Drug Development and Industrial Pharmacy, 34:323–329, 2008
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ISSN: 0363-9045 print / 1520-5762 online
DOI: 10.1080/03639040701662594

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An In Vitro Evaluation of Fenugreek Mucilage as a Potential Excipient for Oral Controlled-Release Matrix Tablet

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A polysaccharide mucilage derived from the seeds of fenugreek, *Trigonella foenum-graceum* L (family Fabaceae) was investigated for use in matrix formulations containing propranolol hydrochloride. Methocel® hypomellose K4M was used as a standard controlled release polymer for comparison purposes. In this study the effect of lactose on the release behaviour of propranolol hydrochloride from matrices formulated to contain the fenugreek mucilage also was investigated. An increase in concentration of the mucilage in matrices resulted in a reduction in the release rate of propranolol hydrochloride comparable to that observed with hypomellose matrices. The rate of release of propranolol hydrochloride from fenugreek mucilage matrices was mainly controlled by the drug:mucilage ratio. However, the mechanism of release from matrices containing drug:mucilage ratios of 1:1, 1:1.25, 1:1.5, and 1:2 remained the same. The kinetics of release, utilising the release exponent n, showed that the values of n were between 0.46–0.57 indicating that the release from fenugreek mucilage matrices was predominantly by diffusion. The presence of lactose in matrices containing mucilage increased the release rate of propranolol hydrochloride. This is due to a reduction in tortuoisity and increased pore size of channels caused by lactose through which propranolol diffuses and therefore diffusion of water into the tablet is facilitated.

Keywords fenugreek mucilage; propranolol hydrochloride; release rate; mechanism of release

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INTRODUCTION

The use of naturally occurring biocompatible polymeric materials has been the focus of recent research activity in the design of dosage forms for oral controlled release administration (Bonferoni et al., 1993; Khullar, Khar, & Agarwal, 1998; Kristmundsottir et al., 1995; Naggar et al., 1992; Vervoort et al., 1998). Polymeric hydrogels are studied for controlled-release applications because of their producing drug release close to zero-order kinetics (Colombo et al., 1985, 1995; Hussain et al., 1994; Mockel & Lippold, 1993; Munday & Cox, 2000; Reynolds et al., 1998; Ughini et al., 2004). Gums from natural sources hydrate and swell on contact with water and have been used for the preparation of single unit dosage forms (Nakano & Ogata, 1984).

Fenugreek seeds contain a high percentage of mucilage (a natural gummy substance present in the coatings of many seeds). Although it does not dissolve in water, mucilage forms a viscous tacky mass when exposed to fluids. Like other mucilage-containing substances, fenugreek seeds swell up and become slick when they are exposed to fluids. The resulting soft mass is not absorbed by the body, but instead passes through the intestines and triggers intestinal muscle contractions (Petropoulos, 2002).

Trigonella Foenum-graceum, commonly known as Fenugreek, is an herbaceous plant of the leguminous family and is native to Western Asia, from where it has spread widely over Europe, the Mediterranean, and the rest of Asia. It is one of the oldest cultivated plants and has found wide applications as a food, a food additive, and as a traditional medicine in every region

where it has been cultivated. The leaves and both the ripe and unripe seeds of *Trigonella Foenum-graceum* are used as vegetables. The seeds also function as a food preservative and are added to pickles, chutneys, and other similar food products (Petropoulos, 2002). The ripe seeds have numerous applications in the traditional medicine system of India. Fenugreek has been used in treating colic flatulence, dysentery, diarrhoea, dyspepsia with loss of appetite, chronic cough, dropsy, enlargement of liver and spleen, rickets, gout, and diabetes (Al-Habori, 2002). The seed is stated to be a tonic. It also is used in post-natal care and to increase lactation in nursing mothers (Al-Habori, 2002).

The aim of the present study is to investigate the suitability of the mucilage as a matrix-forming agent, and propranolol hydrochloride is chosen as a model drug. As hypomellose is one of the widely used hydrophilic polymers in matrix formulations (Li et al., 2005) the present study also compares the release data obtained for matrices containing fenugreek mucilage to those of matrices containing hypomellose.

MATERIALS AND METHODS

Materials

Hypomellose (Hydroxypropyl methylcellulose (HPMC) K4M (Colorcon,UK), lactose (DMV, UK), fenugreek seeds (Maku, Iran), methanol (Merck, Germany), ethanol 96% (Merck, Germany), diethyl ether (Merck, Germany), hexane (Merck, Germany), hydrochloric acid (Merck, Germany), acetone (Merck, germany), n-buthanol (Merck, Germany), and magnesium stearate (BDH, UK) were used as supplied.

Extraction of Mucilage

Fenugreek seeds were purchased from a local market in Maku, Iran. Representative seeds were germinated and the flowering plants were authenticated to be *Trigonella foenum-graceum* L (Fabaceae).

Mucilage extraction and purification were carried out according to the method described by Karawya (1980) with some modifications. The seeds were powdered using pestle and mortar and 100 g of the powder was extracted with hexane to remove lipophilic compounds using a soxhelet apparatus. To remove pigments and to deactivate enzyme, the defatted powder was boiled in ethanol for 20 min (Karawya, 1980). This treated powder was then soaked in 10 litres water and the pH was adjusted to 3.5 using 0.5 M Hydrochloric acid. The mixture was stirred by a mechanical stirrer (IKA, Germany) for 12 h and then filtered through filtration paper (Millipore, UK). The filtrate was centrifuged (5000 g) (BHG, Germany) and the supernatant was concentrated in vacuum to 50% of its initial volume. The resulting solution was mixed with the same volume of 96% ethanol and stored in a refrigerator for 4 h. The precipitated mucilage was separated by centrifugation (5000 g). The collected mucilage was re-suspended in distilled water, agitated for 20 min and re-precipitated one more time to eliminate chloride ions and other impurities. Finally the residue was washed with diethyl ether and acetone and dried overnight at 45°C, resulting in an off-white powder.

Total Hydrolysis of the Mucilage and Sugar Analysis

The mucilage (0.1 g) and 25 ml 2M Hydrochloric acid were refluxed for 2 h at 100°C. The solution was then concentrated under vacuum and the excess acid was removed by repeated codistillation with distilled water. The residue was dissolved in methanol containing a few drops of water and chromatographed on precoated silica gel plates (silica gel GF_{254}, 0.25 mm, Merck) in n-buthanol:acetic acid:water (4:1:5). The thymol-sulfuric acid reagent was used to detect sugars (5 min at 120°C). Quantitative analysis of sugars was performed according to the procedure recommended by Harborne (1998).

IR Spectroscopy

Fourier-trasform infrared spectroscopy (FT-IR) was obtained on a Bomem 2000 FT-IR system (Bomem, Quebec, Canada) using the KBr disk method. Samples were mixed with KBr and compressed to 10 mm discs using a hydraulic press at a pressure of 100 kN for 30 s. The IR scanning range was 450–4000 cm^{-1} and the resolution was 2 cm^{-1}.

Viscosity Determination

1 g of dried and finely powdered fenugreek mucilage was suspended in 75 ml of distilled water for 5 h. Distilled water added up to 100 ml to produce the concentration of 1% w/v. The mixture was homogenized by mechanical stirrer for 2 h and its viscosity determined using a Brookfield viscometer, spindle –LV2 (Brookfield LV-II, USA) at 20 rpm and 25°C.

Preparation of Hydrophilic Matrices

For each mixture, matrices were prepared by mixing propranolol hydrochloride with the fenugreek extract mucilage powder (ratios of drug to mucilage were 1:1, 1:1.25, 1:1.5, and 1:2) or hypomellose in a cube mixer (Erweka, Type UG, Germany) for 10 min. Magnesium stearate was then added to the mixture and was mixed for a further 1 min. The final mixtures were compressed on an 8-mm punch and die using a manual-tableting machine (Riken, Japan) at a constant pressure of 10 kN. To determine the effect of lactose on the release rate of propranolol from matrices containing the mucilage or hypomellose, a constant amount of lactose was added to the formulations. The compositions of all formulations are listed in Table 1. The amount of propranolol hydrochloride was 100 mg in all formulations

TABLE 1
The Composition of Formulations of Matrices

Formulation Code	Propranolol Hydrochloride (mg)	Mucilage (mg)	Hypomellose K4M (mg)	Lactose (mg)	Crushing Strength (kgf)*
F1	100	100	—	—	6.2 ± 0.4
F2	100	125	—	—	7.5 ± 2.8
F3	100	150	—	—	10.8 ± 0.3
F4	100	200	—	—	15.5 ± 1.6
F5	100	150	—	50	12.0 ± 1.6
F6	100	200	—	50	15.2 ± 1.0
F7	100	—	100	—	12.1 ± 1.2
F8	100	—	200	—	11.5 ± 2.5

*Values are mean and standard deviation of 6 determinations.

Crushing Strength Determination

Tablet crushing strength was determined from the force required to fracture the compacts by diametral compression on a motorized tablet hardness tester (Erweka, Germany). The results are the mean and standard deviations of at least five tablets.

In Vitro Dissolution Study

The United State Pharmacopoeia (USP) basket method at 37 ± 0.1°C and a rate of stirring at 100 ± 2 rpm was used for the in vitro dissolution studies. The dissolution media consisted of 900 mL simulated gastric fluid without pepsin (pH 1.2) or simulated intestinal fluid without pancreatin (pH 6.8). The matrices were placed in 900 ml of the simulated gastric fluid (pH 1.2) for 1 h. At appropriate intervals (15, 30, and 60 min), 5 ml of the samples were taken and filtered through a 0.45 μm Millipore filter. The dissolution media was then replaced by 5 ml of fresh dissolution fluid to maintain the constant volume of 900 mL. After 1 h the pH of the dissolution medium was changed from 1.2 to 6.8 using phosphate buffer to simulate intestinal fluid. At appropriate intervals (30, 60, 120, 180, 240, 300, 360, and 420 min) 5 ml of the samples were taken and filtered through a 0.45 μm Millipore filter. The dissolution media was then replaced by 5 ml of fresh dissolution fluid to maintain the constant volume of 900 mL. The samples were analyzed at 289 and 288.5 nm at pH 1.2 and 6.8, respectively, by ultraviolet/visible spectrophotometry (Shimadzu 160A, Japan). The mean of three determinations was used to calculate the drug release rate from each of the formulations.

The release data from controlled release polymeric matrices can be described by Equation 1 proposed by Korsmeyer et al. (1983)

$$Q = K_1 t^n \quad (1)$$

Q is the percentage of drug released at time t, K_1 is a kinetic constant incorporating structural and geometric characteristic of the tablets, and n is the diffusional exponent indicative of the release mechanism.

However, Equation 1 is based on the assumption that release occurs as soon as the matrix is placed in contact with fluid and thus predicts an intercept at the origin. A similar equation with a correction for lag times (*l*) was introduced by Ford et al. (1987, 1991):

$$Q = K_2 (t - 1)^m \quad (2)$$

Where m is the diffusional exponent indicative of the release mechanism. The lag time is the time required for the matrix to hydrate and reach equilibrium before erosion, and the advance of the solvent front occurs through the matrix. Ford et al. (1991) concluded that these lag times in dissolution, despite being relatively constant and small, cannot be ignored when describing release using exponential functions as they improve the fit of the data. Furthermore, such lag times can considerably alter the values of both derived kinetic constants and diffusional exponents. For these reasons, in this study the data between 5 and 60% release were fitted with a computer program (Ford et al., 1991) to Equation 2. Values of m near 0.5 indicate predominantly diffusion control and of 1.0 correspond to zero-order release (Ford et al., 1991).

Furthermore, the release of the drug between 5 and 60%, as a linear function of the square root of time (Higuchi type equation), according to Equation 3 also was calculated:

$$Q = K_3 t^{0.5} + C \quad (3)$$

K_3 is the root time-release rate and C is a constant.

To compare the effects of polymer or diluent concentrations on the drug release, the criteria mean dissolution time (MDT)

and dissolution efficiency (DE) were used as described in Equation 4 and Equation 5, respectively

$$MDT = \frac{\sum_{j=1}^{n} t\Delta M_j}{\sum_{j=1}^{n} \Delta M_j} \quad (4)$$

In Equation 4 (Costa et al., 2003) j is the sample number, n is the number of dissolution sample times, t is the time at mid-point between t and $t - 1$ (easily calculated with $(t + t - 1)/2$) and ΔM_j is the additional amount of drug dissolved between t and $t - 1$. DE is as described below:

$$DE = \frac{\int_0^T Y \times dt}{Y_{100} \times T} \times 100\% \quad (5)$$

In Equation 5 (Khan, 1975), Y is the percent drug release as a function of time, T is the total time of drug release and Y_{100} is 100% drug release.

RESULTS AND DISCUSSION

The yield percentage of the mucilage extraction from fenugreek seeds was 35% w/w and the viscosity of its 1% aqueous dispersion was 484 cP. Analysis confirmed that the sugars existing in mucilage were mannose (66.86%), galactose (33.48%), and xylose (0.35%). The absence of sharp peak at 1700–1800 cm^{-1} in the FT-IR spectrum indicates that there is no carboxyl group in the extracted sample. On the other hand, the presence of peak at 1000–1200 cm^{-1} corresponds to the presence of alcoholic group mostly secondary alcohols. These findings proved that there were no uronic sugars or esters in the structure (Figures 1A, B).

Table 1 shows the composition of each formulation and also the crushing strengths of tablets that were made at 10 kN force. This strengths of tablets increased as the concentration of fenugreek mucilage increased, indicating a good compactibility of the mucilage powders. For example when the amount of mucilage powder was increased from 100 mg to 200 mg, the crushing strengths of the tablet increased from 6.2 to 15.5 kgf. Comparing the crushing strength of mucilage matrices with hypomellose matrices at similar ratios of drug and polymer revealed that at low concentrations of polymer (1:1 ratio of drug:polymer), the crushing strengths of matrices containing hypomellose was greater than the strengths of matrices containing fenugreek extract. However, when the content of polymers was increased from 100 to 200 mg, matrices containing mucilage showed higher

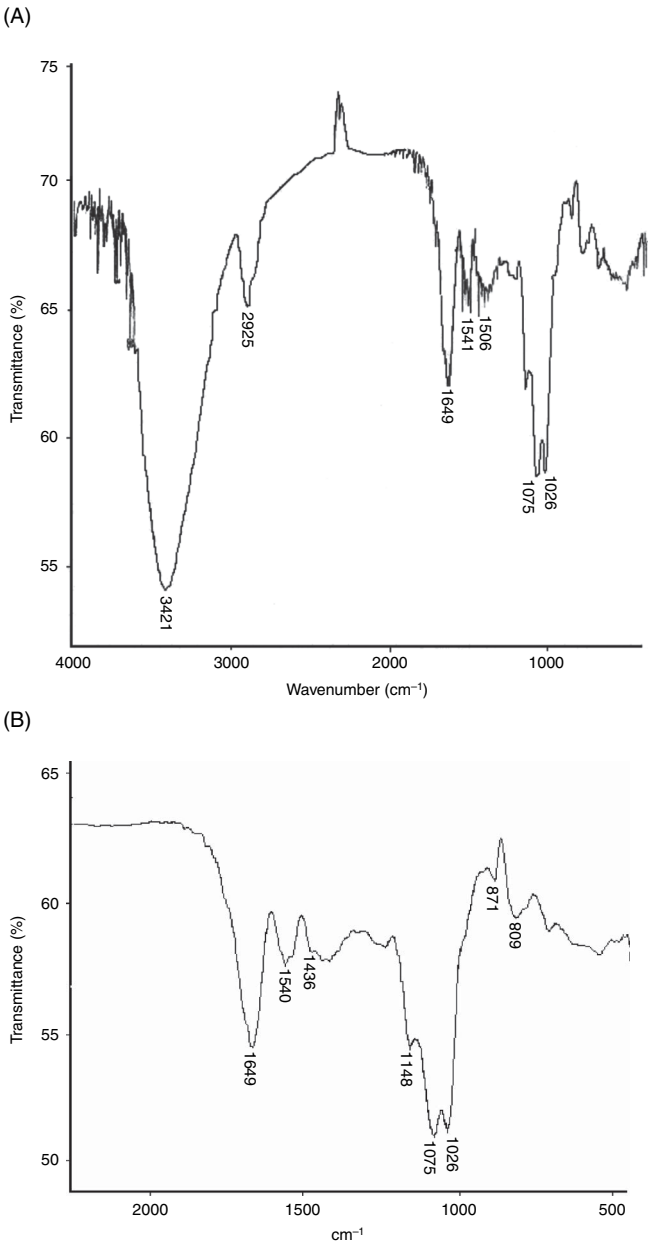

FIGURE 1. FT-IR spectra of fenugreek mucilage powder; (A) between 500–4000 cm^{-1}; (B) 500–2000 cm^{-1}.

strengths than the hypomellose matrices ($p < 0.05$). The content of hypomellose did not significantly affect the crushing strengths of the tablets ($p > 0.05$).

Figure 2 shows the dissolution characteristics of matrices prepared with different mucilage content. In vitro release profiles of propranolol showed that an increase in the percentage of fenugreek mucilage from 100 mg (Formulation F1) to 200 mg (Formulation F4) resulted in a decrease in the release rate of propranolol (Figure 2). For example, the percentages of drug released from the matrices containing 100,

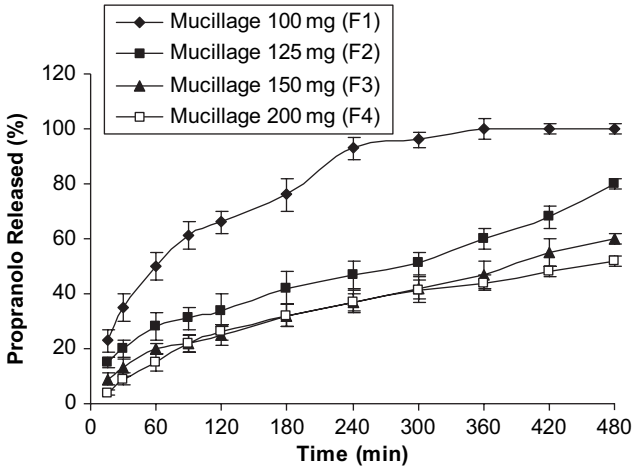

FIGURE 2. Effect of mucilage concentration on the release behaviour of propranolol hydrochloride from matrices.

125, 150, and 200 mg mucilage after 8 h were 100 ± 4, 68 ± 5, 60 ± 2, and 52 ± 3%, respectively. These results were confirmed by dissolution efficiencies and mean dissolution times (Table 2). Matrices containing 200 mg mucilage showed the lowest dissolution efficiency and the highest mean dissolution time, indicating lower release rate for this formulation. For example the dissolution efficiency and mean dissolution time were 34% and 199 min whereas for matrices containing 200 mg mucilage the values were 80% and 97 min, respectively.

The slopes (% $min^{-1/2}$) of the linear portions of the root time dissolution profiles (Figure 1) are given in Table 3. When the log rates of the % $min^{-1/2}$ data (Higuchi model) were plotted as a function of the reciprocal of the mucilage concentration at which they were obtained, a nearly straight line plot was obtained (Figure 3). The general relationship for the line can be expressed by Equation 6:

$$\log R_H = M(1/W) + C \quad (6)$$

where R_H is % $min^{-1/2}$ release rate, M is the slope of derived line, W is weight of mucilage (mg), and C is a constant. The unit of M is % $min^{-1/2}$ mg^{-1} and C is % $min^{-1/2}$ representing the propranolol release rate at a theoretical infinitely high level of mucilage. The coefficient of linear regression of the line was 0.93. The data permitted the release rate to be estimated from a limited number of data points for other polymer contents. A similar relationship was also obtained for promethazine hydrochloride from varying concentrations of different viscosity grades of hypomellose (Ford et al., 1985).

Formulation of sustained release matrices may require the addition of excipients, for instance to alter the size of the tablets, to modify release rates or to increase compaction properties. Therefore, an assessment of the effects of partial replacement of polymer by lactose is important. Figure 4 shows the effect of replacement of mucilage by lactose on the release of propranolol. The presence of lactose resulted in a slight increase in the release rate of the drug from matrices containing 200 mg mucilage but a considerable increase in the release rate of propranolol from the matrices containing 150 mg mucilage. The addition of hydrophilic excipient, lactose, probably increased the release rate by altering the diffusivity of drug in the gel layer. Water diffusivity depends only on the total concentration of viscosity inducing agents in the system irrespective of their nature or polymerization degree (Gao & Fagerness, 1995). Replacement of polymer by lactose decreases tortuoisity and increases pore size of channels through which propranolol diffuses and therefore diffusion of water into the tablet is facilitated. Lactose also decreases the tourtosity of the path of diffusion (Lapidus & Lordi, 1988).

The release profiles of propranolol hydrochloride from matrices containing fenugreek mucilage or hypomellose K4M are shown in Figure 5. The dissolution rate of propranolol from the matrices containing 100 mg hypomellose was slower than that from matrices containing the same amount of fenugreek mucilage. However, when the amount of polymer was increased from 100 mg to 200 mg, the release rate of the drug from fenugreek matrices was slower than from hypomellose matrices. It can be concluded that fenugreek mucilage at a concentration of about 66% w/w (200 mg in formulation F4) is a better release retardant compared to hypomellose at equivalent content. Extracts of fenugreek appear to have major potential for use as a controlled release excipient.

The release kinetics from matrices composed of varying amounts of fenugreek mucilage or hypomellose were analysed using Equations 1, 2, and 3 and are shown in Table 3. As the polymer content increased, the release rate of the drug decreased (values of K_3 in Table 3) whereas the release

TABLE 2
Values of Dissolution Efficiency (DE) and Mean Dissolution Times (MDT) for Different Formulations of Propranolol Hydrochloride

Formulation Code	DE (%)	MDT (min)
F1	80	97
F2	47	168
F3	36	190
F4	34	199
F5	50	151
F6	35	130
F7	67	148
F8	47	171

TABLE 3
The Values of K_1, N, and SS Based on Equation 1; K_2, M, L, and SS Based on Equation 2; K_3, C, and SS Based on Equation 3 for Matrices

Formulation Code	Equation 1			Equation 2				Equation3		
	k	*n*	ss	K	m	*l*	ss	k	C	SS
F1	6.22	0.50	0.27	11	0.38	8.31	4.08	5.43	0.51	13.4
F2	3.86	0.46	47.8	1.8	0.59	−29.3	32.4	3.24	3.10	41.2
F3	1.67	0.57	29.6	0.80	0.69	27.60	18.1	2.71	−2.98	41.5
F4	1.6	0.57	30.5	2.48	0.50	2.90	7.66	2.61	−4.41	16.3
F5	5.61	0.41	42.4	6.33	0.39	4.20	41.1	2.99	6.62	45.8
F6	3.89	0.41	10.1	4.96	0.37	8.64	3.84	2.08	4.40	20.0
F7	6.17	0.44	29.8	9.14	0.37	9.72	10.00	4.25	3.97	40.4
F8	1.49	0.64	22.10	1.82	0.68	5.80	18.5	3.84	−9.07	19.1

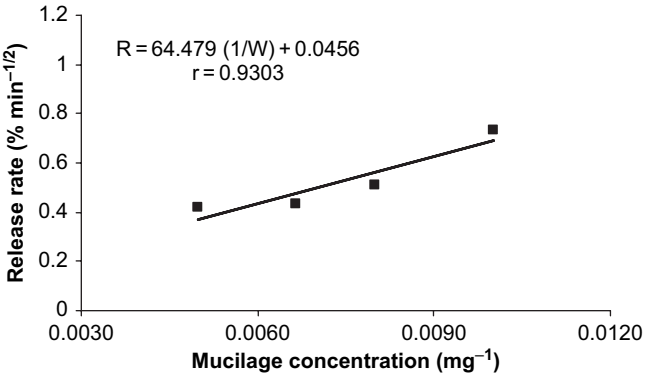

FIGURE 3. Relationship between the release rate of propranolol and the mucilage content in the matrices for formulations F1, F2, F3, and F4.

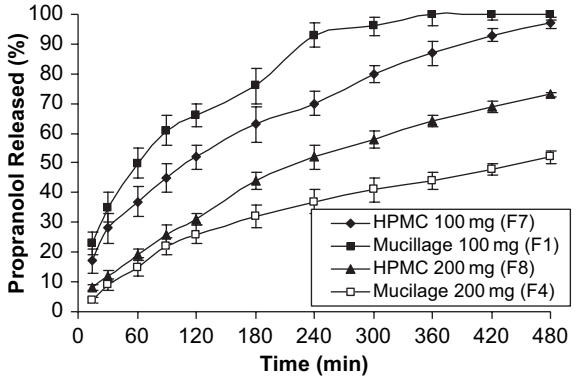

FIGURE 5. Comparison of the release behaviours of propranolol Hydrochloride from matrices containing fenugreek mucilage or hypomellose K4M.

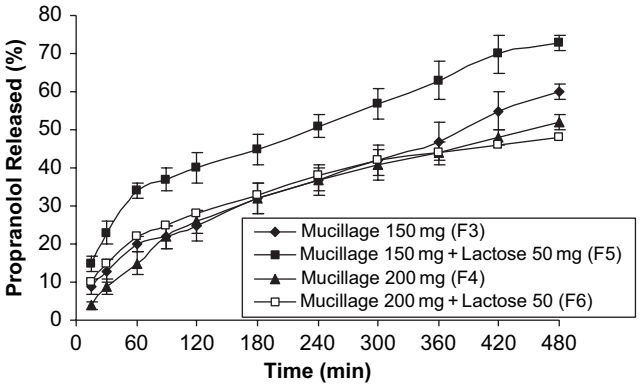

FIGURE 4. The effect of lactose on the release behaviour of propranolol hydrochloride from mucilage matrices.

exponents remained almost unchanged based on Equation 1. A value of n around 0.5 indicates diffusion release mechanisms (Korsemeyer et al., 1983). It is clearly seen that the mucilage content between 100 and 200 mg did not significantly affect the release mechanism. Similar values of *n* of 0.6 (Ranga Rao et al., 1990) and 0.64 (Ford et al., 1987) were found for propranolol hydrochloride release from hypomellose K4M and hypomellose K15M matrices, respectively. 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 (Peppas, 1985). Other values of n obtained for soluble drugs include 0.71 for centperazine release (Baveja & Ranga Rao, 1986) and 0.59 for alperenolol release (Ranga Rao et al., 1990) from matrices containing NaCMC and hypomellose, indicating diffusional-controlled release.

Ford et al. (1991) proved that sum of squares of errors are values that can be used to determine the most appropriate model for a data set. The sum of squares of errors is a measure of the discrepancies between the observed data and the values that would have been predicted by a particular model. Since Equation 2 gave the lowest sums of squares of errors (ss) in comparison to Equation 1, their ss values give an initial guide to the quality of a model; the greater the sums of squares, the poorer the model. Therefore, Equation 2 gives the best fit for the data, suggesting lag time (*l*) in dissolution cannot be

ignored when describing release using exponential functions of time and considerably alter the values of both derived kinetic constants and diffusional exponents.

Negative values of C indicate a burst release of drug and high positive values imply a delay to release. The data in Table 3 indicate that matrices containing 100 to 200 mg fenugreek mucilage had not considerable *l* values. For example, matrices containing 200 mg mucilage has a *l* value of −4.41 min. The small negative value of C indicates that no significant burst release occurred for the matrices containing high concentration of fenugreek mucilage.

CONCLUSION

This study has demonstrated the potential of fenugreek extracts to act as a release retardant excipient in matrix formulation. Binary mixtures of propranolol and mucilage produced matrix tablets with high crushing strength indicating good compactibility of fenugreek mucilage powder. An increase in concentration of mucilage in binary mixtures of drug-mucilage resulted in an increase in crushing strength of tablets. The kinetics of release, utilising the release exponent n, showed that the values of n were between 0.46–0.57 indicating that the release from fenugreek mucilage matrices was predominantly by diffusion. The present study also demonstrated that fenugreek mucilage at a concentration of about 66% w/w is a better release retardant compared to hypomellose at equivalent content. Extracts of fenugreek appear to have major potential for use as a controlled release excipient.

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