Journal of Reports in Pharmaceutical Sciences **2015,4(1), 53-64**

Pharmaceutical Evaluation of *Ziziphus Jujuba* Mucoadhesive Buccal Film

Rahim Bahri-Najafi[a*], Gholam Reza Asghari[b], Hamid Reza Dehlavi[c]

[a]Department of Pharmaceutics, School of Pharmacy and Pharmaceutical Sciences, Isfahan, Pharmaceutical Sciences Research Center, Isfahan University of Medical Sciences, Iran.
[b]Department of Pharmacognosy, School of Pharmacy and pharmaceutical Sciences, Isfahan University of Medical Sciences, Iran.
[c]School of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences, Iran.

ARTICLE INFO

Article Type:
Research Article

Article History:
Received: 2015-02-20
Revised: 2015-04-01
Accepted: 2015-04-15
ePublished:2015-04-20

***Keywords*:**
Buccal film
Caempferol
Eudragit polymer
Gingivitis
Mucoadhesive
Ziziphus jujuba

A B S T R A C T

Buccal mucoadhesive films have attracted great attention among mucoadhesive systems due to their ability to adhere and remain on the oral mucosa and to release their drug content gradually. The aim of the current study was to formulate the *Ziziphus jujuba* aqueous extract as buccal bioadhesive film, which continiously releases the drug at sufficient concentration for reducing the frequency of the administration times. *Ziziphus jujuba* fruit has caempferol compound which considered effective in treating gingivitis because of its anti-bacterial and anti-inflammatory effects. The mucoadhesive films were prepared using hydroxypropyl methylcellulose (HPMC) K4M, K15M and Eudragit RL100 polymers and propylene glycol as plasticizer by using solvent casting method. The physicochemical properties of films such as thickness uniformity, weight variations, swelling index, tensile strength, *ex vivo* adhesion force were evaluated. Films with high concentrations of HPMC K4M and K15M did not have favorable appearance and uniformity. The formulations prepared from Eudragit were transparent, flexible and without bubble. The highest and the lowest percentages of swelling were observed for the films containing HPMC K15M and Eudragit RL100, respectively. Films made of HPMC K15M had adhesion force higher than those containing Eudragit RL100. Drug release kinetics of all formulations followed Higuchi's model and the mechanism of diffusion was considered non-Fickian type. It was concluded that formulations containing Eudragit RL100 were more favorable than others with regard to uniformity and flexibility.

[*]**Corresponding Author: Rahim Bahri-Najafi**, **E-mail: bahrir@pharm.mui.ir**

Introduction

Mucoadhesive drug delivery systems are among the novel drug delivery systems that release the drug in a long time in a slow and controlled manner; providing a high plasma concentration level of the drug and improving the drug efficiency [1]. When buccal muco-adhesive drug formulations come in contact with the mucosa for a long time, they release the drug into blood circulations directly via oral mucosa, and increase the drug bioavailability by reducing the hepatic first pass effect and enzymatic degradation in the gastrointestinal system [2]. Bioadhesion is defined as a state at which two materials, one of which is biological, are held together for a long time through interfacial forces. The adhesion can occur between a biological membrane such as mucosa and a synthetic material like a polymer. In such case, it is referred to as mucoadhesion [3]. The oral mucosa is preferred because of its availability, robust epithelium, and high permeation [4]. Mucoadhesive polymers contain several hydrophilic groups such as hydroxyl, carboxyl, amide and sulphate, which adhere to the mucosa via hydrogen bonds as well as electrostatic and hydrophobic forces. In contact with water, these polymers become hydrated and inflated, and their adhesive parts become exposed [1]. The most appropriate region to place slow-release product in the oral cavity is the upper gum.

Gingivitis ("inflammation of the gum tissue") is a non-destructive periodontal disease. The most common form of gingivitis, and the most common form of periodontal disease overall, is in response to bacterial biofilms (also called plaque) adherent to tooth surfaces, termed *plaque-induced gingivitis*. In the absence of treatment, gingivitis may progress to periodontitis, which is a destructive form of periodontal disease.[5] Ziziphus jujuba commonly called jujube , red date, chinese date or Indian date is a species of *Ziziphus* in the buckthorn family (Rhamnaceae), used primarily as a shade tree that also bears fruit. The fruits and seeds are used in Chinese and Korean traditional medicine, where they are believed to alleviate stress, and traditionally for antifungal, antibacterial, antiulcer, anti-inflammatory, sedative, antispastic, cardiotonic, antioxidant, immunostimulant, and wound healing properties [6] Ziziphus jujuba fruits were used traditionally to improve Gingivitis.

The benefit of the buccal film is that patient does not experience the sensation of presence of the film in the mouth and can follow his or her routine daily activities such as eating, drinking, and talking [4]. Other advantages of this drug formulation is compliance of the patient, ease of taking the drug, and not requiring water to swallow it. Buccal mucoadhesive films of Ziziphus jujuba would be better accepted by the patients for easier and more effective treatment of Gingivitis.

The aim of the current study was preparation and evaluation of buccal mucoadhesive films of Ziziphus jujuba aqueous extract using different types of mucoadhesive polymers; HPMC K4M, K15M and Eudragit RL100, and propylene glycol, as the plasticizer and permeation enhancer; so that the active component can be released at an appropriate rate within 4-6 h after placing the film on the mucosal surface.

Materials and Methods

Materials

Dried fruits of *Ziziphus jujuba* (Kuhpayeh, Esfahan, Iran), HPMC K4M and K15M (Dow Company, USA), Eudragit RL100 (Rohm GmbH & Co.KG. Germany), propylene glycol and acetone (Merck, Germany), ethanol 96% in pharmaceutical grade.

Methods

The fruit of *Ziziphus jujuba* was collected in the kuhpaye from Esfahan province in Iran. The plant material was shade dried at room temperature (20-22˚C) and based on campferol as one of the *Z. jujuba* constituents, was standardized.

HPTLC Standardization of the Ziziphus jujuba extract

Kaempferol is one of the components of *Z. jujuba* fruit pericarp. An accurate and repeatable high-performance thin-layer chromatography method with the help of TLC scanner was done on the fruit pericarp extract for the quantification of

kaempferol . Briefly, 5g of the dried plant material is weighted and extracted with 25 mL water. After acid hydrolysis (1 hrs in 2N HCl, at 95°C), the flavonoids were extracted through ethyl acetate to 5 mL. The sample was spotted in the form of 1 µL spots width on prewashed silica gel TLC AL foil 60 (20 cm × 10 cm with 0.2 mm thickness; E. Merck, Darmstad, Germany) using a Camag nanomat (CAMAG, Muttenz, Switzerland). A constant application rate of 150 nL/s was employed and space between two bands was 10 mm. The slit dimension was kept at 6 mm × 0.45 mm, and 20 mm/s scanning speed was employed. These parameters were kept constant throughout the analysis of samples. The mobile phase consisted of toluene: ethylacetate: formic acid: methanol (30-30-8-2). Plates were developed in ascending order with a CAMAG twin trough glass tank which was pre-saturated with the mobile phase for 30 min; the length of each run was 8 cm. The determination was done at 270 nm using a TLC Scanner 3 (CAMAG, Muttenz, Switzerland). An standard calibration curve in the range of 10 to 200 µg/ml for quantitative analysis was prepared using different concentrations of kaempferol (Sigma Aldrich, USA) as standard material (10, 50, 100, and 200 µg/ml). The relationship between the concentration and peak-height was measured using the minimum square method (R2 value).

HPLC Standardization of the Z. jujuba aqueous pericarp extract

The Rf value for campferol was found to be 0.44 ± 0.022. By the aid of the Camag TLC scanner and wincats software, the calibration curve was determined by linear regression in the range of 10-200 µg/ml (Fig. 1). Then sample obtained from *Z. jujuba* fruit extract was applied and its concentration determined through caempferol calibration curve. Dry extract of the *Z. jujuba* was standardized to % 0.0026 ± 0.0001 (g/100 g) of campferol in the dry plant material.

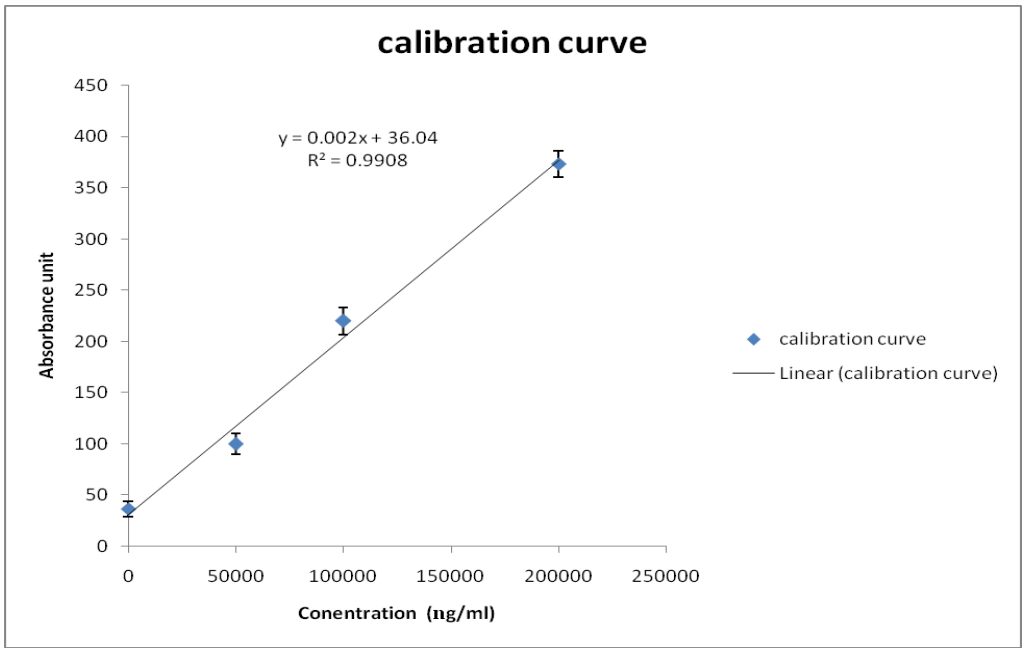

Fig. 1. Calibration curve of *Z. jujuba* aqueous pericarp extract using HPTLC method. Using Camag TLC scanner and wincats software, the calibration curve was determined by linear regression in range of 10-200 µg/ml.

Preparation of the mucoadhesive films

The film was prepared by the solvent casting method. The desired amount of the polymers (HPMC K4M, K15M and Eudragit RL100) were weighed and added to the solvent according to the data given in Table 1. HPMC was dissolved in water and Eudragit was dissolved in alcohol and acetone (v/v 1:4) using a magnetic stirrer (IKA RH, Brazil) at 60 ºC to form a viscous solution. Then, the calculated amount of *Ziziphus jujuba* aqeous extract (10ml equivalent to 69 mg caempfrol) was gradually added to the polymer solution to achieve a transparent and uniform solution. The solution obtained was poured into paraffinized or siliconed plates, and then the plates were placed in the oven (Ehret Gmbh & Co KG, Germany) at 40-55 ºC to evaporate the solvent.

Table 1. The compositions of formulations for *Ziziphus jujuba* buccal mucoadhesive films.

Formulation code	Polymers			10ml *Ziziphus jujuba* aqeous extract equivalent to 69(mg) campferol
	HPMC K4M (mg)	HPMC K15M (mg)	Eudragit RL100 (mg)	
F1	300	-	-	69
F2	400	-	-	69
F3	500	-	-	69
F4	600	-	-	69
F5	700	-	-	69
F6	800	-	-	69
F7	-	300	-	69
F8	-	400	-	69
F9	-	500	-	69
F10	-	600	-	69
F11	-	700	-	69
F12	-	800	-	69
F13	-	-	600	69
F14	-	-	700	69
F15	-	-	800	69
F16	-	-	900	69
F17	-	-	1000	69
F18	-	-	1100	69

Determination of the amount of the campferol in Ziziphu jujuba aqueous extract *film*

The prepared films were dissolved in 100 mL phosphate buffer at pH 6.8. After complete dissolution, the sample absorbance was measured against a blank using the UV-Vis spectrophotometer (UV-1650 PC, Shimadzu, Japan) at the wavelength of 270 nm, and then the drug amount was determined using constructed calibration curves [7].

Study of physicochemical properties of zizphus jujuba aqeous extract films

Appearance of the films was macroscop-ically evaluated. The films should have smooth, soft, transparent appearance without bubble.

Determination of weight and thickness of the films

The weight of three 16 × 25-mm pieces of prepared film was determined using a digital scale (Sartorius Portable GC 803S, Germany), and the thickness was measured by a digital micrometer (Calper GB/T14899-94, China), and the mean values were calculated.

Swelling studies

After determining the primary weight of the film (w_1), the samples were placed on 2% agar plates, and incubated at 37 ºC. At 1-2 h intervals and when the weight became constant, the films were taken away and the extra water on their surface was removed using a filter paper, the weight of inflated films (w_2) were again determined, and the swelling index (SI) was calculated according to following formula [4].

$$SI = (W_2-W_1)/W_1\times100 \quad [1]$$

Film surface pH

The surface pH of buccal film may cause irritation to the buccal mucosa; therefore the surface pH of the films was determined by a pH meter (Metrohm Herisau, Switzerland) using a method described by Bottenberg and coworkers [8]. The 16 × 25 mm piece of film was left in a petridish containing 5 mL distilled water and allowed to swell for 2 h in 37 ºC. The pH was measured by bringing the pH meter electrode near to the surface of the swollen film [4,8].

Determination of mechanical properties of the films

Mechanical properties of the films were determined using SANTAM instrument (STM-1, Iran). In this method, the film was placed between the clamp levers of the equipment, and an extension force at the speed of 30 mm/min was applied to the film. The amount of force and increase in the film length was measured at the time of tearing of the film. The value of film elongation shows the change occurred in the film length after applying the force, which is calculated according to formula below.

Elongation at break (%) = increase in length at breaking point (mm)/original length (mm) × 100 [2]

The maximal force applied to the film, which leads to tearing of it, indicates the tensile strength of the film, and is calculated by formula 3[10,11].

Tensile strength (N/mm^2) = breaking force (N)/cross-sectional area of sample (mm^2) [3]

Study of ex vivo adhesion strength of the film

In this study, mucosal lining of the cow cheek was employed as a model to determine the adhesion strength of the film. To this end, the film was attached to the upper lever of the SANTAM instrument, while a piece of mucosal lining of the cow was made wet by some drops of water and attached to the constant lever of the instrument. Then, the film was kept in full contact with the mucosa for one min. The force required for detachment of the film from the mucosal surface was calculated and reported as the adhesion force of the film [9].

Evaluation of in vitro drug release

Drug release from the selected formulations was performed by a Franz cell (Franz cell device attached bath Gallenkamp Thermostirrer 100, EEC). The film was cut into 16 × 25 mm pieces and placed on 0.45 µm filters in the Franz cell. Phosphate buffer solution with pH 6.8 containing 1% sod was added to the cells and the cells were placed at 37 °C at 50 rpm.

At time intervals of 10, 20, 30, 60, 90, 120, 180, 240, 300 and 360 min, 1 ml of samples were withdrawn and replaced with fresh phosphate buffer. The samples were analyzed by UV-Vis spectrophotometer at the wavelength of 270 nm, and drug concentration was measured using previously constructed calibration curve.

Determination of dissolution parameters and drug release kinetics

The parameters used to compare the drug dissolution profiles were mean dissolution time (MDT) and percentage of dissolution efficiency (%DE)[10].

$$MDT = \sum_{i=1}^{n} t_{mid} \times \Delta M \,/\, \sum_{i=1}^{n} \Delta M \quad [4]$$

where t_{mid} is the midpoints between times t_i and t_{i-1} and ΔM is the amount of the drug dissolved between times t_i and t_{i-1}.

$$DE\% = (AUC_{0-t} / y_{100} \times t) \times 100 \quad [5]$$

where AUC_{0-t} is the area under the dissolution curve up to the time t, and y_{100} is the loading dose.

In order to describe the kinetic of drug release from Zizipus jujuba aqeous extreact buccal films, in vitro release data of selected formulations were fitted in zero order, first order, and Higuchi models.

$$M_t = k_0 t \quad \text{(Zero order)} \quad [6]$$

$$Ln (M_\infty - M_t) = k_1 t \quad \text{(First order)} \quad [7]$$

$$M_t = k_H t^{0.5} \quad \text{(Higuchi)} \quad [8]$$

Furthermore, drug release mechanism was determined according to the Korsmeyer-Peppas equation.

$$Log (M_t/M_\infty) = logk + nlogt \quad [9]$$

Where, M_∞ is the amount of drug released after infinite time, M_t, cumulative amount of drug released at any specified time (t), k, release rate constant, and n, the release exponent [12,13].

Results

The results related to the measurements of weight, thickness, swelling index and drug content are demonstrated in Table 2. The weight of the films was found in the range of 23.4 ± 0.20 to 121.5 ± 0.52 mg and the film thicknesses were observed in the range of 95 ± 3.60 to 283 ± 3.05 mm. The percentage swelling of various formulations ranged between 25.49 ± 0.76 and 61.26 ± 0.44 after 2 h. The assayed drug content of films varied between 6.11 ± 0.031 and 6.27 ± 0.045 mg. The surface pH of all films was found to be in the range of 6.24 ± 0.04 to 6.65 ± 0.03.

The results obtained for adhesion force and the mechanical properties of the films including the percentage of elongation and tensile strength are given in Table 3. The *in vitro* drug release test was performed for selected formulations which are shown in Figs 1-3. As seen, the percentage of drug release from formulations F3, F4, and F5 containing HPMC K4M at the end of 210 min were 87%, 87.6%, and 82.5%, respectively. Formulations F9, F10, and F11 containing HPMC K15M released 87%, 88.8%, and 78.9% of their drug content at the end of 270 min. The drug release percentage for formulations containing Eudragit RL100 F14, F15, F16, F17, and F18 were 93%, 93.3%, 85.5%, 93.9%, and 89% at the end of 360 min, respectively. Parameters related to the drug dissolution including MDT and %DE are also shown in Tables 4-6. Drug release kinetic parameters along with *n*, *k*, and R^2 values are provided in Tables 4-6.

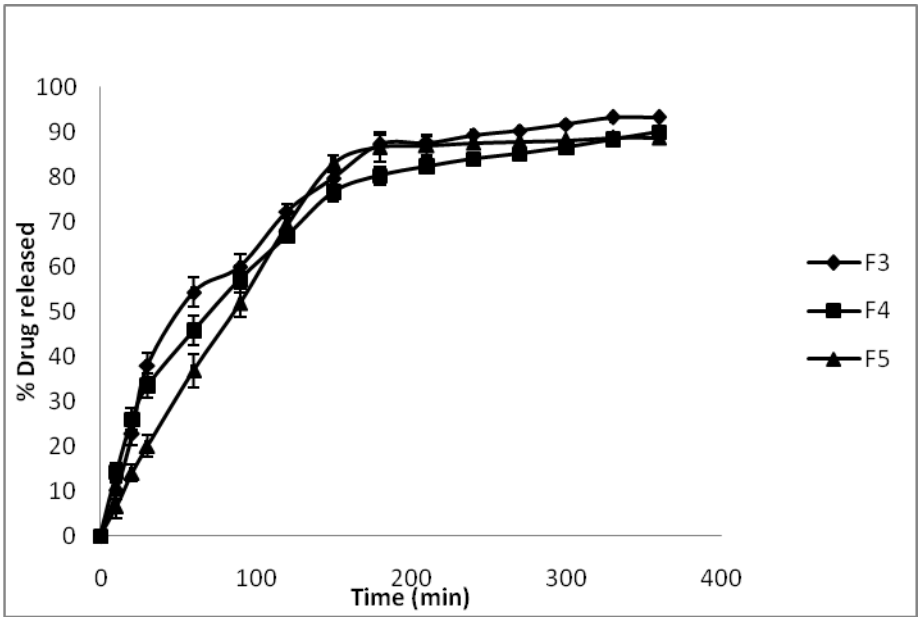

Fig. 2. Drug release profiles of ziziphus jujuba aqueous extract optimized films with HPMC K4M

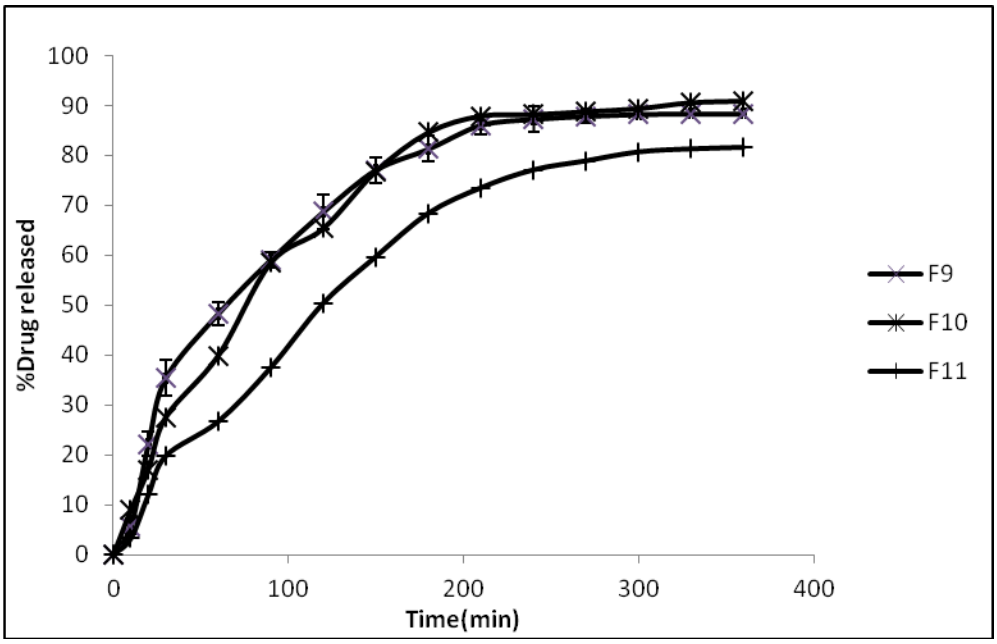

Fig. 3. Drug release profiles of ziziphus jujuba aqueous extract optimized films with HPMC K15M.

Table 2. Physical properties of *ziziphus jujuba* aqeous extract buccal mucoadhesive films.

Formulation code	Mean weight (mg) ± SD	Mean thickness (µm) ± SD	Swelling index (%)		Drug content[Caempferol] (mg) ± SD
			after 1 h	after 2 h	
F1	24.4 ± 0.20	95 ± 3.60	31.27 ± 0.40	45.26 ±0.11	6.16 ± 0.046
F2	27.1 ± 0.40	118 ± 2.64	32.64 ± 0.16	46.78 ± 0.20	6.17 ± 0.031
F3	33.5 ± 0.26	130 ± 2.52	33.06 ± 1.00	49.51 ± 0.67	6.20 ± 0.036
F4	35.8 ± 0.20	141 ± 3.05	36.12 ± 0.70	53.60 ± 0.61	6.23 ± 0.030
F5	43.4 ± 0.26	154 ± 2.08	37.55 ± 0.60	54.87 ± 0.19	6.25 ± 0.041
F6	43.6 ± 0.30	163 ± 2.52	38.19 ± 0.30	55.48 ±0.27	6.23 ± 0.035
F7	27.3 ± 0.26	125 ± 2.52	31.85 ± 0.71	47.52 ± 0.19	6.27 ±0.045
F8	38.8 ± 0.30	133 ± 2.08	32.62 ± 1.50	48.89 ± 0.27	6.11 ± 0.031
F9	37.5 ± 0.20	145 ± 3.55	33.41 ± 0.90	51.36 ± 0.63	6.13 ± 0.052
F10	41.3 ± 0.36	151 ± 3.63	36.67 ± 0.64	55.71 ± 0.80	6.14 ± 0.032
F11	51.8 ± 0.40	162 ± 2.08	39.50 ± 0.27	57.43 ± 0.67	6.21 ± 0.040
F12	56.5 ± 0.20	169 ± 2.52	41.95 ± 0.61	61.26 ± 0.44	6.12 ± 0.056
F13	65.5 ± 0.35	189 ± 2.67	17.43 ± 0.26	25.49 ± 0.76	6.21 ± 0.027
F14	68.9 ± 0.67	221 ± 3.51	18.52 ± 0.20	27.51 ± 0.80	6.18± 0.031
F15	74.6 ± 0.20	247 ± 3.51	18.95 ± 0.87	28.91 ± 0.67	6.13± 0.015
F16	96.6 ± 0.42	256 ± 2.08	21.43 ± 1.50	30.80 ± 0.42	6.19± 0.020
F17	104.6 ± 0.30	266 ± 2.87	22.75 ± 0.72	33.74 ± 0.40	6.12± 0.020
F18	121.5 ± 0.52	283 ± 3.05	25.33 ± 0.52	34.55 ± 0.71	6.15± 0.032

Table 3. Mechanical properties and *ex vivo* bioadhesive strength of *ziziphus jujuba* aqueous extract films.

Formulation code	Elongation at break (%)	Tensile strength)N/mm^2)	Bioadhesion force (N)
F1	52.00	15.88	6.34
F2	50.28	17.72	6.72
F3	46.86	18.32	7.27
F4	45.14	18.57	7.81
F5	40.86	19.89	8.25
F6	39.71	20.19	8.55
F7	38.28	19.27	8.19
F8	37.43	19.41	8.68
F9	35.71	20.75	9.50
F10	32.86	22.15	10.23
F11	30.86	22.58	10.85
F12	26.57	23.40	11.38
F13	77.46	13.61	4.37
F14	74.86	14.03	4.56
F15	74.00	14.28	4.82
F16	72.28	14.91	5.11
F17	70.86	15.10	5.25
F18	65.71	15.71	5.62

Discussion

One of the aims of preparation of novel drug delivery systems is to provide drug formulations with the least adverse effects and maximal therapeutic effect; such that by taking the formulation the patient experience the drug effects more rapidly at lower doses of the drug. To this end, film formulations comprise one of the major drug formulations, which have been studied extensively. Considering the comfort of patients in taking film formulations, the delivery system deserves receiving more attention in the treatment of chronic diseases such as Gingivitis.

Since the mucosa of the oral cavity has non-keratinized epithelium, it has a better penetration for drug release compared with the body skin [1]. Furthermore, it should be noted that mucoadhesive films are more flexible than mucoadhesive tablets and the patients use them with more comfort. Also the films do not have the limitation of relatively short residence time, as observed by the oral gels [1]. Thus, mucoadhesive buccal films of Ziziphus jujuba aqeous extract can be an appropriate alternative for other dosage forms.

The results obtained from evaluation of various formulations demonstrated that the films containing high concentrations of HPMC K4M and K15M do not have desired appearance and uniformity characteristics. Moreover, longer time was required to prepare a transparent and uniform polymer solution and the air bubbles trapped in the polymer solution, were removed with difficulty. In contrast, the formulations containing Eudragit RL100 polymer had a transparent and uniform appearance, without air bubble. Determination of Caempferol content showed that the drug was uniformly dispersed in the film. The films containing both two grades of HPMC showed a higher swelling index than those prepared by Eudragit RL100 (Table 2) .In addition, the results of our study revealed that the inflation percent of films was increased as the polymer concentrations increased.

The film surface pH was measured to determine the possibility of side effect due to acidic or alkaline pH of films that could hurt buccal mucosa [11]. The surface pH of all prepared films was found near the neutral pH indicating its compatibility with buccal pH, causing no irritation to the mucosa and achieves patient compliance.

The results obtained from the tensile strength test of the films showed that formulations containing HPMC K15M had the highest tensile strength and the lowest elongation. However, the buccal films prepared by Eudragit RL100 showed the maximum elongation percent and the minimum tensile strength among the formulations. Increased elasticity of Eudragit films decreases the force required for the film tension. In the study performed by Khan TA and colleagues,[11] mechanical properties of chitosan films were evaluated. They reported an amount of 21.35 to 67.1% for elongation at break and 59.87 to 67.11 (N/mm^2) for tensile strength. For mucoadhesive buccal administration, strong and flexible films are more preferable. In this respect, the buccal films prepared by Eudragit RL100 (F13 in Table 1) was softer and more flexible compared with the other formulations.

From ex-vivo mucoadhesive strength studies, it was observed that adhesion force of the films depends on the type of the polymer used; such that formulations containing HPMC (F12) have higher adhesion force than those prepared by Eudragit RL100 (F13). It was also observed that the mucoadhesive strength of the films was improved as the concentration of the polymers increased. The mucoadhesiveness of the formulations was satisfactory for maintaining buccal films in upper gum for desired period of time. In the study performed by Vinod and coworkers mucoadhesive polymers and their mechanism of mucoadhesion were completely explained [14].

The DE% and MDT were used to compare efficiency of the type and concentrations of the polymers in drug release. According to the values of % DE, it was concluded that drug release was slightly decreased with increasing the polymer concentration. The MDT values of Ziziphus jujuba aqueous extract buccal films with HPMC K4M and HPMC K15M increase as the polymer concentration increase (Tables 4 and 5).

The films containing Eudragit RL100 released the highest amount of the drug up to the end of the drug release time with a slow release profile. The calculated MDT values for all the samples investigated (Table 4-6) support this finding.

As shown in Table 6, formulation F17 containing 1000 mg Eudragit RL100, represented better *in vitro* dissolution profile as compared with the rest of the formulations.

The drug release mechanisms for various formulations were determined by fitting the data into various kinetic models. In all the formulations, correlation coefficient of the Higuchi's model was higher than correlation coefficients of other kinetics (Table 4-6). Thus, in drug release of all formulations, the Higuchi's kinetics was dominant.

Table 4. The release parameters of optimized *ziziphus jujuba* aqeous extract films with HPMC K4M.

Formulation code	Kinetic parameters		Kinetic models (R^2)			Peppas parameters		
	DE (%)	MDT (min)	Zero order	First order	Higuchi	n	k	R^2
F3	61.98	61.40	0.981	0.723	0.989	0.689	36.47	0.945
F4	57.77	62.93	0.979	0.765	0.991	0.572	22.96	0.986
F5	55.95	74.93	0.985	0.800	0.994	0.896	109.65	0.995

Table 5. The release parameters of selected *ziziphus jujuba* aqeous extract films with HPMC K15M.

Formulation code	Kinetic parameters		Kinetic models (R^2)			Peppas parameters		
	DE (%)	MDT (min)	Zero order	First order	Higuchi	N	K	R^2
F9	59.97	72.43	0.977	0.681	0.982	0.775	59.70	0.982
F10	62.64	74.27	0.905	0.737	0.968	0.740	53.21	0.985
F11	49.11	96.50	0.982	0.660	0.993	0.924	167.88	0.953

Table 6. The release parameters of optimized *ziziphus jujuba* aqeous extract films with Eudragit RL100.

Formulation code	Kinetic parameters		Kinetic models (R2)			Peppas parameters		
	DE (%)	MDT (min)	Zero order	First order	Higuchi	n	k	R^2
F14	69.10	93.33	0.986	0.776	0.990	0.733	53.70	0.949
F15	65.14	108.63	0.982	0.689	0.992	0.817	88.92	0.953
F16	57.08	119.63	0.979	0.781	0.986	0.965	228.56	0.946
F17	61.96	122.43	0.985	0.852	0.992	0.815	99.31	0.971
F18	60.29	116.36	0.988	0.673	0.996	0.760	76.91	0.973

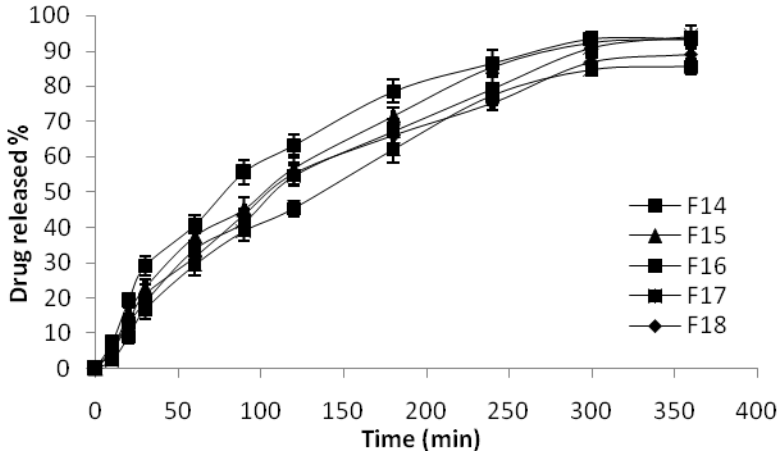

Fig. 4. Drug release profiles of ziziphus jujuba aqueous extract optimized films with Eudragit RL100.

The in vitro release data was fitted into korsmeyer- peppas equation to determine the mechanism of drug release from the films. When *n* value is 0.5 or less, the Fickian diffusion phenomenon dominates, and *n* value between 0.5 and 1 is non-Fickian diffusion (anomalous transport). The mechanism of drug release follows case-II transport when the *n* value is 1 and for the values of *n* higher than 1, the release is characterized by super case-II transport [12, 13]. Drug diffusion for all formulations was of non-Fickian type. Non-Fickian drug release means that the drug is released from the film via diffusion mechanism and also another process called chain relaxation [15]. The diffusion that is not according to the Fickian type is a step toward continuous and uniform drug release; as it is similar to the drug release of zero order [16].

Conclusion

Comparing the results obtained in the present study, the most appropriate formulation was F16, containing Eudragit RL100, which showed desirable physical and appearance characteristics, and released almost 96% of its drug content within six hours in a controlled and slow manner according to the non-Fickian model.

Conflict of interest

Authors certify that no actual or potential conflict of interest in relation to this article exists.

Acknowledgements

Financial assistance from Faculty of Pharmacy, Isfahan University of Medical Sciences is gratefully acknowledged.

References

[1] Shaikh R, Singh TRR, Martin James Garland MJ, Woolfson AD, Donnelly RF. Mucoadhesive drug delivery systems. JSBP. 2011;3:89.
[2] Saurabh R, Malviya R, Sharma PK. Trends in buccal film: Formulation characteristics, recent studies and patents. European J Appl Sci. 2011;3:93-101.
[3] Tangri P, Madhav NS. Oral mucoadhesive drug delivery systems: a review. IBJ. 2011;2229:7499.
[4] Muzib YI, Kumari KS. Mucoadhesive buccal films of glibenclamide: Development and evaluation. Int J Pharm Investig. 2011;1:42.
[5] Martin JA, Grill AC, Matthews AG, Vena D, Thompson VP, Craig RG, et al. Periodontal diagnosis affected by variation in terminology. JOP. 2013;84:606-13.
[6] Mahajan R, Chopda M. Phyto-Pharmacology of Ziziphus jujuba Mill-A plant review. Pharmacogn Rev. 2009;3:320.

[7] Ramniklal HP. Design and optimization of oral osmotic pump based controlled release for glipizide. 2010.
[8] Bottenberg P, Cleymaet R, Muynck C, Remon J, Coomans D, Michotte Y, et al. Development and testing of bioadhesive, fluoride-containing slow-release tablets for oral use. J Pharm Pharmacol. 1991;43:457-64.
[9] Patel Geeta M, Patel Anita P. A novel effervescent bioadhesive vaginal tablet of ketoconazole: Formulation and in vitro evaluation. Int J Pharm Tech Res. 2010;2:656-67.
[10] Gohel M, Panchal M. Novel Use of Similarity Factors f 2 and S d for the Development of Diltiazem HCl Modified-Release Tablets Using a 32 Factorial Design. DRUG DEV IND PHARM. 2002;28:77-87.
[11] Goudanavar P, Bagali R, Patil S, Chandashkhara S. Formulation and in-vitro evaluation of mucoadhesive buccal films of Glibenclamide. Der Pharm Letter. 2010;2:382-7.
[12] Dash S, Murthy PN, Nath L, Chowdhury P. Kinetic modeling on drug release from controlled drug delivery systems. Acta Pol Pharm. 2010;67:217-23.
[13] Kanjickal DG, Lopina ST. Modeling of drug release from polymeric delivery systems—a review. CRIT REV THER DRUG. 2004;21.
[14] Vinod K, Rohit Reddy T, Sandhya S, David Banji VRB. Critical review on mucoadhesive drug delivery systems. Hygeia JD Med. 2012;4:1-5.
[15] Verma A, Bansal A, Ghosh A, Pandit J. Low molecular mass chitosan as carrier for a hydrodynamically balanced system for sustained delivery of ciprofloxacin hydrochloride. Acta Pharm. 2012;62:237-50.
[16] Colombo P, Conte U, Gazzaniga A, Maggi L, Sangalli M, Peppas N, et al. Drug release modulation by physical restrictions of matrix swelling. Int J Pharm. 1990;63:43-8.

