Research Article

Assessment of the Role of Ginsenoside Rb1 Active Substance in Alginate/Chitosan/Lovastatin Composite Films

Thi-Loc Thach,¹ Thuy-Chinh Nguyen¹,² An-Quan Vo,² Minh-Thanh Do¹,² Quang-Tung Nguyen,³ Tuan-Anh Nguyen¹,³ Long-Giang Bach¹,⁴ and Hoang Thai¹,⁵

¹Vinh University, 182 Le Duan, Vinh City, Nghe An Province, 460000, Vietnam

²Institute for Tropical Technology, Vietnam Academy of Science and Technology, 18, Hoang Quoc Viet, Cau Giay, Ha Noi, 100000, Vietnam

³Hanoi University of Industry, Minh Khai Commune, Tu Liem, Ha Noi, 100000, Vietnam

⁴NTT Institute of High Technology, Nguyen Tat Thanh University, 300A Nguyen Tat Thanh, District 4, Ho Chi Minh City, 700000, Vietnam

⁵Graduate University of Science and Technology, Vietnam Academy of Science and Technology, 18 Hoang Quoc Viet, Cau Giay, Ha Noi, 100000, Vietnam

Correspondence should be addressed to Thuy-Chinh Nguyen; thuychinhhn@gmail.com and Hoang Thai; hoangth@itt.vast.vn

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This article reports the effect of ginsenoside Rb1 on some properties, morphology, and the drug release process of the chitosan (CS)/alginate (AG)/lovastatin (LOV) composite films prepared by a solution method using different contents of ginsenoside Rb1. The ratio of AG/CS was fixed at 4/1 (wt./wt.%), the content of LOV was 10 wt.%, and the content of ginsenoside Rb1 was changed from 1 to 5 wt.%. The results of scanning electron microscopy and Fourier transform infrared spectroscopy analysis showed that the composite films have a heterogeneous structure and the ginsenoside Rb1 content influenced on the structure of composite films. The presence of ginsenoside Rb1 did not influence on the melting temperature of these films but caused a significant difference in the melting enthalpy of the films. The ginsenoside Rb1 was also contributed positively on the LOV release from these films in different pH buffer solutions. The LOV release process from these films included two stages (fast/burst release and slow/control release). It was increased remarkably by the synergic effect of LOV and ginsenoside Rb1 in the drug release process. From the obtained results, we suggested that ginsenoside Rb1 plays an important role not only in the enhancement of health and immunity as general but also as an efficient agent in control of the LOV size as well as LOV drug release from the composite films.

1. Introduction

Panax notoginsengs as well as ginsengs are herbaceous plants whose root is used as a medicine to make the most rare and nutritious Oriental medicine. They not only have been widely applied in Asian countries such as Vietnam, China, Japan, and Korea but also have been used in pharmaceuticals in the US and Russia for the few past decades. Ginsenoside Rb1 which was found in the ginseng is used as a drug (inhibit the chemoinvasion in blood vessels) to reduce the blood glucose levels, prevent the fat decomposition, and stimulate the insulin production. In addition, ginsenoside Rb1 has great

effects in the blood circulation, prevention of the blood fat disease, or atherosclerotic effect on the health. In particular, ginsenoside Rb1 could act directly on the central nervous system, help to reduce extremes of the excitement, inhibit cancer cells, regulate nerves, and help to improve our memory [1].

Lovastatin (LOV) is a naturally occurring fermentation compound discovered in 1970. It is found in oyster mushrooms and red yeast rice [2]. The LOV is a competitive inhibitor of hydroxyl methyl glutaryl coenzyme (HMG-CoA), prevents HMG-CoA conversion into mevalonate—a precursor of cholesterol. The LOV also inhibits the cholesterol biosynthesis, decreases cholesterol in liver cells, and rouses the

synthesis of LDL (low-density lipoproteins) receptors, thus leading to the increase in the transport of LDL in the blood and the decrease in the plasma cholesterol levels [3, 4]. The main application of LOV is to treat the blood lipid disorders and to prevent the cardiovascular diseases [5]. However, the limitation of LOV is the low half-life (3–4 hours) and LOV undergoes extensive first-pass metabolism so the bioavailability of LOV in use is low and variable. Therefore, using biopolymers as LOV carriers to improve the bioavailability and stability of LOV as well as control of LOV release is attractive to scientists. On the other hand, preparation of the nanocomposites based on the polymer matrix has been a new approach for the model medicine technology [6].

Chitosan is a deacetylated derivation of chitin, which was scientifically named as poly-(1,4)-2-amino-2-deoxy- β -D glucopyranose or poly-(1,4)-2-amino-2-deoxy- β -D-glucose. Chitosan (CS) is a sort of polysaccharide that is plentiful in shells of crustaceans like shrimps and crabs. The unique combination of a number of physicochemical properties, such as biocompatibility, high reactivity, biodegradability, immunomodulatory activity, bacteriostatic, selectivity, and excellent sorption capacity, created the applications of chitosan [7] in food industry, agriculture, biology, paper industry, etc. [8, 9]. In biomedicine and pharmaceutical, CS has been used as a film to heal wounds and regenerate bone tissue [2, 10]. In particular, CS is also an important ingredient in glucosamine preparation [9]. However, the disadvantage of CS is it is very sensitive to the moisture, which limits the use of this natural polymer. To overcome its disadvantage, combination of CS with relatively stable moisture-resistant polymers such as alginate (AG) [9–11], polylactic acid [12, 13], polyethylene glycol fumarate [14], poly (vinyl alcohol) [15], and glucomannan [16] is a suitable solution. Among the above biopolymers, AG is a potential candidate for the combination with CS thanks to the reaction between AG and protonated CS to form the polyelectrolyte complex [17]. On the other hand, the AG can be biodegradable and completely safe in human and animal tests. The CS-AG system gives advantages for the encapsulation as well as transportation of drugs. Especially, the amazing long-term mechanical property and viability provided by the CS film are of great advantage when studying this system for *in vivo* cell-based therapy [18].

In our previous study, we prepared and investigated the characteristics, morphology of the AG/CS/LOV composite films, and ability to control *in vitro* drug release from these composite films [8, 19–22]. The results indicated that the AG/CS ratio of 4/1 and the LOV content of 10 wt.% (compare with the mass total of AG and CS) were most suitable for preparation of the AG/CS/LOV composite film. This film had higher drug loading ability, thermal stability, and better control drug release in comparison with the films which use a different AG/CS ratio and LOV content [19]. Although the compatibilizers were used to improve the compatibility of components in AG/CS/LOV composite films, LOV bars in the composite films are still quite large in size [8, 19, 20, 22] and the LOV release process from the composites in buffer solutions was difficult to control in the early hours of testing [19, 21]. The question here is how to improve the LOV dispersion in AG/CS blend and control the drug

release from the AG/CS/LOV films better. In another study, we recognized that ginsenoside Rb1 could disperse evenly in AG/CS blend [19]. Recently, the AC82R5Lx films which had ginsenoside Rb1 content fixed at 5 wt.% and LOV content varied have been prepared by a solution method. The results showed that LOV and ginsenoside Rb1 had a synergistic effect which influenced positively on the morphology, properties, and drug release ability of these films [23]. Therefore, in this work, the ginsenoside Rb1 was chosen as a stable agent and compatibilizer for the AG/CS/LOV system. The ginsenoside Rb1 content in the composite films was varied from 1 to 5 wt.% to find the most suitable weight of ginsenoside Rb1. We expect that the combination of ginsenoside Rb1 and LOV in AG/CS blend will not only reduce the cholesterol concentration for treatment of cardiovascular diseases for patients but also increase in the immunity, strengthening the health of ginsenoside Rb1 thanks to the synergistic effect of ginsenoside Rb1 and LOV.

2. Experimental

2.1. Materials. Sodium alginate (AG) is in white powder, viscosity of 300–500 mPa·s; chitosan (CS) is in powder with a deacetylation degree > 75–85%, polymer density index of 1.61×10^5 Da; and lovastatin (LOV) purity $\geq 98.0\%$ were provided by Sigma-Aldrich Co., ginsenoside Rb1 (Rb1) (extracted from *Panax pseudoginseng* by the National Institute of Medicinal Materials, Vietnam). Ethanol, acetic acid 1%, and CaCl_2 , were analytical grade chemicals and were used as received.

2.2. Synthesis of AC82L10Rx Composite Films. The solution method was used to prepare the AG/CS/LOV/ginsenoside Rb1x composite films (abbreviation AC82L10Rx) [8]. Firstly, AG and CS with calculated weights were dissolved in distilled water and 1% acetic acid solution, respectively, whereas LOV and ginsenoside Rb1 were dissolved in ethanol solvent (drug solution). Next, the drug solution was dropped into the solution of AG which was added with CaCl_2 and stirred on a magnetic stirrer. After that, the CS solution was dropped to mixture of AG and drug, and the above mixture was ultrasonicated three times for 15 minutes. Then, the composite mixture was poured into the petri dish and the solvent has naturally evaporated for 24 hours. Finally, film production was dried at 50°C for 8 hours. The mass of AG, CS, and LOV was fixed at 0.8 grams, 0.2 grams, and 0.01 grams, respectively. The mass of ginsenoside Rb1 was changed: 0 gram, 0.001 grams, 0.003 grams, and 0.005 grams. Abbreviations of the samples are AC82L10R0, AC82L10R1, AC82L10R3, and AC82L10R5, respectively.

2.3. Characterization. Fourier transform infrared spectroscopy (FTIR) spectra of LOV, ginsenoside Rb1, AG/CS blend, and AC82L10Rx composite films were recorded on a Nicolet/Nexus 670 spectrometer (USA) with a wavenumber ranging from 400 to 4000 cm^{-1} , at room temperature by 32 scans with 8 cm^{-1} resolution.

Morphology of the LOV, ginsenoside Rb1, and obtained AC82L10Rx composite films coated by platinum was

FIGURE 1: FTIR spectra of AC82L10Rx composite films.

TABLE 1: Position of peaks for main characteristic groups in AC82L10Rx composite films.

Samples Vibrations	Wavenumber (cm ⁻¹)			
	AC82L10R0	AC82L10R1	AC82L10R3	AC82L10R5
$\nu_{\text{NH}_2\text{-OH}}$	3386.44	3378.73	3332.73	3324.73
ν_{CH}	2931.32	2931.32	2931.32	2931.32
$\nu_{\text{NH}_3\text{OC}}$	2159.92	2175.35	2167.63	2167.63
$\nu_{\text{C=O}}$	1604.51	1604.51	1604.51	1604.51
$\delta_{\text{-NH}_2}$	1411.66	1411.66	1411.66	1411.66
$\nu_{\text{C-O-C}}$	1041.39	1033.68	1033.68	1033.68

conducted using a S-4800 FESEM instrument (Hitachi, Japan). Thermal property of the LOV, ginsenoside Rb1, and AC82L10Rx composite films was surveyed on a DSC-60 thermogravimetric analyzer (Shimadzu) in nitrogen atmosphere from room temperature to 400°C at a heating rate of 10°C/min.

2.4. Drug Release and Kinetic Studies. Study on simulation of drug release in some simulated fluids similar to typical digestive organs in the human body such as

- (i) pH = 2: corresponding to the lower portion of the stomach where drugs are staying from 1 to 3 hours
- (ii) pH = 4.5: corresponding to the upper portion of the stomach where drugs are staying from 30 to 60 minutes; corresponding to the small intestine where drugs are staying from 1 to 5 hours and the large intestine where drugs are staying for 10 hours
- (iii) pH = 6.8: corresponding to the colon region in the body where drugs are staying from 10 to 15 hours
- (iv) pH = 7.4: corresponding to the duodenum region in the body where the drugs are staying from 30 to 60 minutes

The drug release process of LOV and Rb1 was performed as follows: 0.015 grams of the composite films were immersed in 200 ml of buffer solutions. The solutions were stirred at 37°C at 120 rpm and after every 1 hour, 5 ml of the sample solution was withdrawn to monitor the release of LOV and Rb1 with a UV-Vis spectrophotometer. At the same time, 5 ml of fresh buffer solution was added to maintain constant volume of 200 ml. The experiment was performed in 32 hours and done in triplicate. The percentage of release drug was determined by the equations:

$$\text{LOV release [\%]} = \frac{C_t}{C_0} \times 100 \quad (1)$$

$$\text{Rb1 release (\%)} = \frac{C'_t}{C'_0} \times 100, \quad (2)$$

where C_0 and C_t represent the amount of loaded drug and amount of released drug at the initial time and testing time, respectively.

2.5. Drug Release Kinetic Study. The drug release mechanism from the polymer matrix usually is calculated according to some popular kinetics as depicted below [24–26]:

Zero-order kinetic (ZO):

$$W_t = W_0 + k_1 t, \quad (3)$$

First-order kinetic (FO):

$$\log C_t = \log C_0 - \left(\frac{k_2 t}{2.303} \right), \quad (4)$$

Hixson-Crowell's cube-root equation (HCW):

$$(100 - W) \left(\frac{1}{3} \right) = 100^{1/3} - k_3 t, \quad (5)$$

Higuchi's square root of time equation (diffusion model) (HG):

$$W_t = k_4 t, \quad (6)$$

Power law equation or Korsmeyer-Peppas model (diffusion/relaxation model) (KMP):

$$\left(\frac{M_t}{M_\infty} \right) = k_5 t^n, \quad (7)$$

where C_0 and C_t is drug concentration at the initial time and testing time, respectively; W_0 and W_t is the weight of the drug at the initial time and testing time, respectively; k is the drug release constant; M_t/M_∞ is the fractional drug release into dissolution medium; and n is the diffusional constant that characterizes the mechanism of drug release transport.

FIGURE 2: FESEM images of AC82L10Rx composite films.

FIGURE 3: DSC diagrams of AC82L10Rx composite films.

To find the most suitable kinetic model for the release process of LOV and ginsenoside Rb1 from the AC82L10Rx composite films, the data of drug release content were calculated according to Equation (3)–Equation (7).

3. Results and Discussion

3.1. FTIR Spectra. Figure 1 presents the FTIR spectra of AC82L10Rx composite films while the FTIR spectra of CS, AG, LOV, and Rb1 are shown in our previous articles [8, 17, 19–22]; therefore, they were not presented here. From Figure 1, it can be seen that the characteristic peaks of AG, CS, LOV, and ginsenoside Rb1 appeared in the FTIR spectra of AC82L10Rx composite films. For example,

TABLE 2: DSC parameters obtained from DSC diagrams of AG, CS, LOV, Rb1, and AC82L10Rx composite films.

Samples	Endothermic DSC		Exothermic DSC peak (°C)
	Temperature (°C)	Enthalpy (J/g)	
AG	119.7	358.6	240–260°C
CS	106.8	130.6	—
LOV	174.6	—	—
Rb1	98.9	186.7	—
AC82L10R0	134.05 181.64	444.59 —	240.62
AC82L10R1	133.75 178.82	401.57 —	241.42
AC82L10R3	130.05 180.71	415.77 —	239.67
AC82L10R5	133.49 178.39	383.04 —	243.86

the peaks at 2931 cm^{-1} and 1604 cm^{-1} were contributed $-\text{C}-\text{H}$ and $-\text{C}=\text{O}$ groups, respectively [7]. The peak corresponding to stretching vibration of the $\text{C}-\text{O}-\text{C}$ group was featured at 1033 cm^{-1} ; the NH_2 group was assigned at 1411 cm^{-1} . The saccharide ring structure was found at 779 cm^{-1} and 948 cm^{-1} ; a broad band from 3200 cm^{-1} to 3500 cm^{-1} was assigned to the stretching vibration of the hydroxyl group [10]. The peaks of the $-\text{NH}_3\text{OC}$ group which were formed by the electrostatic interaction between the protonated amino groups of CS and the carboxylate groups of AG dissociated to COO^- groups were located at 2167 cm^{-1} and 2360 cm^{-1} [27]. With the addition of ginsenoside Rb1 into the AG/CS/LOV composite films, it was recognized to have a strong shift in NH_3OC and the hydroxyl group in the FTIR spectra of CS, AG, LOV,

FIGURE 4: Content of LOV released from AC82L10Rx composite films in pH 2 and pH 4.5 buffers.

TABLE 3: The content of LOV and Rb1 released from AC82L10Rx composite films in pH 2 solution.

Time	Content of released LOV (%)				Content of released Rb1 (%)		
	AC82L10	AC82L10R1	AC82L10R3	AC82L10R5	AC82L10R1	AC82L10R3	AC82L10R5
0	0	0	0	0	0	0	0
1	47.08	21.41	13.55	20.06	21.27	11.95	21.48
2	50.30	42.25	34.50	46.79	31.03	24.72	33.26
3	53.57	58.64	64.27	57.58	44.10	50.55	40.98
4	56.01	61.35	75.40	67.61	60.58	66.25	52.27
5	59.33	71.16	78.59	72.67	65.35	78.68	59.60
6	64.43	84.24	84.18	74.68	73.25	82.65	68.36
7	68.79	90.59	91.30	79.83	78.30	85.24	77.81
8	72.36	92.01	94.76	80.89	83.44	88.56	82.80
9	75.98	94.41	97.23	87.15	85.63	90.88	92.99
10	78.77	94.79	97.65	92.48	84.77	92.17	95.60
11	79.82	95.11	98.01	93.73	86.87	93.42	96.95
12	82.52	95.63	98.10	94.29	87.44	94.14	97.36
16	84.35	96.38	98.30	95.37	87.75	94.65	98.21
20	84.39	97.41	98.33	96.15	87.99	95.33	98.77
24	84.31	97.70	98.49	96.79	88.32	96.27	99.28
28	84.09	98.24	98.80	96.95	88.91	96.46	99.36
32	84.61	98.83	98.84	97.60	89.31	96.89	99.51

ginsenoside Rb1, and AC82L10Rx composite films (Table 1). This proved that the presence of ginsenoside Rb1 could lead to the stronger electrostatic interaction between AG and CS as well as increase the intermolecular hydrogen bond between ginsenoside Rb1, LOV, AG, and CS [28].

3.2. Morphology. Figure 2 presents the FESEM images of the AC82L10Rx composite films at different contents of ginsenoside Rb1. It can be seen that the presence of ginsenoside Rb1 in the composite film helped the dispersion of LOV to become more evenly in the AG/CS matrix and the size of LOV bars were significantly decreased. For instance, LOV

had a bar and rod shape with a size in the range from 30 μm to 40 μm in the AG/CS matrix (AC82L10R0) and LOV size was reduced to 5 μm to 10 μm when adding 5 wt.% of ginsenoside Rb1. This result exhibited that ginsenoside Rb1 can play an important role in auxiliary dispersion and as a compatibilizer in the AC82L10Rx composite films thanks to the increase in intermolecular hydrogen bond of the components in this film. As a result, the agglomeration of LOV in the composite films was decreased.

3.3. Thermal Behavior Analysis. The DSC diagrams of AC82 and AC82L10Rx composite films with different ginsenoside

TABLE 4: The content of LOV and Rb1 released from AC82L10Rx composite films in pH 4.5 solution.

Time	Content of released LOV (%)				Content of released Rb1 (%)		
	AC82L10	AC82L10R1	AC82L10R3	AC82L10R5	AC82L10R1	AC82L10R3	AC82L10R5
0	0	0	0	0	0	0	0
1	17.99	16.20	15.19	24.90	16.34	21.26	15.27
2	29.99	29.89	28.71	31.61	36.81	30.83	42.41
3	42.76	42.85	40.04	52.86	45.43	40.64	50.63
4	51.34	52.74	49.33	57.83	56.10	50.10	58.95
5	61.32	62.00	57.68	68.75	67.86	64.83	66.38
6	69.15	69.00	63.18	74.61	79.85	72.60	76.31
7	77.85	77.68	73.15	80.77	84.86	80.98	83.69
8	81.43	82.32	79.96	84.31	89.51	91.52	89.73
9	83.97	87.28	84.32	85.94	93.05	92.70	92.06
10	87.56	91.85	87.81	87.88	94.63	93.87	94.21
11	90.86	93.25	90.88	88.11	95.18	93.70	95.25
12	91.36	94.16	92.17	88.86	95.68	94.21	95.68
16	93.07	96.19	95.58	92.82	96.85	95.76	96.24
20	94.93	97.63	97.01	93.92	97.54	94.94	97.21
24	95.82	98.58	97.72	94.69	98.45	96.35	97.54
28	96.62	99.03	98.38	95.00	98.60	97.49	98.03
32	96.93	99.25	99.11	95.38	99.17	97.99	98.41

TABLE 5: The content of LOV and Rb1 released from AC82L10Rx composite films in pH 6.8 solution.

Time	Content of released LOV (%)				Content of released Rb1 (%)		
	AC82L10	AC82L10R1	AC82L10R3	AC82L10R5	AC82L10R1	AC82L10R3	AC82L10R5
0	0	0	0	0	0	0	0
1	23.12	23.97	21.09	16.79	21.29	19.42	28.88
2	36.43	36.58	30.10	30.86	43.71	27.14	37.63
3	47.31	47.80	43.82	49.02	57.03	32.42	50.45
4	59.27	60.82	52.62	54.01	67.20	40.71	57.20
5	68.28	68.91	65.59	63.02	75.94	48.94	63.93
6	76.43	77.24	71.76	74.44	83.17	57.52	70.01
7	83.05	84.31	81.16	81.09	87.57	67.91	80.73
8	87.17	88.14	89.82	86.73	90.76	80.15	86.68
9	90.35	91.04	92.10	91.20	91.00	88.37	89.83
10	91.34	93.40	93.33	93.73	92.40	92.16	91.87
11	92.78	94.68	93.88	94.89	92.59	93.10	92.67
12	93.60	95.20	94.79	95.99	93.38	93.73	93.34
16	95.03	96.73	96.83	97.11	96.08	95.43	95.62
20	95.85	97.89	97.52	98.16	97.90	96.40	97.36
24	96.24	98.04	98.44	98.57	98.43	97.56	97.94
28	96.95	99.16	98.78	98.78	98.49	98.00	98.99
32	97.23	99.51	99.28	99.01	98.90	98.77	99.90

Rb1 contents are shown in Figure 3. In our previous literature, the dehydration process of chitosan occurred at 106.8°C [19]. There is an endothermic peak at nearly 100°C which was evidenced for the dehydration of AG. The decomposition of AG was determined by an exothermic peak at 240-260°C [29]. Two endothermic peaks corresponding to

the loss of adsorbed water and the melting point of the LOV were placed at 174.6°C and 264.7°C, respectively [21, 30]. The melting point of ginsenoside Rb1 was observed at 99°C [20, 31].

From data in Table 2, the melting temperature of AC82L10R0 composite film was significantly lower than

TABLE 6: The content of LOV and Rb1 released from AC82L10Rx composite films in pH 7.4 solution.

Time	Content of released LOV (%)				Content of released Rb1 (%)		
	AC82L10	AC82L10R1	AC82L10R3	AC82L10R5	AC82L10R1	AC82L10R3	AC82L10R5
0	0	0	0	0	0	0	0
1	52.80	43.53	34.73	16.62	42.67	44.05	38.38
2	55.44	52.35	52.95	24.07	65.29	75.93	51.16
3	59.73	78.27	60.42	38.58	77.88	81.72	64.84
4	62.45	84.29	73.00	58.55	85.46	85.84	78.04
5	66.83	84.04	78.91	69.18	91.06	90.01	89.34
6	71.28	88.59	87.20	81.63	95.69	92.47	94.51
7	77.47	89.45	91.46	91.29	96.65	93.14	94.97
8	82.17	93.83	93.69	94.37	96.76	95.54	95.90
9	86.96	94.53	95.72	96.89	96.80	96.52	96.99
10	90.18	94.61	96.02	97.85	97.04	96.74	97.30
11	91.74	94.99	96.64	97.99	97.25	97.08	97.96
12	92.58	95.13	96.87	98.00	97.38	97.12	98.58
16	92.65	96.79	97.39	98.45	98.06	97.53	98.82
20	92.90	97.14	97.72	98.70	98.45	98.12	98.90
24	92.82	98.21	98.38	99.04	98.83	98.72	99.13
28	92.91	98.31	98.85	99.14	98.95	98.88	99.19
32	93.05	98.50	98.91	99.14	99.81	98.98	99.19

AG, CS, and LOV [16]. The AC82L10R0 film has two endothermic peaks at close to 130°C and 180°C characterized for the dehydration and melting of the polymer matrix. The decomposition of the biopolymers took place which was represented by an exothermic peak at close 240°C similar to the decomposition of AG.

When adding ginsenoside Rb1 into the AC82L10R0 film, the melting temperature of these AC82L10Rx composite films was fixed but their melting enthalpy had a great change. The decrease in the melting enthalpy with the increase in the ginsenoside Rb1 content in the composite films can confirm the reduction in the relative crystal degree of the composite films. It can affect on the drug release as discussed below.

3.4. Drug Release Study. Figure 4 displays that the content of LOV was released from the AC82L10Rx composite films with the various contents of ginsenoside Rb1 from 0 to 5% in pH 2 (a) and pH 4.5 (b) buffer solutions. Tables 3–6 list the LOV content released from the AC82L10Rx composite films in different pH buffer solutions. It can be clearly seen that the ginsenoside Rb1 content added into the AC82L10R0 composite film affected remarkably the LOV release from these films. For all investigated pH buffer solutions, the AC82L10Rx composite films exhibited the drug release according to 2 steps: rapid release stage at the first time of testing and slow release stage (as controlled) in the following time. This was similar to the drug release process from AG/CS blends which are loading some other drugs like oxaliplatin, verapamil, or antineoplastic drugs [32–34] as well as novel extended-release formulation of LOV [26]. In pH 2 solution, after 12 hours of testing, the LOV release content from the AC82L10R0 composite film only reached to 82.52% while LOV released from films containing ginseno-

side Rb1 was much more than 94.00%. After 32 hours of testing, the LOV content release from the AC82L10R0 and AC82L10Rx composite films had a maximum value of 84.61% and ca. 98%, respectively. When the content of ginsenoside Rb1 in the films was increased, the percentage of LOV release was slightly decreased after 32 hours of testing. For example, in pH 4.5 solution, the LOV content was released from the AC82L10R1 composite film has reached to 99.25% whereas the LOV content released from AC82L10R3 and AC82L10R5 composite films has reached to 95.11 wt.% and 99.38%, respectively. This means that ginsenoside Rb1 had a strong effect on the LOV release from the AG/CS composite films and vice versa. It may be explained by a strong interaction between the LOV and ginsenoside Rb1, between drugs and the polymer matrix to create a better drug release control. Thus, the combination of LOV and ginsenoside Rb1 could create a positive impact to control the drug release as a synergistic effectiveness between the LOV and ginsenoside Rb1.

In general, the content of LOV and Rb1 released from the composite films in medium solution was greater and more stable than that in acidic solution. For instant, after 32 hours of immersing, the LOV content released from the AC82L10Rx films in pH 2 solution containing various Rb1 contents was 84.81–98.84% while the LOV released from the AC82L10Rx films in pH 7.4 solution has reached 94.00–99.00%. Besides, the Rb1 content released from the AC82L10R1 in pH 7.4 solution was nearly 100% whereas the content of Rb1 released from AC82L10R1 in pH 2 solution was only 89.31%. This can be explained by the NH_2 group in CS that was protonated by the proton in the acidic environment, leading to the formation of a proton layer on the surface of the composite films, causing a decrease of diffusion ability of drug into the pH solution. These results were

TABLE 7: Regression coefficient (R^2) and release constant (k) obtained from kinetic equations reflecting LOV release from the AC82L10Rx films in different pH solutions.

pH	Samples	Step	ZO		FO		HG		HW		KMP		
			k	R^2	k	R^2	k	R^2	k	R^2	k	n	R^2
2	AC82L10R0	Fast	4.10^{-4}	0.99	-0.03	0.99	1.10^{-3}	0.96	-4.10^{-4}	0.99	0.32	0.1	0.98
		Slow	2.10^{-5}	0.8	1.10^{-3}	0.79	2.10^{-5}	0.82	-6.10^{-6}	0.90	0.76	0.08	0.96
	AC82L10R1	Fast	1.10^{-4}	0.95	-0.16	0.78	5.10^{-4}	0.98	-4.10^{-5}	0.95	0.24	0.69	0.97
		Slow	3.10^{-6}	0.97	6.10^{-3}	0.96	2.10^{-5}	0.99	-9.10^{-7}	0.97	0.87	0.04	0.99
	AC82L10R3	Fast	1.10^{-4}	0.86	-0.21	0.66	6.10^{-4}	0.94	-5.10^{-5}	0.86	0.17	0.91	0.92
		Slow	8.10^{-7}	0.85	0.08	0.98	7.10^{-6}	0.88	-3.10^{-7}	0.85	0.95	0.01	0.91
	AC82L10R5	Fast	9.10^{-5}	0.84	-0.12	0.59	4.10^{-4}	0.93	-3.10^{-5}	0.84	0.26	0.60	0.90
		Slow	3.10^{-6}	0.89	5.10^{-3}	0.98	2.10^{-5}	0.93	-9.10^{-7}	0.89	0.84	0.04	0.96
4.5	AC82L10R0	Fast	1.10^{-4}	0.96	-0.14	0.81	5.10^{-3}	0.99	-4.10^{-5}	0.96	0.35	0.70	0.99
		Slow	4.10^{-6}	0.96	4.10^{-3}	0.94	4.10^{-5}	0.97	1.10^{-6}	0.95	0.81	0.06	0.99
	AC82L10R1	Fast	1.10^{-4}	0.97	-0.17	0.83	5.10^{-3}	0.99	-4.10^{-5}	0.97	0.17	0.77	0.99
		Slow	4.10^{-6}	0.89	5.10^{-3}	0.96	4.10^{-5}	0.93	-1.10^{-6}	0.89	0.80	0.07	0.96
	AC82L10R3	Fast	1.10^{-4}	0.98	-0.152	0.82	5.10^{-3}	0.99	-4.10^{-5}	0.97	0.16	0.77	0.99
		Slow	5.10^{-6}	0.88	3.10^{-3}	0.83	4.10^{-5}	0.92	-2.10^{-6}	0.88	0.72	0.09	0.91
	AC82L10R5	Fast	1.10^{-4}	0.96	-0.18	0.82	5.10^{-3}	0.99	-5.10^{-5}	0.96	0.22	0.74	0.98
		Slow	2.10^{-6}	0.91	7.10^{-3}	0.95	2.10^{-5}	0.94	-8.10^{-7}	0.91	0.88	0.04	0.97
6.8	AC82L10R0	Fast	1.10^{-4}	0.98	-0.16	0.88	5.10^{-4}	0.99	-4.10^{-5}	0.98	0.28	0.65	0.99
		Slow	4.10^{-6}	0.86	6.10^{-3}	0.98	3.10^{-5}	0.90	-1.10^{-6}	0.86	0.69	0.05	0.93
	AC82L10R1	Fast	1.10^{-4}	0.96	-0.14	0.84	5.10^{-4}	0.99	-4.10^{-5}	0.96	0.24	0.63	0.99
		Slow	3.10^{-6}	0.92	5.10^{-3}	0.97	3.10^{-5}	0.95	-1.10^{-6}	0.92	0.83	0.05	0.97
	AC82L10R3	Fast	1.10^{-4}	0.99	-0.18	0.93	5.10^{-4}	0.99	-4.10^{-5}	0.99	0.19	0.71	0.99
		Slow	4.10^{-6}	0.89	6.10^{-3}	0.95	3.10^{-5}	0.93	-1.10^{-6}	0.89	0.82	0.06	0.96
	AC82L10R5	Fast	1.10^{-4}	0.97	-0.19	0.81	5.10^{-4}	0.99	-4.10^{-5}	0.97	0.18	0.79	0.98
		Slow	3.10^{-6}	0.83	6.10^{-3}	0.99	3.10^{-5}	0.88	-9.10^{-7}	0.83	0.86	0.04	0.92
7.4	AC82L10R0	Fast	6.10^{-6}	0.86	-0.3	0.99	8.10^{-4}	0.95	-2.10^{-4}	0.78	0.12	0.05	0.96
		Slow	1.10^{-5}	0.99	5.10^{-3}	0.99	9.10^{-5}	0.98	-7.10^{-7}	0.92	0.65	0.01	0.88
	AC82L10R1	Fast	1.10^{-4}	0.80	-0.09	0.66	4.10^{-4}	0.88	-3.10^{-5}	0.80	0.44	0.40	0.91
		Slow	3.10^{-6}	0.93	6.10^{-3}	0.93	2.10^{-5}	0.96	-9.10^{-7}	0.93	0.87	0.04	0.98
	AC82L10R3	Fast	1.10^{-4}	0.95	-0.11	0.82	4.10^{-4}	0.99	-4.10^{-5}	0.95	0.36	0.48	0.99
		Slow	2.10^{-6}	0.95	7.10^{-3}	0.97	2.10^{-5}	0.97	-6.10^{-7}	0.95	0.91	0.03	0.98
	AC82L10R5	Fast	2.10^{-4}	0.97	-0.32	0.76	7.10^{-4}	0.99	-6.10^{-5}	0.97	0.08	0.29	0.96
		Slow	1.10^{-6}	0.80	7.10^{-3}	0.98	9.10^{-6}	0.85	-4.10^{-7}	0.80	0.94	0.02	0.88

complied with the LOV content released from the composite materials in some literatures [31, 35].

In comparison to LOV, the Rb1 content released from the composite films was more stable and better at every buffer solution. After 32 hours of survey, the ginsenoside Rb1 content released from all samples was over 98%. This showed that ginsenoside Rb1 associated with the AG/CS polymer blend weaker than LOV with the AG/CS polymer blend; therefore, it is easily released from the composite films. Almost all the samples had a prolonged half-life compared with that of LOV and Rb1 in previous studies [8, 19–22], which indicated that the effectiveness of the drug release was increased when LOV was combined with ginsenoside Rb1 in the AG/CS polymer blend. In pH2 solution, the released ginsenoside Rb1 content was increased with the

increase of its initial concentration in the sample, but in the different pH solution, the ginsenoside Rb1 content released from the AC82L10R3 composite film was always lower than that from the AC82L10R1 and AC82L10R5 composite films at the same testing time. This may express that at the Rb1 content of 3 wt.%, the structure of the film was the closest; the links of the drug to the polymers contribute effectively to control the release process of ginsenoside Rb1.

3.5. Drug Release Kinetic Study. Analyzing the release of pharmaceuticals from the composite polymer is described by the liberal kinetic equation. A range of kinetic models involving the process of drug release are selected from the most important mathematical equations. However, the mechanism of drug release depends on the dose, pH, and

TABLE 8: Regression coefficient (R^2) and release constant (k) obtained from kinetic equations reflecting Rb1 release from the ACLR films in buffer solutions.

pH	Samples	Step	ZO		FO		HG		HGW		KMP		
			k	R^2	k	R^2	k	R^2	k	R^2	k	n	R^2
2	AC82L10R1	Fast	1.10^{-5}	0.91	-0.12	0.76	4.10^{-5}	0.97	-3.10^{-6}	0.91	0.22	0.64	0.98
		Slow	1.10^{-7}	0.98	5.10^{-3}	0.99	1.10^{-6}	0.98	-5.10^{-8}	0.98	0.82	0.03	0.97
	AC82L10R3	Fast	3.10^{-5}	0.95	-0.21	0.99	1.10^{-4}	0.88	-1.10^{-5}	0.95	0.16	0.67	0.89
		Slow	9.10^{-7}	0.90	6.10^{-3}	0.95	7.10^{-6}	0.94	-3.10^{-7}	0.90	0.86	0.04	0.96
	AC82L10R5	Fast	4.10^{-5}	0.87	-0.2	0.68	2.10^{-4}	0.94	-1.10^{-5}	0.87	0.08	0.95	0.94
		Slow	8.10^{-7}	0.91	5.10^{-3}	0.99	7.10^{-6}	0.95	-3.10^{-7}	0.91	0.52	0.04	0.96
4.5	AC82L10R1	Fast	1.10^{-5}	0.97	-0.2	0.82	6.10^{-5}	0.99	-5.10^{-6}	0.97	0.18	0.80	0.98
		Slow	3.10^{-7}	0.88	7.10^{-3}	0.96	3.10^{-6}	0.92	-1.10^{-7}	0.89	0.85	0.04	0.95
	AC82L10R3	Fast	4.10^{-5}	0.99	-0.21	0.96	1.10^{-4}	0.98	-1.10^{-5}	0.99	0.20	0.70	0.99
		Slow	9.10^{-7}	0.89	7.10^{-3}	0.91	8.10^{-6}	0.91	-3.10^{-7}	0.89	0.85	0.04	0.92
	AC82L10R5	Fast	6.10^{-5}	0.95	-0.19	0.73	3.10^{-4}	0.98	-2.10^{-5}	0.95	0.19	0.78	0.94
		Slow	1.10^{-6}	0.79	7.10^{-3}	0.98	1.10^{-5}	0.83	-5.10^{-7}	0.79	0.85	0.04	0.86
6.8	AC82L10R1	Fast	2.10^{-5}	0.95	-0.21	0.83	6.10^{-5}	0.98	-5.10^{-6}	0.95	0.22	0.76	0.98
		Slow	5.10^{-7}	0.89	4.10^{-3}	0.84	4.10^{-6}	0.93	-2.10^{-7}	0.89	0.79	0.07	0.96
	AC82L10R3	Fast	3.10^{-5}	0.99	-0.17	0.98	1.10^{-4}	0.95	-1.10^{-5}	0.99	0.17	0.70	0.96
		Slow	1.10^{-6}	0.94	4.10^{-3}	0.95	1.10^{-5}	0.97	-4.10^{-7}	0.94	0.81	0.06	0.99
	AC82L10R5	Fast	5.10^{-5}	0.99	-0.12	0.91	2.10^{-4}	0.99	-2.10^{-5}	0.99	0.28	0.54	0.99
		Slow	2.10^{-6}	0.93	3.10^{-3}	0.86	2.10^{-5}	0.96	-7.10^{-7}	0.93	0.79	0.07	0.98
7.4	AC82L10R1	Fast	2.10^{-5}	0.92	-0.16	0.82	5.10^{-5}	0.97	-5.10^{-6}	0.92	0.45	0.47	0.98
		Slow	2.10^{-7}	0.94	9.10^{-3}	0.90	1.10^{-6}	0.97	-6.10^{-8}	0.94	0.92	0.02	0.97
	AC82L10R3	Fast	4.10^{-5}	0.77	-0.13	0.63	1.10^{-4}	0.85	-1.10^{-5}	0.77	0.49	0.43	0.88
		Slow	8.10^{-7}	0.69	8.10^{-3}	0.95	7.10^{-6}	0.76	-3.10^{-7}	0.69	0.86	0.04	0.82
	AC82L10R5	Fast	9.10^{-5}	0.99	-0.16	0.98	3.10^{-4}	0.99	-3.10^{-5}	0.99	0.50	0.40	0.99
		Slow	1.10^{-6}	0.65	9.10^{-3}	0.94	8.10^{-6}	0.74	-3.10^{-7}	0.65	0.92	0.03	0.82

properties of the polymer and drug. Parameters of the regression equation such as regression coefficient (R^2) and release constant (k) from zero kinetic models (ZO), first order (FO), Higuchi (HG), Hixson-Crowell (HCW), and Korsmeyer-Peppas (KMP) reflecting the release of LOV and Rb1 from the AG82L10Rx composite films in pH 2, pH 4.5, pH 6.8, and pH 7.4 solutions are listed in Tables 7 and 8.

From the results in Table 7, it can be seen that in four buffer solutions, both of rapid-release and slow-release stages of drugs do not comply with only one kinetic model because of the different dependencies of interactions between the components in the composite films and different dispersions of LOV into the polymer matrix. The regression coefficients (R^2) corresponding to the LOV fast-release stage from the AC82L10R0 composite film with different kinetic models were higher than that from the composite films containing Rb1. In contrast, the regression coefficient (R^2) corresponding to the LOV slow-release stage from the AC82L10R0 composite film was lower than that from the AC82L10Rx films.

The regression coefficients of the kinetic models that release drugs LOV and Rb1 from the composite films were relatively high and the Korsmeyer-Peppas (KMP) kinetic model was suitable with the R^2 value nearly 0.9. Observing the n values in the Kosmeyer equation, it is clearly recognized

that the slow-release process of both LOV and Rb1 followed the Fickian diffusion mechanism the Fick law ($n < 0.45$) while the fast-release process of LOV was non-Fickian transport in the acid environment. In the base environment, the LOV release process did not follow Fickian diffusion at both stages [26].

4. Conclusion

The chitosan (CS)/alginate (AG)/lovastatin (LOV) composite films using the ratios of AG/CS = 8/2, LOV content = 10 wt.%, and ginsenoside Rb1 content = 0, 1, 3, and 5 wt. % (AC82L10Rx composite films) were prepared successfully by solution method. The slight shift of characteristic peaks in FTIR spectra of AC82L10Rx composite films in comparison with the FTIR individual spectrum of AG, CS, LOV, and Rb1 can prove that they had interacted strongly to each other. The FESEM images illustrated the positive effect of Rb1 content added in the reduction in the size and agglomeration of LOV bars in the composite films. The melting temperature and melting althany of AC82L10Rx composite films were lower than those of the AC82L10 film. The process of LOV release from the AC82L10Rx composite films in various pH solutions includes 2 steps: rapid-release stage and slow-

release stage as controlled. The content of LOV released from the AC82L10Rx films was higher than that from the AC82L10R0 composite film. When increasing the Rb1 content, the ability of LOV release from the AC82L10Rx films was raised at the same pH solution. The regression coefficient and release constant obtained from kinetic equations reflecting the LOV release from the AC82L10Rx films in buffer solutions were relatively high. The KMP model had the highest regression coefficient which was always higher 0.9 for all of samples. In conclusion, the combination of LOV and Rb1 gave a synergistic effect for LOV and Rb1 release from the AC82L10Rx films.

Data Availability

The [DATA TYPE] data used to support the findings of this study are included within the supplementary information file(s).

Conflicts of Interest

There are no conflicts to declare.

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Supplementary Materials

Data of FTIR spectra of samples. (*Supplementary Materials*)

References

- [1] C.-Z. Wang, X. Luo, B. Zhang et al., "Notoginseng enhances anti-cancer effect of 5-fluorouracil on human colorectal cancer cells," *Cancer Chemotherapy and Pharmacology*, vol. 60, no. 1, pp. 69–79, 2007.
- [2] J. Liu, J. Zhang, Y. Shi, S. Grimsgaard, T. Alraek, and V. Fonnebo, "Chinese red yeast rice (*Monascus purpureus*) for primary hyperlipidemia: a meta-analysis of randomized controlled trials," *Chinese Medicine*, vol. 1, no. 1, pp. 4–11, 2006.
- [3] P. J. Neuvonen, J. T. Backman, and M. Niemi, "Pharmacokinetic comparison of the potential over-the-counter statins simvastatin, lovastatin, fluvastatin and pravastatin," *Clinical Pharmacokinetics*, vol. 47, no. 7, pp. 463–474, 2008.
- [4] N. Gunde-Cimerman and A. Cimerman, "Pleurotus Fruiting Bodies Contain the Inhibitor of 3-Hydroxy-3-Methylglutaryl-Coenzyme A Reductase—Lovastatin," *Experimental Mycology*, vol. 19, no. 1, pp. 1–6, 1995.
- [5] J. A. Tobert, "Lovastatin and beyond: the history of the HMG-CoA reductase inhibitors," *Nature Reviews Drug Discovery*, vol. 2, no. 7, pp. 517–526, 2003.
- [6] A. L. Volynskii and N. F. Bakeev, "A new approach to the preparation of nanocomposites based on a polymer matrix," *Polymer Science Series C*, vol. 53, no. 7, pp. 1203–1216, 2011.
- [7] R. Y. Milusheva and S. S. Rashidova, "Bioactive properties of nanochitosan *Bombyx mori*," *Polymer Science, Series C*, vol. 59, no. 1, pp. 29–34, 2017.
- [8] N. T. Chinh, T. T. Loc, L. D. Giang, N. T. T. Trang, T. T. Mai, and T. Hoang, "Effect of polyethylene oxide on properties of chitosan/alginate/lovastatin composites," *Vietnam Journal of Science and Technology*, vol. 54, no. 2A, pp. 156–162, 2018.
- [9] Y. Sun, J. Zhang, S. Wu, and S. Wang, "Preparation of d-glucosamine by hydrolysis of chitosan with chitosanase and β -d-glucosaminidase," *International Journal of Biological Macromolecules*, vol. 61, pp. 160–163, 2013.
- [10] N. T. N. Tu and P. T. Mai, "Application of chitosan in pharmaceutical chemistry," *Vietnam Pharmaceutical Journal*, vol. 3, pp. 14–15, 1995.
- [11] K. Y. Lee and D. J. Mooney, "Alginate: Properties and biomedical applications," *Progress in Polymer Science*, vol. 37, no. 1, pp. 106–126, 2012.
- [12] N. T. T. Trang, N. T. Chinh, N. V. Giang, D. T. M. Thanh, T. D. Lam, and T. Hoang, "PLA/CS/Nifedipine Nanocomposite Films: Properties and the In Vitro Release of Nifedipine," *Journal of Electronic Materials*, vol. 45, no. 7, pp. 3581–3590, 2016.
- [13] N. T. Chinh, N. T. T. Trang, N. V. Giang et al., "In vitronifedipine release from poly(lactic acid)/chitosan nanoparticles loaded with nifedipine," *Journal of Applied Polymer Science*, vol. 133, no. 16, article n/a, 2016.
- [14] A. H. Doulabi, H. Mirzadeh, and M. Imani, "Miscibility study of chitosan/polyethylene glycol fumarate blends in dilute solutions," *Journal of Applied Polymer Science*, vol. 127, no. 5, pp. 3514–3521, 2013.
- [15] L. Liu, Y. Wang, X. Shen, and Y. e. Fang, "Preparation of chitosan-g-polycaprolactone copolymers through ring-opening polymerization of ϵ -caprolactone onto phthaloyl-protected chitosan," *Biopolymers*, vol. 78, no. 4, pp. 163–170, 2005.
- [16] J. Du, R. Sun, S. Zhang, L.-F. Zhang, C.-D. Xiong, and Y.-X. Peng, "Novel polyelectrolyte carboxymethyl konjac glucomannan-chitosan nanoparticles for drug delivery. I. Physicochemical characterization of the carboxymethyl konjac glucomannan-chitosan nanoparticles," *Biopolymers*, vol. 78, no. 1, pp. 1–8, 2005.
- [17] K. Dominika, Z. K. Anna, K. Zaneta, O. Maciej, and J. Andrzej, "Effect of film-forming alginate/chitosan polyelectrolyte complex on the storage quality of pork," *Molecules*, vol. 22, no. 1, pp. 98–113, 2017.
- [18] L. Baruch and M. Machluf, "Alginate–chitosan complex coacervation for cell encapsulation: Effect on mechanical properties and on long-term viability," *Biopolymers*, vol. 82, no. 6, pp. 570–579, 2006.
- [19] N. T. Chinh, N. T. H. Ly, T. T. Mai et al., "Characteristic and properties of chitosan/alginate polymer blend carrying lovastatin drug," *Vietnam Journal of Science and Technology*, vol. 54, no. 2B, pp. 118–124, 2016.
- [20] N. T. Chinh, H. Thai, L. T. Thach, G. D. Le, and T. P. Ngo, "Effect of Polycaprolactone on Characteristics and Morphology of Alginate/Chitosan/Lovastatine Composite Films," *Vietnam Journal of Science and Technology*, vol. 56, no. 4A, p. 13, 2018.
- [21] T. Hoang, K. Ramadass, T. T. Loc et al., "Novel Drug Delivery System Based on Ginsenoside Rb1 Loaded to Chitosan/Alginate Nanocomposite Films," *Journal of Nanoscience and Nanotechnology*, vol. 19, no. 6, pp. 3293–3300, 2019.

- [22] L. D. Minh, N. T. Chinh, L. D. Giang, T. C. Le, D. T. K. Quyen, and T. Hoang, "Prediction of service half-life time of high density polyethylene/organo-modified calcium carbonate composite exposed naturally at Dong Hoi - Quang Binh," *Vietnam Journal of Chemistry*, vol. 56, no. 6, pp. 767–772, 2018.
- [23] T. Hoang, T. D. Lam, T. T. Loc et al., "Effect of both lovastatin and ginsenoside Rb1 on some properties and in-vitro drug release of alginate/chitosan/lovastatin/ginsenoside Rb1 composite films," *Journal of Polymers and the Environment*, vol. 27, no. 12, pp. 2728–2738, 2019.
- [24] A. Dev, N. S. Binulal, A. Anitha et al., "Preparation of poly(lactic acid)/chitosan nanoparticles for anti-HIV drug delivery applications," *Carbohydrate Polymers*, vol. 80, no. 3, pp. 833–838, 2010.
- [25] N. T. T. Trang, N. T. Chinh, N. V. Giang et al., "Hydrolysis of green nanocomposites of poly(lactic acid) (PLA), chitosan (CS) and polyethylene glycol (PEG) in acid solution," *Green Processing and Synthesis*, vol. 5, no. 5, 2016.
- [26] S. Dash, P. N. Murthy, L. Nath, and P. Chowdhury, "Kinetic modeling on drug release from controlled drug delivery systems," *Acta Poloniae Pharmaceutica*, vol. 67, no. 3, pp. 217–223, 2010.
- [27] M. S. Eldin, A. M. Omer, M. A. Wassel, T. M. Tamer, M. S. Abd Elmonem, and S. A. Ibrahim, "Oval smart pH sensitive chitosan grafted alginate hydrogel microcapsules for oral protein delivery: I. preparation and characterization," *International Journal of Pharmacy and Pharmaceutical Sciences*, vol. 7, no. 10, pp. 331–337, 2015.
- [28] A. Dong, M. Ye, H. Guo, J. Zheng, and D. Guo, "Microbial transformation of ginsenoside Rb1 by *Rhizopus stolonifer* and *Curvularia lunata*," *Biotechnology Letters*, vol. 25, no. 4, pp. 339–344, 2003.
- [29] J. P. Soares, J. E. Santos, G. O. Chierice, and E. T. G. Cavalheiro, "Thermal behavior of alginic acid and its sodium salt," *Eclética Química*, vol. 29, no. 2, pp. 57–64, 2004.
- [30] M. I. Yoshida, M. A. Oliveira, E. C. L. Gomes, W. N. Mussel, W. V. Castro, and C. D. V. Soares, "Thermal characterization of lovastatin in pharmaceutical formulations," *Journal of Thermal Analysis and Calorimetry*, vol. 106, no. 3, pp. 657–664, 2011.
- [31] P. Sandhya, G. Kodali, and A. Fatima, "Formulation and in-vitro characterization of gastro retentive mucoadhesive tablets of lovastatin," *International Journal of Biological & Pharmaceutical Research*, vol. 5, no. 1, pp. 71–77, 2014.
- [32] N. H. Minh, G. B. Long, H. N. Dai et al., "PEGylated PAMAM dendrimers loading oxaliplatin with prolonged release and high payload without burst effect," *Biopolymers*, vol. 110, no. 7, p. e23272, 2019.
- [33] P. George and B. Nikolaos, "Swelling studies and in vitro release of verapamil from calcium alginate and calcium alginate-chitosan beads," *International Journal of Pharmaceutics*, vol. 323, pp. 34–42, 2006.
- [34] Y. Cui-Yun, Z. Xi-Chen, Z. Fang-Zhou, Z. Xian-Zheng, C. Si-Xue, and Z. Ren-Xi, "Sustained release of antineoplastic drugs from chitosan-reinforced alginate microparticle drug delivery systems," *International Journal of Pharmaceutics*, vol. 357, pp. 15–21, 2008.
- [35] L. Ochoa, M. Igartua, R. M. Hernández, A. R. Gascón, M. A. Solinis, and J. L. Pedraz, "Novel extended-release formulation of lovastatin by one-step melt granulation: In vitro and in vivo evaluation," *European Journal of Pharmaceutics and Biopharmaceutics*, vol. 77, no. 2, pp. 306–312, 2011.