



# The effect of *Plantago major* mucilage on the release profile and bioadhesive properties of propranolol HCl buccoadhesive tablets in comparison with current polymers

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## ABSTRACT

**Background:** Drug delivery via buccal mucosa offers distinct advantages over peroral administration. Plant gums and exudates are getting screened for their use as pharmaceutical adjuvant. The aim of this study is to investigate the suitability of the *Plantago major* seed mucilage as a mucoadhesive agent, and propranolol hydrochloride is chosen as a model drug. **Methods:** Mucoadhesive tablets of propranolol were formulated using four mucoadhesive polymers namely Carbopol 934P, HPMC K4M, Tragacanth and plantago major mucilage. The swelling, erosion, mucoadhesive force and *in vitro* drug release were studied. **Results:** Maximum bioadhesive strength was observed with Carbopol 934P and the lowest bioadhesive strength was seen with tragacanth. The results also showed that bioadhesive strength increased with increase in the amount of polymers. As the amount of polymers increased from 40 mg to 160 mg per tablet, initial drug release as well as drug release in the latter hours was decreased. The lowest release rate was observed with formulation F6 containing Carbopol 934P and the highest release rate was observed with formulation F7 containing tragacanth. Formulations that contain carbopol 934P showed highest bioadhesive force. Also the bioadhesion force increased as the polymer amount increased. The highest and lowest percent of swelling were observed with F2 and F8, respectively. The kinetic of drug release have changed by increase in amount of mucilage. **Conclusions:** The mucilage of *Plantago major* can be used as bioadhesive polymer in bioadhesive formulations.

## Introduction

The development of bioadhesive controlled release systems has been the subject of many studies in recent years. These formulations can improve the effectiveness of drugs by maintaining the plasma drug concentration at the therapeutic levels for prolonged periods of time, inhibiting the dilution of drug in the body fluid, and allowing targeting and localization of a drug at a specific adsorption site. <sup>1</sup> Drug delivery by mucoadhesive systems have certain advantages over per oral administration. In recent years, special attention is given to the development of adhesive systems for drug administration. These dosage forms can be administered by different routes (e.g. ocular, buccal, nasal, rectal, vaginal), either for local therapy or for systemic transmucosal 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 the exposure of drug to gastrointestinal tract. <sup>2</sup> 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. Mediated by mucoadhesive polymers, the residence time of dosage forms on the GI- mucosa should be prolonged, which allows a sustained drug release at a given target site to maximize the therapeutic effect. <sup>3</sup> Typical polymers that have been used as mucoadhesive drug carriers are poly acrylic acid, poly methacrylic acid, cellulose derivatives, poly ethylene oxide, lectin and chitosan, PAA and its cross-linked commercial forms <sup>4</sup>. Carbopol and polycarboxylic acid exhibit strong mucoadhesive properties. <sup>5</sup> Many attempts have been undertaken to improve the mucoadhesive properties of polymers by preparing copolymers, polymer conjugates or interpolymer complexes. <sup>6,7</sup> Mucilage and gums are well known since ancient times for their medicinal use. Today, the gums are being used as sources of pharmaceutical excipients. Mucilage generally are carbohydrate polymers 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.<sup>9,10</sup> Mucilage from natural sources hydrate and swells on contact with water and has been used for the preparation of single unit dosage forms.<sup>11</sup>

*Plantago major* L. is a perennial plant that belongs to the Plantaginaceae family. The plant produces large amount of seeds. The seeds are located in capsules (8-16 per capsules) and become sticky in humid water due to the swelling of the polysaccharides present in the seed coat. The seeds contain the monosaccharide, disaccharide, and trisaccharide. The outer seed coat contains carbohydrate polymers that swell in contact with water and form mucilage with high viscosity. These polysaccharides are composed of xylose, arabinose, galacturonic acid, glucuronic acid, rhamnose, galactose, and glucose.<sup>12</sup>

In this study, mucoadhesive strength of the *Plantago major* seed mucilage is compared with Typical mucoadhesive polymers. The propranolol hydrochloride has also been used as a model drug. Hydroxypropyl methylcellulose (HPMC), carbopol, and tragacanth are used as bioadhesive polymers in mucoadhesive formulations, the present study also compares the release, swelling, and erosion data obtained for buccoadhesive matrices containing *Plantago major* seed mucilage to those of mucoadhesive matrices containing HPMC, carbopol and tragacanth.

### Materials and methods

Propranolol Hydrochloride powder was purchased from Rouz-daru Co. (Tehran, Iran). HPMC K4M (Colorcon, UK), Carbopol 934P (B.F.Goodrich USA), and

Tragacanth were used as bioadhesive polymers. *Plantago major* seed was purchased from herbal drug market (Sari, Iran). Other chemicals such as NaOH, HCl, magnesium stearate, and potassium di-hydrogen phosphate were obtained from Merck, Germany.

### Swelling Factor

The *Plantago major* seeds (1 g by weight) were put in to graduate stoppered cylinders that were later filled with distilled water at room temperature up to the 25 ml mark. Except for intermittent agitation, the cylinders were left undisturbed for 24 h and the volume of swollen seed layer was then recorded by observation of the water gel boundary. The test was done triplicate and result showed in mean.<sup>13</sup>

### Extraction of Mucilage

*Plantago major* seed mucilage was extracted based on method was used in our previous study.<sup>10</sup> Briefly, ten milliliters of 0.1 N Hydrochloride was heated to boiling in a 100-ml Corning flask. The flask was removed from the flame and 1-g test sample of dry seed was added to it. Heating was resumed and the process of dissolution of the seed husk was watched. When all seeds had changed colour, the flask was finally removed from the flame and the solution was filtered through clean muslin cloth, while still hot. In order to separate residual traces of mucilage, the seeds were washed twice in 5 ml 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 5 h. Finally, the supernatant liquid was decanted off and the beaker containing the precipitate was dried an oven maintained at 50°C.

**Table 1.** Formulation composition of investigated propranolol hydrochloride mucoadhesive matrix tablets

Formulation Code	Total mass (mg)					
	Propranolol hydrochloride (mg)	<i>P. major</i> mucilage (mg)	Carbopol 934P (mg)	Tragacanth (mg)	HPMC K4M (mg)	Mg stearate (mg)
F1	80	40	-	-	-	1.2
F2	80	80	-	-	-	1.6
F3	80	160	-	-	-	2.4
F4	80	-	40	-	-	1.2
F5	80	-	80	-	-	1.6
F6	80	-	160	-	-	2.4
F7	80	-	-	40	-	1.2
F8	80	-	-	80	-	1.6
F9	80	-	-	160	-	2.4
F10	80	-	-	-	40	1.2
F11	80	-	-	-	80	1.6
F12	80	-	-	-	160	2.4

### Preparation of mucoadhesive Matrix Tablets

For preparation of a 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 10 min. Magnesium stearate (1% w/w) was then added, followed by further mixing for 2 min. mixed and introduced into the die and compacted at

constant compression pressure using 1% (m/m) magnesium stearate. The tablet properties (crushing strength, friability, mass variation, and content uniformity) were determined by standard procedure.<sup>14,15</sup>

### **In vitro release studies**

The dissolution tests were performed to the basket method (USP pharmacopoeia 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 definite time intervals. The dissolution media was then replaced by fresh dissolution fluid to maintain a constant volume. The solution was passed through a filter (Watman, USA) and then the 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**

The tablet properties (crushing strength, mass variation, and friability) were determined by standard procedure.<sup>14</sup> The tensile strength (*T*) of tablet 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 the tablets (*n* = 10) using the Erweka hardness tester (TBH 30MD, Germany). The *T* values were computed from equation below:

$$T = \frac{2P}{\pi Dt} \quad \text{Eq.(1)}$$

where *P* is the load applied on the tablet that causes diametric fracture of the tablet of diameter, *D*, and *t* is the tablet thickness (*m*). The content uniformity of drug in tablets was confirmed based British pharmacopoeia method.<sup>10</sup>

### **Drug release kinetics**

In order to describe the kinetics of drug release from mucoadhesive tablets, various mathematical equation models (zero-order, first-order, Higuchi) were tested

$$Q_t = K_0 t \quad \text{Eq.(2)}$$

$$\ln Q_t = \ln Q_0 - K_1 t \quad \text{Eq.(3)}$$

$$Q_t = K_H t^{1/2} \quad \text{Eq.(4)}$$

Where *Q<sub>t</sub>* is the amount of drug released in time *t*, *Q<sub>0</sub>* is the initial amount of drug in tablet and *k<sub>0</sub>*, *k<sub>1</sub>* and *k<sub>H</sub>* 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 Peppas and Korsemayer equation

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

Where *M<sub>t</sub>* corresponds to the amount of drug released in time *t*, *M<sub>∞</sub>* is the total amount of drug that must be released at infinite time, *K<sub>p</sub>* is a constant and "n" is the

release exponent indicating the type of drug release mechanism. The value of *n* for a cylinder is < 0.45 for Fickian release, > 0.45 and < 0.89 for non-Fickian release, 0.89 for the case II release and > 0.89 for super case II type release.<sup>16</sup> Criteria for selecting the most appropriate model were based on best goodness of fit and smallest sum of squared residuals.

### **Determination of bioadhesive strength**

To evaluate the bioadhesion strength, a tensile tester apparatus was designed similar to a tensile tester apparatus (Instron model 4301) and the bioadhesive strength of the 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 of abdominal skin of rat (mucosa part) was fixed on the head of diffusion cell and filled with phosphate buffer with pH 6.8. The same conditions were exactly used according to previously published method.<sup>17</sup>

### **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 weight, 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 blotted with a tissue paper to remove excess test liquid and re-weighed. The percent water uptake, i.e., degree of swelling due to absorbed test liquid, was estimated at each time point using following equation:

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

Which, %WU is the percent of water uptake, *W<sub>s</sub>* is the weight of swelled matrix in certain time, and *W<sub>i</sub>* is the initial starting weight in the matrix tablet (n=3).<sup>18</sup>

### **Matrix erosion studies**

The standard USP/NF dissolution apparatus No. 1 (Caleva 8ST, Germany) was used for this purpose. The dry matrices were 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 50° C.<sup>18</sup> The percentage matrix erosion (%E) at time, *t*, was estimated from equation No. 6:

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

$$\%Remaining = 100 - \%E \quad \text{Eq. (8)}$$

Where *W<sub>i</sub>* is the initial starting weight of the matrix and *W<sub>t</sub>* is the weight of matrix subjected to erosion for time, *t* (n=3).

### **Statistical analysis**

A one-way ANOVA with a Tukey's post hoc (by SPSS

12), test was used to analyzed the dissolution and bioadhesion 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 1 g of *P. major* was  $14.3 \pm 1.06$  mL ( $637.2 \pm 43.9\%$ ) according to the above method.

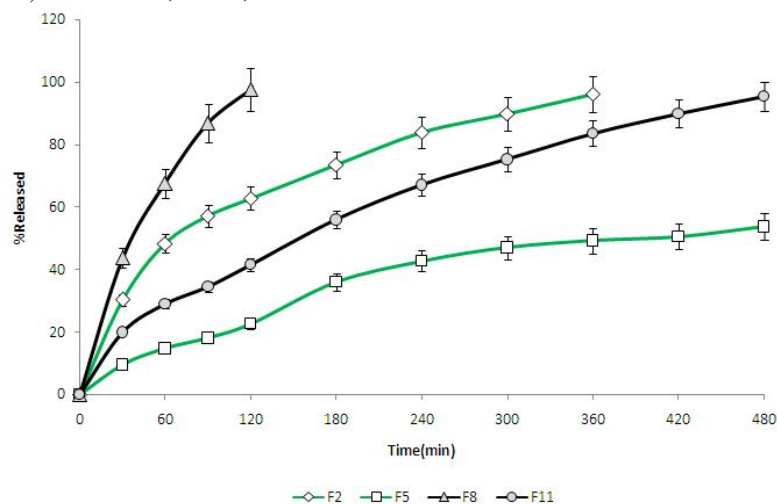
**Table 2.** Characteristics of propranolol hydrochloride tablets prepared with different ratios of *P. major* mucilage, HPMC K4M, and tragacanth.

Formulation Code	Hardness* (kg.cm <sup>-2</sup> ) (n=10)	Friability* (% w/w) (n= 10)	Tensile strength* (MN.m <sup>-2</sup> ) (n=10)	Assay* (%) (n=20)
F1	3.65 ± 0.16	1.22 ± 0.11	0.43 ± 0.05	99.44 ± 2.31
F2	3.83 ± 0.21	1.02 ± 0.06	0.45 ± 0.06	100.07 ± 2.14
F3	4.11 ± 0.19	0.96 ± 0.06	0.51 ± 0.06	100.21 ± 3.17
F4	3.27 ± 0.19	1.01 ± 0.05	0.33 ± 0.07	99.56 ± 3.16
F5	3.48 ± 0.29	0.98 ± 0.07	0.39 ± 0.05	100.27 ± 2.78
F6	3.57 ± 0.25	0.91 ± 0.05	0.42 ± 0.06	99.78 ± 2.11
F7	4.76 ± 0.29	0.92 ± 0.05	0.58 ± 0.07	98.51 ± 3.16
F8	4.95 ± 0.36	0.85 ± 0.07	0.65 ± 0.05	100.37 ± 2.93
F9	5.57 ± 0.35	0.81 ± 0.05	0.74 ± 0.06	99.18 ± 2.47
F10	4.91 ± 0.28	0.91 ± 0.05	0.61 ± 0.07	99.54 ± 2.68
F11	5.23 ± 0.37	0.82 ± 0.07	0.68 ± 0.06	100.34 ± 3.14
F12	5.42 ± 0.31	0.72 ± 0.06	0.73 ± 0.05	98.78 ± 2.85

\* Data are shown as mean ± SD,

The bioadhesive matrix tablets were prepared according to Table 1 and were analyzed as described above. The release rate of propranolol from matrix tablets (1:1 drug: polymer) as a function of time as shown in Fig. 1. As the amount of polymers increased from 40 mg to 160 mg per tablet, initial drug release as well as drug release in the latter hours was decreased. The percent of cumulative drug release after 2 h for formulation containing 40 mg *P. major* mucilage (F1), Carbopol 934P (F4), Tragacanth (F7), and HPMC K4M (F10) were 73.97, 53.66, 100 and

70.99%, respectively. Whereas the percent of cumulative drug release after 2 h for the formulations containing 160 mg *P. major* mucilage (F3), Carbopol 934P (F6), Tragacanth (F9), and HPMC K4M (F12) were 47.47, 12.31, 61.09, and 28.84%, respectively. The lowest release rate was observed with formulation F6 containing Carbopol 934P and the highest release rate was observed with formulation F7 containing tragacanth. The significant difference was observed between formulations ( $P < 0.001$ ).



**Figure 1.** Comparison of release behaviour of propranolol HCl from matrices containing 1:1 of drug/mucilage (F2), carbopol (F5), Tragacanth (F8) and HPMC (F11) (n = 3).

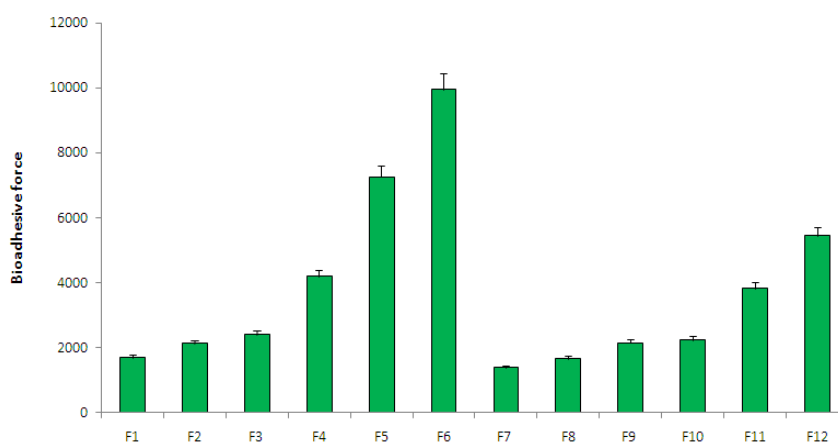
Dissolution rate data were analyzed based on Eqs. (2-5) and their results are listed in table 3. The results showed that altering the type and amount of polymer was affected on the release kinetic of propranolol from buccoadhesive tablets and the highest correlation coefficient were achieved with the various models. The results showed that by changing the type and amount of drug release kinetics of polymer changes and the highest correlation coefficient were achieved with the various models. The results showed that in formulations containing *P. major* mucilage as a controlling-release agent (F1-F3), the kinetic of release changed by increase in amount of mucilage. These results showed that in F1 the highest correlation coefficient was achieved with the Higuchi model. The release rate was so fast that kinetic analysis

could not be fitted accurately in Peppas model. Increasing in amount of *P. major* mucilage in F2 (containing 1:1 of drug: mucilage ratio) changed the kinetic of release and the best fitting was observed in Peppas model. The value of *n* in Peppas model was 0.542 and showed the diffusion type release.<sup>16</sup> The bioadhesion strength of mucoadhesive tablets were evaluated by method that described by Akbari et al.<sup>17</sup> The bioadhesive strengths of the mucoadhesive tablets are shown in Fig.2. Maximum bioadhesive strength was seen with Carbopol 934P and the lowest bioadhesive strength was seen with tragacanth ( $P<0.001$ ). The results also show that bioadhesive strength increased with increase in the amount of polymers ( $P<0.01$ ).

**Table 3.** The kinetics data of propranolol hydrochloride release from investigated mucoadhesive tablets.

Formulation code	Zero-order model			First-order model			Higuchi model			Peppas model			
	$K_0$ (%.min)	$r^2$	ss	$K_1$ (min <sup>-1</sup> )	$r^2$	ss	$K_H$ (%.min <sup>-1/2</sup> )	$r^2$	ss	$K_p$ (%.min <sup>-n</sup> )	<i>n</i>	$r^2$	ss
F1	0.005	0.978	13003	0.076	0.778	5057.1	0.082	0.995	775.7	----	----	----	----
F2	0.004	0.919	13020	0.053	0.882	8801.0	0.086	0.963	140.6	----	----	----	----
F3	0.005	0.962	7036.5	0.047	0.777	19858	0.099	0.993	5842	----	----	----	----
F4	0.003	0.926	13769	0.037	0.748	32723	0.072	0.976	2734	---	---	---	---
F5	0.001	0.914	19455	0.001	0.944	8178.0	0.029	0.968	12727	0.010	0.66	0.979	682.0
F6	0.005	0.991	22530	0.006	0.996	17088	0.013	0.994	2406.9	0.009	0.54	0.994	117.5
F7	0.002	0.874	31325	0.016	0.668	306.00	0.048	0.954	2836.4	-----	----	----	----
F8	0.001	0.961	37758	0.016	0.668	4531.0	0.041	0.996	6919.0	0.127	0.331	0.992	9.077
F9	0.001	0.995	32270	0.012	0.552	14319	0.041	0.985	1726.5	0.114	0.304	0.935	121.4
F10	0.002	0.933	25202	0.017	0.689	18771	0.052	0.978	500.40	0.053	0.478	0.985	35.65
F11	0.002	0.979	22884	0.006	0.957	2240.6	0.047	0.993	2626.5	0.042	0.484	0.963	166.7
F12	0.001	0.979	18369	0.002	0.982	5196.9	0.032	0.985	13299	0.012	0.643	0.970	833.8

$k_0$ : 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;

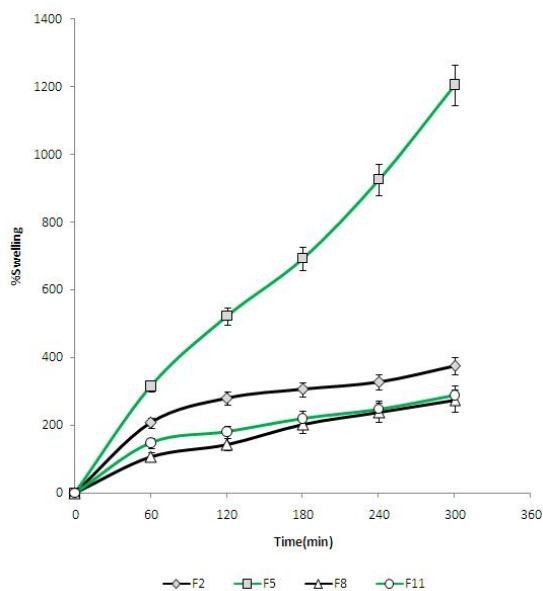


**Figure 2.** Comparison of bioadhesive force (N/m<sup>2</sup>) of matrices containing 1:1 of drug/mucilage (F2), carbopol (F5), Tragacanth (F8) and HPMC (F11) (n = 3).

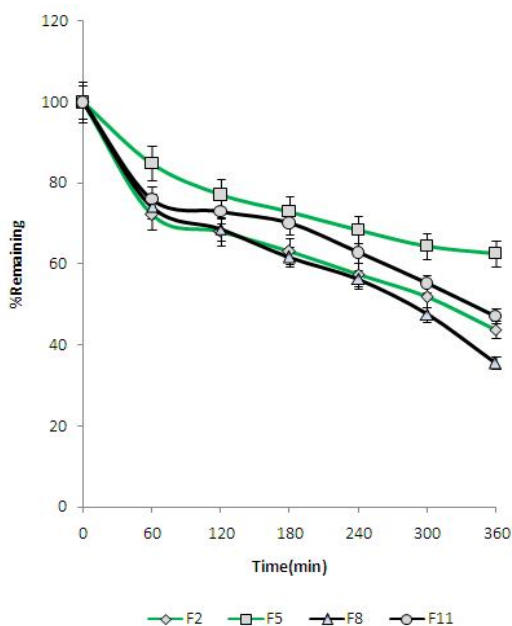
The swelling of the polymers used *P. major* mucilage, Carbopol 934P, Tragacanth, and HPMC K4M, could be determined by water uptake of the tablet. In this study the swelling of formulation that contain 1:1 ratio of drug and polymer (F2, F5, F8, and F11) were investigated. The percent of swelling of the tablets

were determined by the method described previously (Fig. 3). The complete swelling of the tablet was achieved in various time after beginning the test and significant difference was seen between polymers ( $P<0.01$ ). The complete swelling was achieved in 240 min, 240 min, 180 min, and 120 min for F2, F5, F8,

and F11 respectively. The highest and lowest percent of swelling were seen with F2 and F8, respectively. The hydration and erosion rates of tablets were measured, after the immersion of the 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. 4). Weight loss from the tablets was in constant progression until the end of test.



**Figure 3.** Comparison of swelling of matrices containing 1:1 of drug/mucilage (F2), carbopol (F5), Tragacanth (F8) and HPMC (F11) (n = 3)



**Figure 4.** Comparison of erosion of matrices containing 1:1 of drug/mucilage (F2), carbopol (F5), Tragacanth (F8) and HPMC (F11) (n = 3).

## Discussion

Values of the tensile strength and friability for all formulations are presented in Table 2. The values of hardness (from  $3.65 \pm 0.16$  to  $4.11 \pm 0.19$  kg.cm<sup>-2</sup> in F1 and F3 respectively) and tensile strength increased (from  $0.43 \pm 0.05$  to  $0.51 \pm 0.06$  MN.m<sup>-2</sup> in F1 and F3 respectively) with increase in the concentration of mucilage while friability decreased with increase in mucilage concentration (from  $1.22 \pm 0.11$  to  $0.96 \pm 0.06$  % 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.<sup>14</sup> However, 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 tablet. The content uniformity test showed that the drug content was between 98.78-101.09 %.

There has been much interest expressed in the use of oral cavity membranes as sites of drug administration. Both the buccal and sublingual sites have advantages compared with other routes, including rapid onset of action, high blood levels, avoidance of the first-pass effect and possible degradation of drug as a result of its exposure to the gastrointestinal tract. In addition, there is excellent accessibility and the drug can be applied, localized and removed easily.<sup>19</sup>

Bioadhesive force means the force with which tablets bind to buccal mucous membranes. The bioadhesive forces of the tablet are affected by the shape of the tablet, the swelling degree of the tablet and the nature of the tablet components.<sup>20</sup>

Many polymers have been studied for use as mucoadhesive polymers. A mucoadhesive polymer should have properties such as proper hydrogen-bonding functional groups, suitable wetting properties, swelling/water load properties, and sufficient flexibility for entanglement with the tissue mucus network.

Mechanisms of polymer attachment to mucosal surfaces are not yet fully understood. However, certain theories of bioadhesion have suggested that it might occur via physical entanglement (diffusion theory) and/or chemical interactions, such as electrostatic, hydrophobic, hydrogen bonding, and Van der Waals interactions (adsorption and electronic theories).<sup>21</sup>

Formulations that contain carbopol 934P were having highest bioadhesive force because the carbopol 934P has a higher viscosity than the other three polymers. Also the bioadhesion force increased as the polymer amount increased. 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. 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 unstable interaction amongst the

polymer and the mucosal layer resulting in poor mucoadhesive properties.<sup>22</sup> The increased sites for bond formation can explain the increase in bioadhesion with an increase in amount.

Tragacanth containing formulation (F2) was having lowest bioadhesive force because the tragacanth has a lower viscosity than the other three polymers, while formulation containing carbopol 934P showed higher bioadhesion force due to higher viscosity. HPMC is a long chained, non-ionic polymer and so its mucoadhesion is attributable to the formation of physical bonds or hydrogen bonding with the mucus components. HPMC possesses a large number of hydroxyl groups that are responsible for adhesion. *Plantago major* contain mucilaginous matter consisting of hydrophilic polycarbohydrides mainly in the seed coat. The polycarbohydrides have variable amounts of xylose, arabinose, galacturonic acid and glucuronic acid as main components. They 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.

From the above results it was found that polymers having high molecular weight and high viscosity exhibited higher adhesion. Chandira et al. prepared the mucoadhesive tablets of Clarithromycin by using the Carbopol 974P, HPMC K15M and HPMC K4M. They found that polymers having high molecular weight and high viscosity exhibited higher adhesion. HPMC K15M and Carbopol 974P were found to be having good mucoadhesive strength. HPMC and carbopol possesses hydroxy and carboxy groups respectively required for bioadhesion.<sup>21</sup> Akbari et al evaluated the effect of fillers on the bucoadhesive propranolol hydrochloride tablets. The results showed that bioadhesion force increased by increasing in the amount of polycarbohydril. It is clear that the formation of very thin and strong gel layer at the boundary might be necessary for adhesion. The viscosity of this layer is increased by adding polycarbohydril and therefore the bioadhesion strength increases.<sup>17</sup>

Also Maniyar et al. stated that the strength of mucoadhesion can be influence by polymer amount.<sup>23</sup> Drug release from carbopol 934P was lesser owing to its high viscosity and also due to less permeability of water to carbopol 934P. Also the viscosity grade and the amount of the polymer used affecting the drug release rate.

Comparative dissolution profile (Fig. 1) showed that an increase in the percentage of *P. major* mucilage from 40 mg (F1) to 160 mg (F3) resulted in a decrease in the release rate of propranolol. The results showed that the release rates of matrices containing carbopol 934P were slower, and drug release rates in formulations containing tragacanth were higher than the drug release from matrices containing *P. major* mucilage and HPMC K4M for all investigations). Odeku and Fell

reported that an increase in the percentage of Khaya gum from 60% to 90% w/w mucilage containing matrices resulted in a significant decrease in the release rate of paracetamol.<sup>9</sup> Similar results were observed in glibenclamide matrix tablets containing dried mucilage of *Aloe barbadensis* as a release retardant excipient.<sup>24</sup> The same results were reported in aminophylline matrix tablets containing *Adansonia digitata* mucilage too. The drug release retardation efficiency of the *Adansonia digitata* mucilage tablets at equal polymer amount was less than that of HPMC.<sup>25</sup>

The adhesion increases with the degree of hydration until a point where over hydration leads to an abrupt drop in adhesive strength due to disentanglement at the polymer tissue interface<sup>26</sup>. The results of swelling and erosion studies in phosphate buffer (pH 6.8) are shown in Fig. 3. The changes in weight, characteristic of water uptake and swelling, started from the beginning and continued until 360 min of experiment, in the except of F8 which disintegrated after 3h. There was significant ( $P < 0.001$ ) difference in percent swelling of the tablets with different polymers. The percent swelling of formulations containing Carbopol 934P were found to be higher than that of other formulations. The formulations containing tragacanth showed the lowest swelling in comparison with other formulations. It can also be concluded that the viscosity of polymer had major influence on swelling process and matrix integrity. The high initial uptake of water may be due to the faster hydration rate of HPMC.

In hydrophilic polymeric matrix systems, the carrier on the surface of the matrix initially hydrates during dissolution to generate an outer viscous gel layer. This phase is then sequentially followed by matrix bulk hydration, swelling and erosion.<sup>27</sup> The results of matrix erosion are shown in Fig. 4. Weight loss from the tablets increased progressively with the erosion of time. The extent of erosion in formulations containing *P. major* mucilage (F1-F3) was more than HPMC and carbopol matrices and lower than tablets containing tragacanth. These erosion profiles confirm the release pattern of propranolol hydrochloride from *P. major* mucilage containing matrix tablets. 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.<sup>20</sup>

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 I and II. According to our previous study, *P. major* mucilage thermogram exhibits a very broad endothermic peak at 95.2°C which is associated with the loss of water from the carbohydrate polymer and propranolol hydrochloride showed an endothermic peak around its melting point (164.2±0.1°C). The matrix tablet containing 1:1 of

drug: *P. major* mucilage ratio in both matrix tablet and physical mixture showed the same peak in this area, which indicates that there is no interaction between drug and *P. major* mucilage during the formulation process.<sup>10</sup> From above finding it can be concluded that the delayed dissolution rate of propranolol hydrochloride is not due to the formation of complex between the drug and *P. major* mucilage, or changes in crystallinity of the drug.

In our previous study, FT-IR spectral confirmed the above conclusion. In case of pure *P. major* mucilage, a broad band appeared around 3437.5 cm<sup>-1</sup> corresponds to OH stretching, wave number 1742.9 cm<sup>-1</sup> depicts the stretching zone of C=O, and 1040.1 cm<sup>-1</sup> depicts the stretching vibration of C-O group which was characteristics of polysaccharides. The FT-IR spectrum of propranolol hydrochloride, revealed the presence of peaks at 2964.9 cm<sup>-1</sup> due to the presence of a secondary amine group, peaks at 3280.6 cm<sup>-1</sup> due to the hydroxyl group (secondary), the aryl alkyl ether displayed a stretching band at 1267.8 cm<sup>-1</sup> and the peak at 979.9 cm<sup>-1</sup> was due to  $\alpha$ -substituted naphthalene.<sup>10</sup> The FT-IR spectrum of the blend of mucilage and drug, major characteristic peaks of propranolol hydrochloride were retained. The peaks at 2960.38 cm<sup>-1</sup> due to the presence of a secondary amine group, 3281.37 cm<sup>-1</sup> due to the hydroxyl group (secondary), the aryl alkyl ether displayed a stretching band at 1267.87 cm<sup>-1</sup> and the peak at 970.0 cm<sup>-1</sup> was due to  $\alpha$ -substituted naphthalene. This confirmed no physical or chemical interactions amongst the components of the formulation and compatibility of the drug with the natural carbohydrate polymer.

### Conclusion

The aim of this study was to investigate the suitability of natural mucilage as a mucoadhesive agent. This study has demonstrated the potential of *Plantago major* seed mucilage to act as a controlled release excipient and bioadhesive agent in matrix formulation.

An increase in amount of mucilage in binary mixtures of drug-mucilage resulted in an decrease in drug release from tablets. The kinetics of release showed that the best fitting was observed in Higuchi model. This mucilage as a natural compound have advantages like oral safety, and inexpensively. The present study demonstrated that *P. major* mucilage have major potential for use as a bioadhesive and controlled release excipient.

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