

Formulation and evaluation of Gastro-retentive drug delivery system using Fenugreek gum as novel matrixing agent

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Abstract

The purpose of this study was to evaluate efficiency of fenugreek gum for developing gastro retentive floating tablets of Sumatriptan succinate when used alone or in combination with established polymers. The floating Tablet were prepared by direct compression and wet granulation technique and evaluated for various parameters like physical characterization, hardness, friability, weight variation, drug content uniformity, swelling index and in-vitro buoyancy and drug release. Fenugreek gum was efficient as release retardant and floating agent when used alone or in combinations with HPMC. The results indicated that fenugreek gum effectively sustained release for 12 hrs with parameters such as floating lag time, buoyancy, and floating time in acceptable range. In-vitro drug release kinetics evaluated using the linear regression method was found to follow the Higuchi release kinetics equation. This suggests that fenugreek gum can be a novel hydrophilic polymer in designing of FDDS.

Keywords: Fenugreek gum, Sumatriptan succinate, Gastro Retentive Drug Delivery, Floating System, Controlled Release.

1. Introduction

Modified release systems, have been developed to improve the pharmacokinetic profiles of active pharmaceutical ingredients (APIs) and patient compliance, as well as reducing side effects [1,2]. Generally, the absorption of APIs from oral drug delivery systems (DDS) is precluded by several physiological difficulties, such as inability to restrain and localize the drug delivery system within desired regions of the GIT and the high variable nature of gastric emptying process [3]. The maximum achievable sustained drug release is subject to inter individual variations, with an average gastrointestinal (GI) transit time of around 24 h in humans [4]. This variation, may lead to unpredictable bioavailability and times to achieve peak plasma levels, since the majority of drugs are preferentially absorbed in the upper part of the GIT [3]. It is well recognized that stomach may be used as “depot” for sustained-release (SR) dosage forms, both in human and veterinary applications. [5-7]. The retention of oral dosage forms in the upper GIT causes prolonged contact time of drug with the GI mucosa, leading to higher bioavailability, and hence

therapeutic efficacy, reduced time intervals for drug administration, potentially reduced dose size and thus improved patient compliance [8]. Therefore, extended release DDS possessing gastric retention properties may be potentially useful [9-14]. Gastro-retentive DDSs exhibiting controlled drug release are significantly important for drugs which are: Acting locally in the stomach (e.g. antibiotics against *Helicobacter Pylori*, antacids and misoprostol) [15-19]. Absorbed incompletely due to a relatively narrow window of absorption in the GIT, such as cyclosporin, ciprofloxacin, furosemide, L-DOPA, *p*-aminobenzoic acid and riboflavin [3,20-25]. Unstable in the intestinal or colonic environment such as captopril [26] or exhibit low solubility at high pH values such as verapamil HCl, diazepam and chlorthalidone [27-30].

Polymers are principle excipient in pharmaceutical dosage forms especially with modified release. They may be used in taste masking, stabilization and protection in oral drug delivery systems. Also, they can bind to the particles of solid dosage formulations and change the flow characteristics of liquid dosage

formulations. There is a need of new polymer materials to suit the development of newer dosage forms and release patterns. The present work is aimed at evaluating potential of fenugreek gum as natural hydrophilic polymeric material for development of floating gastro-retentive drug delivery system using Sumatriptan succinate used as a model drug.

2. Materials and Methods

2.1 Materials

Sumatriptan succinate was obtained as research sample from Centuar Pharmaceuticals Pune India. Fenugreek Gum powder was purchased from local market [Wonder Herbs Pvt Ltd Hyderabad]. All other ingredients were of laboratory or analytical grade and procured from SD Fine Chem, Mumbai.

2.2 Methods

2.2.1. Characterization of Fenugreek gum:

Solubility of fenugreek gum was checked with different solvents. Fenugreek gum powder was evaluated for parameters such as pH, specific gravity, surface tension, water content, ash content and swelling index, bulk density, tapped density etc. using official tests or standard tests.

Swelling index of fenugreek gum was determined by using modified method [10]. One gram of fenugreek gum powder (#100 mesh passed) was accurately weighed and transferred to a 100mL stoppered measuring cylinder. The initial volume of the powder in the measuring cylinder was noted. The volume was made up to 100 mL mark with distilled water. The cylinder was stoppered, shaken gently and set aside for 24 h. The volume occupied by the gum sediment was noted after 24 h.

Swelling index (SI) is expressed as a percentage and calculated according to the following equation.

$$\text{swelling index (SI)} = \frac{X_t - X_0}{X_0} \times 100$$

XO is the initial height of the powder in graduated cylinder and Xt denotes the height occupied by swollen gum after 24 h.

The content from the measuring cylinder from the above test were filtered through a muslin cloth and the water was allowed to drain completely into a dry 100mL graduated cylinder. The volume of water collected was noted and the difference between the original volume of the mucilage and the volume drained was taken as water retained by sample and was referred to as water retention capacity or water absorption capacity.

2.2.2 Formulation development:

In the present study of gastro retentive floating matrix tablets, direct compression method and wet granulation method were evaluated as tableting technique for preparing tablets.

2.2.2.1. Direct Compression

Tablets were prepared by direct compression technique using varying amounts of different polymers. The drug, polymers and other excipients were passed through sieve number 100 and weighed accurately. Sumatriptan succinate was mixed with the natural polymers like fenugreek gum powder, xanthan gum, synthetic polymers like carbopol, HPMC K4M, MC, sodium alginate either individually or in combination. To this mixture sodium bicarbonate, PVP K-90, MCC, lactose were mixed at required quantities according to the designed formulations for 5min in mortar and pestle and finally lubricated. The blend was compressed using 8 mm concave punch to an average weight of 300 mg using Karnavati multi stationed tablet compression machine. Various formulations of tablets are given in Table 1.

2.2.2.2 Wet granulation

Wet granulation technique, designed powder floating formulation mixture was mixed with alcohol in required amount to make it into a wet mass which is then sieved into granules from mesh #20. The obtained granules were dried at 45°C for 24 hours to get dried granules for compression. Granules were compressed to get tablets in similar manner as explained in previous section.

Table 1: Formulations of Sumatriptan Floating Tablets

Formulations	F1	F2	F3	F4	F5	F6	F7
Sumatriptan succinate	16.7	16.7	16.7	16.7	16.7	16.7	16.7
Fenugreek gum powder	50	30	30	25	25	30	32
HPMC K4M	-	20	20	25	15	25	25
Carbopol	-	-	-	-	16.3	-	-
Sodium bicarbonate	11	10	10	10	12	11	11
PVP K90	2.3	2	2	4.3	-	-	-
MCC	13	11.3	10	12	12	-	12.3
Lactose	-	8	9.3	-	-	14.3	-
Magnesium stearate	1	1	1	1	1	1	1
Talc	1	1	1	1	2	2	2

2.2.3. Evaluation of post compression parameters

The floating tablets were evaluated for post compression parameters like thickness, weight variation, hardness, friability, drug content uniformity and *in vitro* dissolution studies. Official or standard evaluation tests were used for evaluation. Procedures for some of the tests are given below. All the studies were performed in triplicate, and the results were expressed as mean $\pm$ SD.

2.2.3.1. Drug content uniformity

A representative sample of thirty tablets was selected and out of these, ten tablets were analyzed individually by UV spectrophotometry at 260 nm. As per the specifications, at least nine tablets should have drug content in the range of 85.0% to 115.0% of label claim and no tablet should be outside the range of 75.0% to 125.0% of the label claim.

Drug content was calculated as follow

The regression equation from calibration curve is represented as:

$$y = mx + c$$

y= absorbance; m= slope; x= concentration; c= y-intercept

$$\text{Concentration (x)} = \frac{\text{absorbance (y)} - \text{intercept (c)}}{\text{slope (m)}} \times 100$$

$$\text{Drug content (in mg)} = \text{Concentration (x)} \times \text{Dilution factor}$$

Finally, the percentage drug content can be calculated by the formula:

$$\% \text{ Drug content} = \frac{\text{Drug content}}{\text{Label claim}} \times 100$$

2.2.3.2. In-vitro dissolution studies

Release of the drug *in vitro*, was determined by estimating the dissolution profile.

Dissolution test was carried out using USP type-II apparatus at 50 rpm with 900 ml of 1.2 pH 0.1N HCl for 12 hours. The temperature was maintained at $37 \pm 0.5^\circ \text{C}$. Aliquots of dissolution medium were withdrawn at 0.5 hr initially for one hour and after each hour thereafter.

The samples were filtered, diluted and analysed by UV spectrophotometric method at 226 nm using 1.2 pH, 0.1N HCl as blank.

2.2.3.3 In-vitro buoyancy studies

The time taken for tablet to emerge on surface of medium is called the floating lag time (FLT) The tablets were placed in a 250-mL beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time. Duration of time the dosage form to constantly remain on surface of medium is called the total floating time (TFT).

2.2.3.4 Swelling characteristics (water uptake study)

The swelling properties were determined by placing the tablet in the dissolution test apparatus, in 900 ml of 0.1 N HCl at $37 \pm 0.5^\circ \text{C}$. The tablets were removed periodically from dissolution medium, after draining free from water by blotting paper; the tablets were measured for weight gain. Swelling characteristics were expressed in terms of percentage water uptake (WU %) show relationship between swelling index and time [31].

$$\text{WU\%} = \frac{[\text{weight of swollen tablet} - \text{initial weight of tablet}]}{[\text{initial weight of tablet}]} \times 100$$

2.2.3.5. In Vitro Drug Release Kinetic Studies:

Kinetic model had described drug dissolution from solid dosage form where the dissolved amount of drug is a function of test time. In order to study the exact mechanism of drug release from the tablets, drug release data was analyzed according to zero order [Khan GM, 2001], first order [Morkhade DM, 2006], Higuchi square root, Korsmeyer-Peppas model. The criteria for selecting the most appropriate model were chosen on the basis of goodness of fit test. The data were processed for regression analysis using graph pad prism.

2.2.3.6. Stability studies

The optimized Sumatriptan succinate floating tablets of optimized formulations were packed and subjected to accelerated stability studies as per ICH guidelines ($40^\circ \text{C} \pm 2^\circ \text{C}$ /75 % $\pm$ 5 % RH). The sample were withdrawn periodically at the end of 30, 60, 90 days, respectively and evaluated for the different parameters i.e., physical appearance, weight variation, hardness, drug content, friability, floating lag time, total floating time, buoyancy on disturbing and *in-vitro* drug release.

3. Results and Discussion:

3.1. Characterization of fenugreek gum

The fenugreek gum was evaluated for various physicochemical properties. The results are given in Table 2.

Table 2: Physicochemical Properties of Fenugreek gum

Parameter	Result
Solubility	Slightly soluble in cold water, But quickly dissolves in warm water, forms viscous colloidal solution, insoluble in ether, acetone, chloroform, methanol, ethanol.
pH (1% solution)	6.23±0.2
Specific gravity (0.01% solution) g/ml	1.0005±2.3X10 ⁻⁴
Water content (%)	71±5.2
Total ash	0.967±0.015
Water soluble ash	0.847±0.015
Melting point	232°-240°C
Acid insoluble ash	0.01±0.005
Swelling index	8±0.2

The results comply with the reported one and desired one. Based on these results it can be conclude that fenugreek gum powder is a suitable material to be used as release retarding polymer for using in a formulation development of FDDS.

3.2. Evaluation of pre compression parameters

All the formulations when evaluated for the various common pre-compression parameters have shown the evaluation parameters in acceptable range only. The results of evaluation of pre compression parameters are given in Table 3.

Table 3: Evaluation of pre compression parameters

Formulation Code	Bulk density (gm/cm ³) ±S.D	Tapped density (gm/cm ³) ±S.D	Carr's index (±S.D %)	Hausner's ratio (±S.D %)	Angle of repose (°)
F1	0.486±0.011	0.562±0.041	13.58±0.71	0.864±0.031	23.71 ±S 0.51
F2	0.468±0.005	0.564±0.013	15.29±0.56	0.829±0.014	21.52 ±S 0.59
F3	0.483±0.114	0.569±0.096	16.72±0.32	0.848±0.052	25.32 ±S 0.38
F4	0.446±0.032	0.567±0.038	17.60±0.27	0.786±0.031	26.42 ±S 0.72
F5	0.453±0.147	0.534±0.025	15.64±0.13	0.848±0.041	24.75 ±S 0.34
F6	0.550±0.025	0.592±0.012	17.26±0.24	0.929±0.036	25.29 ±S 0.12
F7	0.580±0.071	0.614±0.052	17.18±0.56	0.944±0.017	22.79 ±S 0.51

It can be seen from the results that angle of repose values are less than 30 indicating good flow, Hausner's ratio values were less than 1.25 and Carrs' index values were in the range of 13-17 suggesting the good flow properties of the powder formulation and superior tableting capacity.

3.3. Evaluation of post compression parameters:

The results of post-compression parameters like friability, hardness and weight variation are well within the limits and following the Indian pharmacopoeial standard limits. The results are given in table 4.

Table 4: Evaluation of post compression parameters for formulations F1-F7

Formulation Code	Thickness (mm)	Diameter (mm)	Hardness (kg/cm ²)	Friability (%)	Weight variation (mg)	Drug content (%)
F1	3.1 ±0.01	8.00±0.03	4.5±0.03	0.82±0.04	298±0.511	97.34±0.005
F2	3.2 ±0.05	8.00±0.01	4.7±0.02	0.86±0.06	300±0.001	99.34±0.024
F3	3.2±0.03	7.8±0.03	4.2±0.02	0.69±0.02	299±0.024	97.36±0.021
F4	3.32 ±0.04	7.7±0.03	4.4±0.04	0.67±0.07	301±0.521	98.29±0.008
F5	3.26 ±0.04	7.5±0.02	5.0±0.01	0.71±0.01	296±0.011	98.47±0.012
F6	3.2 ±0.01	8.00±0.04	4.7±0.04	0.76±0.04	297±0.010	98.84±0.005
F7	3.3 ±0.04	7.9±0.05	4.9±0.02	0.85±0.02	298±0.012	98.64±0.006

The post-compression data suggests that the tableting properties were good with all the formulation mixtures. The tablets showed friability within limit of 1%, weight variation within limit of 5%. Hardness

was found to be in the range of 3.5-5 kg/cm². Drug content for all the batches was between 97-99%.

Drug Release Study

The drug release from the different formulations was in the range of 90.342 to 99.892%. The results are presented in figure 1 given below.

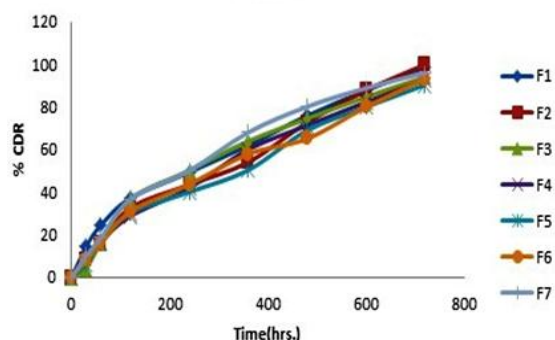


Figure 1: In-vitro drug release profile of different formulations

The *in vitro* dissolution studies indicate that fenugreek gum has good release retarding capacity directly proportional to concentration. At lower concentration it was not able to sustain drug release for longer time. Its efficiency increases when used in combination with HPMC making it able to retard release even at lower concentration. Formulation F5 has shown more sustained release out of all the formulations which is formulated with 25% fenugreek, 15% HPMC and 16.3% of Carbopol suggesting the release retarding capacity of fenugreek gum in combination. The 3:2 ratios of fenugreek and HPMC K4M have shown almost 100% drug release as in the case of F2 in 12 hrs. The drug release ranges of different formulations suggest that fenugreek based tablets have shown sustained drug release up to 12 hours. From this study it can be concluded that the fenugreek gum is having release retardant capacity either alone and/or in combination.

Release Kinetics:

In order to study the kinetics of drug release process in all formulations, various equations were used, such as zero-order rate equation, which describe

the system where the release rate is independent of the concentration of dissolved species. The first order equation describes the release from the systems where dissolution rate is dependent on concentration of dissolving species. Higuchi square root equation describes the release from the system where solid drug is dispersed in matrix, and the rate of drug release is related to rate of diffusion. The Korsemeyer-Peppas equation is used to analyze the release of drug pharmaceutical polymeric dosage forms, when the release mechanism is not well known or when more than one type of release phenomenon could be involved. The dissolution data obtained was plotted as cumulative percentage drug release vs. time as zero-order, Log cumulative percentage drug retained vs. time as first order release kinetics, cumulative percentage drug release vs. square root of time as Higuchi equation, and Log of fraction of drug released vs. Log time as per Korsemeyer-Peppas equation. The parameters of model fitting of the release profile of all the formulations shown in Table 5.

In controlled or sustained release formulations diffusion, swelling and erosion are the three most important rate controlling mechanisms followed. The drug release from the insoluble polymeric system is mostly by diffusion and best described by Fickian diffusion. But in case of formulations containing swellable polymers, other processes include relaxation of polymer chain, imbibition of water causing polymers to swell and changing them from initial glassy to rubbery state. Due to swelling considerable volume expansion takes place leading to moving diffusion boundaries complicating the solution of Fick's second law of diffusion. So to explore the release pattern, results of the *in-vitro* release data were fitted to Korsemeyer and Peppas equation which characterize the transport mechanism.

Table 5: Release kinetic profile of different formulations

Formulation code	Zero-order	First-order	Higuchi	Korsemeyer-peppas	
	R ²	R ²	R ²	R ²	N
F1	0.983	0.854	0.993	0.793	0.55
F2	0.986	0.830	0.982	0.769	0.53
F3	0.941	0.663	0.991	0.776	0.59
F4	0.985	0.865	0.994	0.840	0.88
F5	0.981	0.789	0.986	0.713	0.56
F6	0.979	0.808	0.991	0.762	0.69
F7	0.955	0.789	0.995	0.765	0.75

All the formulations in this study were best expressed by Higuchi's classical diffusion equation, as the plots showed the range of R² coefficients is 0.982-0.995. The linearity of the plot (data not shown)

indicated that the release process was diffusion-controlled. Thus the amount of drug release was dependent in the matrix drug loaded. As concentration reduced on drug release, the diffusion path increased

resulting in a drug release at comparatively slower rate in later phase.

Korsmeyer-Peppas equation is a generalization of the observation that superposes two apparently independent mechanism of drug transport describes drug release from a swelling polymer. The 'n' value gives an indication of the release mechanism; When $n = 1$, the release independent of time (zero-order), $n = 0.5$ for Fickian diffusion. When n is between 0.5 and 1.0, diffusion non Fickian transport or anomalous diffusion are implicated. When n is more than 1.0 super case II transport is apparent. The n value in this model indicates the diffusional exponent. From the R^2 coefficients and the n values of all the formulations given in the table 5. The 'n' value for the formulations was in the range of 0.5-1.0, indicating non-Fickian diffusion i.e. the rate of drug release is due to drug diffusion and polymer relaxation. This means that drug diffusion and polymer relaxation have an essential role in drug release. However as indicated by the values of R^2 coefficients of both the models i.e., Higuchi and Korsmeyer-Peppas were found to be efficient in describing the drug release of Sumatriptan succinate from the floating tablets.

4. Conclusion

From the results indicate that the drug polymer ratio, viscosity of polymer and gas generating agents influence the release of drug and floating characteristics from the prepared floating tablets of Sumatriptan succinate. The floating tablets prepared with fenugreek gum as polymer showed satisfactory results with short floating lag time, long total floating time and controlled drug release up to 12 hrs. The drug release data were explored for the type of release mechanism followed. The best fit with the highest determination R^2 coefficients was shown by both of models Higuchi followed by Korsmeyer-Peppas model which indicate the drug release via diffusion and non-Fickian diffusion mechanism. Drug content, physical appearance & comparable release profile of floating tablets after 3 months indicates the stability of formulation. Thus it can be concluded that fenugreek gum can be used as a novel hydrophilic polymer in formulation and development of sustained release floating tablets.

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