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ORIGINAL ARTICLE

Characteristic Comparison of an Intraoral Thin Film Containing Astaxanthin Nanoemulsion Using Sodium Alginate and Gelatin Polymers

Sodyum Aljinat ve Jelatin Polimerleri Kullanılmış Nanoemülsiyon Astaksantin İçeren İntraoral İnce Filmin Karakteristiğinin Karşılaştırılması

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ABSTRACT

Objectives: The present study was conducted to compare the characteristics of a thin film containing an astaxanthin-loaded nanoemulsion (TFANE) using two kinds of natural polymers, namely sodium alginate and gelatin.

Materials and Methods: An astaxanthin nanoemulsion was prepared by using the self-nanoemulsifying method, followed by incorporation into a polymer matrix system by the solvent casting method to form TFANE. A characteristic comparison between the sodium alginate and gelatin matrix systems was carried out by comparing the physical and mechanical film properties. At the end of the study, *in vitro* dissolution tests were also assessed.

Results: An intraoral film with good physical and mechanical properties containing an astaxanthin-loaded nanoemulsion was developed successfully using a natural polymer matrix system. The film, made from a gelatin matrix system containing an astaxanthin nanoemulsion, was more flexible and harder than films made from a sodium alginate matrix system, where all of the films have ideal characteristics for intraoral delivery. The dissolution test results showed that, with both sodium alginate and gelatin, more than 90% of the drug was released at 15 minutes.

Conclusion: Gelatin as a natural polymer appears to be promising for the preparation of an intraoral thin film delivery system.

Key words: Astaxanthin, nanoemulsion, thin film, solvent casting method

ÖZ

Amaç: Bu çalışma, astaksantin yüklü nanoemülsiyon (TFANE) içeren ince filmin özelliklerini sodyum aljinat ve jelatin olmak üzere iki çeşit doğal polimer kullanılarak karşılaştırmak amacıyla yapılmıştır.

Gereç ve Yöntemler: Astaksantin nanoemülsiyon, kendiliğinden nanoemülsifikasyon yöntemi kullanılarak hazırlandı, ardından TFANE elde etmek için çözücü döküm yöntemi ile polimerler matris sistemine dahil edildi. Sodyum aljinat ve jelatin matris sistemlerinin karşılaştırması, fiziksel ve mekanik film özellikleri karşılaştırılarak gerçekleştirilmiştir. Çalışmanın sonunda *in vitro* çözünme testleri de değerlendirildi.

Bulgular: İyi fiziksel ve mekanik özelliklere sahip astaksantin yüklü nanoemülsiyon içeren intraoral film, doğal polimer matris sistemi kullanılarak başarıyla geliştirilmiştir. Tüm filmlerin intraoral ilaç taşınımı için ideal özelliklere sahip olduğu; astaksantin nanoemülsiyon içeren jelatin matris sisteminden yapılan filmin, sodyum aljinat matris sisteminden yapılan filmlerden daha esnek ve daha sert olduğu tespit edilmiştir. Çözünme testi sonuçları, hem sodyum aljinat hem de jelatinin 15 dakikada ilacın %90'ından daha fazla salındığını gösterdi.

Sonuç: Doğal bir polimer olarak jelatin, intraoral ince film ilaç taşıyıcı sisteminin hazırlanması için umut verici görünmektedir.

Anahtar kelimeler: Astaksantin, nanoemülsiyon, ince film, çözücü döküm yöntemi

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INTRODUCTION

Astaxanthin is a lipophilic pigment with a reddish color, synthesized naturally by algae or plants. As a member of the xanthophyll group of compounds, which comprises oxygenated derivatives of carotenes, astaxanthin contains conjugated double bonds, hydroxyl groups, and ketone groups and possesses both lipophilic and hydrophilic properties. Its unique structure gives astaxanthin strong antioxidant power and superior biological activity to that of other antioxidants, owing to its ability to forms linkages with the cell membrane.[1-3]

In humans, the bioavailability of carotenoids is low and variable (10%-50% of a given dose), due to their low solubility in gastrointestinal tract juices, leading to poor absorption in the small intestine.[3] Another factor that lowers the bioavailability of astaxanthin is its degradation in the gastrointestinal tract and the possibility of first-pass metabolism. A pharmacokinetic study by Choi et al.[1] showed that the hepatic and gastrointestinal elimination extraction ratios of astaxanthin were 0.490 and 0.901, respectively. The value of the elimination extraction ratio ranges between 0 and 1, where a value close to 1 indicates that the drug is eliminated by the intended organ.[1]

To overcome these drawbacks, an astaxanthin nanoemulsion was developed. A nanoemulsion preparation may offer an improvement in dissolution and absorption rates, while also improving the drug release profile.[4,5] Furthermore, to facilitate its use in patients; the astaxanthin nanoemulsion was incorporated into a polymer matrix system to create a thin film for intraoral use. This research was extended to develop a new dosage form to maximize the use of astaxanthin. In this research, astaxanthin was encapsulated in oil in an oil-in-water nanoemulsion system. This nanoemulsion was developed by the self-nanoemulsifying method. Then, two different natural polymers, sodium alginate and gelatin, were selected to obtain the best film matrix that was able to incorporate the astaxanthin nanoemulsion. Both physical and mechanical evaluations of thin film containing an astaxanthin-loaded nanoemulsion (TFANE) were performed, including pH and viscosity of film-forming mixtures, film thickness, film weight uniformity, film disintegration time, tensile strength, percent elongation, and film morphology.

MATERIALS AND METHODS

Materials

Astaxanthin (Astareal® L10) was purchased from Fuji Chemical Industries (Japan). Sunflower oil was purchased from Jan Dekker International (The Netherlands). Polyoxy-35-castor oil (Kolliphor® RH40) was purchased from BASF (Indonesia). Polyethylene glycol 400 (PEG 400) was purchased from Merck (Indonesia). Sodium alginate was purchased from Merck (Indonesia). Poly [butyl methacrylate, (2-dimethylaminoethyl) methacrylate, methyl methacrylate] 1:2:1 (Eudragit® EPO) was purchased from Evonik Industries (Thailand). Gelatin was purchased from Global Capsules Ltd (Bangladesh). All other chemicals used were of pharmaceutical grade.

Preparation of the astaxanthin nanoemulsion

The astaxanthin nanoemulsion was prepared by using the self-nanoemulsifying method with the optimized ratio of oil phase to surfactant to co-surfactant determined in a previous study.[6] Forty milligrams of astaxanthin was added to the 1-gram mixture of oil phase (sunflower oil), surfactant (Kolliphor® RH40), and co-surfactant (PEG 400) in the ratio 1:8:1, respectively. This mixture was then mixed with a mixing speed of 100 rpm for 30 minutes using a magnetic stirrer (IKA® C-MAG HS7), followed by sonication for 1 hour (Krisbow®). A nanoemulsion was formed by addition of deionized water with mild stirring.

Optimization of thin film preparation

In this study, sodium alginate and gelatin were used as thin film-forming polymers, with PEG 400 as a plasticizer. The experiment to optimize both the polymer and the plasticizer concentration that produced the best thin-layer preparation was designed by using Design-Expert® Version 12 Software with the Simple Lattice Design method. A thin film was formed by pouring the wet mixture (WME) into a petri dish with a flat, clean surface of diameter 10 cm and dried for 48 hours at ambient temperature (30˚C±5˚C). After drying, the film thickness and film disintegration time were evaluated. The experimental design results from the software are given in Table 1.

Preparation of TFANE

A quantity of 1.25 g of the astaxanthin nanoemulsion was dispersed slowly into a mixture of the optimized polymer matrix

Table 1. Experimental designs of thin film preparation

Formula	Components			
	Sodium Alginate (g)	Gelatin (g)	PEG 400 (g)	Deionized water
F1	0.125	-	0.625	Add up to 25 mL
F2	0.281	-	0.500	
F3	0.438	-	0.375	
F4	0.594	-	0.250	
F5	0.750	-	0.125	
F6	0.438	-	0.375	
F7	0.125	-	0.625	
F8	0.750	-	0.125	
F9	-	0.25	0.250	
F10	-	0.25	0.250	
F11	-	1.00	0.156	
F12	-	0.75	0.188	
F13	-	1.25	0.125	
F14	-	0.75	0.188	
F15	-	1.25	0.125	
F16	-	0.50	0.219	

PEG: Polyethylene glycol

system and 0.01 g Eudragit® EPO (in 2.5 mL ethanol 96%). The final mixing was performed by adding deionized water up to 25 mL and mixing with a magnetic stirrer (IKA® C-MAG HS7) in 100 rpm for 1 hour. A thin film was formed by pouring this WME onto the flat, clean surface of a petri dish with a diameter of 10 cm and dried for 48 hours at ambient temperature (30˚C±5˚C). Then, the TFANE was cut into a 3x3 cm square.

Physical, chemical, and mechanical characterizations of TFANE

Visual observation and pH determination

Visual observation included observation of the color, odor, and clarity of the WME. The pH of the WME was determined by using a calibrated pH meter (Mettler® Toledo).

Film thickness and weight uniformity

Film thickness was determined by using a micrometer (Mitutoyo®) at three different locations on the film. Meanwhile, the weight uniformity of the thin film was determined by weighing six pieces of thin film (with a size of 3x3 cm) using an analytical balance (Mettler Toledo XS204). It is important to know these parameters because they are directly related to the accuracy of doses in the film. The thickness requirement for thin film dosage form must be in the range of 0.005 to 0.2 mm.[7]

Film disintegration time

The film disintegration time was determined visually in a petri dish containing 10 mL of phosphate buffer, pH 6.8 at 37˚C with shaking every 10 s. Disintegration time is the time at which the film begins to break or collapse. The disintegration time of a good thin film is less than 60 s.[7]

Tensile strength and percent elongation

Mechanical stress tests of TFANE were performed by using a universal testing machine (Oriented UCT-5T). Dry film was cut into pieces of uniform size using a sharp-bladed cutting mold. Film (with area exposed to the stress of 25 mm x 4 mm) was sandwiched between two machine jaws. The load was given to the film gradually (at a speed of 30 mm/minute) and automatically until the film shredded. The test was carried out at 23˚C and 50% relative humidity. Tensile strength is calculated by the applied load at rupture divided by the cross-sectional area of the film. Percent elongation is defined as a strain of the film. Strain is basically the deformation of the strip divided by the original dimension of the sample.

Film morphology

The film morphology of TFANE was examined by scanning electron microscopy (SEM). The sample was sized according to the specimen container, followed by smearing with silver paste at several points before the sample was placed. The sample was dried at 20˚C. The sample was fine coated as a voltage of 1.2 kV, current of 6-7.5 mA, and air pressure of 0.2 torrs for 4 minutes to obtain a sample with a thickness of approximately 400 Å.

Assay of astaxanthin in TFANE

The assay was carried out by dissolving the TFANE (with a size of 3x3 cm) in a volumetric flask containing 10 mL of phosphate buffer pH 6.8 for 30 minutes. Then, the absorbance was measured by ultraviolet-visible spectrophotometry (Genesys™ 10S) at a maximum wavelength of 472 nm. The astaxanthin concentration in the TFANE was calculated by estimating the astaxanthin content in the individual film. The limit of the assay is 85%-115%.[8]

In vitro dissolution test

In vitro dissolution tests were performed using a USP 41 apparatus 2, paddle apparatus. Nine hundred milliliters of phosphate buffer (pH 6.8) was used and maintained at 37˚C ±5˚C, and the paddle was set at 50 rpm. A film sample of 9 cm^2 (3x3 cm) was cut and added to the medium. Five milliliters of samples were removed at predetermined time points at 1; 2; 3; 4; 5; 10; 15; and 20 minutes, and the same amount was replaced with fresh buffer. The withdrawn samples were filtered and analyzed using a spectrophotometer at a wavelength of 472 nm. The percentage release was calculated, and the relationship between time and percentage release was plotted.

Statistical analysis was not used in this research.

RESULTS AND DISCUSSION

Preparation of the astaxanthin nanoemulsion

Self-nanoemulsifying dosage forms are anhydrous homogenous liquid mixtures consisting of an oil, surfactant, drug, and co-surfactant, which spontaneously form an oil-in-water nanoemulsion upon dilution with water under gentle stirring.[4,5] Adding a surfactant and co-surfactant to such systems enhances drug dissolution and formulation dispersibility during dilution with the aqueous medium of GIT. During dilution with water, the active substance dissolves in the oil phase and/or surfactant, which forms a film between the oil and water phases.[4] The appropriate type and ratio of the oil phase, surfactant, and co-surfactant are critical parameters in the formation of nanoemulsion. Based on our previous study, the best ratio between sunflower oil as the oil phase, Kolliphor® RH40 as the surfactant, and PEG 400 as the co-surfactant was 1:8:1, respectively.[6] Our results showed that the astaxanthin nanoemulsion had droplet sizes in the nano-range (26-27 nm) with a polydispersity index less than 0.5 (0.2-0.3) and a zeta potential value more than (-20) mV.

Optimization of thin film preparation

In the preliminary study, prior to formulation of the astaxanthin nanoemulsion in the polymer matrix systems, optimization of polymers and plasticizer concentrations were carried out by using Design-Expert® version 12 Software with Simple Lattice Design method. This software is a tool to determine the optimal variations in polymers and plasticizer concentrations in a thin film preparation. Using this software will produce eight experimental designs for each of the natural polymers that were used. Critical evaluations including film disintegration time and film thickness were carried out to find the best thin film characteristics. The results of the evaluation in the preliminary screening of thin film-matrix systems are given in Table 2. All of the formulas had good characteristics of both disintegration

time and thickness (Table 2). The best characteristic of thin film from both sodium alginate and gelatin were determined by using Simplex Lattice Design modeling. The film thickness and film disintegration time parameters were used to determine the optimum film formulation to be used in the TFANE preparation. The results of data analysis from the model are presented in Figure 1.

Based on the contour plots in Figure 1, it can be seen that the effects of application of sodium alginate and gelatin in the matrix systems were similar. Although the shape of the

Table 2. The results of preliminary screening on optimization of polymer matrix systems

Parameters	Formula							
	F1	F2	F3	F4	F5	F6	F7	F8
Film thickness (mm)*	0.137±0.001	0.159±0.001	0.182±0.001	0.192±0.001	0.203±0.001	0.178±0.001	0.131±0.001	0.205±0.001
	F9	F10	F11	F12	F13	F14	F15	F16
	0.132±0.001	0.135±0.001	0.171±0.001	0.152±0.001	0.199±0.002	0.145±0.002	0.197±0.001	0.144±0.002
	F1	F2	F3	F4	F5	F6	F7	F8
Film disintegration time (s)*	28.78±0.015	35.43±0.015	44.3±0.020	51.55±0.015	56.32±0.020	42.17±0.020	23.94±0.021	59.33±0.015
	F9	F10	F11	F12	F13	F14	F15	F16
	23.03±0.015	24.58±0.021	49.68±0.030	43.89±0.035	58.42±0.020	45.93±0.025	58.00±0.010	33.96±0.020

*Values are given as the mean ± standard deviation (n=3)

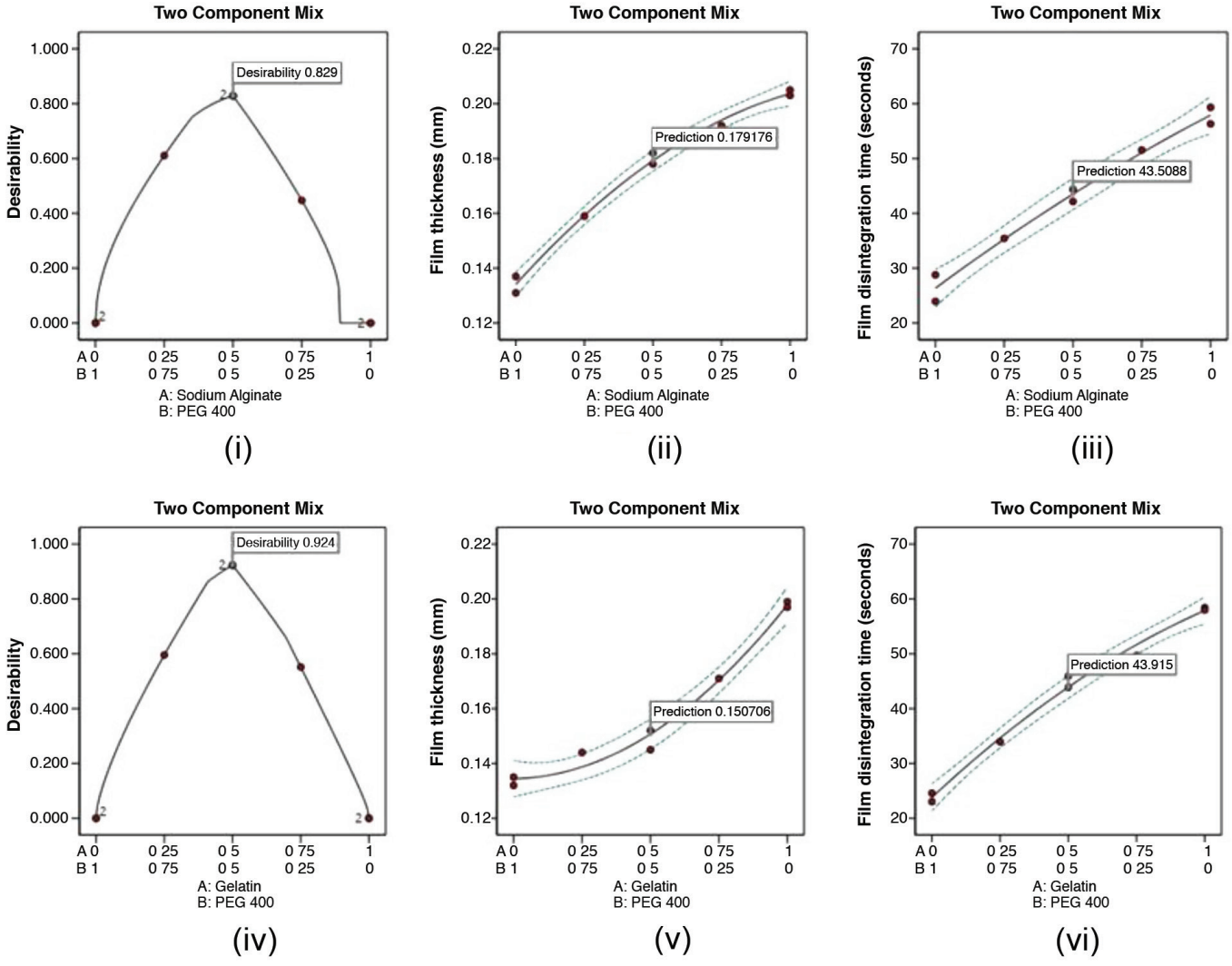

Figure 1. Data analysis of thin film optimization using Simplex Lattice Design modeling. (i)-(iii) for sodium alginate and (iv)-(vi) for gelatin

PEG: Polyethylene glycol

contour plot in film thickness was different, sodium alginate has a convex quadratic shape, whereas gelatin had a concave quadratic shape. The higher of the two polymer concentrations, the longer of the film disintegration time needed and the greater the film thickness. In contrast to the effects of PEG on film thickness and disintegration time, with the higher PEG concentration, a thinner film was produced and the film disintegrated faster. The polymer concentration is an important factor in the development of the thin film. The integrity of fast-dissolving oral films is dependent upon the nature of the selected polymer and its concentration. Different polymers are employed to modulate the diverse properties of films.[9,10] PEG also has good film-forming properties either alone or in combination with other polymers.[11] The disintegration rate of the polymers is decreased by increasing the molecular weight and its concentration of the polymer film matrix system.[12,13] In thin film development, mechanical properties such as tensile strength and percent elongation are improved by adding a plasticizer to the formulations.[12] The mechanical properties of a thin film depends on the plasticizer concentration;[13] thus, proper selection of a plasticizer is very important as improper selection may cause cracking and splitting of the film.[12,14]

The desirability value in Figure 1 (i) showed the highest value (0.829) in a mixture of sodium alginate and PEG 400 with a film thickness of approximately 0.179176 mm and a film disintegration time of approximately 43.5088 s, whereas Figure 1 (iv) shows the highest value (0.924) in a mixture of gelatin and PEG 400 with a film thickness of approximately 0.150706 mm and a film disintegration time of approximately 43.915 s. The desirability value can range from zero (outside of the limits) to one (at the goal). Desirability is simply a mathematical method to determine the optimum (closed to one).[15] Thus, it can be concluded that the two best polymer matrix systems for the preparation of TFANE were mixtures containing 1.75% (w/v) sodium alginate and 1.5% (w/v) PEG 400 and those comprising 3% (w/v) gelatin and 0.75% (w/v) PEG 400.

Preparation of TFANE

The film properties of astaxanthin nanoemulsions prepared with both sodium alginate and gelatin are presented in Table 3. In this study, the films prepared using a 10-mm-diameter petri dish showed good weight homogeneity. All films showed a disintegration time of less than 60 s, which related to ease of drug release from the matrix system. The ideal intraoral film should have the following mechanical properties: High tensile strength and high percent elongation. The astaxanthin nanoemulsion incorporated into the gelatin matrix system had a higher tensile strength and higher percent elongation values than the sodium alginate matrix system (Table 3). Tensile strength is the maximum stress applied to a point at which the film breaks, whereas percent elongation indicates the ability to stretch when a stress is applied. Hard and brittle films demonstrate high tensile strength,[16] which means that the film made from sodium alginate was relatively smoother than that made from gelatin. The percent elongation of the gelatin matrix system was greater than that of the sodium alginate matrix system, which means that the film made from gelatin was more flexible than that made from sodium alginate.

Referring to a study conducted by Lakshmi et al.[17], Eudragit® EPO was selected as the second polymer because the film made from this polymer showed good tensile strength. Other studies have also shown that Eudragit® EPO has taste-masking properties to prevent a negative impact on patient compliance, which is a major consideration when developing an oral formulation.[18,19]

Visual observation of the TFANE was conducted by observing its organoleptic properties. The TFANE was orange in color, odorless, with a smooth surface, and transparent (Figure 2). The morphology of the surface film was observed by SEM (Figure 3). Clear differences were observed between the TFANE containing sodium alginate and gelatin matrix systems, in which the film made from sodium alginate showed a grainier texture than that made from gelatin.

At the end of the study, *in vitro* dissolution tests were performed to compare the drug release profiles of the sodium alginate and gelatin matrix systems. The plotted curves of percentage release over time are shown in Figure 4. The films formed by sodium alginate and gelatin released >90% of the drug within 15 minutes. These results indicate that there was no difference

Table 3. Physical and mechanical properties of TFANE

Parameters	Polymer matrix systems	
	1.75% (w/v) sodium alginate + 1.5% (w/v) PEG 400	3% (w/v) gelatin + 0.75% (w/v) PEG 400
Visual properties of WME	Orange, clear, and odorless	Orange, clear, and odorless
pH of WME*	6.56±0.05	6.80±0.01
Film thickness (mm)*	0.196±0.001	0.184±0.008
Weight uniformity/sheet 3x3 cm (g)*	0.221±0.002	0.202±0.007
Film disintegration time (s)*	48.69±0.10	47.64±0.70
Tensile strength (MPa)*	2.01±0.16	5.33±0.40
Percent elongation (%)*	12.76±1.17	77.15±7.29
Assay of astaxanthin (%)*	98.85±0.54	98.73±0.47

*Values are given as mean ± standard deviation (n=6), TFANE: Thin film containing an astaxanthin-loaded nanoemulsion, PEG: Polyethylene glycol, WME: Wet mixture

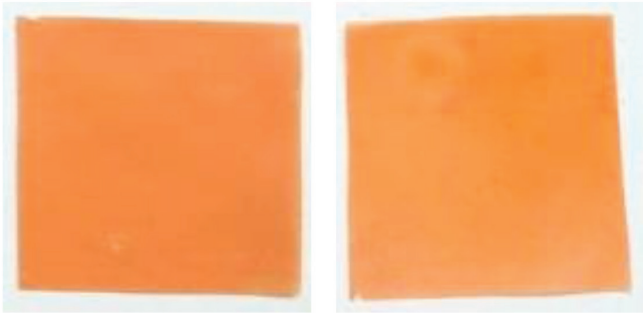

Figure 2. Visual observation of TFANE. (A) TFANE was contained the sodium alginate matrix system and (B) TFANE was contained the gelatin matrix system

TFANE: Thin film containing an astaxanthin-loaded nanoemulsion

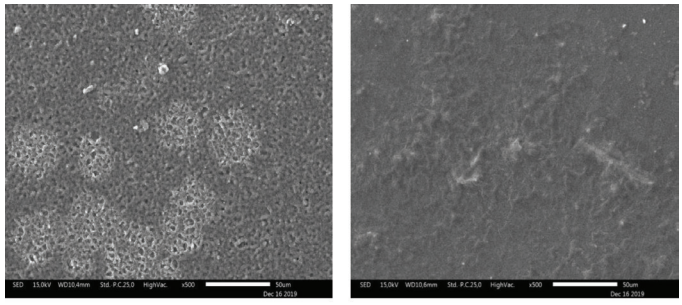

Figure 3. The morphology of TFANE at 500x magnification. (A) TFANE was contained the sodium alginate matrix system, and (B) TFANE was contained the gelatin matrix system

TFANE: Thin film containing an astaxanthin-loaded nanoemulsion

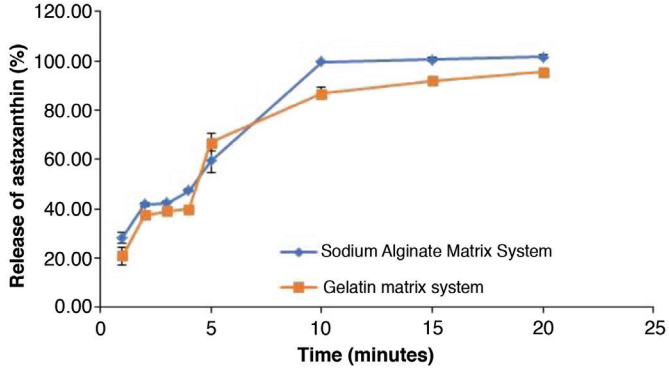

Figure 4. *In vitro* drug release from TFANE prepared using sodium alginate and gelatin polymers

TFANE: Thin film containing an astaxanthin-loaded nanoemulsion

regarding drug release between films made from sodium alginate and those made from gelatin.

CONCLUSION

An intraoral film containing an astaxanthin-loaded nanoemulsion with good physical and mechanical properties was successfully developed using a natural polymer matrix system. The film made from a gelatin matrix system containing astaxanthin nanoemulsion was more flexible and harder than film made from a sodium alginate matrix system, whereas all of the films had the characteristics that made them ideal for intraoral delivery. There was no difference regarding drug release from films made by sodium alginate or gelatin. Gelatin as a natural polymer appears to be promising for the preparation of an intraoral thin film delivery system.

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