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Original Article

Pharmaceutical and Biomedical Research

Evaluation of *Ocimum basilicum* L. seed mucilage as rate controlling matrix for sustained release of propranolol HCl

Majid Saeedi[1,2*], Katayoun Morteza-Semnani[3,4], Jafar akbari[1], Mohammad Hossein Bazargani[1], Gholamreza Amin[5]

[1]Department of Pharmaceutics, Faculty of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran
[2]Pharmaceutical Sciences Research Center, Mazandaran University of Medical Sciences, Sari, Iran
[3]Department of Medicinal Chemistry, Faculty of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran
[4]Traditional and Complementary Medicine Research Center, Mazandaran University of Medical Sciences, Sari, Iran
[5]Department of Pharmacognosy, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran

Received: Oct 25, 2014, Revised: 22 Dec 2014, Accepted: Jan 3, 2015

Abstract

Polysaccharide mucilage derived from the seeds of *Ocimum basilicum* L. (family Lamiaceae) was investigated for use in matrix formulations containing propranolol hydrochloride. Basil mucilage was extracted and several tablets were formulated. The effect of mucilage on drug release rate was evaluated in comparison with tablets containing two kinds of hydroxypropyl methylcellulose (HPMC K4M and HPMC K100M) as standard polymer. The release data were fitted to several models for kinetic evaluation. The results showed that hardness decreased and friability of tablets increased as the concentration of mucilage increased. The rate of release of propranolol HCl from *O. basilicm* mucilage matrices was mainly controlled by the drug: mucilage ratio. Drug release was slower from the HPMC K4M and HPMCK100M containing tablets compared to the mucilage containing matrices than the drug release from matrices containing *O. basilicum* seed mucilage in similar ratios. Formulations containing *O. basilicm* mucilage were found to exhibit suitable release pattern. The results of kinetic analysis showed that in tablets containing *O. basilicm* mucilage the highest correlation coefficient was achieved with the zero order model. The swelling and erosion studies revealed that, as the proportion of mucilage in tablets was increased, there was a corresponding increase in percent swelling and a decrease in percent erosion of tablets.

Keywords: *Ocimum basilicum*, mucilage, release, HPMC, swelling, erosion

Pharm Biomed Res 2015; 1(1): 18-25 DOI: 10.18869/acadpub.pbr.1.1.18

Introduction

Hydrophilic matrices have been used extensively to produce controlled release oral drug delivery. The use of naturally occurring biocompatible polymeric materials has been the focus of recent research activity in the design of these dosage forms (1-5). Polymeric hydrogels are studied for controlled release applications because of their producing drug release close to zero-order kinetics (6,7). Mucilages and gums are well known since ancient times for their medicinal use (8). In recent times, increasing attention has been given to the application of gums of various sources as pharmaceutical excipients. Plant gums and exudates are getting screened for their use as pharmaceutical adjuvants. Mucilages generally are Polysacchar ides which are polymeric in nature of natural substances 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 (9-11). Gums from natural sources hydrate and swell on contact with water and have been used for the preparation of single unit dosage forms (12).

Basil or *Ocimum basilicum* L. (locally known as Reyhan) is a member of genus *Ocimum*. This genus comprise between 50 and 150 species of herbs and shrubs. This plant distributes in the tropical regions of Asia, Africa, and Central and South America (13,14). Basil is one of the endemic plants in Iran that is produced and used

*E-mail: majsaeedi@yahoo.com

as a pharmaceutical plant in high quantity. This plant have several traditional uses in urinary tract inflammation, chest and long complaints, diuretic, reconstituent, flatulence, nerves tonic, colic ulcer, dyspepsia, inflammation, diarrhea, appetizer, expectorant, galactogogue, and influenza (15).

The outer pericarp (or outer epidermis) of basil seeds, when soaked in water, soon swells into a gelatinous mass. The high mucilage content of basil seeds can make it a novel source of edible gum (16). The mucilaginous layer of the swollen seeds has a large capacity for hydration (17). The polysaccharides extracted from basil seed by cold water extraction and alcohol precipitation, have been reported to have two major fractions: (i) an acid-stable core glucomannan (43%) having a ratio of glucose to mannose 10:2, and (ii) a (1-4)-linked xylan (24.29%) having acidic side chains at C-2 and C-3 of the xylosyl residues in acid-soluble portion. Also a minor fraction of glucan (2.31%) as a degraded cellulose material with DP = 80 has been reported (16).

The aim of present study is to investigate the suitability of the basil seed mucilage as a matrix-forming agent, and propranolol hydrochloride is chosen as a model drug. As hydroxypropyl methylcellulose (HPMC) is one of the widely used hydrophilic polymers in matrix formulations (18). The present study also compare the release, swelling and erosion data obtained for matrices containing basil seed mucilage to those of matrices containing HPMC.

Materials and methods

Materials

Propranolol HCl (Rouz-daru Co., Tehran, Iran) was received as gratis sample. HPMC K4M and HPMC K100M (Colorcon, UK), NaOH, KCl, HCl, magnesium stearate, Soybean Casein Digest Agar (SCDA) medium (Merck, Germany) and potassium di-hydrogen phosphate (Fluka, Switzerland) were used as supplied.

Extraction of mucilage

Ocimum basilicum seeds were purchased from a local market in Sari, Iran. The basil seeds were carefully cleaned removing dusts, stones and chaffs. The cleaned seeds were then packed in plastic bags, sealed and preserved in a dry and cool place until the gum extraction step.

Mucilage extraction and purification were carried out according to the method described by Anroop et al. with some modifications (8). The cleaned seeds were defatted with petroleum ether (60-80) in a Soxhlet (Iran). The defatted material (25 g) was soaked in distilled water (500 mL) at room temperature and stirred with a double bladed mixer (Ika-werk, Germany) 500 rpm for 24 h. The resulting mass strained through muslin cloth. To the filtrate, acetone was added until precipitation was complete. The precipitated mucilage was filtered through muslin cloth and the mucilaginous residue was spread on glass plates and dried at 40 $^{\circ}$C. The extracted polysaccharide (4 g) was dispersed in 200 mL water with stirring for 12 h and ethanol was added in different proportion. First the concentration of ethanol was made up to 20% in the solution. Some impurities that precipitated were removed by centrifugation (Hettich universal D-7200, Germany). The ethanol concentration was further increased to 60% to precipitate the remaining polysaccharides. The precipitated gum was filtered, treated with acetone to remove the traces of water and dried in an oven 40°C. The characteristics of mucilage were evaluated based on Saeedi et al. study (19).

Preparation of matrix tablets

A series of formulations containing a fixed amount of propranolol HCl (80 mg), and several amounts of *Ocimum basilicum* seeds mucilage powder (ratio of drug to mucilage were 1:0.5, 1:0.75, 1:1, 1:1.5, 1:2) or HPMC K4M and HPMC K100M (ratio of drug to polymer were 1:0.5, 1:1, 1:2) were sufficiently blended for 10 min. Magnesium stearate (1% w/w) was then added, followed by further mixing. The resultant powder mixture was compressed into tablets using a single punch machine (Korsch, Germany), with 10 mm diameter flat punch. All matrices were stored in desiccators for at least 3 days to allow for tablet relaxation before use. The compositions of all formulations are listed in Table 1. The amount of propranolol HCl was 80 mg in all formulations.

Evaluation of tablets

Tablet properties (crushing strength, mass variation, and friability) were determined by the standard procedure. The tensile strength (T) of tablets, which is a measure of the stress necessary to cause diametric fracture of the compact, was determined from the mean data obtained from the hardness test carried out on

tablets (n = 10) using an Erweka hardness tester (TBH 30MD, Germany) (19).

Table 1 Formulation composition of investigated propranolol hydrochloride matrix tablets

Formulation Code	Formulation composition					Total mass (mg)
	Propranolol hydrochloride (mg)	*Ocimum basilicum* mucilage (mg)	HPMC K4M (mg)	HPMC K100M (mg)	Mg stearate (mg)	
F1	80	40	-	-	1.2	121.2
F2	80	60	-	-	1.4	121.4
F3	80	80	-	-	1.6	161.6
F4	80	120	-	-	2	182
F5	80	160	-	-	2.4	242.4
F6	80	-	40	-	1.2	121.2
F7	80	-	80	-	1.6	161.6
F8	80	-	160	-	2.4	242.4
F9	80	-	-	40	1.2	121.2
F10	80	-	-	80	1.6	161.6
F11	80	-	-	160	2.4	242.4

Content uniformity of the drug in tablets was confirmed based on the British Pharmacopoeia method (20).

In vitro drug release

The USP basket method was used for all *in vitro* dissolution studies. Distilled water containing hydrochloric acid 0.2 mol L^{-1} (pH 1.2) and phosphate buffer pH 7.4 without enzymes were used as dissolution media (19). The dissolution profile of propranolol HCl was determined according to the USP basket method at 100 rpm, in 900 mL maintained at 37.0 ± 0.5 °C in a dissolution tester apparatus (Caleva 8ST, Germany). The amount of propranolol hydrochloride was determined in all formulations before dissolution study. The matrices were placed in 900 mL of distilled water containing hydrochloric acid (pH 1.2) for 2 h. The samples were withdrawn at predetermined time intervals (30, 60, 90, and 120 min), filtered and assayed spectrophotometrically at 289 nm using a UV/Visible spectrophotometer (Varian, Australia). After 2 h, the dissolution medium pH was changed from 1.2 to 7.4 using phosphate buffer. The samples were withdrawn at predetermined time intervals (3, 4, 5, 6, 7, and 8 h) and analyzed by the mentioned method. The mean of three determinations was used to calculate drug release from each of the formulations (21).

Data treatment

Various mathematical equations have been proposed for kinetic analysis of drug release from evaluated formulations. The zero order rates Eq. 1 describe the systems, where the drug release is independent of its concentration. The first order rate Eq. 2 describes the release from systems, where the release is concentration dependent. According to Higuchi model Eq. 3, the drug release from insoluble matrix is directly proportional to square root of time and is based on Fickian diffusion (22).

$$Q_t = k_0 t \quad \text{eq.1}$$

$$Ln\ Q_t = ln\ Q_0 - k_1 t \quad \text{eq.2}$$

$$Q_t = k_H t^{1/2} \quad \text{eq.3}$$

Where Q_t is the amount of drug released in time t, Q_0 is the initial amount of drug in tablet and k_0, k_1 and k_H are release rate constant for zero order, first order and 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 Ritger and Peppas and Korsemayer equation

$$M_t / M_\infty = K_p t^n \quad \text{eq.4}$$

Where M_t corresponds to the amount of drug released in time t, M_∞ is the total amount of drug that must be released at infinite time, K_p is a constant and "n" is the release exponent indicating the type of drug release mechanism.

In cylindrical shape matrices, a release exponent of 0.45 can serve as an indication for Fickian diffusion. If $0.45 < n < 0.89$ anomalous transport could be obtained, and if "*n*" approaches to 0.89 the release mechanism can be described as polymer swelling mechanism. Criteria for selecting the most appropriate model were based on best goodness of fit and smallest sum of squared residuals (23).

Matrix swelling studies

Swelling of the matrices can be measured by their ability to absorb water and swell. The study was carried out in a USP/NF dissolution apparatus No. 1 (Caleva 8ST, Germany). Dry polymer matrices were accurately weighed, placed in dissolution baskets, and immersed in 900 mL of phosphate buffer (pH 7.4) maintained at 37 °C in dissolution vessels. At regular intervals, the pre-weighed basket-matrix system was withdrawn from the dissolution vessel, lightly blotted with a tissue paper to remove excess test liquid and reweighed. The percent water uptake, *i.e.*, degree of swelling due to absorbed test liquid, was estimated at each time point as the mean of three determinations (24).

Matrix erosion studies

A standard USP/NF dissolution apparatus No. 1 (Caleva 8ST, Germany) was used for this purpose. Dry matrices were weighed, placed in dissolution baskets, and subjected to dissolution in 500 mL of 0.05 mol L^{-1} phosphate buffer (pH 7.4), 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 50 °C (24). The percentage matrix erosion (*%E*) at time *t*, was estimated as mean of three determinations.

Statistical analysis

ANOVA followed Tukey test was used to determine significant differences between groups and "$P < 0.05$" was considered significant (SPSS software Chicago, USA).

Results

Ocimum basilicum seeds mucilage was extracted as cited method. The mean yield percentage of extraction was 10.2% ± 0.8. The swelling factor of basil seed mucilage was 10.4 ml based on above method. The viscosity of 1% aqueous dispersion of extracted mucilage was 618 cP. The pH of 1% aqueous solution of *Ocimum basilicum* seed mucilage was 4.6 ± 0.4. The limit for chloride was not more than 0.1% and the heavy metal content was less than 20 parts per million. The microbial limit test showed that there was no *E.Coli* and *Salmonella spp.* in one gram of mucilage.

Table 2 shows the characteristics of investigated tablets. The results of tablet hardness in formulations containing basil seed mucilage showed decrease in hardness by increasing in mucilage concentration. This difference was significant between F1, F4 and F5 ($p = 0.01$ and $p = 0.001$ respectively). This decrease in tablet hardness was not significant in formulations containing HPMC K4M and K100M. The comparison of formulations showed higher hardness in formulations containing HPMC K4M versus tablets which prepared by basil seed mucilage. The friability of investigated tablets showed that friability of tablets increased by increasing in mucilage concentration. This difference was significant from F1 to F5 ($p < 0.05$). This result was observed in formulations containing HPMC K100M too (F9 and F11).

Table 2 Characteristics of propranolol hydrochloride tablets prepared with different ratios of *O. basilicum* mucilage, HPMC K4M, and HPMC K100M

Formulation Code	Hardness* ($kg.cm^{-2}$) (n =10)	Friability* (% *w/w*) (n = 10)	Assay* (%) (n = 20)
F1	8.52 ± 0.28	0.638 ± 0.06	101.60 ± 3.72
F2	8.29 ± 0.67	0.666 ± 0.05	99.80 ± 2.87
F3	8.11 ± 0.65	0.664 ± 0.08	99.76 ± 4.11
F4	7.59 ± 0.53	0.680 ± 0.05	99.83 ± 3.26
F5	7.19 ± 0.64	0.746 ± 0.07	100.70 ± 3.14
F6	9.28 ± 0.74	0.648 ± 0.06	101.70 ± 3.55
F7	8.93 ± 0.69	0.678 ± 0.09	99.93 ± 3.56
F8	8.53 ± 0.61	0.694 ± 0.07	99.63 ± 4.14
F9	8.99 ± 0.65	0.658 ± 0.05	99.93 ± 3.21
F10	8.49 ± 0.53	0.704 ± 0.08	100.30 ± 3.17
F11	8.33 ± 0.71	0.742 ± 0.08	101.36 ± 3.74

* Data are shown as mean ± SD,

The release profiles of tablets are shown in figures 1, 2, and 3. The dissolution data in F1-F5 showed that, release rate decreased by in increasing in mucilage content ($p < 0.001$). This result was observed in tablets containing HPMC K4M and HPMC K100M too. Drug release was slower from the HPMC K4M and HPMCK100M containing tablets compared to the mucilage containing matrices than the drug release from matrices containing *O. basilicum* seed mucilage in similar ratios ($p < 0.001$). The release rates in

formulations containing HPMC K100M were slower than others.

Dissolution rate data were analyzed based on the cited equations and the results are shown in Table 3. The results show that in formulations containing basil seed mucilage as a controlling-release agent (F1-F5), the highest correlation coefficient was achieved with the zero order model. The release kinetic was changed in formulations containing HPMC K4M by increasing in polymer concentration from zero order in F6 to Peppas model in F7 and F8. This result was observed in formulations containing HPMC K100M, and release kinetic was changed from first order in F9 to Higuchi model in F10 and F11.

Swelling and erosion studies were carried out on all tablets. The results of these tests are provided as the percentage weight change and erosion percentage of tablet mass, as shown in figures 4 and 5. Matrices containing a higher proportion of mucilage showed a lower degree of swelling with time ($p < 0.001$). The percent swelling of formulations containing *O. basilicum* seed mucilage was found to be lower than that of formulations containing HPMC K4M and HPMC K100M ($p < 0.001$). The highest percent swelling was observed in formulations containing HPMC K100M. These results were observed for erosion percent too.

Table 3 The kinetic of propranolol hydrochloride release from tablets prepared with different amounts of *Ocimum basilicum* mucilage, HPMC K4M, and HPMC K100M

Formulation code	Zero-order model			First-order model			Higuchi model			Peppas model			
	K_0 %.min^{-1}	r^2	*ss*	K_1 min^{-1}	r^2	*ss*	K_H %.min$^{-1/2}$	r^2	*ss*	K_p %.min^{-n}	*n*	r^2	*ss*
F1	0.0024	0.998	1984	-0.008	0.796	191271	0.0620	0.975	487951	0.0011	1.1420	0.993	267
F2	0.0020	0.997	784	-0.005	0.913	82671	0.0543	0.976	444240	0.0013	1.0729	0.994	261
F3	0.0016	0.997	245	-0.003	0.925	27207	0.0442	0.962	346238	0.0016	1.000	0.996	183
F4	0.0015	0.998	951	-0.003	0.963	26945	0.0416	0.969	435238	0.0011	1.050	0.994	337
F5	0.0014	0.998	721	-0.002	0.967	21541	0.0393	0.968	465502	0.0011	1.0459	0.996	263
F6	0.0020	0.996	4582	-0.005	0.819	168286	0.0543	0.960	701295	0.0009	1.1371	0.993	312
F7	0.0013	0.995	5948	-0.002	0.961	38656	0.0354	0.955	771150	0.0005	1.1370	0.996	354
F8	0.0011	0.995	6389	-0.001	0.973	29528	0.0299	0.956	784636	0.0004	1.1421	0.996	353
F9	0.0011	0.971	24333	-0.002	0.987	12861	0.0283	0.984	496	0.0355	0.4617	0.965	399
F10	0.0009	0.967	23816	-0.001	0.980	14121	0.0235	0.992	530	0.0197	0.5239	0.992	130
F11	0.0006	0.965	27052	-0.001	0.973	20310	0.0156	0.987	314	0.0183	0.4738	0.984	234

k_0: zero order release rate constant, k_1: first order release rate constant, k_H: Higuchi model release rate constant, k_p: Peppas model release rate constant, *n:* release exponent in Peppas model, r^2 : definition coefficient, *ss* : sum of squares of errors;

Discussion

The swelling factor of 1g of basil seeds was 10.4 ml. Kadam et al. reported 2.5 mL for swelling factor of *O. basilicum* seeds (25). The viscosity of 1% aqueous dispersion of extracted mucilage was 618 cP. The pH of 1% aqueous solution of basil seed mucilage was 4.6 ± 0.4 and between 4-5 acceptable ranges. The limit for chloride, heavy metal content, and the microbial limit test was established based on Iranian pharmacopoeia (26).

The mechanical properties of pharmaceutical tablets are quantifiable by the hardness and friability of the tablets. There are no clear limits for acceptance or rejection of tablet batches probably because in the case of tensile strength, the desired hardness is largely dependent on the intended use of the tablet (27). Yadav et al. studied the *O. basilicum* seed mucilage as binder. Their results showed that increasing the concentration of mucilage increased the tablets' hardness (28). For friability, conventional compressed tablets that lose < 1% w/w of their mass during the friability test are generally considered acceptable (26). Values of the hardness and friability for all formulations are presented in Table 2. The values of hardness decreased with increase in the concentration of mucilage while friability increased with increase in mucilage concentration for tablets.

Nokhodchi et al. have been reported the same results in propranolol hydrochloride matrix tablets which prepared by fenugreek mucilage as an excipient for controlling the drug release (11). Similar results have been observed in propranolol HCl matrices containing *Plantago major* seed mucilage by Saeedi et al (21). 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 (27).

Comparative dissolution profile (Fig.1-3) showed that an increase in the percentage of *O. basilicum* seed mucilage from 40 mg (formulation F1) to 160 mg (formulation F5) resulted in a decrease in the release rate of propranolol. The drug release was slower from the HPMC K4M and HPMC K100M containing tablets compared to the mucilage containing matrices; Saeedi et al reported that an increase in the percentage of *P. major* seed mucilage containing matrices resulted in a significant decrease in the release rate of propranolol HCl (21). Similar results were observed in glimepiride matrix tablets containing dried mucilage of *Aloe barbadensis* as a release controlling agent (29). Sabale et al. reported the effect of calendula mucilage as release rate controlling agent in chlorpheniramine maleate buccoadhesive tablets (30).

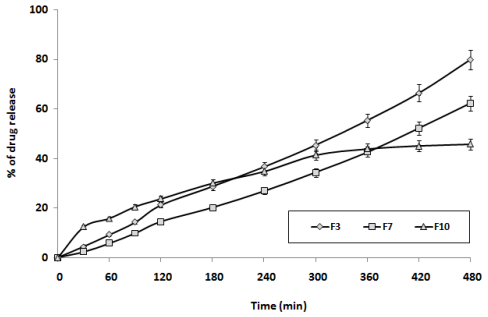

Figure 1 Comparison of the release behaviors of propranolol hydrochloride from matrices containing 1:0.5 of drug: *O. basilicum* seed mucilage, HPMC K4M or HPMC K100M, (n = 4).

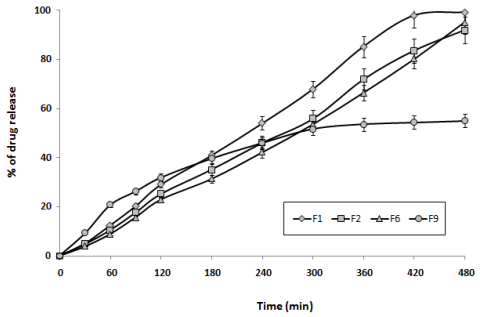

Figure 2 Comparison of the release behaviors of propranolol hydrochloride from matrices containing 1:1 of drug: *O. basilicum* seed mucilage, HPMC K4M or HPMC K100M, (n = 4).

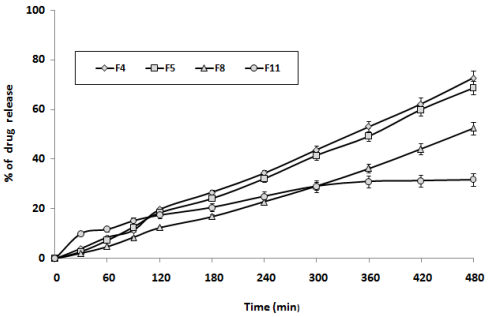

Figure 3 Comparison of the release behaviors of propranolol hydrochloride from matrices containing 1:2 of drug: *O. basilicum* seed mucilage, HPMC K4M or HPMC K100M, (n = 4).

The drug release profile was generally linear, especially 1-3 hours after initial release for all the formulae. Such linear drug release from hydrophilic matrices has been attributed to synchronization between swelling and erosion of the polymer a maintaining a constant gel layer. During the dissolution studies, the outer parts of the tablet appeared to be hydrated after being placed in the in the dissolution medium. There was a progressive increase in the size of this hydrated layer, followed by a gradual loss in integrity resulting from the hydrodynamic stress induced by agitated dissolution medium (31). The hydrated gel layer persisted for a considerable part of the dissolution process. This could be attributed to an increase in the viscosity of the hydrated layer with the increase in mucilage concentration, which thus improved its resistance to erosion and release.

In formulations containing *O. basilicum* seed mucilage (F1-F5) the highest correlation coefficients were achieved with zero order model. The values of *n* in Peppas model in F9-F11 were 0.462, 0.524, and 0.474 respectively. These values indicated that release mechanism were similar and based on anomalous transport of drug from matrix. Similar values of *n* of around 0.6 were found for propranolol hydrochloride release from hydroxypropyl methylcellulose matrices (32).

The swelling and erosion evaluations were carried out in all formulations. The results of these studies in phosphate buffer (pH 7.4) are shown as the percentage weight change and percentage of erosion, as shown in figures 4 and 5. The formulations absorbed water from dissolution media and swelled.

The changes in weight, characteristic of water uptake and swelling, started from the beginning and continued until 300 min of experiment. Matrices tablets containing a lower proportion of mucilage showed a lower degree of weight gain with time ($p < 0.001$). The percent swelling of formulations containing HPMC K4M and HPMC K100M were found to be higher than that of formulations containing *O. basilicum* seed mucilage
($p < 0.001$). The formulations containing HPMC K100M showed the highest swelling in comparison with other formulations ($P < 0.01$). Hardikar et al. reported high swelling factor for extracted basil mucilage in their study (33).

The matrix erosion measured the weight loss from matrix tablets immersed in dissolution media as a function of time. The percentage of the matrices' erosion is shown in figure 5 and reflects the amount of polymer dissolved and the erosion of matrix during the dissolution process. Weight loss from the matrices increased progressively with the erosion time. The extent of erosion in formulations containing *O. basilicum* mucilage (F1-F5) was more than HPMC (F6-F11) matrices ($p < 0.001$). There was significant ($p < 0.000$) increase in percent of the tablet erosion with increase in *O. basilicum* mucilage concentrations (formulations F1-F5).

Singh et al. studied the *Mimosa pudica* seed mucilage as sustained release excipient in diclofenac sodium matrix tablets. The swelling and erosion studies revealed that, as the proportion of mucilage in tablets was increased, there was a corresponding increase in percent swelling and decrease in percent erosion of tablets (34).

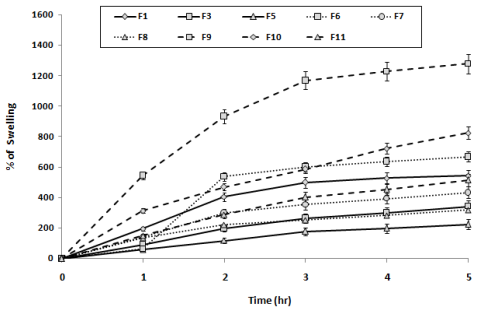

Figure 4 The percentage of swelling (weight change) of different formulations of propranolol hydrochloride matrices containing *O. basilicum* seed mucilage, HPMC K4M or HPMC K100M, (n = 3).

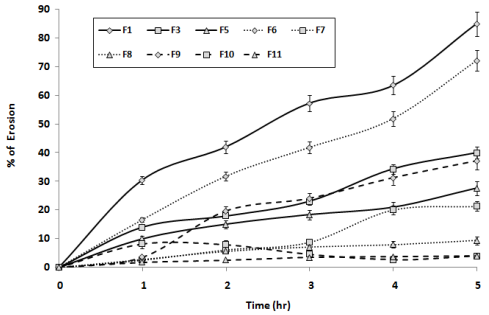

Figure 5 The erosion percentage of different formulations of propranolol hydrochloride matrices containing *O. basilicum* seed mucilage, HPMC K4M or HPMC K100M, (n = 3).

Conclusion

This study has demonstrated the potential of *O. basilicum* seed mucilage to act as a release retardant excipient in matrix tablets. An increase concentration of mucilage in binary mixtures of drug-mucilage resulted in a decrease in release rate. The kinetics of release showed that the mechanism was fitted in zero-order model. The present study demonstrated that *O. basilicum* mucilage have major potential for use as a controlled release excipient.

Acknowledgment

This work was supported by a grant from the research council of the Mazandaran University of Medical Sciences.

Conflict of interest

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

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