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RESEARCH ARTICLE

FORMULATION AND OPTIMIZATION OF SUSTAINED RELEASE FLOATING GASTRO RETENTIVE TABLET OF NIFEDIPINE USING NATURAL POLYMER

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ABSTRACT:

Aim of the present study was Formulation and optimization of sustained release floating tablet of Nifedipine using natural polymer. Nifedipine is having low oral bioavailability and low half-life of about 2 to 4 hrs hence there is a need to formulate Sustained drug delivery for nifedipine for oral delivery. Nifedipine, a calcium channel blocker antihypertensive drug, is a poorly water soluble drug and belongs to BCS class II. The objective of the research work was to formulate and optimize sustained release matrix tablet using fenugreek a natural polymer, different grade of hydroxy propyl methyl cellulose (HPMC) for optimum delivery of Nifedipine.

Keywords: Nifedipine, Natural Polymer, HPMC, Sustained release

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INTRODUCTION:

Sustained release dosage form is a modified dosage form that prolongs the therapeutic activity of the drug. Sustained release products provide an immediate release of drug that promptly produces the desired therapeutic effect which is followed by gradual release of additional amounts of drug to maintain this effect over a predetermined period of time.[1]

Nifedipine, a dihydropyridine derivative, is effectively being used drug in the management of various CVDs such as angina, mild to moderate hypertension, myocardial infection, etc.[2] Nifedipine is a suitable drug candidate for sustained release administration due to its short elimination half-life of 2 to 4 h, its rapid and complete drug absorption over the entire gastrointestinal tract, despite its low water solubility (10mg/l), and the relationship between drug plasma concentrations and blood pressure reduction.[3] The importance of reduced peak plasma level of this drug in order to avoid adverse effects such as reflex tachycardia has also been reported.[4]

Trigonella foenum-graecum L. (Fenugreek) belongs to the Leguminosae family. Fenugreek seeds have been widely used in food as a flavour component and seasoning and in Iranian folk medicine as a tonic.[5] In clinical, pharmacological and biological tests, extracts and fractions of Fenugreek seeds are reported to have glucose and lipid- lowering properties and antioxidant and antiphlogistic effects. Phytochemical studies on *Trigonella foenum-graecum* L. revealed that carbohydrates and mucilages (mainly galactomannans), proteins, fixed oils, flavonoids and saponins were the main components of the seeds.[6]

Rationale of the study

Since Fenugreek seeds produce high viscosity mucilage at low concentration levels, the objective of the present investigation was to evaluate the binder effects of this mucilage in matrix tablet of nifedipine. The present works want to apply a concept of synergistic effect of fenugreek (lipid- lowering properties) and nifedipine as antihypertensive agent.

Material and method

Materials

Nifedipine was generously gifted by Unique Pharmaceuticals Ltd. Gujarat. Crude Fenugreek purchased from local farmer of Bhopal (M.P.). Fenugreek gum extracted from crude

Trigonella foenum-graecum L was carried out at college laboratory (Sagar institute of pharmaceutical science, Bhopal (M.P.) and gum was extracted in Pharmaceutics research lab, scan research laboratories, Bhopal, (M.P.), Lactose, magnesium stearate and talc, Citric acid, and Sodium bi carbonate were purchased from S.D fine chemicals, Mumbai.

Instruments

UV Vis Double beam Spectrophotometer - Labindia 3000+. FT IR instrument - Bruker alpha. Electronic weighing balance - Wensar. Digital pH meter - Khera, Tablet punching machine - Shakti. Tablet dissolution tester USP - Labindia DS 8000. Hardness tester- Pfizer hardness tester. Friability tester- Electctronic India.

Methods

Method of isolation and extraction of Fenugreek gum

About 2kg of fresh seeds of *Trigonella foenum-graecum* L were obtained from a local market. The seeds were sliced, homogenized and extracted with cold water containing 1% (w/v) sodium metabisulphate. The crude mucilage was centrifuged at 4000 rpm for 5 min and the gum was precipitated from the supernatant with acetone. The precipitated gum was washed several times with acetone; the obtained product was dried under vacuum in a desiccator. This was stored in a well closed amber colored specimen bottle till ready for use.

Characterization of Fenugreek Gum [7]

Particle size

Sieving is the most widely used method for measuring particle size distribution because it is inexpensive, simple and rapid with little variation between operators. The procedure involves the mechanical shaking of a sample through a series of successively smaller sieves and the weighing of the portion of the sample retained on each sieve. For determining particle size sieve was used. 10 gm of powder was taken and passed through the sieve no. 85.

Angle of Repose

Angle of repose has been used as indirect method of quantifying powder flow ability, because their relationship with interparticle cohesion. This is the angle θ as defined by the equation;

$$\mathbf{Tan\ \theta = 2h / D}$$

The value of angle of repose will be high if the powder is cohesive and low if the powder is non-cohesive. Powder with angle of repose greater than 50^0 have unsatisfactory flow property, where as minimum angle of repose close to 25^0 corresponds to very good flow property.

Bulk Density

The bulk density of a powder is dependent on particle packaging and changes as the powder consolidates. Bulk density of powder is defined as the ratio of the mass of the powder and its bulk volume. Bulk density of powder is calculated by using the formula;

$$\mathbf{\rho_b = M / V_b}$$

For determining bulk density 10 gm powder was taken and transferred into graduated 100 ml measuring cylinder. The volume occupied was determined. By using the formula the bulk density was calculated.

Tap Density

The tape density of powder is defined as the ratio of the mass of the powder and its volume after tapping. Tapped density is determined by placing graduated cylinder containing a known mass of drug or formulation on a mechanical tapper apparatus, which is operated for a fixed number of taps (~1000) until the powder bed volume has reached a minimum. Tape density of powder is calculated by using the formula;

$$\mathbf{\rho_t = M / V_t}$$

Weight of powder (M)

Tape volume of powder (V_t)

For determining tape density 10 gm powder was taken and transferred into graduated 100 ml measuring cylinder. The volume occupied after tapping (~ 1000) was determined. By using the formula the tape density was calculated.

Tape Density (Carr's compressibility index)

A simple test has been developed to evaluate the flow ability of a powder by comparing the bulk density and tape density of a powder and the rate at which it packed down. A useful empirical guide is given by Carr's compressibility index**.**

$$\text{Carr's index (\%)} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}}$$

Loss on Drying

The moisture in a solid can be expressed on a wet-weight or dry–weight basis. On a wet-weight basis, the water content of a material is calculated as a percentage of the weight of the wet solid, whereas on the dry-weight basis, the water is expressed as a percentage of the weight of the dry solid.

In the pharmacy, the term loss on drying, commonly referred to as LOD, is an expression of moisture content on wet-weight basis, which is calculated as;

$$\text{\% LOD} = \frac{\text{Wt. of water in sample}}{\text{Total wt. of wet sample}} \text{ X } 100$$

For determination of LOD, 1gm powder was taken and placed in a previously dried and flat weighing bottle. Powder dried in an oven at 105^0C until two consecutive weighing do not differ by more than 5 mg

Swelling Index

Carryout simultaneously not fewer than three determinations for any given material. Introduce 1 gm of the powder, previously reduced to the required fineness and accurately weighed, into a 25 ml glass Stopperd measuring cylinder. The internal diameter of the cylinder should be about 16 mm, the length of the graduated portion about 125 mm, marked

in 0.2 ml divisions from 0 to 25 ml of water and shake the mixture thoroughly every 10 min for 1 hr. allow standing for 3 hr at room temperature. Calculate the mean value of the individual determinations, related to 1 gm of powder.

Preparation of sustained release floating tablets

Floating tablets containing nifedipine were prepared by wet granulation technique using variable concentrations of fenugreek mucilage. Different tablets formulations were prepared by wet granulation method. All the powders were passed through 60 mesh sieve. Required quantity of drug, and lactose were mixed thoroughly. Then, polymer dissolve in granulating agent (isopropyl alcohol) was added slowly with uniform mixing the get a wet mass. The wet mass was passed through sieve no 10 to obtain wet granules. The granules were dried at 50ºC for 5 to 6 hrs in try dryer. The dried granules were passed through sieve.no.22, after blending with lubricants were compresses into tablet compression machine using tablet compression machine. Each tablet contained 20mg of nifedipine and other pharmaceutical ingredients as listed in table 1 in each section.

Table 1. Formulation of colon targeted matrix tablet of Nifedipine

S. No.	Tablet	Formulation Code					
	Ingredients (mg/tab)	F1 10%FG	F2 20% FG	F3 30% FG	F4 40% FG	F5 50% FG	F6 60% FG
1	Nifedipine	20	20	20	20	20	20
2	Fenugreek gum	50	100	150	200	250	300
3	Lactose	335	285	235	185	135	85
4	Sodium bi carbonate	20	20	20	20	20	20
5	Citric acid	10	10	10	10	10	10
6	Talc	10	10	10	10	10	10
7	Magnesium stearate	5	5	5	5	5	5
8	Total (wt)	450	450	450	450	450	450

Table 2. Results of Characterization of Fenugreek Gum

Particle size	Angle of Repose	Bulk Density	Tape Density	Carr's index	LOD	Swelling Index
NMT- 180	40.39^0C	0.666	0.909	26.73	11.12%	NMT-10

Evaluation of tablets [8]

Weight variation test

To study weight variation twenty tablets of the formulation were weighed using a wensar electronic balance and the test was performed according to the official method. Twenty tablets were selected randomly from each batch and weighed individually to check for weight variation.

Drug content

20 tablets were weighed individually and powdered. The powder equivalent to average weight of tablets was weighed and drug was extracted in 0.1 N HCL content was determined measuring the absorbance at 240 nm after suitable dilution using a UV- Vis double beam spectrophotometer Labindia 3000+.

Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Pfizer hardness tester. It is expressed in kg/cm2. Three tablets were randomly picked and hardness of the tablets was determined.

Thickness

The thickness of the tablets was determined by using Vernier calipers. Five tablets were used, and average values were calculated.

Friability test

The friability of tablets was determined using Roche Friabilator. It is expressed in percentage (%). Ten tablets were initially weighed and transferred into friabilator. The friabilator was

operated at 25rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again. The % friability was then calculated by, %F =1-(loss in weight/ initial weight) 100 % Friability of tablets less than 1% are considered acceptable.

In-vitro dissolution study

In-vitro dissolution study was performed by using USP dissolution test apparatus (Apparatus 1, Basket type) at 100 rpm for 12 h in 0.1 N HCl (900 ml). At the end of different time period 10 ml of the sample were taken and analyzed for Nifedipine content at 240 nm by double beam UV-visible spectrophotometer. A 10 ml fresh and filtered dissolution medium (buffers) was added to make the volume after each sample withdrawal.[9]

Kinetic data analysis.

The drug release kinetic studies were carried out for bi-layer tablets of nifedipine were evaluated using the linear regression method.

(1) Zero order kinetic models—cumulative % of drug released versus *T*

(2) First order kinetic model—log cumulative percent drug remaining versus *T*

(3) Higuchi's model—cumulative percent drug released versus square root of *T*

(4) Korsmeyer equation/Peppa's model—log cumulative percent drug released versus log

Formulation development of sustained release gastro retentive tablet.

Optimized formulation of F-1 for sustained release used for formulation of gastro retentive tablet.

Evaluation of sustained release gastro retentive tablet.[10]

Evaluation parameters of sustained release gastro retentive tablet were performed according to I.P. specifications. Parameters such as weight variation were performed by taking average weight of 20 tablets, Hardness test was performed by Monsanto hardness tester, Thickness of the tablet was measured using Verniercaliper, Friability test was performed by taking 6 tablets in Roche friabilator and % friability was calculated. In vitro drug release studies of sustained release gastro retentive Bi-layer tablets were carried out using USP dissolution apparatus type II in 900mL of 0.1N HCl up to 12 hours. Samples were collected at regular intervals of time and filtered. The collected samples were filtered and observed in UV spectrophotometer.[11]

Result & Discussion

In all sustained release gastro retentive Bi-layer formulations (F1 to F6), were performed according to I.P. specifications, Hardness of all tablet was found between (6.7 – 7.2) kg/cm^2 , Friability test of tablets was found less than 1 %, Weight variation test of tablets was found between(452.45 - 455.7 mg), Thickness was found in the range of (3.9 – 4.2 mm), Drug Content test of tablets was found between(98.32 - 99.13 %). This result is giving in table no 3.

Table 3. Results of Post compression parameters

Formulation	Parameters				
	Weight variation	**Drug content**	**Hardness**	**Thickness**	**% Friability**
F1	450±0.735	98.32±0.089	6.7±0.115	4.0±0.005	0.178
F2	450±0.821	99.13±0.113	7.0±0.288	4.2±0.004	0.098
F3	450±0.639	98.83±0.093	6.9±0.172	4.0±0.005	0.118
F4	450±0.997	98.86±0.085	7.2±0.152	3.9±0.002	0.158
F5	450±0.719	98.47±0.113	6.8±0.354	4.0±0.004	0.139
F6	450±0.714	99.03±0.103	6.9±0.267	4.1±0.004	0.099

The sustained release gastro retentive Bi-layer formulation F1-F6 having Nifedipine with Fenugreek gum used in various ratio were showed drug release in 12hrs. It was observed F1 formulation gave better result with Fenugreek gum natural polymer in the concentration 50 mg or (15%). The higher concentration of polymer gave long time release of drug. The percent of Nifedipine released from sustained release tablets containing 10 % of fenugreek gum at the end of 12 hrs was found to be 87.0.13 %

In-vitro buoyancy study of sustained release tablets of Nifedipine of all formulation (F1- F6). In vitro drug release studies of sustained release tablets of all 6 formulation were optimizes in 12 hrs. In the % Cumulative Drug Release of Formulation (F1-F6) were obtained (50.289 to 87.013). This result is giving in table no 4.

The F1 formulation was optimizes in all six formulation. The dissolution study of sustained release tablets of Nifedipine shows release up to 12 hours was found to be 87.0.13 %.

Table 4. Results of *In-vitro* dissolution study

Time(hrs)	Cumulative % drug release					
	Formulation code					
	F1	F2	F3	F4	F5	F6
0.5	5.065	4.12	2.883	2.738	2.374	1.865
1	21.124	19.261	16.226	12.374	11.754	8.859
1.5	33.531	30.904	22.961	18.854	16.779	13.558
2	45.742	41.034	29.072	27.508	23.781	20.555
4	60.486	54.838	36.996	34.221	33.259	29.957
6	68.410	61.375	43.588	41.697	39.750	36.808
8	74.635	68.016	50.432	47.436	45.111	41.114
10	83.505	77.017	56.186	52.726	51.438	48.119
12	87.013	79.966	58.945	54.470	53.539	50.289

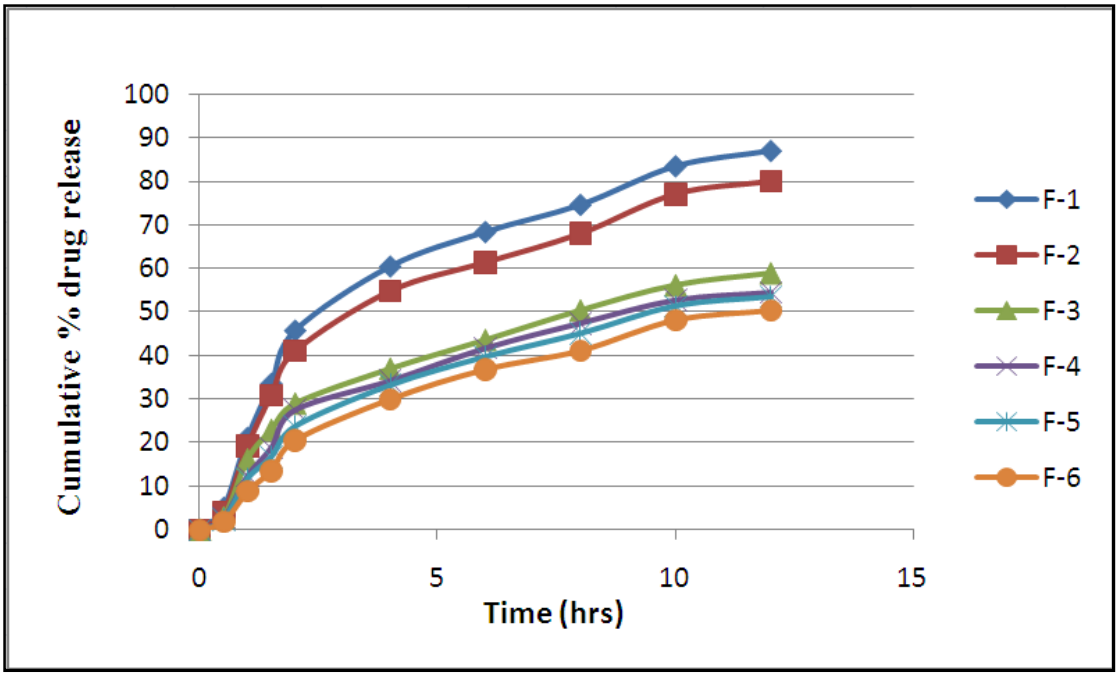

Figure 1. Cumulative percent of Nifedipine released from floating matrix tablet containing varying proportion of fenugreek

Conclusion

The floating gastro retentive tablet formulations of nifedipine were prepared by wet granulation technique using various proportion of polymer. Six batches were prepared with various percentage of fenugreek to retard the drug release in to the stomach. From the *in-vitro* dissolution studies it was found to be that formulation F1 with 10% fenugreek retard drug release in the stomach and small intestine effectively. Formulation F1 with 10 % guar gum emerged to be the best one, because it exhibits the best overall general appearance, hardness of 7.2 ± 0.152 Kg/cm^2, friability of 0.158 % & percentage drug released at the end of 12 h *in-vitro* dissolution studies.

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