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

Astaksantin Nanoemülsiyon Içeren İntraoralİntraoral Ince Filmin Sodyum Aljinat ve Jelatin Polimerleri ile Karşılaştırılması

Short Title:
Characteristics Comparison of Intraoral Thin Film Containing Astaxanthin Nanoemulsion

Astaksantin Nanoemülsiyon Içeren İntraoral Ince Filmin Özellikleri Karşılaştırması

Lusi NURDIANTI[1,2], Taofik RUSDIANA[1]*, Iyan SOPYAN[1], Norisca Aliza PUTRIANA[1], Hanifa Rifdah AIMAN[1], Tengku Ruhul FAJRIA[1]
[1]Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, Padjadjaran University, Bandung, Indonesia
[2]Pharmacy Department, Bakti Tunas Husada Institute of Health Science, Tasikmalaya, Indonesia

*Corresponding Author: Taofik Rusdiana
Corresponding Author Address: Raya Bandung Sumedang Road KM.21, Hegarmanah, West Java 45363 Bandung - Indonesia
Corresponding Author Phone: +62227796200
Corresponding Author Email: t.rusdiana@unpad.ac.id
ORCID: https://orcid.org/0000-0002-3321-2179
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ABSTRACT
Objectives: The present study was conducted to compare the characteristics of thin film containing astaxanthin-loaded nanoemulsion (TFANE) using two kinds of natural polymers, namely sodium alginate and gelatin.
Materials and Methods: Astaxanthin nanoemulsion was prepared by using self-nanoemulsifying method, followed by incorporation into the polymers matrix system by

solvent casting method to forming TFANE. Characteristics comparison between sodium alginate and gelatin matrix systems were carried out by comparing the physical and mechanical film properties. At the end of the study, in vitro dissolution tests were also assessed.
Results: A good physical and mechanical properties of intraoral film containing astaxanthin-loaded nanoemulsion was successfully developed using natural polymers matrix system. The Film made from a gelatin matrix system containing astaxanthin nanoemulsion was more flexible and harder than films made from sodium alginate matrix system, where all of the films have ideal characteristics for intraoral delivery. The dissolution test results showed that both sodium alginate and gelatin were released more than 90% of the drug at 15 minutes.
Conclusion: Gelatin as a natural polymer appears to be promising for the preparation of an intraoral thin film delivery system.
Keywords: astaxanthin, nanoemulsion, thin film, solvent casting method

ÖZ
Amaç: Bu çalışmaçalışma, Astaksantin yüklü nanoemülsiyon (TFANE) içeren ince filmin özelliklerioözelliklerini sodyum aljinat ve Jelatin olmak üzere iki çeşit doğal polimer kullanılarak karşılaştırmak amacıyla yapılmıştır.
Gereç ve Yöntem: Astaksantin nanoemülsiyon, kendinden nanoemülsifiye yöntemi kullanılarak hazırlandı, ardından tfane oluşturmak için solvent döküm yöntemi ile polimerler matris sistemine dahil edildi. Sodyum aljinat ve jelatin matris sistemleri arasındaki özellikler karşılaştırması, fiziksel ve mekanik film özellikleri karşılaştırılarak gerçekleştirilmiştir. ÇalışmanınÇalışmanın sonunda inin vitro çözünme testleri de değerlendirildi.
Bulgular: Astaksantin yüklü nanoemülsiyon içeren intraoral filmin iyi bir fiziksel ve mekanik özellikleri, doğal polimerler matris sistemi kullanılarak başarıyla geliştirilmiştir. Astaksantin nanoemülsiyon içeren bir jelatin matris sisteminden yapılan Film, TümTüm filmlerinfilmlerin intraoral doğum için ideal özelliklere sahip olduğu sodyum aljinat matris sisteminden yapılan filmlerden daha esnek ve daha sertti. Çözünme testi sonuçlarısonuçları, hem sodyum aljinat hem de jelatinin 15 dakikada ilacın %90'ından daha fazla salındığını gösterdi.
Sonuç: Doğal bir polimer olarak Jelatin, intraoral ince film dağıtım sisteminin hazırlanması içiniçin umut verici görünmektedir.
Anahtar kelimeler: astaksantin, nanoemülsiyon, ince film, solvent döküm yöntemi

INTRODUCTION

Astaxanthin is a lipophilic pigment with a reddish colour, which is naturally synthesized by algae or plants. As a xanthophyll group, which is oxygenated derivatives of carotenes, astaxanthin contains conjugated double bonds, hydroxyl- and keto-groups with lipophilic and hydrophilic properties. Because of its unique structure makes astaxanthin acts as a strong antioxidant and it showed better biological activity than other antioxidants, because their ability to link with membrane cell.[1-3]

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

To overcome these drawbacks, the development of astaxanthin nanoemulsion was carried out. Nanoemulsion preparation may offer an improvement in dissolution rates and extents of absorption, while nanoemulsion may also improve the release performance.[4,5] Furthermore, to facilitate its use in patients; astaxanthin nanoemulsion was incorporated into the polymer matrix system to create a thin film for intraoral use purposes. This research was further research to develop a new dosage form to maximize the use of astaxanthin. In this research, astaxanthin was encapsulated in oil in the oil-in-water nanoemulsion system. This nanoemulsion was developed by self-nanoemulsifying method. Then, two different natural polymers such as sodium alginate and gelatin were selected to obtain the best film matrix which was able to incorporate astaxanthin nanoemulsion. Both physical and mechanical evaluations of 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 (Netherland). 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 astaxanthin nanoemulsion

Astaxanthin nanoemulsion was prepared by using self-nanoemulsifying method with the optimized ratio between the oil phase, surfactant, and co-surfactant, which refers to a previous study.[6] Forty milligrams of astaxanthin were added into the 1 gram mixture of oil phase (Sunflower oil), surfactant (Kolliphor® RH40), and co-surfactant (PEG 400) with 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®). Nanoemulsion was formed after the 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. Design of experiment for optimization both of polymers and plasticizer concentrations that were able to produce the best thin layer preparation were carried out by using Design-Expert® Version 12 Software with Simple Lattice Design method. Thin film was formed by pouring wet mixture into the flat and clean surface petri dish in diameter of 10 cm and dried for 48 hours at ambient temperature (30±5ºC). After dried, film thickness and film disintegration time were evaluated. The designs of experimental results from the software are given in Table 1.

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	

Preparation of TFANE

An amount of 1.25 g astaxanthin nanoemulsion was dispersed slowly into the mixture of the optimized polymers matrix system and 0.01 g Eudragit® EPO (in 2.5 mL Ethanol 96%). The final mixing was done by added the deionized water up to 25 mL and mixed by using a magnetic stirrer (IKA® C-MAG HS7) in 100 rpm for 1 hour. Thin film was formed by pouring this wet mixture (WME) into the flat and clean surface petri dish in diameter of 10 cm and dried for 48 hours at ambient temperature (30±5ºC). Then, the TFANE was cut into a size of 3x3 cm.

Physical, chemical, and mechanical Characterizations of TFANE

Visual observation and pH determination

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

Film thickness and weight uniformity

Film thickness was carried out by using a micrometer (Mitutoyo®) at three different locations on the film. Meanwhile, the weight uniformity of thin film was determined by weighing 6 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 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

Film disintegration time was determined visually in a petri dish containing 10 ml of phosphate buffer pH 6.8 at 37ºC where the container was shaken in 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 uniform sized pieces using 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. A Strain is basically the deformation of 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 20ºC. The sample was put into the fine coat in voltage condition of 1.2 kV, ampere of 6-7.5 mA, and air pressure of 0.2 torrs for 4 minutes to obtain a sample with a thickness of about 400 Å.

Assay of astaxanthin in TFANE

The assay was carried out by dissolving 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 UV-Visible Spectrophotometer (Genesys™ 10S) at a maximum wavelength of 472 nm. Assay of astaxanthin in TFANE was calculated by estimating the astaxanthin content in the individual film. Limit of the assay is 85-115%.[8]

In vitro dissolution test

In vitro dissolution tests were performed using USP 41 apparatus 2, paddle apparatus. Nine hundred milliliters of phosphate buffer (pH 6.8) was used and was maintained at 37±5ºC while the paddle was set at 50 rpm. A film sample of 9 cm^2 (3x3 cm) was cut and taken into the medium. Five milliliters of samples were taken at predetermined time points at 1; 2; 3; 4; 5; 10; 15; 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.

RESULTS AND DISCUSSION

Preparation of astaxanthin nanoemulsion

Self-nanoemulsifying dosage forms are anhydrous homogenous liquid mixtures consisting of oil, surfactant, drug, and co-surfactant, which spontaneously form oil-in-water nanoemulsion upon dilution with water under gentle stirring.[4,5] Adding surfactant and co-surfactant into

systems enhances drug dissolution and formulation dispersibility during dilution with the aqueous medium of GIT. During dilution with water, active substance dissolves in the oil phase and/or surfactant, which forms a film between the oil and water phase.[4] The appropriate type and ratio of the oil phase, surfactant and co-surfactant are critical parameters in formation of nanoemulsion. Based on our previous study, the best ratio between sunflower oil as oil phase, Kolliphor® RH40 as surfactant, and PEG 400 as co-surfactant was 1:8:1, respectively.[6] Our results showed that astaxanthin nanoemulsion had droplets size in the nano-range (26-27 nm) with polydispersity index was less than 0.5 (0.2-0.3) and zeta potential value was more than (-20) mV.

Optimization of thin film preparation

In the preliminary study, before the formulation of the astaxanthin nanoemulsion into 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 find out the optimal variations in polymers and plasticizer concentrations in thin film preparation. Using this software will produce 8 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 characteristic. The results of the evaluation in the preliminary screening of thin film matrix systems are given in Table 2.

Parameters	Formula							
Film thickness (mm)*	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
	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
Film disintegration time (s)*	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
	28.78 ± 0.015	35.43 ± 0.015	44.36 ± 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).

In Table 2, it can be seen that all of the formulas have good characteristics in both of disintegration time and also thickness. The best characteristic of thin film from both of 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.

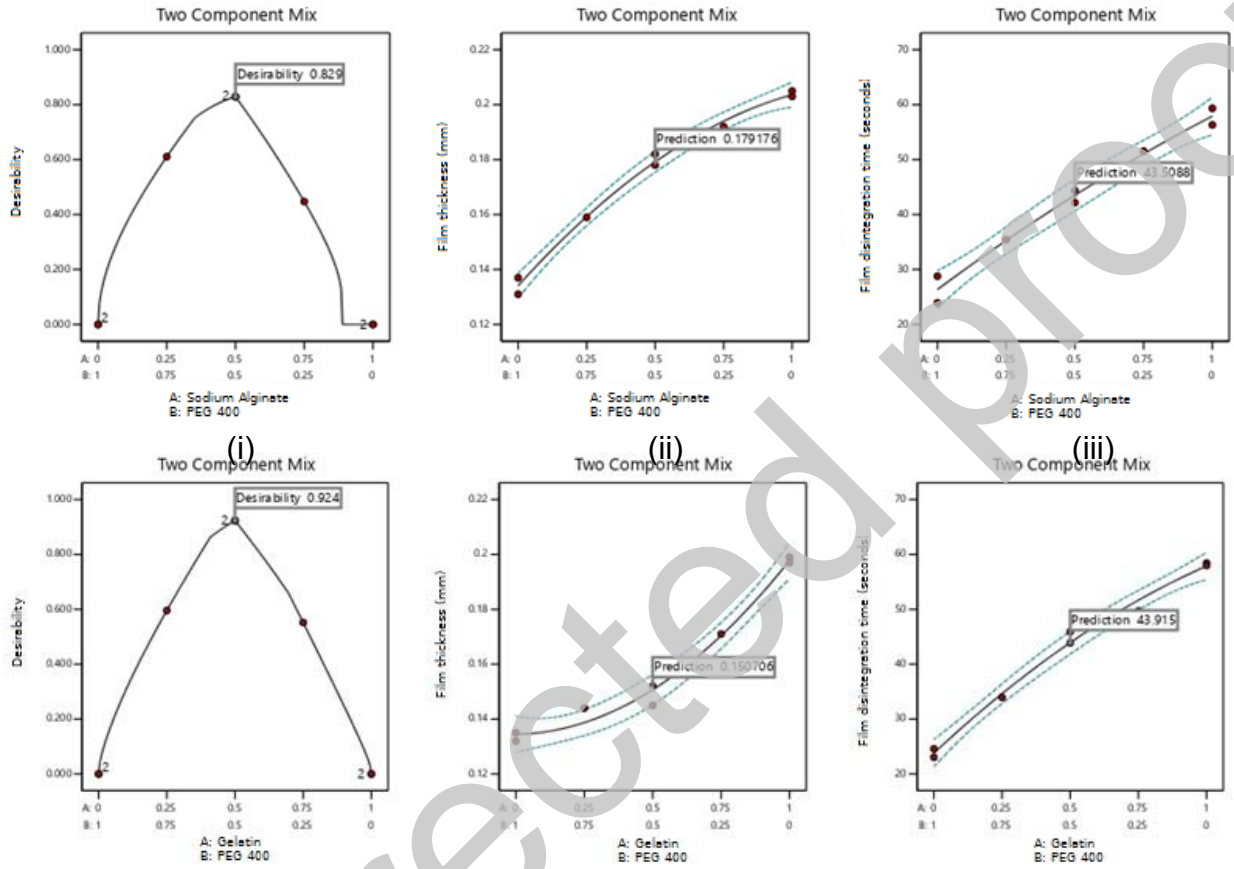


Figure 1. Data analysis of thin film optimization using Simplex Lattice Design modeling. (i) – (iii) for sodium alginate and (iv) – (vi) for gelatin.

Based on the contour plots in Figure 1, it can be seen that the effects of application sodium alginate and gelatin in the matrix systems were similar. Although the shape of the contour plot in film thickness was different, sodium alginate has a convex quadratic shape while gelatin has a concave quadratic shape. The higher of both polymers concentration, the longer of the film disintegration time needed, as well as the increasing of film thickness. Contrary to the effects of PEG on film thickness and disintegration time, where the higher of PEG concentration, the thinner of the film produced and the faster of the film disintegrated. The concentration of polymers is an important factor in the development of the thin film. The integrity of fast dissolving oral films is dependent upon the selection of polymer nature and its concentration. Different polymers are employed to modulate diverse properties of films.[9,10] Polyethylene glycol (PEG) also has a 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 the thin film development, mechanical properties such as tensile strength and percent elongation are improved by adding a plasticizer to the formulations.[12] Mechanical property of thin film is plasticizers concentration-dependent.[13] The proper selection of plasticizers is very important. The 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 film thickness around 0.179176 mm and film disintegration time around 43.5088 s. While, Figure 1 (iv) showed the highest value (0.924) in mixture of gelatin and PEG 400 with film thickness around 0.150706 mm and film disintegration time around 43.915 s. Desirability value is the value from zero (outside of the limits) to one (at the goal). Desirability is simply a mathematical method to find the optimum (closed to one).[15] So, it can be concluded that for the mixture contains of 1.75% (w/v) sodium alginate with 1.5% (w/v) PEG 400 and 3% (w/v) gelatin with 0.75% (w/v) PEG 400 were the best polymer matrix systems for the preparation of TFANE.

Preparation of TFANE

The film properties containing astaxanthin nanoemulsion prepared with both sodium alginate and gelatin are presented in Table 3.

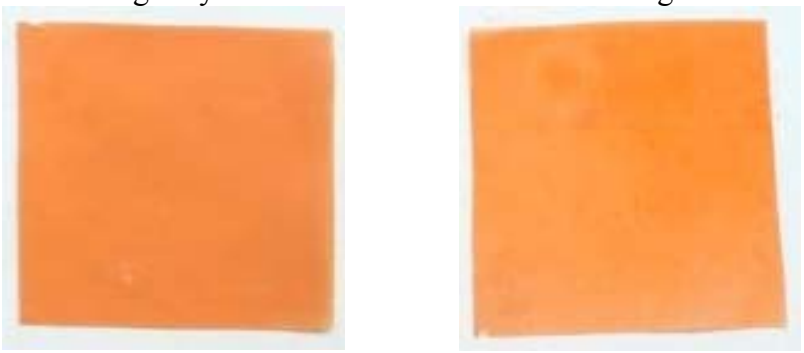
Parameters	**Polymer Matrix Systems**	
	1.75% (w/v) Sodium Alginate + 1.5% (w/v) PEG 400	**3% (w/v) Gelatin + 0.75% (w/v) PEG 400**
Visual properties of WME	Orange, clear, and odorless	Orange, clear, and odorless
pH of WME*	6.56 ± 0.05	6.80 ± 0.01
Film thickness (mm)*	0.196 ± 0.001	0.184 ± 0.008
Weight 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).

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

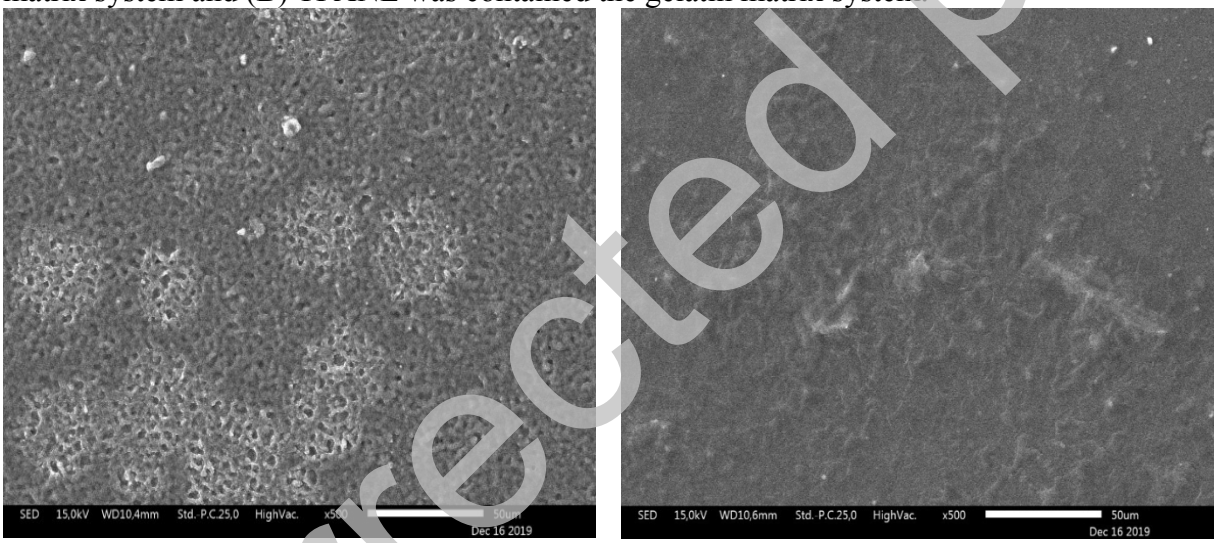
Refer to the study conducted by Lakshmi, *et al.*[17], Eudragit® EPO was selected as the second polymer because the film made by this polymer showed good tensile strength. Other studies have also shown that Eudragit® EPO, which has taste-masking properties to prevent a negative impact on patient compliance,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

Visual observation of TFANE was done by observing the organoleptic, where the TFANE had orange color, odorless, smooth surface, and transparent (Figure 2). The morphology of the surface film was observed by SEM (Figure 3). Clear differences were observed between TFANE contained sodium alginate and gelatin matrix system, which film made from sodium alginate showed more grainy-textured than the film made from gelatin.



(A) (B)

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



(A) (B)

Figure 3. The morphology of TFANE with a magnification of 500 times. (A) TFANE was contained the sodium alginate matrix system and (B) TFANE was contained the gelatin matrix system.

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

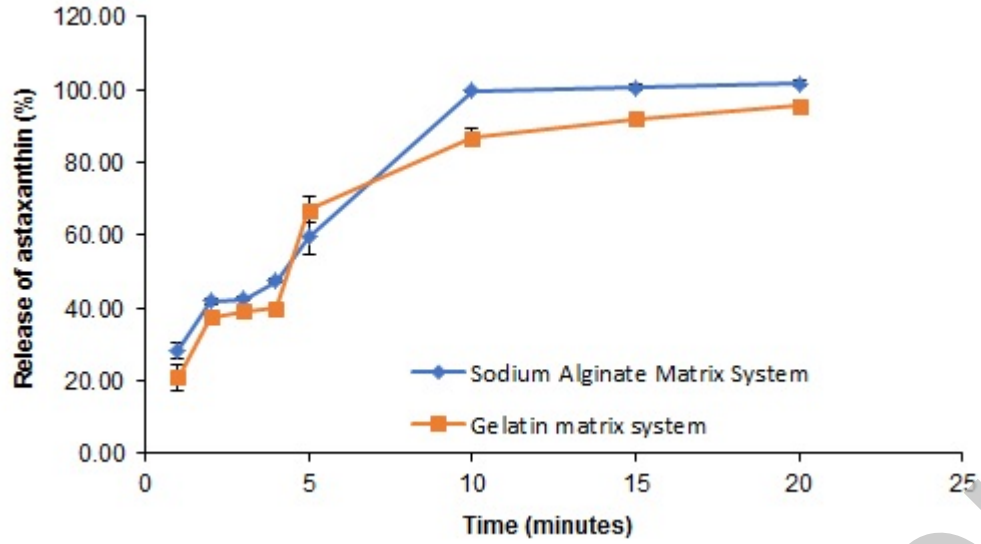


Figure 4. In vitro drug release from TFANE prepared using sodium alginate and gelatin polymer.

CONCLUSION

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

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