Original Article

Pharmaceutical and Biomedical Research

The effect of *Plantago major* seed mucilage combined with carbopol on the release profile and bioadhesive properties of propranolol HCl buccoadhesive tablets

Jafar Akbari[1,2], Majid Saeedi[1,2*], Katayoun Morteza-Semnani[2,3], Behnaz Zarrabi[1], Seyyed Sohrab Rostamkalaei[4], Hamid Reza Kelidari[2]

[1]Department of Pharmaceutics, Faculty of Pharmacy, Mazandaran University of Medical Science, Sari, Iran
[2]Pharmaceutical Sciences Research Center, Mazandaran University of Medical Science, Sari, Iran
[3]Department of Medicinal Chemistry, Faculty of Pharmacy, Mazandaran University of Medical Science, Sari, Iran
[4]Student Research Committee, Mazandaran University of Medical Science, Sari, Iran

Abstract

Buccoadhesive drug delivery systems have distinct advantages in comparison with oral administration. Plant exudates like gum or mucilage are being studied for their use as pharmaceutical adjuvant. The aim of this study is to evaluate the properties of the *Plantago major* seed mucilage as a mucoadhesive agent and propranolol hydrochloride is chosen as a model drug**.** Mucoadhesive tablets of propranolol hydrochloride were formulated by combination of two mucoadhesive polymers include Carbopol 934P and *Plantago major* mucilage, and properties such as *in vitro* drug release, swelling, erosion, mucoadhesive force were studied. The results show increase in bioadhesive strength and decrease in release rate with increase in percent of Carbopol 934P, as F13 (containing Carbopol 934P alone) and F8 (containing mucilage alone) show the highest bioadhesive strength and highest release rate respectively and these results were matched to swelling results which decrease in swelling of matrices results in decrease in bioadhesion. Matrices with both *Plantago major* mucilage and Carbopol have the optimum drug release in bioadhesive formulation of propranolol tablets.

Keywords: *Plantago major,* mucilage, mucoadhesive, DSC, FTIR

Introduction

The development of mucoadhesive polymers may be traced back to 1947, when gum tragacanth and dental adhesive powders were combined to form a vehicle for applying penicillin to oral mucosa. An improvement in this system resulted when CMC and petrolatum were combined to form the vehicle (1). In recent years, much interest has been shown in the development of bioadhesive systems. These dosage forms can be administered by different routes such as ocular, buccal, nasal, rectal, vaginal) either for local therapy or for systemic drug delivery. In particular, the buccal route appears to offer a series of advantages compared with other routes, such as rapid onset of action, high blood supply, avoidance of first pass effect and exposure of drug to gastrointestinal tract (2). Buccal drug delivery necessitates the use of

* E-mail: **majsaeedi@gmail.com**

mucoadhesive polymers as a means of prolonging the resistance time of the dosage form on the absorbing membrane as well as localizing drugs in a particular region (3). Mucoadhesion is provided by the formation of non-covalent bonds such as hydrogen bonds and ionic interactions or physical entanglements between the mucus gel layer and polymers (4). Typical polymers that have been used as mucoadhesive drug carriers are poly acrylic acid, poly meth acrylic acid, cellulose derivatives, poly ethylene oxide, lectin and chitosan, PAA and its cross-linked commercial forms (5). By active using of copolymers, polymer conjugates and inter polymer complexes, the mucoadhesive properties of polymers have been improved. The following characteristics are the basic requirements needed for a successful buccal delivery: a bio-adhesive to retain the drug in oral cavity and maximize the intimacy of contact with mucosa, a vehicle that releases the drugs at an appropriate rate under the conditions prevailing in the mouth and strategies for overcoming the low permeability of the oral mucosa. the bioadhesive bonds are formed by three steps: wetting and swelling of mucoadhesive polymer, entanglement of polymer and mucin chains, and formation of weak chemical bonds between entangled chains and polymer (6). Mucilage and gums are well known since ancient times for their medicinal use. Today the gums are being used as pharmaceutical excipients. Mucilage generally are carbohydrate polymer which obtained from woody and non woody plant parts such as bark, seeds, sap, roots, rhizomes, fruits, and leaves. Mucilage are used for their binding, thickening,

stabilizing, humidifying properties, disintegrating and release controlling in medicines (7, 8). Mucilage from natural sources hydrate and swells on contact with water and has been used for the preparation of single unit dosage forms (9). *Plantago major* is a member of Plantaginaceae family (10). The plant produces large amount of seeds. The seeds are located in capsules (8-16 per capsule) and become sticky in humid condition due to swelling of the polysaccharides present in the seed coat. The seeds contain the monosaccharides, disaccharides and trisaccharides. The outer seed coat, contain carbohydrate polymers that swell in contact with water and form mucilage with high viscosity. These polysaccharides are composed of xylose, arabinose, galactorunic acid, glucuronic acid, rhamnose, galactose and glucose (11). In this work, the *Plantago major* seed mucilage characteristics such as mucoadhesive strength, swelling, erosion and drug release rate in addition to carbopol 934P (a muccoadhesive polymer) were studied.

Materials and methods

Propranolol Hydrochloride powder, HCl, Potassium di-hydrogen phosphate were obtained from Merck, Germany. Carbopol 934P (B.F. Goodrich, USA), *Plantago major* seed was purchased from herbal drug market (Sari, Iran) and NaOH from Dr. Mojallali (Iran). Mg stearate was obtained from Roche (Germany).

Extraction of mucilage
10 mL of 0.1 N HCl was heated to boil in a 100 mL corning flask. The flask was removed

from the flame and 1g test sample of dry seed was added to it. Heating resumed and the process of dissolution of the seed husk was observed. When all seeds had changed color the flask was finally removed from the flame and the solution (while being hot) was filtered through clean muslin cloth. The seeds were washed up to three times in 5ml of hot water and the solution obtained each time was filtered. The combined filtrate, containing the dissolved mucilage was mixed with 60 mL of 95% ethyl alcohol, stirred and allowed to stand for 5h. Finally the supernatant liquid was decanted off and the beaker containing the precipitate was dried an over maintained at 50 ^{o}C for 10 hours (8).

Preparation of mucoadhesive Matrix Tablets

For preparation of mucoadhesive tablets a 9 mm flat faced punches on a hydraulic press were used. The materials for each tablet (Table 1) were weighed and were sufficiently blended in a planetary mixer (Erweka, Germany) for 10min. magnesium stearate (1%w/w) was then added, followed by further mixing for 2 min. mixed and introduced into the die and compacted at compression using 1% (M/M) magnesium stearate. The tablet properties (crushing, strength, friability, mass variation and content uniformity) were determined by current procedure (13,14).

Table1 Formulation comparison of investigated propranolol hydrochloride mucoadhesive matrix tablets

Formulation code	Propranolol HCl (mg)	*P. major* mucilage (mg)	Carbopol 934P (mg)	Mg stearate (mg)
F1	80	10	70	1.6
F2	80	20	60	1.6
F3	80	30	50	1.6
F4	80	40	40	1.6
F5	80	50	30	1.6
F6	80	60	20	1.6
F7	80	70	10	1.6
F8	80	40	-	1.2
F9	80	80	-	2.4
F10	80	160	-	1.2
F11	80	-	40	1.6
F12	80	-	80	1.6
F13	80	-	160	2.4
F14	-	160	-	1.6
F15	-	-	160	1.6

In vitro drug release studies

The dissolution tests were performed to the basket method (USP pharmacopeia 24). A dissolution apparatus (Caleva 8ST, Germany) was employed with a stirring rate of 100 rpm. The dissolution medium was 900 mL phosphate buffer (pH 6.8). Samples of the solution were withdrawn at benefit time intervals. The dissolution media was replaced by fresh dissolution fluid to maintain a constant volume. The solution was passed through a filter (Watman, USA) and then concentration of propranolol hydrochloride in solution was measured with an ultraviolet spectrophotometer (Varian, Australia) at a wavelength of 289 nm after suitable dilution with the dissolution medium when necessary (n = 3).

Evaluation of tablets

Properties include friability crushing strength, mass variation of tablets were determined by standard procedure (13). The content uniformity of active ingredient was confirmed based on British pharmacopoeia method (8). The tensile strength (T) of tablets (measure of the stress necessary to cause diametric fracture of the compact) was determined from the mean data obtained from the hardness test that we did on tablets (n = 10) Using the Erweka hardness tester (TBH30MD, Germany). The T values were computed from the following equation:

$$T = 2p/\pi * D_t \qquad \text{Eq. (1)}$$

P: Load applied on the tablet that causes diametric fracture of the tablet that causes diametric fracture of the tablet

D_t : Thickness of tablet (m)

Drug release kinetics

Various mathematical equations were tested for describing the kinetics of drug release from mucoadhesive tablets (zero-order, first order, Higuchi)

$$Q_t = K_0 \cdot t \qquad \text{Eq. (2)}$$
$$ln Q_t = ln Q_0 - K_{1t} \qquad \text{Eq. (3)}$$
$$Q_t = K_H \, t^{1/2} \qquad \text{Eq. (4)}$$

Q_t : The amount of drug released in time t
Q_0 : The initial amount of drug in tablet
$K_0 . K_1 K_H$: Release rate constant for zero order, first order, Higuchi model, respectively

In order to define a model which will represent a better fit for the formulations, dissolution data can be further analyzed by Peppas and Korsemayer equation.

$$\frac{M_t}{M_\infty} = K_p \, t^n \qquad \text{Eq. (5)}$$

M_t: Amount of drug released in time t
M_∞: Total amount of drug that must be released at infinite time
K_p: Constant
n: release exponent indicating the type of drug release mechanism
n: for a cylinder is <0.45 for Fickian release >0.45 and <0.89 for non- Fickian
0.89 for the case2 release
>0.89 for super case 2 type release (15).
Criteria for selecting the most appropriate model were based on the best goodness of fit and smallest sum of squared residuals.

Determination of bioadhesive strength

For this purpose a tensile tester apparatus was designed similar to a tensile tester apparatus (Instron model 4301) and the

bioadhesive strength of tablets was measured according to previously published method by a tensile tester apparatus. After isolation of hairless abdominal skin of the rat the dorsal section (mucosa part) was fixed on the head of diffusion cell and filled with phosphate buffer with pH 6.8. The same conditions were used exactly according to previously published method (16).

Matrix swelling studies
The study was carried out in the USP/NF dissolution apparatus No.1 (Caleva 8ST, Germany). the dry polymer matrices were accurately weighted, placed in dissolution baskets, and immersed in 900 mL phosphate buffer (pH 6.8) maintained at 37°C in the dissolution vessels. At regular intervals, the pre-weighed basket-matrix system was withdrawn from the dissolution vessel, lightly bottled with a tissue paper to remove exes test liquid and re-weighed. The percent water uptake (degree of swelling due to absorbed liquid) was estimated in certain times according to the following equation:

$$\%WU = \frac{W_s - W_i}{W_i} * 100 \qquad \text{Eq. (6)}$$

%WU: The percent of water uptake (n=3).
W_s: The weight of swelled matrix in certain time (n = 3).
W_i: The initial starting weight in the matrix tablet (n = 3).

Matrix erosion studies
The standard USP/NF dissolution apparatus No.1 (Caleva8ST, Germany) was used for this purpose, the dry matrix was weighed, placed in dissolution baskets, and subjected to dissolution in 500 mL of 0.05 M phosphate buffer (pH 6.8) maintained at 37°C with the basket rotating at 100 rpm. At regular intervals basket-matrix assemblies were removed from the dissolution vessels and dried to a constant weight in a hot air oven at 60°C (17).
The percentage of matrix erosion (%E) at time, (t) was estimated from the following equation:

$$\%E = \frac{W_i - W_t}{W_i} * 100 \qquad \text{Eq. (7)}$$

W_i: The initial starting weight of the matrix
W_t: The weight of matrix subjected to erosion for time t
And the percentage of remaining matrix, compute from the Eq. (8)
%Remaining = 100-%E   Eq. (8) (n = 3)

Statistical analysis
A one-way ANOVA with a turkey's post hoc (SPSS 12), test was analyzed the dissolution and bio adhesive data obtained for each batch of formulation in order to compare the rate of drug release from the mucoadhesive tablets. The confidence limit was set at 95%.

Results
The swelling factor of 1g of *P. major* was 14.3 ± 1.06 mL (637.2 ± 43.9%) according to the above method. Sharma and Koul reported 8.33 mL swelling factor for *P. major* in their study (12). The yield of mucilage extraction from *P. major* seeds was 20.9%. The characteristics of evaluated tablets are shown in table 2.

Mucoadhesive tablets were prepared and analyzed as described above. The release rate of propranolol from matrix tablets increased, as the ratio of mucilage: Carbopol 934P increased in formulation F1 to F7 (Fig. 1). And results show the release rate decreases, as the amount of mucilage and carbopol increased in formulation F8-F13 (Fig. 2). The lowest release rate was with formulation F1 (Containing 10 mg *P. major* mucilage and 70 mg Carbopol 934P) and the highest release rate was with formulation F7 (Containing 70 mg *P. major* mucilage and 10 mg Carbopol 934P) and the percent of cumulative drug release after 2hr for F8-F13 were 56.24, 45.2, 32.18, 73.98, 22.68, 12.31 respectively. The lowest release rate was observed with formulation F13 (Containing 160 mg Carbopol 934P) and the highest was with F11 (Containing 40 mg Carbopol 934P). The significant difference was observed between formulations ($p < 0.001$).

Table 2 Characteristics of propranolol hydrochloride tablets prepared with different ratios of *P. major* mucilage and Carbopol934P.

Formulation code	Hardness*(Kg/cm²) (n = 10)	Friability (%w/w) (n = 10)	Tensile strength*(MN/m²) (n = 10)	Assay (%) (n = 20)
F1	3.65 ± 0.16	1.22 ± 0.11	0.43 ± 0.05	79.7 ± 1.4
F2	3.82 ± 0.22	1.03 ± 0.05	0.45 ± 0.06	80.1 ± 1.5
F3	4.10 ± 0.19	0.96 ± 0.06	0.52 ± 0.06	79.6 ± 2.8
F4	3.25 ± 0.18	1.02 ± 0.04	0.33 ± 0.07	80.2 ± 2.1
F5	3.48 ± 0.29	0.98 ± 0.07	0.39 ± 0.05	78.8 ± 0.8
F6	3.57 ± 0.25	0.91 ± 0.05	0.42 ± 0.06	79.5 ± 0.7
F7	4.75 ± 0.29	0.92 ± 0.05	0.58 ± 0.07	81.4 ± 0.81
F8	4.95 ± 0.37	0.86 ± 0.06	0.65 ± 0.05	78.0 ±1.2
F9	5.57 ± 0.35	0.81 ± 0.05	0.74 ± 0.06	81.1 ± 0.83
F10	4.91 ± 0.28	0.91 ± 0.05	0.61 ± 0.07	78.9 ± 1.7
F11	5.23 ± 0.32	0.82 ± 0.07	0.68 ± 0.06	79.3 ± 0.8
F12	5.38 ± 0.23	0.86 ± 0.08	0.67 ± 0.04	80.2 ± 1.3
F13	4.98 ± 0.34	0.83 ± 0.06	0.72 ± 0.05	79.4 ± 0.6

*Data are shown as mean ±SD
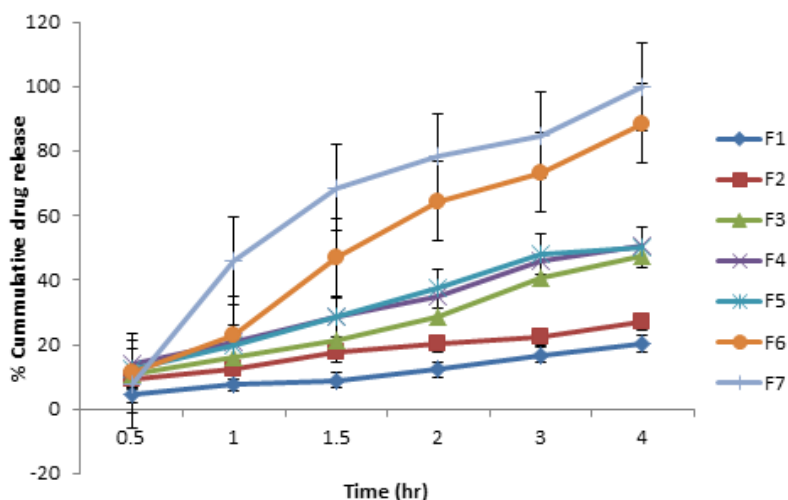
Figure 1 Comparison of release profile of propranolol hydrochloride from formulation F1-F7 (n = 3).
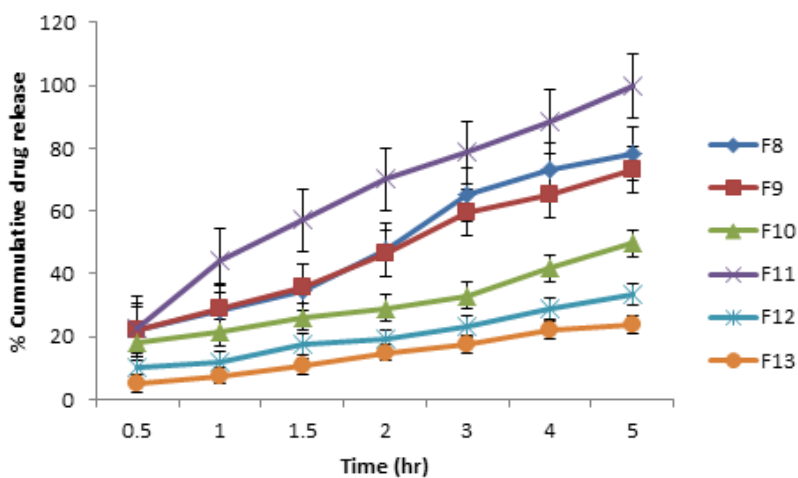

Figure 2 Comparison of release profile of propranolol hydrochloride from formulation F8-F13 (n = 3)

Dissolution rate data were analyzed based on equations 2-5 and their results are listed in table3. The results showed that the amount and type of the polymer affect the release kinetic of propranolol from tablets, the highest correlation coefficient were achieved with the various models.

Table 3 The kinetic release parameters for propranolol mucoadhesive tablets formulations

| Formulation code	Zero-order model			First-order model			Higuchi model			Peppas model			
	K_0 %min	r^2	ss	K_1 1/min	r^2	ss	K_H	r^2	ss	K_p %min	n	r^2	ss
F1	0.0006	0.9840	11174.2	-0.0008	0.9916	6057.4	0.0180	0.9915	38045.5	0.0037	0.7317	0.9942	247.6
F2	0.0007	0.9767	24065.7	-0.0010	0.9843	15075.4	0.0199	0.9865	1678.9	0.0143	0.5445	0.9895	241.0
F3	0.0012	0.9422	18732.6	-0.0020	0.9797	5384.8	0.0336	0.9859	13427.0	0.0112	0.6661	0.9862	447.9
F4	0.0011	0.9307	24724.6	-0.0021	0.9797	9808.2	0.0329	0.9866	1549.4	0.0186	0.6013	0.9890	202.6
F5	0.0013	0.9383	22472.4	-0.0025	0.9512	5085.0	0.0359	0.9714	6260.3	0.0163	0.6274	0.9627	753.5
F6	0.0032	0.9383	22472.4	-0.0025	0.9512	5085.0	0.0753	0.9685	104829	0.0014	1.2773	0.9761	262.5
F7	0.0038	0.8037	9718.2	-0.0372	0.7381	622808	0.0853	0.8987	267147	0.000	2.5919	1.000	0.000
F8	0.0014	0.8816	36561.4	-0.0046	0.9920	5342.3	0.404	0.9629	2177.9	0.0296	0.6154	0.9982	7.4021
F9	0.0014	0.9252	30572.9	-0.0037	0.9909	5654.2	0.0401	0.9629	2177.9	0.0305	0.5653	0.9682	11.04
F10	0.0012	0.9777	25318.1	-0.0023	0.9990	8388.2	0.0334	0.9972	846.0	0.0266	0.5295	0.9936	92.4625
F11	0.0033	0.9256	13794.9	-0.0283	0.8097	20277.1	0.0727	0.9761	2712.8	-	-	-	-
F12	0.0010	0.9162	19318.2	-0.0016	0.9468	8041.4	0.0292	0.9694	12964.4	0.0100	0.6630	0.9795	668.3
F13	0.005	0.9915	22530.7	-0.0006	0.9963	17088.9	0.0131	0.9940	2406.9	0.00089	0.549	0.9948	117.5
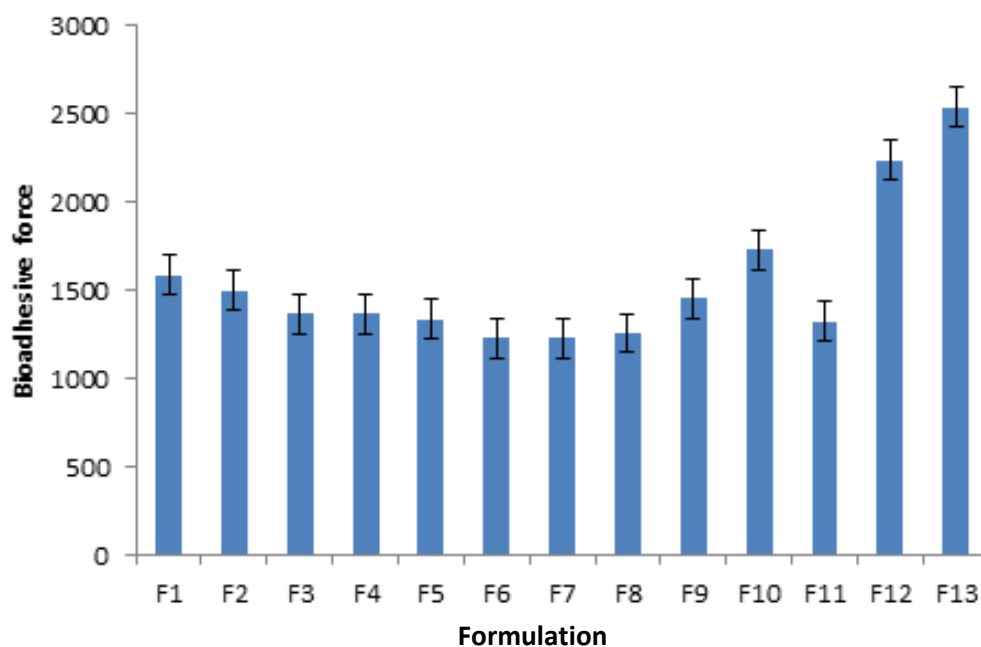
Figure 3 Comparison of bioadhesive force (N/m²) of formulations F1-F13

The bioadhesive strengths of mucoadhesive tablets are shown in Figure 3. The results show that all of the tablets have good bioadhesive strength, although the formulations with high ratio of Carbopol 934P: mucilage have higher bioadhesive strength but this difference were not significant between F1-F7 ($p < 0.01$). The results Also show that bioadhesive strength increased with increase in the amount of mucilage and carbopol 934P, so that the maximum bioadhesive strength was seen in F13.

The swelling of the polymers could be determined by water uptake of the tablet .The percent of swelling of the tablets were computed according to the method described previously. In this study the swelling of formulation F1-F7 were investigated (Fig. 4), The percent of polymers in each formulation was mentioned previously in table1. The F6 and F7 matrices disintegrated after 5 and 3 hours respectively. The hydration and erosion rates of tablets were measured, after the immersion of tablets in the test medium, to relate the observed phenomena of drug release with the rates or polymer hydration. The matrix erosion measured by the weight loss from matrix tablets immersed in dissolution media as a function of time (Fig. 5). Weight loss from the tablets was in constant progression until the end of test and the results show that the percent of erosion increased with the increase in the ratio of mucilage: carbopol 934P (Fig. 5), and also comparison between F9 & F14 showed that the absence of active ingredient in F14 resulted lower percentage of erision (Fig. 6).
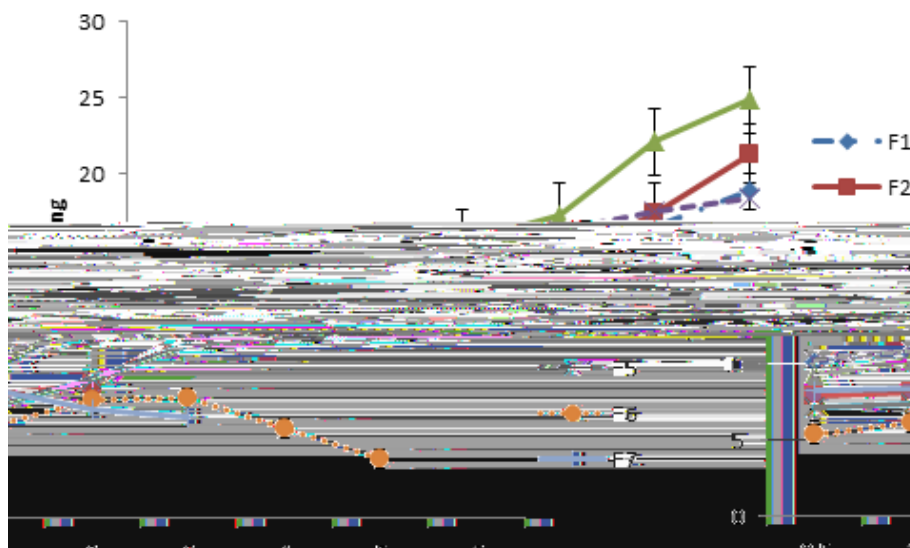
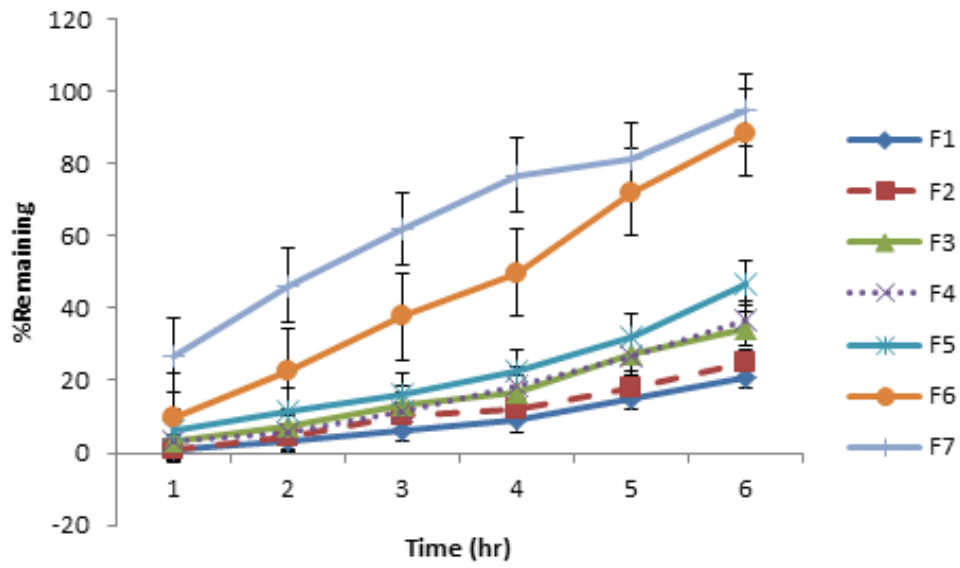**Figure 4** Comparison of swelling in F1-F7 formulations.

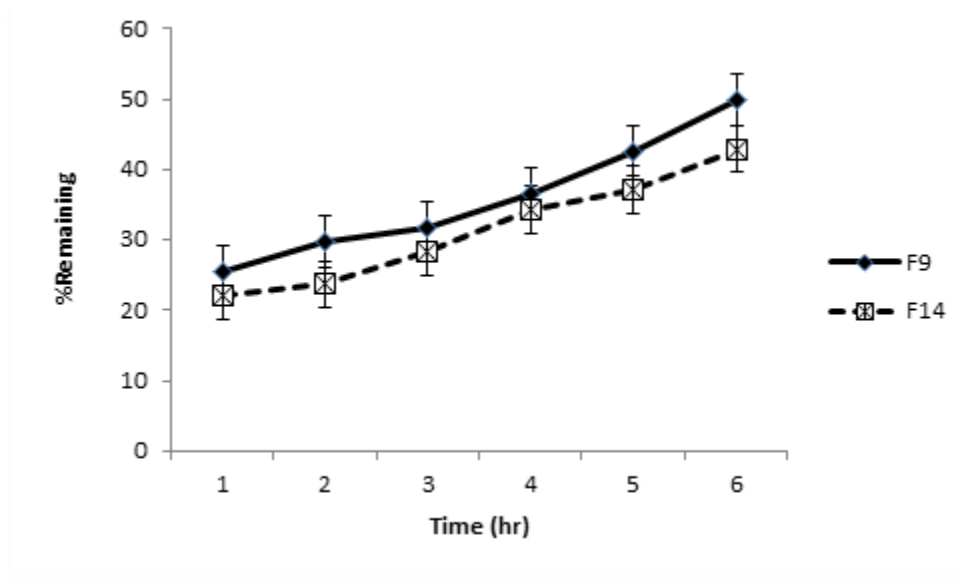**Figure 5** Comparison of erosion in F1-F7 formulations.

Figure 6 Comparison of erosion in F9 & F14 formulations.

Discussion

Values of the tensile strength and friability for all formulation are presented in Table 2.The values of hardness (from 3.6 ± 0.16 to 4.11 ± 0.19 kg/cm² in F1 and F3 respectively) and tensile strength increased (from 0.43 ± 0.5 to 0.51 ± 0.06 MN/m² in F1 and F3 respectively) with increase in the concentration of mucilage while friability decreased with increase in mucilage concentration (from 1.22 ± 0.11 to 0.96 ± 0.06% w/w in F1 and F3 respectively) for tablets prepared by direct compression .It is well known that polymers undergo plastic deformation, which subsequently leads to the formation of more solid bonds resulting in tablets with more resistance to fracture and abrasion (13).

When the polymer is "contaminated" by other materials such as the drug, the number of solid bonds between the particles decreased, leading to a decrease in the tensile strength of the tablets. The content uniformity test showed that the drug content was between 98.78-101.09%.

The buccal route offers an attractive alternative for systemic drug delivery because of better patient compliance, ease of dosage form removal in emergencies, robustness, and good accessibility. Use of buccal mucosa for drug absorption was first attempted by Sobrero in 1847, and since then much research was done to deliver drugs through this route. Today research is more focused on the development of suitable delivery devices, permeation enhancement, and buccal delivery of drugs that undergo a first-pass effect, such as cardiovascular drugs, analgesics and peptides. In addition studies have been conducted on the development of controlled or slow release delivery systems for systemic or local therapy of diseases in the oral cavity (18).

Bio adhesive force means the force with which tablets binds to buccal mucous membranes. The bio adhesive forces of tablet are affected by the shape of the tablet, the swelling degree of the tablet and the nature of the tablet components (19).

Mucoadhesion defined as the state in which two materials, at least one biological in nature, are held together for an extended period of time by interfacial forces, the phenomena of bioadhesion occur by a complex mechanism. Till data, six theories have been proposed which can improve our understanding for the phenomena of adhesion and can also be extended to explain the mechanism of bio adhesion. The theories include: (a) the electronic theory, (b) the wetting theory, (c) the adsorption theory, (d) the diffusion theory, (e) the mechanical theory, (f) the cohesive theory. The electronic theory proposes transfer of electrons amongst the surfaces resulting in the formation of an electrical double layer thereby giving rise to attractive forces. The wetting theory postulates that if the contact angle of liquids on the substrate surface is lower, then there is a greater affinity for the liquid to the substrate surface. If two such substrate surface is brought in contact with each other in the presence of the liquid, the liquid may act as an adhesive amongst the substrate surface. The adsorption theory proposes the presence of intermolecular forces, viz. hydrogen binding, and Van der Waal's forces, for the adhesive interaction amongst the substrate surfaces. The diffusion theory assumes the diffusion of the polymer

chains, present on the substrate surfaces, across the adhesive interface thereby forming a networked structure. The mechanical theory explains the diffusion of the liquid adhesives into the micro-cracks and irregularities present on the substrate surface thereby forming and interlocked structure which gives rise to adhesion. The cohesive theory proposes that the phenomena of bio adhesion are mainly due to the intermolecular interactions amongst like-molecules (20).

Formulations that contain Carbopol 934P had higher bio adhesive force in comparison to those had *P. major* mucilage, also the bio adhesion force increased as the amount of polymer increased, because of the increase in sites for bond formation. Formation of hydrogen bonds between the hydrophilic functional groups of the mucoadhesive polymers and the mucus layer is a prerequisite for extensive and longer mucoadhesion. The amount of the polymer also plays a significant role in the process of mucoadhesion. At lower amounts of the polymer chains, there is an inadequate and unsuitable interaction among the polymer and mucosal layer resulting in poor mucoadhesive properties (21).

P .major contain mucilaginous matter consisting of hydrophilic polysaccharides mainly in the seed coat, this polysaccharide has variable amounts of xylose, arabinose, galacturonic acid that swell in contact with water and form mucilage with high viscosity.

Formation of hydrogen bonds between the hydrophilic functional groups of the mucoadhesive polymers and the mucus layer or the mucosal surface is a

prerequisite for extensive and longer mucoadhesion (22).

Vimal Kumar Yadav et al. studied Means of improving the bio adhesive properties of Drug Delivery Systems and the results shows that with the increase in the chain length of the polymers there is an increase in the mucoadhesive property of the polymer. Flexible Polymer chains help in the better penetration and entanglement of the polymer chains with that of mucosal layer thereby improving the bio adhesive property. The flexibility of the polymer chains is generally affected by the cross linking reaction and the hydration of the polymer network. The Higher the crosslinking density, the lower is the flexibility of the polymer chains (20).

Akbari et al evaluated the effect of fillers on the buccoadhesive propranolol tablets. It was investigated that by increasing in the amount of poly carbophil the bioadhesion force increased. Because the viscosity of the thin gel layer that is necessary for adhesion is increased by adding polycarbophil so the bio adhesion increases (16).

Comparison of the drug release profile of the tablets is shown in   Fig. 1.The test was performed in phosphate buffer (pH 6.8) and the samples studied at various times. Comparison showed that with increase in the amount of P.major mucilage and decrease in the amount of Carbopol 934P (F1 to F7) the drug release rate increases. and also for the formulation that have only one kind of polymer (F8 to F13) the drug release rate decreased with the increase in amount of polymer (Fig. 2)

Sabale et al studied the Calendula mucilage as a mucoadhesive substance and they demonstrated that with the increase in the

amount of mucilage in the matrices the rate of drug release decreased (23).

Odeku and Fell investigated that the increase in the percentage of Khaya gum from 60 to 90% mucilage containing matrices resulted in a significant decrease in the release rate of paracetamol (13). Also in one study the researchers evaluate *Aloe barbadensis* miller mucilage as a component of control released matrices they understood that with an increase in the amount of mucilage in matrices the drug release rate decreases (24).

Swelling and erosion test was done in phosphate buffer (pH 6.8) are shown in fig. 4 & 5. The data is not exhibiting a regular process in swelling in formulation F1 to F3 (p < 0.01) we had an increase in the swelling percentage and from F4 to F7 we had a decrease in swelling complete disintegration was observed in F6 and F7 after 5hours and 3 hours respectively. High percentage of swelling in the F14 and F15 shows that the swelling in tablets that do not contain drug is higher than others. The friability was increased with the increase in amount of the mucilage and decrease in Carbopol 934P in formulation F1 to F7 (p < 0.05). Comparison of formulations F9 and F14 showed that erosion percentage in matrices with drug is higher than the matrices without it (p < 0.005) because of the solubility of the drug that increases the erosion, and comparison of formulations F12 and F15 that contain Carbopol934P shows that the percentage of erosion in matrices with drug is higher than the matrices with it (p < 0.01)

The adhesion increases with the degree of hydration until a point were over hydration leads to an abrupt drop in adhesive strength due to disentanglement at the polymer tissue interface (25). In hydrophilic polymeric matrix systems, the carrier on the surface of the matrix initially hydrates during dissolution to generate an outer viscous layer. This phase is then sequentially followed by matrix bulk hydration, swelling and erosion (26).

Adequate swelling behavior of a buccoadhesive system is an essential property for uniform and prolonged release of drug and effective mucoadhesion. Singh et al. studied the *Mimosa pudica* seed mucilage as a sustained release excipient in diclofenac sodium tablets and they understood as the amount of mucilage was increased in tablets percent swelling increased and percent erosion decreased (19).

Polymorphic changes of the drug may affect the dissolution rate and bioavailability. Bartolomei et al. reported that (R, S) propranolol hydrochloride existed in two crystalline forms, designated that α, β.

According to the DSC test we did in our previous study *P. major* mucilage has a very broad endothermic peak at 95.2 ^{o}C the presence of this peak is because the loss of water from the carbohydrate polymer, and Propranolol thermograms showed an endothermic peak about 164.2 $\pm$ 0.1 ^{o}C, that is around its melting point. We tested the matrix tablet containing 1:1 of drugs: *P. major* mucilage ratio in both mixture tablet and physical mixture and it showed the same peak in this area which indicates no interaction between drug and mucilage during the formulation process (8). From this finding we understand the delayed dissolution rate of propranolol is not because of complex formation between the drug and *P. major* mucilage or changes in crystallinity of the drug.
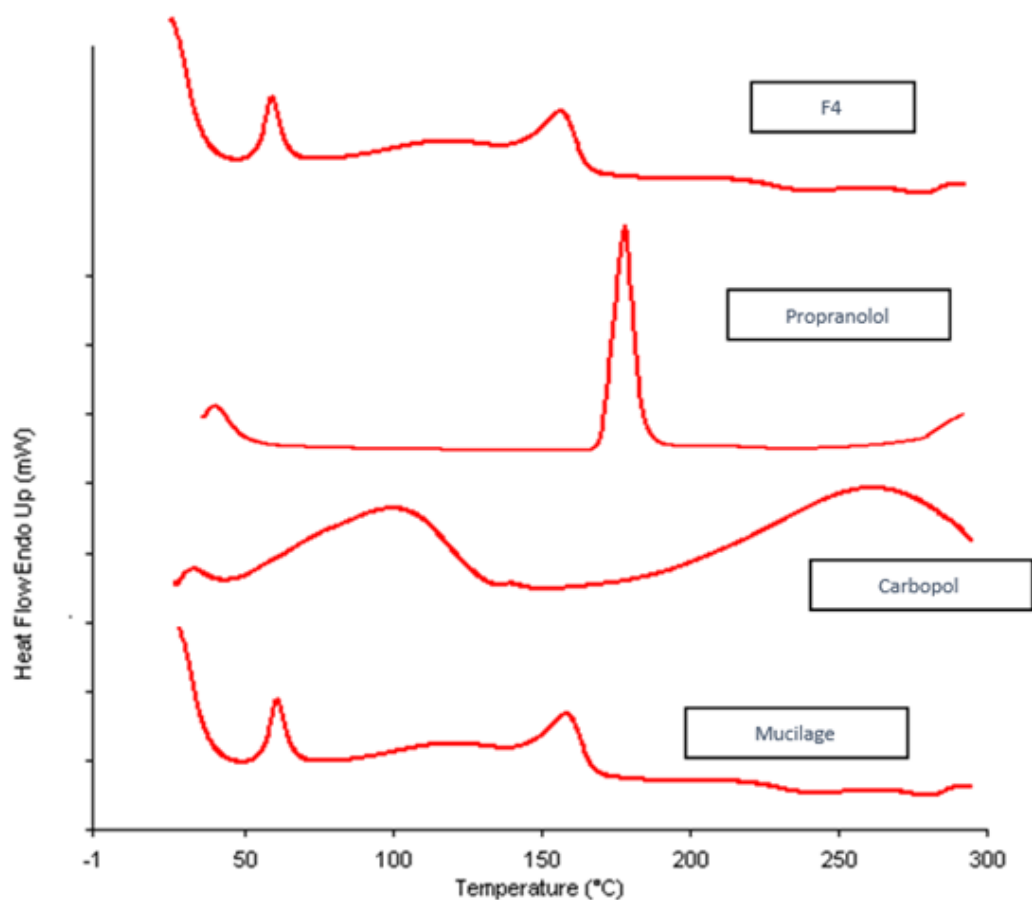
Figure 6 DSC thermograms of mucilage, Carbopol, Propranolol and formulation No. 4.

FT-IR spectral confirmed the above conclusion, *P. major* mucilage showed a broad band around 3437.5 1/cm corresponds to OH stretching, wave number 1742.9 1/cm depicts the stretching vibration of C=O, and 1040.1 1/cm depicts the stretching vibration of C-O group which was a characteristics of a polysaccharide. and the test for propranolol hydrochloride showed a peak at 2964.9 1/cm due to the presence of a secondary amine group, peaks at 3280.6 1/cm due to the secondary hydroxyl group. A peak at 1267.8 showed The presence of stretching bond of aryl alkyl ether, and a peak at 979.9 1/cm was due to α-substituted naphthalene (8). The FT-IR spectrum of the tablets contain 1:1 ratio of drug and *P. major* mucilage showed the same peak in the same area, which indicates no physical or chemical interactions amongst the components of the formulation and compatibility of the drug with the *P. major* mucilage.
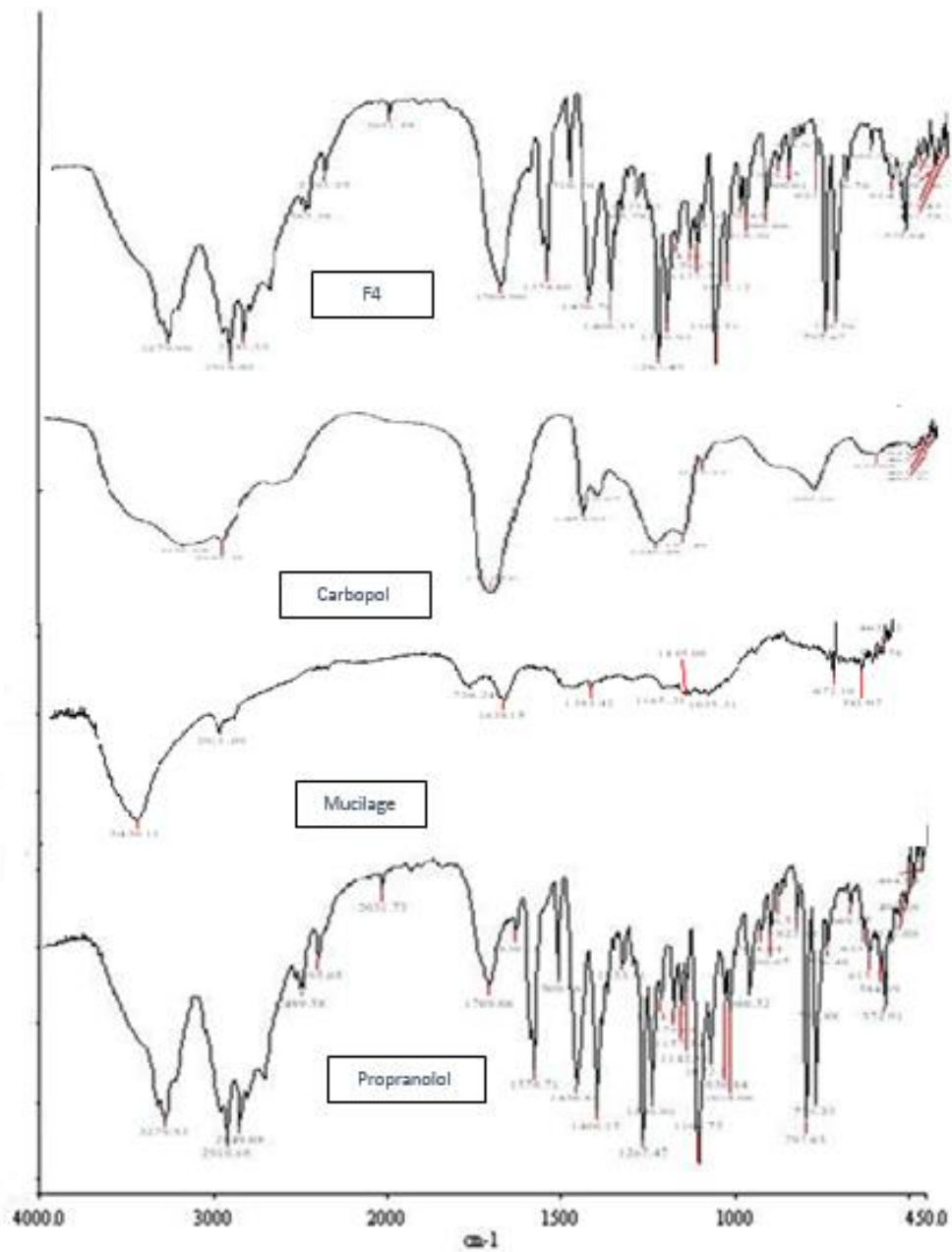
Figure 7 FTIR spectra of pure propranolol powder, mucilage, Carbopol and F4.

Conclusion

The main aim of this work was to isolate *P. major* seed mucilage and evaluate this natural polymer as a component for release the drug from the buccal tablets and its adhesion to oral cavity mucosa together with Carbopol 934P. In conclusion the use of *P. major* mucilage in addition to carbopol can optimize the drug release in propranolol buccoadhesive tablets.

Conflict of interest

The authors declared no potential conflict of interest with respect to the authorship, and/or publication of this study.

References

1. Bernkop-Schnurch A. Mucoadhesive systems in oral drug delivery. Drug Discov Today Technol 2005; 2:83-7.

2. Ahn JS, Choi HK, Cho CS. A novel mucoadhesive polymer prepared by template polymerization of acrylic acid in the presence of chitosan. Biomaterials 2001; 22: 923-8.

3. Hassan N, Khar RK, Ali M, Ali J. Development and evaluation of buccal bioadhesive tablet of an anti-emetic agent ondansetron. AAPS Pharm Sci Tech 2009;10:1085-92.

4. Roy SK. Prabhakar B. Bioadhesive polymeric platforms for transmucosal drug delivery systems – a review. Trop J Pharm Res 2010; 9: 91-104.

5. Chun MK, Cho CS, Choi HK. Mucoadhesive drug carrier based on interpolymer complex of poly(vinyl pyrrolidone) and poly(acrylic acid) prepared by template polymerization. J Control Release 2002;81:327-34.

6. Moghimipour E, Aghel N, Adelpour A. Formulation and Characterization of Oral Mucoadhesive Chlorhexidine Tablets Using Cordia myxa Mucilage. Jundishapur J Nat Pharm Prod 2012;7:129-33.

7. Saeedi M, Morteza-Semnani K, Sagheb-Doust M. Evaluation of *Plantago major* L. seed mucilage as a rate controlling matrix for sustained release of propranolol hydrochloride. Acta Pharm 2013;63: 99-114.

8. Sinha VR, Al-Azaki AA, Kumar RV. Novel Lannea Woodier gum matrices for controlled release of drugs. Carbohydr Polymers 2011; 83:1492-8.

9. Jani GK, Shah DP. Evaluation of mucilage of Hibiscus rosasinensis Linn as rate controlling

matrix for sustained release of diclofenac. Drug Dev Ind Pharm 2008;34:807-16.

10. Turel I, Ozbek H, Erten R, Oner AC, Cengiz N, Yilmaz O. Hepatoprotective and anti-inflammatory activities of *Plantago major* L. Indian J Pharmacol 2009;41:120-4.

11. Samuelsen AB. The traditional uses, chemical constituents and biological activities of *Plantago major* L. A review. J Ethnopharmacol 2000;71:1-21.

12. British Pharmacopoeia 1993: HMSO, London, UK.

13. Odeku OA, Fell JT. Effects of the method of preparation on the compression, mechanical, and release properties of khaya gum matrices. Pharm Dev Technol 2006;11:435-41.

14. Peppas NA. Analysis of Fickian and non-Fickian drug release from polymers. Pharm Acta Helv 1985;60:110-1.

15. Akbari J, Nokhodchi A, Farid D, Adrangui M, Siahi-Shadbad MR, Saeedi M. Development and evaluation of buccoadhesive propranolol hydrochloride tablet formulations: effect of fillers. Farmaco 2004;59:155-61.

16. Pornsak Sriamornsaka B, Thirawonga N, Korkerd K. Swelling, erosion and release behavior of alginate-based matrix tablets. Eur J Pharm Biopharm 2007;66:435-50.

17. Sharma PK, Koul AK. Mucilage in seeds of *Plantago ovata* and its wild allies. J Ethnopharmacol 1986;17:289-95.

18. Birudaraj R, Mahalingham R, Li X, Jasti B. Advances in buccal drug delivery. Crit Rev Ther Drug Carrier Syst 2005;22:295-330.

19. Choi HG, Kim CK. Development of omeprazole buccal adhesive tablets with stability enhancement in human saliva. J Control Release 2000;68:397-404.

20. Yadav VK, Kumar R, Yadav JS, Kumar B. Mucoadhesive polymers: means of improving the mucoadhesive properties of drug delivery system. J Chem Pharm Res 2010;2:418-32.

21. Roy S, Pal K, Anis A, Pramanik K, Prabhakar B. Polymers in mucoadhesive drug-delivery systems: A brief note. Designed Monomers Polymers 2009;12:483-95.

22. Alladi KK, Suram R, Bela M, Kiran S, Ramesh V, Narendera Y. Formulation and characterization of Clarithromycin controlled release bioadhesive tablets. J Chem Pharm Res 2011;3:684-90.

23. Sabale V, Patel V, Paranjape A. Evaluation of Calendula mucilage as a mucoadhesive and controlled release component in buccal tablets. Res Pharm Sci 2014:9:39-48.

24. Saeedi M, Akbari J, Morteza-Semnani K, Azarashk A. Evaluation of Buccoadhesive Propranolol Hydrochloride Formulations Containing *Plantago psyllium* Seed Mucilage and Carbopol 934P. Iranian J Pharm Sci 2014;10:1-18.

25. Eouani C, Picerelle P, Prinderre P, Bourret E, Joachim J. *In-vitro* comparative study of buccal mucoadhesive performance of different polymeric films. Eur J Pharm Biopharm 2001;52:45-55.

26. Sinha Roy D, Rohera BD. Comparative evaluation of rate of hydration and matrix erosion of HEC and HPC and study of drug release from their matrices. Eur J Pharm Sci 2002;16:193-9.