient was developed by Jayanudin, et al. [9]. The current study aimed to analyze the release of red ginger oleoresin from the chitosan which was cross-linked with TPP and to determine the diffusivity coefficient of the red ginger oleoresin microcapsules.

2. Material and methods

2.1 Materials

The red ginger oleoresin was obtained from Lansida Group Ltd, which resulted from the extraction of the red ginger with a solvent of 96% (v/v) ethanol. Meanwhile, the sodium tripolyphosphate which was obtained from Sigma-Aldrich was used as a cross-linking agent. Glacial acetic acid, as a solvent for chitosan, was obtained from Merck. The technical grade chemicals such as toluene, n-hexane, and petroleum ether were obtained from Tri Jaya Dinamika Ltd. Chitosan, with a degree of deacetylation (DD) of 87.2%, was obtained from Biotech Surindo Ltd, while the corn oil was obtained from Surya Agung Ltd.

2.1.1 Preparation of the red ginger oleoresin-loaded chitosan microcapsules

Chitosan microcapsules filled with the red ginger oleoresin were prepared by the emulsion cross-linking technique reported by Jayanudin et al. [23]. Red ginger oleoresin as much as 4 g was added to 40 mL of chitosan solution at various concentrations, and it was stirred using IKA-Werk Ultra-Turrax for 30 min to form the first emulsion. Then, the first emulsion was added to 150 mL of corn oil, and it was stirred for 1 h to form the second emulsion, namely oil in water in oil (O/W/O). A total of 20 mL of TPP solution at various concentrations was gradually dropped into the second emulsion while stirring. Then, an acetic acid solution of 2%v/v was added to adjust the pH level and constantly stirred for 3 h. Microcapsules containing red ginger oleoresin were separated using a centrifuge and then washed with petroleum ether and hexane. Furthermore, microcapsules chitosan was dried in an oven at 65°C. The release analysis of the red ginger oleoresin from the microcapsules was conducted in a phosphate buffer medium. Table 1 shows the formulations for the preparation of red ginger oleoresin microcapsules.

Table 1 The formulations for the preparation of microcapsule chitosan filled with red ginger oleoresin.

Formulation	Concentration of chitosan solution (w/v)	Concentration of TPP solution (w/v)	pH
F1	1	5	5
F2	2	5	5
F3	3	5	5
F4	4	5	5
F5	4	7	5
F6	4	9	5
F7	4	5	6
F8	4	5	4

2.1.2 Release analysis of the red ginger oleoresin

Analysis of the red ginger oleoresin released from the microcapsules was conducted by modifying an analysis method reported by Jayanudin, et al. [9]. A phosphate buffer solution was made by mixing 200 mL of 0.2 M KH_2PO_4 solution with 0.2 M NaOH solution until the pH of the buffer phosphate was equal to 7.4. The release analysis of the red ginger oleoresin from the chitosan microcapsules was conducted by inserting 0.2 g of the red ginger oleoresin microcapsules into 200 mL of the phosphate buffer with a pH of 7.4. The mixture was stirred at 150 rpm at 37.4°C. The concentration of the red ginger oleoresin in the phosphate buffer was analyzed using a UV-Vis spectrophotometer with the following procedures: Samples as much as 5 mL were taken at certain time intervals and analyzed for the absorbance value using the UV-Vis spectrophotometer (Thermo Thermo Scientific Genesys 10 uv) with a wavelength of 283 nm. Furthermore, the concentration of oleoresin in the phosphate buffer solution was determined using a linear equation of a standard solution curve. Meanwhile, the standard solution curve was made by analyzing the absorbance of oleoresin in the buffer phosphate at various concentrations which were 20 mg/L, 40 mg/L, 60 mg/L, 80 mg/L, 100 mg/L, 200 mg/L, 300 mg/L, 400 mg/L, and 500 mg/L. Furthermore, the standard solution curve was made for the absorbance value vs oleoresin concentration. The linear relationship between the absorbance and the concentration was shown by the linear equation. Therefore, the red ginger oleoresin concentration in phosphate buffer solution was determined by converting the absorbance value from the spectrophotometer analysis using the linear equation. This study used the diffusion model of the red ginger oleoresin release proposed by Jayanudin, et al. [9] to determine the diffusion coefficient, as shown in the Equation (1) was the diffusion model for the red ginger oleoresin release.

$$C_{Aw} = \frac{C_{A0}}{\left(1+\frac{V_m H_l}{V_w H_d}\right)}\left\{\frac{V_m}{V_w}\frac{H_l}{H_d} + \exp\left[-A_m \frac{D_{AB}}{\delta}\left(\frac{H_d}{V_m}+\frac{H_l}{V_w}\right)t\right]\right\} \quad (1)$$

The wall thickness was determined using the Equation (2).

$$\delta = \frac{d\left[1-\sqrt[3]{\frac{\rho_{oleo}}{\rho_k+\rho_{oleo}\left(\frac{1}{x}-1\right)}}\right]}{2} \quad (2)$$

The oleoresin concentration in the release medium was then used to determine the cumulative release using the Equations (3) and (4) reported by Chandrasekaran, et al. [29].

$$\text{Amount of red ginger oleoresin release} = \frac{\text{concentration} \times \text{dissolution bath volume} \times \text{dilution factor}}{1000} \quad (3)$$

$$\text{Cumulative release (\%)} = \frac{\text{Volume of sample withdrawn (mL)}}{\text{Bath volume}} \text{ x } \left(P(1-t)\right) + Pt \quad (4)$$

Where: ρ_k, ρ_{oleo}: Density of chitosan and red ginger oleoresin [g/cm^3]; d_{avg} : Average diameter of the microcapsules [μm]; δ: Thickness of the microcapsule wall [μm]; n: The release exponent; D_{AB}: The diffusion coefficient $\left[\frac{cm^3}{sec}\right]$; t: Time [h]; Pt: Percentage release at time t; $P(1-t)$: Percentage release previous to 't'. H_I is equilibrium constant in phase I and H_d is quilibrium constant in phase II.

3. Results and discussion

3.1 Determination of the cumulative release of the red ginger oleoresin from the microcapsules

The preparation of chitosan microcapsules filled with red ginger oleoresin has been successfully carried out in the study of Jayanudin, et al. [23]. The study, however, only focused on the yield, encapsulation efficiency, and microcapsule characterization. Therefore, the current study analyzed the red ginger oleoresin released from the microcapsules to determine its diffusivity coefficient. To do it, this study was carried out in a phosphate buffer medium with a pH of 7.4 and a temperature of 37°C, which is also called the simulated intestinal fluid (SIF) medium. Differences in the chitosan concentration, pH, and TPP concentration can affect the percentage of cumulative release.

3.2 Effect of the chitosan concentration on the cumulative release percentage of red ginger oleoresin

Figure 1 shows the different profiles of the cumulative release of red ginger oleoresin which was caused by the different chitosan solution concentrations. There was an insignificant difference found in the first one hour with the cumulative release percentage of 30.44± 2% (F4), 29.47±1.83 (F3), 30.58±1.9 (F2), and 31.76±1.66% (F1). A clear difference was noticeable from the 2nd h to the 72nd h. The cumulative release for 72 h was 57.78±1.7 (F4), 61.85±1.59% (F3), 63.88±2.09% (F2), and 65.06±1.54% (F1).

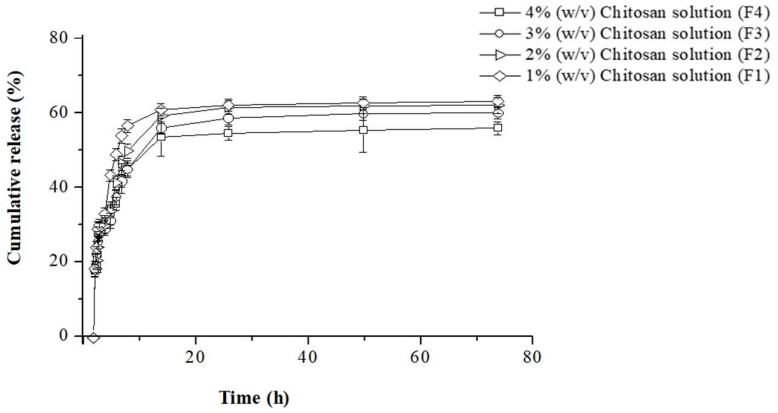

Figure 1 The release profile of the red ginger oleoresin microcapsules at a variation of the chitosan solution concentrations. The red ginger oleoresin microcapsules were prepared with a TPP solution concentration of 5% (w/v) and a pH of 5. Mean ± SD, n = 3. Equilibrium constant in phase I (H_I) and quilibrium constant in phase II (H_{II})

Overall, the increase in the concentration of chitosan solution caused the release of red ginger oleoresin to be lower. The increase in the concentration of chitosan solution increased the viscosity of the chitosan solution and made the microcapsule walls denser because the cross-linking between the chitosan and the TPP functional groups was stronger. The release process started from the absorption of the medium solution by the microcapsules, which caused swelling. This swelling process loosened the cross-linking network between aldehyde and amines, so the red ginger oleoresin diffused more easily into the release medium. The increase in the density of the microcapsule walls weakened the swelling ability of the microcapsules, which resulted in a lower amount of red ginger oleoresin being released. In line with this study, Hou, et al. [30], Jarudilokkul, et al. [31], and Deng, et al. [32] also reported that an increase in the concentration of chitosan solution led to a decrease in the cumulative release. The characterization of the red ginger oleoresin microcapsules with chitosan as the wall material cross-linked with TPP was analyzed using Fourier transform infrared (FTIR). FTIR analysis only showed an interaction between the chitosan and TPP functional groups to form the peak of 1211.30 cm^{-1} (P-O) and 1157.29 cm^{-1} (P=O).

3.3 Effect of the concentration of TPP solution

The differences in the cumulative release percentage were influenced by the concentration of TPP solution as shown in the (Figure 2).

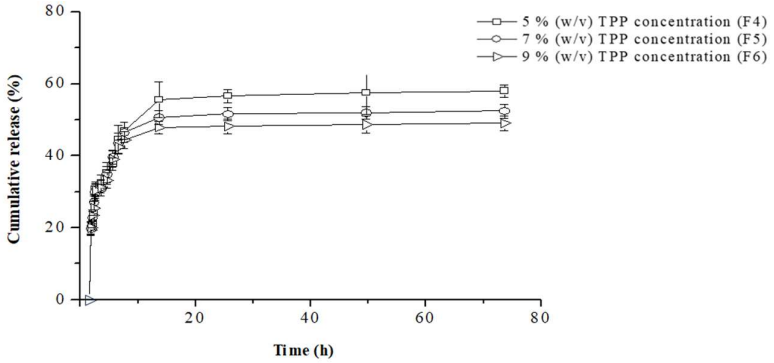

Figure 2 The effect of TPP concentrations on the red ginger oleoresin released from chitosan microcapsules prepared with a chitosan concentration of 4% (w/v) and a pH of 5. Mean ± SD, n = 3.

Figure 2 shows the profiles of the red ginger oleoresin release from the microcapsules, which were influenced by the TPP solution concentration as a cross-linking agent. An insignificant difference occurred in the first hour because the medium solution adsorbed by the microcapsule wall was still low. The swelling process increased from the 2nd h to the 72nd h, so a significant difference in cumulative release percentage was observed clearly in that time range. The cumulative release percentage for 72 h was 57.78±1.7% (F4), 52.23±1.95% (F5), and 48.82±2.1% (F6).

Therefore, it can be concluded that the higher the TPP solution concentration, the lower the cumulative release of the red ginger oleoresin from the microcapsules will be. This conclusion was also in line with that in studies of Lin, et al. [33] and Mulia, et al. [34]. This was because the higher the concentration of the TPP solution, the higher the cross-linking activity occurred in the microcapsules containing the red ginger oleoresin, thereby producing a more compact wall structure, and reducing a diffusion rate [35]. An increase in the concentration of TPP increased the interaction between the oxygen from polyanions and the hydrogen from photosrated amines in chitosan through the hydrogen bonds. This increase in the cross-linking slowed down the release process [36]. The more compact the cross-linking process slowed the swelling process because less phosphate buffer solution was absorbed.

3.4 Effect of pH of the mixture on the percentage of cumulative release

The addition of TPP increased the pH level. The pH of the mixture can be adjusted by adding 2% (v/v) glacial acetic acid. Differences in pH affected the activity of the TPP cross-linking agent, the strength of the microcapsule wall, and the release process. The effect of the pH of the mixture on the percentage of cumulative release is provided in the (Figure 3).

Differences in the cumulative release profile of the red ginger oleoresin from the microsphere chitosan due to the differences in pH level can be seen in the (Figure 3). The variation of the pH level was conducted in the microsphere chitosan preparation process. Figure 3 shows that there was an insignificant difference between pHs of 4-6. The highest cumulative release was 60.73±2.25% (at a pH of 4 for 72 h), while the lowest cumulative release was 57.78 ±1.7% (at a pH of 5 for 72 h).

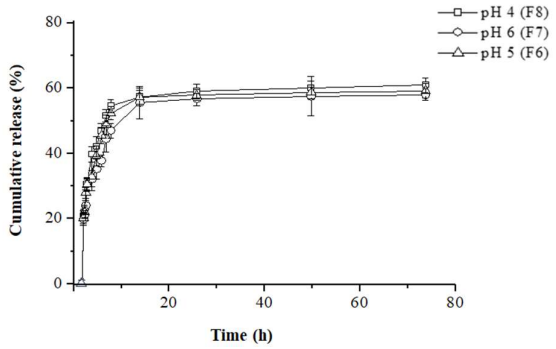

Figure 3 The profiles of the red ginger oleoresin released from the microcapsules at a variation of pH levels. Red ginger oleoresin microcapsules were prepared with a chitosan solution concentration of 4% (w/v) and a TPP solution concentration of 5% (w/v). Mean ± SD, n = 3.

The ionization of the TPP is controlled by the pH value. Ionic interactions between the chitosan solution and the TPP solution are obtained at an acidic pH level when the phosphate ions from the TPP solution interact with NH_3^+ from the chitosan solution. Meanwhile, deprotonation by hydroxyl ions is obtained at an alkaline pH level because hydroxyl ions and phosphate ions from TPP compete to interact with NH_3^+ from chitosan. The emulsification of the gelation process at an alkaline pH weakens the ionic interactions and then the cross-linking, which results in the formation of less dense chitosan microparticles [35,37]. Hence, it can be concluded that the higher the pH value, the higher the cumulative release value will be.

This study, however, found different results. The red ginger oleoresin microcapsules prepared at a pH of 4 resulted in a higher cumulative release compared to those at a pH of 6. The addition of TPP solution for the cross-linking process increased the pH of the emulsion. To decrease the pH to an appropriate level, acetic acid was added. Consequently, the chitosan solution was dissolved and facilitated the red ginger oleoresin to diffuse out during the microcapsule solidification process. The red ginger oleoresin was stuck on the microcapsule surface and partially mixed with the emulsion in the oil phase. This may explain why at pH 4, the encapsulation efficiency value was lower, and the cumulative release was higher compared to those at pHs of 5-6.

It can be concluded that the higher the TPP solution concentration, the lower the cumulative release of the red ginger oleoresin from the microcapsules will be. This conclusion was similar to studies by Lin, et al. [33] and Mulia, et al. [34]. The reason was that a higher concentration of the TPP solution led to a higher cross-linking activity that occurred in the microcapsules containing the red ginger oleoresin, thereby producing a more compact wall structure, and reducing a diffusion rate [35]. The increase in the concentration of TPP increased the interaction between the oxygen from polyanions and the hydrogen from photosrated amines in chitosan through the hydrogen bonds. This increase in the cross-linking slowed down the release process [36]. The more compact cross-linking process slowed the swelling process because less phosphate buffer solution was absorbed.

3.5 Modeling of the red ginger oleoresin release from the microcapsules using TPP as a crosslinking agent

Mathematical modeling was conducted to predict the oleoresin release from the red ginger oleoresin microcapsules and to determine the diffusion coefficient value using a model written in the Equation (1). Before the concentration of the red ginger oleoresin released in the medium was calculated through the Equation (1), the wall thickness of the microcapsules was first determined using the Equation (2) (Jayanudin, et al. [23]). Furthermore, the calculated wall thickness value was used to determine the red ginger oleoresin concentration using Equation (1), which was then used to determine the cumulative release using Equation (3) and (4). The fitting between the calculated data (modeled data) and the experimental data is shown in Figure 4.

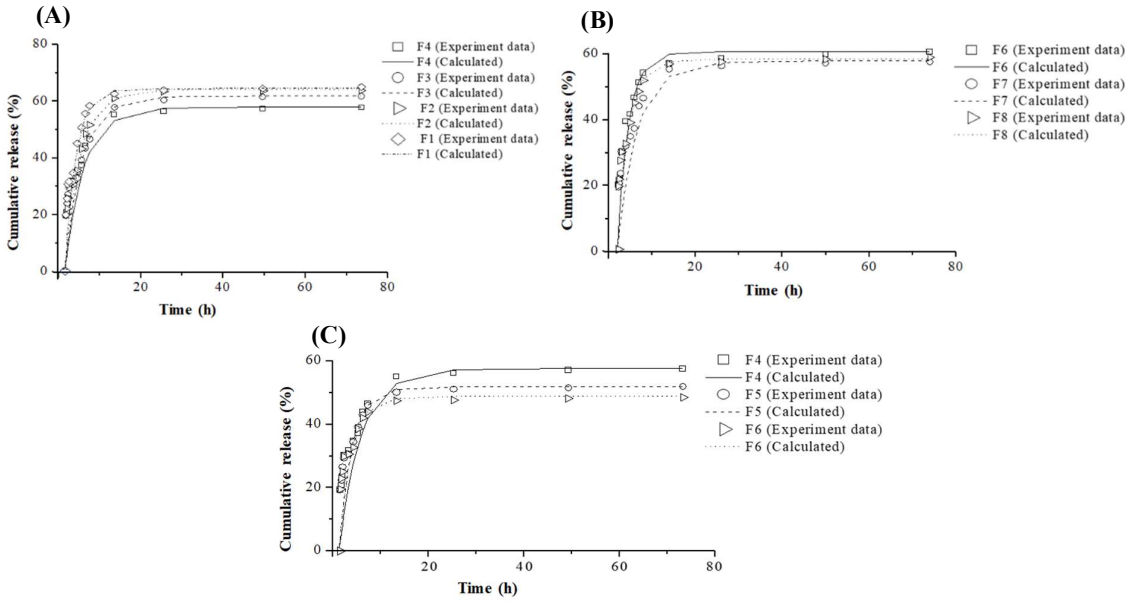

Figure 4 Comparison between the experimental cumulative percentage release data and the calculated data (modeled data): (A) effect of the concentration of chitosan, (B) effect of the pH, and (C) effect of the concentration of TPP.

Comparison between the experimental data and the calculated data showed good coefficient of determination (R^2) values of 0.81-0.98. At the beginning of the release (from the 15th min to the 2nd h), the experimental

cumulative release data and the calculated data that were obtained from the modeling had a fairly large deviation of 3%-20%; however, after the 2nd h, the deviation value was smaller. Figures 4 (A-C) show the experimental data compared with the calculated data at the variation of the concentration of chitosan solution, the pH level, and the concentration of sodium TPP solution, respectively. The highest R^2 value was obtained from the F4 with a value of 0.98. Based on the R^2 value shown in the (Figure 4), it was concluded that the calculated data obtained from the modeling fairly represented the experimental data of this research. Some formulations had low R^2 values. Those were due to the large deviation between the experimental data and the calculated data in a release time range of 1-7 days. In that time range, the experimental cumulative release data was higher than the calculated data, there might have been oleoresin attached to the surface of the microcapsules so that the experimental concentration data was greater than the calculated data obtained through the mathematical model which did not consider the oleoresin attached to the surface of the microcapsules. The used model assumed that the oleoresin was concentrated in the core and then diffused out of the microcapsules.

By using the equation (1), the values of the diffusion coefficient and equilibrium constants were obtained. These values correspond to the mass transfer of red ginger oleoresin, starting from the inner microcapsule wall layer to the outer wall. Table 2 shows the increase in the concentration of chitosan and TPP solutions decreased the diffusion coefficient (D_{AB}). This diffusion coefficient value was related to the diffusion rate of the red ginger oleoresin through the microcapsule wall. The increase in the concentrations of chitosan and TPP solutions made the microcapsule walls denser, which reduced the diffusion rate and D_{AB} values. The results of this study were the same as the results of a previous study using GST as a cross-linking agent in the preparation of the red ginger oleoresin chitosan microcapsules [9]. Various pHs contributed to the fluctuation in the D_{AB} value. However, at a pH of 5, the D_{AB} value was smaller than that at pHs of 4 and 6.

Table 2 Diffusion coefficient and equilibrium constant values on the red ginger oleoresin microcapsules using TPP as a crosslinking agent.

Parameter	$D_{AB}\left(\frac{cm^2}{sec}\right)$	H_d	H_I	R^2
F1	4.55×10^{-10}	15.3	1683	0.9
F2	4.53×10^{-10}	15.3	3350.7	0.89
F3	4.35×10^{-10}	12.2	3782	0.84
F4	4.01×10^{-10}	17.9	12367.11	0.98
F5	3.99×10^{-10}	13.2	6336	0.83
F6	3.49×10^{-10}	12.1	2904	0.81
F7	4.69×10^{-10}	13.1	4309.9	0.89
F8	4.86×10^{-10}	13.3	4134.97	0.88

Equilibrium constant in phase I (H_I) and quilibrium constant in phase II (H_d)

Table 2 also shows the equilibrium constant values of H_d and H_I representing the inner and outer wall equilibrium constants, respectively. The H_d value was smaller than the H_I value because the outer layer walls were in direct contact with the phosphate buffer and absorbed it so that the microcapsule walls were softer than the inner walls. The diffusion coefficient is the rate at which one material can diffuse into another material. The diffusion coefficient or diffusivity depends on various factors such as molecular size, pressure, temperature, viscosity, surface area, etc. Table 2 shows that the increase in the chitosan and TPP concentrations decreased the diffusion coefficient and had a direct effect on the decrease in the release rate. The higher the density of the microcapsule wall, the lower the value of the diffusion coefficient would be due to the tighter molecular structure that inhibited the release rate of the red ginger oleoresin.

4. Conclusion

The preparation of the red ginger oleoresin microcapsules with chitosan wall material which was cross-linked with sodium TPP has been successful. Variation of the concentrations of chitosan and TPP solutions, and also pH level affected the cumulative amount of the red ginger oleoresin released from the microcapsules. The cumulative release percentage decreased with an increase in the concentrations of chitosan and TPP solutions. Meanwhile, the effect of pH resulted in an irregular cumulative release percentage. The increase in the concentration of chitosan and sodium tripolyphosphate also decreased the value of the diffusion coefficient and affected the rate of diffusion. The decrease in the cumulative release was caused by the lower diffusion rate of the ginger red oleoresin through the microcapsule walls, which was indicated by the low diffusivity coefficient. Based on the results of this study, the best formulation for preparing the red ginger oleoresin microcapsules based on the

mathematical modeling (with R^2 of 0.98) was with 4% (w/v) concentration of chitosan, 5% (w/v) concentration of sodium tripolyphosphate, and a pH of 5.

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