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FORMULATION DEVELOPMENT AND EVALUATION OF GASTRORETENTIVE MUCOADHESIVE TABLETS FOR TREATMENT OF HYPERLIPIDEMIA

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Abstract

Objective: The present study concerns the development of mucoadhesive tablets of simvastatin which were designed to prolong the gastric residence time after oral administration. **Methods:** Fenugreek seeds mucilage and their combinations were used to formulate the mucoadhesive simvastatin tablets. Tablets were prepared using direct compression method and were evaluated for parameters such as weight variation, hardness, friability, drug content, swelling index, *in vitro* drug release study, *in vitro* mucoadhesive strength study. **Results:** All the formulation showed compliance with pharmacopeia standards. Among all the formulations, F4 with the combination of Fenugreek seeds mucilage showed greater *in vitro* drug release (99.45% at the end of 8 hrs), good swelling and better mucoadhesive strength than other mucilage combinations. So, the formulation (F4) was selected as optimized. The drug release of optimized formulation follows the Higuchi kinetic model, and the mechanism is found to be non Fickian/anomalous according to Korsmeyer–Peppas. First order was maximum i.e. 0.960 hence indicating drug release from formulations was found to follow First order release kinetics. **Conclusion:** The simvastatin tablets based on swelling and mucoadhesive mechanisms, sustained *in vitro* drug release signify better bioavailability. Such a formulation would improve patient compliance and increase the efficacy of therapy for treatment of hyperlipidemia.

KEYWORDS: Mucoadhesive tablets, Simvastatin, Fenugreek mucilage, Mucoadhesive mechanism.

INTRODUCTION

The primary aim of oral controlled drug delivery system is to deliver drugs for longer period of time to achieve better bioavailability, which should be predictable and reproducible. But this is difficult due to number of physiological problems such as fluctuation in the gastric emptying process, narrow absorption window and stability problem in the intestine.[1] To overcome these problems, different approaches have been proposed to retain dosage form in stomach. These include bioadhesive or mucoadhesive systems,[2] swelling and expanding systems[3,4] floating systems[5,6] and other delayed gastric emptying devices.

In clinical, Fenugreek seeds are reported to have glucose and lipid-lowering properties. Phytochemical studies on T. foenum-graecum revealed that carbohydrates and mucilages (mainly galactomannans), proteins, fixed oils, flavonoids and saponins were the main components of the seeds. Fenugreek is known to have several pharmacological effects such as hypoglycemic, hypocholestrolemic, antioxidant, and appetite stimulation. Furthermore, this plant has gastro protective activity[7] and histopathological examination of liver and brain has revealed that, aqueous extract of fenugreek seeds offer a significant protection against ethanol toxicity.

Simvastatin is HMG Co-A (3-hydroxy-3-methylglutaryl-CoA) reductase inhibitors widely used in the treatment of hyper cholesterolemia, as it reduces levels of low-density lipoproteins and triglycerides, and raises high-density lipoprotein levels. Simvastatin undergoes extensive first pass metabolism in liver due to which the oral bioavailability is less dose size i.e., in few mg. Hence, it is suitable candidate for mucoadhesive drug delivery[8] Since Fenugreek seeds produce high viscosity mucilage at low concentration levels, the objective of the present investigation was to evaluate mucoadhesive tablets of simvastatin by employing Fenugreek seeds mucilage for prolonged gastrointestinal absorption.

MATERIALS AND METHODS

Materials

Fenugreek seeds were procured from the local market. Simvastatin was collected as a gift sample from Aurobindo Pharma Ltd., Hyderabad. All other chemicals used were of analytical grade and were used as received.

Extraction and isolation of fenugreek mucilage

Fenugreek seeds (250g) were soaked in double distilled water at room temperature and then boiled with sufficient amount of double distilled water under stirring condition in a water bath until slurry was prepared. Then the slurry was cooled and kept in refrigerator overnight to settle out undissolved materials. The upper clear solution was decanted off and centrifuged at 1000 rpm for 30 minutes. The supernatant was separated and concentrated at 50-55º C on a water bath to a third of its original volume. Solution was cooled down to room temperature and was poured into thrice volume of acetone by continuous stirring. The precipitate was washed repeatedly with acetone and dried.[9]

Evaluation of mucilage

Determination of percentage yield

Percentage yield of mucilage was determined using this formula.

$$\% \text{ Yield} = \frac{\text{Practical Yield}}{\text{Theoretical Yield}} * 100$$

Physico-chemical characterization of mucilage

The separated mucilage was evaluated for swelling index, loss on drying, density, compressibility index and angle of repose.[10,11]

Determination of swelling index

The swelling index is the volume in ml occupied by 1g of drug; including any adhering mucilage after it has been swollen in an aqueous liquid for 4h. The swelling index of Fenugreek mucilage powder, was determined according to the BP, 2001. One gram of mucilage powder was taken in a 25 ml ground glass stoppered cylinder graduated over a height of 120 to 130 mm in 0.5 divisions. To this 25 ml of water was added and this was shaken vigorously every 10 m for 1h and then allowed to stand for 24 h. The volume occupied by mucilage was measured. The swelling index was calculated from the mean of three determinations.

Swelling Index % (SI) = (W2 – W1/W1) x 100 ---------- (1)

W1= Initial Volume in ml

W2= Final Volume in ml

Loss on drying of isolated mucilage

Loss on drying was directly measured by IR moisture balance (Labgo Infrared Moisture Balance). Firstly calibrated the instrument by knob then taken 5.000 gm sample (powder) and set the temp at 100°C to 105°C for 15 minutes and constant reading set the knob and check % moisture.

Method for preparation of simvastatin mucoadhesive tablet

Simvastatin, polymers, and excipients were mixed thoroughly and passed though sieve 60. The tablets with different composition (table 1) were prepared by direct compression technique on a rotary punch tablet compression machine (Rimek mini press, MT-II, India). The powder was weighed and individually filled in the die cavity (8 mm diameter), and constant pressure was applied. The tablets were evaluated for various parameters like thickness, average weight, hardness, drug content, Swelling Index, mucoadhesive strength and in vitro drug release.[12]

Optimization of mucoadhesive tablets of simvastatin

Table 1: Various formulations of simvastatin mucoadhesive tablets.

Excipients (mg)	F1	F2	F3	F4	F5	F6
Simvastatin	10	10	10	10	10	10
HPMC K4	25	50	25	50	25	50
Fenugreek mucilage	10	10	10	10	10	10
Sodium alginate	10	20	-	-	5	10
Gum tragacanth	-	-	10	20	5	10
MCC	75	40	75	40	75	40
Talc	10	10	10	10	10	10
Mg Stearate	10	10	10	10	10	10
Total Weight	150	150	150	150	150	150

Evaluation of powder blend

Bulk density

Bulk density was determined by measuring the volume of a known mass of powder sample that has been passed through a screen into a graduated cylinder or through a volumetric measuring apparatus into a cup. A known quantity of powder was poured into the measuring cylinder carefully level the powder without compacting, if necessary and read the unsettled apparent volume, Vo, to the nearest graduated unit.[13,14] Calculated the bulk density, in gm per ml gm/ml, by the formula

Bulk density = Bulk Mass/ Bulk Volume

Compressibility index (Carr's index)

Compressibility index (C.I.) is an important measure that can be obtained from the bulk and tapped densities. Carr's index a material having values of less than 20% to 30% is defined as the free flowing material.[13,14] It was calculated as per given formula:

$$C.I. = \frac{\text{Tapped density- Bulk density}}{\text{Tapped density}} \times 100$$

Hausner ratio

It indicates the flow properties of the powder and it can be measured by the ratio of tapped density to bulk density.[13,14]

Hausner ratio = Tapped density / Bulk Density

Evaluation of tablets

General appearance

Five tablets from various batches were randomly selected and organoleptic properties such as color, odor, taste, shape, were evaluated. Appearance was judged visually. Very good (+++), good (++), fair (+) poor (-), very poor (- -).

Thickness and Diameter

Thickness and diameter of tablets were determined using Vernier caliper. Five tablets from each batch were used, and an average value was calculated.[15,16]

Drug content

Twenty tablets were taken and amount of drug present in each tablet was determined. The tablets were crushed in a mortar and the powder equivalent to 10mg of drug was transferred to 10ml standard flask. The powder was dissolved in 5 ml of 0.1 N HCl and made up to volume with of 0.1 N HCl. The sample was mixed thoroughly and filtered through a 0.45µ membrane filter. The filtered solution was diluted suitably and for drug content by UV spectrophotometer at λ max of 232.0 nm using 0.1 N HCl blank.[17]

Hardness

For each formulation the hardness of five tablets was resolved utilizing the Monsanto hardness tester (Cadmach).[15,16]

Friability

The friability of sample of 10 tablets was estimated utilizing a Friability tester (Electro Lab). Ten tablets were weighed, rotated at 25 rpm for 4 minutes. Tablets were reweighed after removal of fines (dedusted) and the percentage of weight loss was calculated.[18]

Uniformity of weight

Twenty tablets were randomly selected from each batch individually weighed, the average weight and standard deviation of 20 tablets was calculated.[19]

Swelling index

Swelling study of individual polymers and combinations was carried out using eight-stage USP type 1 (basket) Dissolution Test Apparatus (Lab India, DS 8000) at 50 rpm, and 0.1 N HCl was used as medium, and the temperature was maintained at 37 ± 0.5°C. Weight of individual tablet was taken prior to the swelling study (W_1). The tablet was kept in a basket. The weight of tablet was taken at time interval of 2, 4, 8, 12 hours (W_2).[20] Percent hydration (swelling index) was calculated using the formula:

$$\text{Swelling index} = (W_2 - W_1) \times 100/W_2$$

Where W_1 is the initial weight of tablet and W_2 is the weight of hydrated tablet.

Determination of mucoadhesive strength

The working of a double beam physical balance formed the basis of the bioadhesion test assembly. The left pan was removed and hung with a stainless steel chain. A Teflon block with 1.5 in height and 1.5 in diameter was hung with the stainless steel chain to balance the weight of the other pan. The height of the total set up was adjusted to accommodate a glass container or beaker below it leaving a head space of about 0.5 cm in between. Block of 2 inch height and 1.5 inch diameter was kept inside the glass vessel, which was then positioned below the top hung Teflon block. Suitable weights were added on the right pan to balance the beam of the balance. The porcine gastric mucosa was attached with the mucosal side upward onto the lower Teflon block which was then placed in the glass vessel. Sufficient simulated gastric fluid was filled into the beaker so that the surface of the fluid just touches the mucosal surface to Teflon block. A tablet was fixed to the bottom portion of the cylindrical shaped base with ‘feviquick’ glue. The string with tablet was hung in such a way that the tablet was just in contact with the surface of the mucosal side of pig stomach when the balance was in a balanced position. The balance was left in a balanced position for fixed time of 5 minutes and then slowly weights were increased on the right pan until the tablet detaches from the surface

of the intestinal mucosa. The weights on right side pan gave the mucoadhesive strength of the tablet in grams.[21-23] From mucoadhesive strength, the bioadhesion force was calculated per unit area of the tablet as follows.

$$F=\frac{Ww \times G}{1000 \times A}$$

Where F is the bioadhesion force (kg/m/s^2), Ww is the mass applied (g), g is the acceleration due to gravity (cm/s^2) and A is the surface area of the patch (cm^2).

Dissolution rate studies

In vitro drug release of the sample was done using USP-type II dissolution apparatus (Paddle type). The dissolution medium, 900 ml 0.1 N HCl was set into the dissolution flask maintaining the temperature of 37±0.5 $^{\circ}$C and rpm of 75. One simvastatin tablet was set in every container of dissolution apparatus. The mechanical assembly was permitted to keep running for 10 hours. Sample measuring 5 ml were pulled back after each 1 hour up to 2 hours using 10ml pipette. The new disintegration medium (37 $^{\circ}$C) was supplanted each time with a similar amount of the sample and takes the absorbance at 232.0 nm using spectroscopy.[24,25] The plot of cumulative percentage drug release V/s time (hrs) for preliminary formulations were plotted.

RESULTS AND DISCUSSION

The separated mucilage was evaluated for swelling index, loss on drying, density, compressibility index and angle of repose. In physico-chemical characterization of mucilage appearance was found to be mucilaginous, colour was brown and state was solid.

Table 2: Physico-chemical characterization of mucilage.

S. No.	Physico-chemical characterization	Results of mucilage
1.	Appearance	Mucilaginous
2.	Colour	Brown
3.	State	Solid

The swelling index of isolated mucilage was found to be 150.35±0.637%. The loss on drying of isolated mucilage was found to be 87.966±0.0498%. Tablet powder blend was subjected to various pre-compression parameters Table 3. The angle of repose values indicates that the powder blend has good flow properties. The bulk density and tapped density of all the formulations was found to be in the range showing that the powder has good flow properties.

The compressibility index and Hauser's ratio of all the formulations was found within limit which show that the powder has good flow properties.

Table 3: Result of pre-compression properties of simvastatin powder blend.

F. Code	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Compressibility index	Hausner ratio
F1	0.245	0.365	32.877	1.490
F2	0.263	0.374	29.679	1.422
F3	0.252	0.336	25.000	1.333
F4	0.241	0.372	35.215	1.544
F5	0.236	0.368	35.870	1.559
F6	0.248	0.361	31.302	1.456

The data obtained of post-compression parameters such as hardness, thickness, friability, weight variation and amount of drug content are shown in table 4. Tablets obtained were of uniform weight (due to uniform die fill) with acceptable variation as per IP specifications. The low standard deviation (S.D) values indicating efficient mixing of drug, disintegrant and excipients. The percentage drug content of all the tablets were found in the range of 98.78±0.15to 99.45±0.2 percentage, which was within the acceptable limits. Hardness of the tablets was found to be 5.1±0.2-5.3±0.3kg/cm^2. The thickness of tablets was found to be 2.11±0.01to 2.15±0.01mm. The result revealed that the tablets of all the formulations showed uniform thickness. In all the formulations, the friability values were less than 1% and meet the Indian pharmacopoeia (I.P) limits.

Table 4: Results of post compression properties of Simvastatin mucoadhesive tablets.

Formulation code	Thickness* (mm)	Hardness (kg/cm^2) n=3	Weight variation (mg) n=3	Friability (%) n=3	Drug content (%) n=3
F1	2.11±0.02	5.1±0.2	203±2	0.658±0.002	98.89±0.45
F2	2.13±0.03	5.2±0.1	205±2	0.623±0.008	98.98±0.32
F3	2.14±0.01	5.1±0.2	198±3	0.785±0.015	98.78±0.15
F4	2.15±0.01	5.3±0.3	203±2	0.856±0.007	99.45±0.23
F5	2.10±0.02	5.2±0.1	199±3	0.784±0.014	99.02±0.18
F6	2.11±0.01	5.2±0.2	202±2	0.658±0.011	98.85±0.21

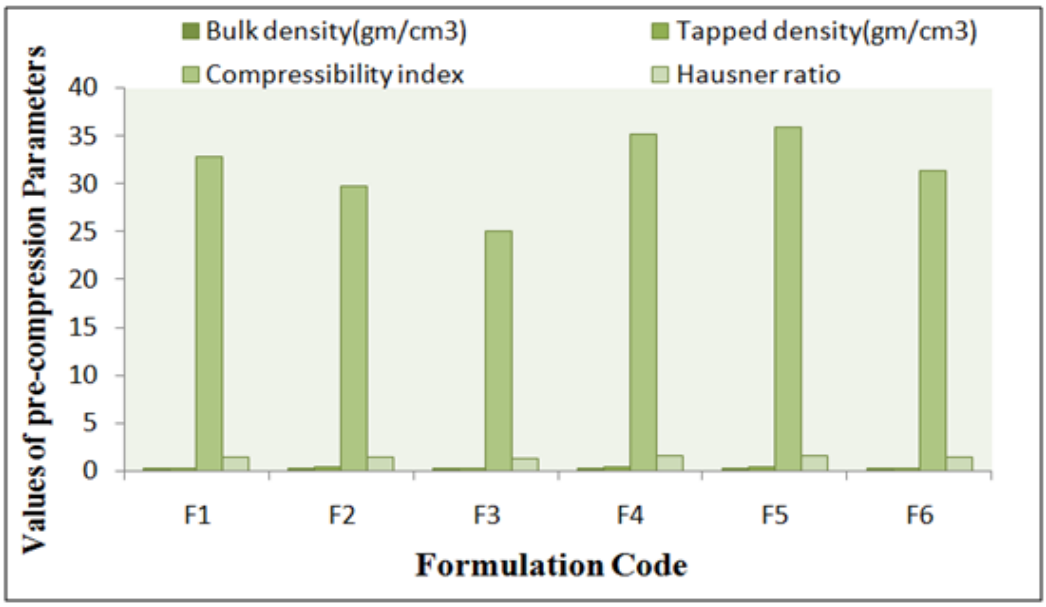

Figure 1: Result of pre-compression properties of Simvastatin.

The swelling behaviour of a bioadhesive system is an important property for uniform and prolonged release of drug and bioadhesion. The swelling behaviour depends upon nature of polymer, concentration of polymer and pH of the medium. The swelling of all the tablets was increased as the time proceeds because the polymer gradually absorbs water due to hydrophilicity of the polymer. The outermost hydrophilic polymer layer hydrates/swells first and as the hydrated layer progressively dissolves or disperse, the hydration swelling process will continuous towards new expose surfaces thus maintaining the integrity of dosage form . Swelling index increased as the weight gain by tablet increased proportionally with rate of hydration. In swelling study it was found that the amount of mucilage play important role in swelling of matrix and leads to the drug diffusion. All the formulations were more water soluble and rapidly get hydrated above 50% within 4 hours.

Table 5: Results of swelling index of simvastatin mucoadhesive tablets.

Formulation Code	% Swelling Index			
	2 hrs.	4 hrs.	8hrs.	12hrs.
F1	45.56	65.58	85.56	99.23
F2	52.32	72.32	92.32	105.65
F3	55.65	69.98	83.35	92.65
F4	64.56	75.65	95.56	105.98
F5	78.89	98.89	102.32	120.32
F6	65.58	83.32	98.87	100.65

All the formulation showed good mucoadhesion. The bioadhesive strength study was performed on the modified physical balance to measure the force (N) required for detaching the tablet. The bioadhesion characteristics were affected by the type and concentration of the bioadhesive polymers. Viscosity of the polymer also affected the bioadhesive strength of the tablet.

Table 6: Results of determination of mucoadhesive strength.

S. No.	Formulation code	Force of adhesion
1.	F1	1.15
2.	F2	1.22
3.	F3	1.08
4.	F4	1.14
5.	F5	1.25
6.	F6	1.05

From the overall dissolution profiles, it was concluded that the drug release rate decreased as the concentration of the polymer increased, in batch (F1-F6) which was also affected by the type of polymer used.

Table 7: *In-vitro* drug release study of mucoadhesive tablets.

Time	% Cumulative drug release					
(hr)	F1	F2	F3	F4	F5	F6
0.5	33.45	30.45	28.98	25.65	22.65	12.25
1	55.48	45.58	40.65	39.98	34.85	32.25
1.5	69.98	58.89	50.65	46.65	42.32	40.95
2	98.85	68.78	61.56	58.78	56.65	51.47
3	-	99.12	88.98	73.36	69.98	60.36
4	-	-	98.85	85.65	75.65	69.98
6	-	-	-	92.56	83.65	76.65
8	-	-	-	99.45	91.65	80.65
12	-	-	-	-	99.45	86.65

The results of *in vitro* disintegration time of all the formulations were found to be within the prescribed limits and satisfied the criteria of fast dissolving tablets.

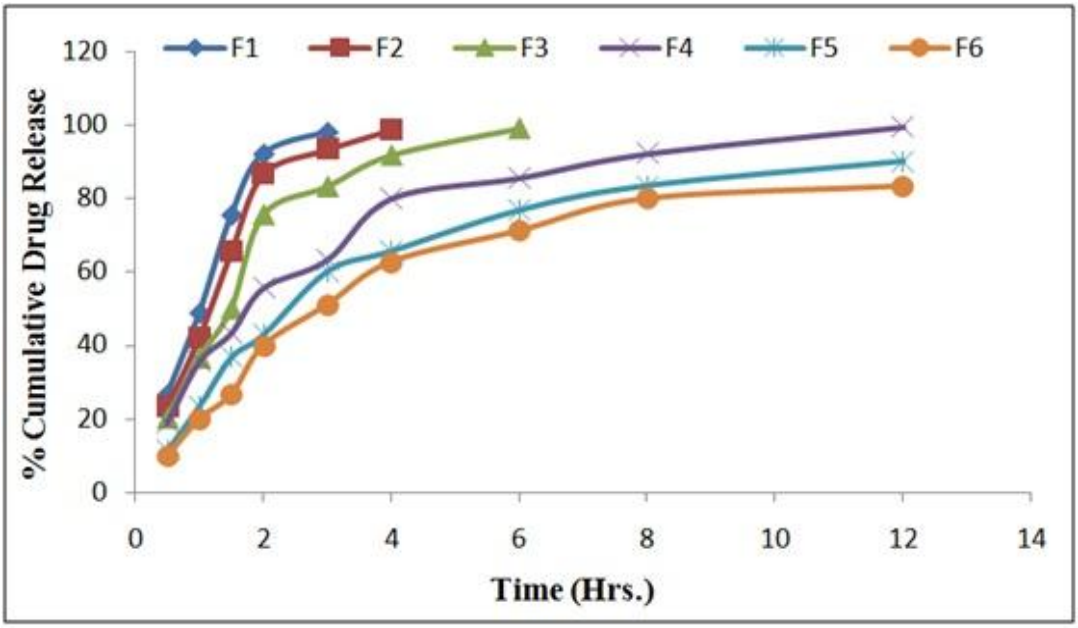

Figure 2: *In-vitro* drug release study of mucoadhesive tablets.

The cumulative percentage of the drug released for formulation F4 showed better drug release and the kinetic studies revealed that the drug release from all the formulations followed first order release. The *in vitro* drug release data of the optimized formulation was subjected to goodness of fit test by linear regression analysis according to zero order, first order kinetic equation, higuchi's and korsmeyer's models in order to determine the mechanism of drug release. When the regression coefficient values of were compared, it was observed that 'r' values of first order was maximum i.e. 0.960 hence indicating drug release from formulations was found to follow first order release kinetics.

Table 8: Interpretation of diffusional release mechanisms.

Release exponent (*n*)	Drug transport mechanism	Rate as a function of time
0.5	Fickian diffusion	$t^{-0.5}$
0.5<*n*<1.0	Anomalous transport	t^{n-1}
1.0	Case-II transport	Zero-order release
Higher than 1.0	Super Case-II transport	t^{n-1}

Table 9: *In-vitro* drug release data for optimized formulation F4.

Time (h)	Square Root of Time(h)$^{1/2}$	Log Time	Cumulative*% Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
0.5	0.707	-0.301	18.89±0.45	1.276	81.11	1.909
1	1.000	0.000	35.56±0.32	1.551	64.44	1.809
1.5	1.225	0.176	43.32±0.25	1.637	56.68	1.753
2	1.414	0.301	55.58±0.65	1.745	44.42	1.648
3	1.732	0.477	63.32±0.78	1.802	36.68	1.564
4	2.000	0.602	79.98±0.41	1.903	20.02	1.301
6	2.449	0.778	85.56±0.23	1.932	14.44	1.160
8	2.828	0.903	92.14±0.25	1.964	7.86	0.895
12	3.464	1.079	99.45±0.36	1.998	0.55	-0.260

Table 10: Regression analysis data of simvastatin mucoadhesive tablets formulation F-4.

Batch	Zero order	First order	Higuchi	Korsmeyer-Peppas
	r^2	r^2	r^2	r^2
F4	0.797	0.960	0.923	0.938

Drug content in the weighed amount of powder of all formulations was found to be uniform. All these results indicate that the powder possessed satisfactory flow properties, compressibility, and drug content. Tablets of different formulations were subjected to various evaluation tests, such as thickness, uniformity of weight, drug content, hardness, friability, and in vitro dissolution. All formulations showed uniform thickness. In a weight variation test, pharmacopoeias limit for the percentage deviation for tablets of more than 155 mg is ±5%. Average percentage deviation of all tablet formulations was found to be within the above limit, andhence all formulations passed the test for uniformity of weight as per official requirements.[26] Good uniformity in drug content was found among different batches of tablets and percentage of drug content was more than 95%.Tablet hardness is not an absolute indicator of strength.[27] Another measure of a tablet's strength is friability. Conventional compressed tablets that lose less than 1% of their weight are generally considered acceptable. In the present study, percentage friability for all formulations was below 1%, indicating that friability was within the prescribed limits.[27] All tablet formulations showed acceptable Pharmacotechnical properties and complied with the inhouse specifications for weight variation, drug content, hardness, and friability.

CONCLUSION

The results of experimental studies of mucoadhesive tablets of simvastatin proved that the blend of Fenugreek seeds mucilage showed good flow properties, tablet evaluation tests are

within the acceptable limits, the kinetic studies revealed that all the formulations followed first order drug release. The formulations prepared with Fenugreek seeds mucilage showed a rapid drug release formulation. Thus the results of the above study clearly indicated that simvastatin may be formulated as mucoadhesive tablets using Fenugreek seeds mucilage by direct compression method.

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