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Design and Evaluation of a Sustained Release Enteric Coated Dosage Form of Fluoxetine Hydrochloride

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ABSTRACT

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The purpose of present study was to develop once a day sustained release enteric coated tablet of Fluoxetine HCl by direct compression method. Design was prepared for nine batch using fenugreek mucilage at 40%, 50% and 60% concentration ; HPMC at 10%, 15% and 20%; Compritol ATO 888 at 10%, 15% and 20% and ethyl cellulose at 2%, 3% and 4% concentration. Fenugreek mucilage was extracted from dried ripe seeds of *Trigonella foenum-graecum* (Fabaceae). Cellulose acetate phthalate was used as enteric coating agent. The tablets were characterized for weight variation, crushing strength, friability, drug content and in vitro drug release study. All the formulations were complied with standard specifications. The Drug excipients compatibility study was performed by DSC and IR Spectroscopy and no incompatibility was found. The results of *in vitro* dissolution studies indicated that formulations X2, X5 and X8 released 7.03%, 7.03%, 4.75% of Fluoxetine respectively at the end of 2 hour and 98.17%, 78.12%, 65.45% of Fluoxetine respectively at the end of 24 hour. Increased release rate was observed in polymer in the order HPMC K 100M > ethyl cellulose > Compritol ATO 888. Formulation X2 (50% fenugreek mucilage and 15% HPMC K 100M) could extend drug release up to 24 hour and it exhibited satisfactory drug release within first 2 hours and total release pattern was very close to marketed product. The mechanism of drug release was found to be diffusion coupled with erosion. Optimized formulation was found to be stable when exposed to 40^0C/ 75 % of relative humidity for 3 month.

Keywords: Delayed release, Fluoxetine HCl, HPMC K 100M, Fenugreek mucilage.

INTRODUCTION

Successful pharmacotherapy is dependent on many factors. Efficacy is obviously important; other factors that are often overlooked include availability of optimal dosage and delivery forms, treatment compliance and reduction of side effects. In psychiatric medicine, innovative dosage forms or delivery systems have been developed to address issues that contribute to successful pharmacotherapy.

Depressive disorders are highly prevalent, affecting an estimated 19 million adult Americans in a given 1-year period (NIMH, 2002). The treatment of psychiatric illness frequently requires long term treatment and, as with most chronic illnesses, poor treatment compliance is a widespread phenomenon. Fluoxetine hydrochloride is a Selective Serotonin Reuptake Inhibitor (SSRI) used in divided daily doses (20 mg) every 2 to 3 times for the treatment of many mental disorders, which require long term treatment. The increased need for patient compliance and demand for improved therapeutic efficacy of Fluoxetine Hydrochloride necessitates sustained release drug delivery system with reduced dose. Generally, primary objectives of sustained drug delivery are to ensure safety and to improve efficacy of drugs as well as patient compliance, which can be achieved by better control of plasma drug levels and less frequent dosing.[22] The most convenient way to achieve sustained release of active agent involves physical blending of drug with polymer matrix, followed by direct compression. Different polymers viz. hydroxypropylmethylcellulose (HPMC), ethylcellulose, glyceryl behenate and fenugreek mucilage etc. were tried to control release of the drug up to 24 hour.

The past research acknowledged the use of fenugreek mucilage as a potential non-toxic and safe pharmaceutical excipient (controlled release polymer) in tablet[17]. These particulars explicate the rationale, as to why proposed article concerns the use of fenugreek mucilage for sustained drug delivery.

Hydroxypropyl methylcellulose (HPMC), a semisynthetic derivative of cellulose, has its popularity for the formulation of controlled release (CR) dosage forms as a swellable and hydrophilic polymer.[18,19,20] Its nontoxic property, ease of handling, ease of compression, ability to accommodate a large percent of drug, negligible influence of the processing variables on drug release rates, and relatively simple tablet manufacturing technology make it an excellent carrier material.[10,21]

Numbers of patents have been granted for delayed release Fluoxetine formulation[1]. The present research work was undertaken to fabricate low-cost delayed release tablets of

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Fluoxetine hydrochloride without infringing existing patents using HPMC K 100M and fenugreek mucilage as matrixing agents. Another reason of using combinations of HPMC K 100M and fenugreek mucilage was to overcome the disadvantages of individual matrixing agents. Hydroxypropyl methylcellulose forms firm gel but do not hydrate quickly. On the other hand, fenugreek mucilage hydrates very quickly.

Moreover, higher Fluoxetine levels (60-100 mg) in uncoated dosage form is associated with side effects, such as nausea, vomiting (gastrointestinal intolerance) presumably due to local irritation or the increased plasma levels shortly after dosing resulting in reduced patient compliance.[1] To overcome these side effects, enteric coating of Fluoxetine is done.

In the present study, it was attempted to develop sustained release enteric coated tablet of Fluoxetine HCl to be taken once a day using combination of fenugreek mucilage and HPMC K 100M and to elucidate the effect of Fenugreek mucilage: Compritol 888 ATO, HPMC K 100M, Ethyl cellulose weight ratio on the release kinetics of Fluoxetine from delayed release tablet.

MATERIALS AND METHOD

Materials

Fluoxetine HCl was gifted by Cadila Pharmaceuticals Ltd., India. Ethyl cellulose and HPMC K 100M were obtained as gift samples from Colorcon Asia Pvt. Ltd., India. Compritol ATO 888 was gifted by Gattefosse Corp., USA. A gift sample of cellulose acetate phthalate was received from G.M. Chemicals, India. Fenugreek mucilage was extracted from seeds of *Trigonella foenum-graecum* L., a member of the family Fabaceae. Mg.stearate, talc and microcrystalline cellulose were procured from Atul Chemicals, Anand/Chemdyes Corporation, India. All other chemicals and reagents used were of pharmaceutical or analytical grade.

Tablets were compressed using Rotary tablet compression machine, Rimek machinery 10 station, RSB4-1, Ahmedabad, India. Analysis was performed using UV Visible Spectrophotometer, Shimadzu UV- 230V, Kyoto, Japan.

Isolation of fenugreek mucilage[2]

Fenugreek seeds (200 g) were soaked in 1.5 L of distilled water at room temperature for 1hour and then boiled under stirring condition in a water bath until the slurry was formed. The solution was cooled and kept in a refrigerator overnight to settle out undissolved materials. The upper clear solution was decanted and centrifuged at 500 rpm for 20 minutes. The supernatant was separated and concentrated at 60^0C on a water bath to one third of its original volume. The solution was cooled to the room temperature and was poured into thrice the volume of acetone with continuous stirring. The precipitate was washed repeatedly with acetone and dried at 50-60^0C under vacuum. The dried material was powdered and kept in a desiccator. **Characterization of fenugreek mucilage.**[3,4]

Swelling Index

One gram of powder was placed in a 25 ml ground-glass-stoppered cylinder graduated over a height of about 120 to 134 mm in 5 ml divisions. The powder was moistened with 1 ml of ethanol (96% v/v), water was added up to 25 ml and the cylinder was closed. It was shaken vigorously every 10 min for 1 hour and then allowed to stand for 3 hour. The volume occupied by the powder was measured including any adhering mucilage. Three tests were carried out at the same time. Swelling index was calculated from the mean of the three tests.

Particle size distribution

The particle size of the fenugreek mucilage powder was analysed by optical microscope.

Flow property of fenugreek mucilage powder

The flow property of fenugreek mucilage powder was characterized in terms of angle of repose, carr's index (% Compressibility) and hausner's ratio. Angle of repose was measured by direct funnel method. The $\tan^{-1}$ of the (height of pile/ radius of surface) gave angle of repose.

$$\% \text{ Compressibility} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Bulk density}} \times 100 \quad \text{.....(1)}$$

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \quad \text{..... (2)}$$

pH

The pH of each of 1% suspension was measured using a pH meter to check any hydrolysis or microbial decomposition of suspensions. The change in pH is attributed to hydrolysis or microbial decomposition.

Viscosity

1 gm dried and finely powdered fenugreek mucilage was suspended in 75 ml distilled water for 5 hour. Distilled water was added up to 100 ml to produce the concentration of 1% w/v. The mixture was homogenized by mechanical stirrer for 2 hour and its viscosity was determined using a Brookfield viscometer, spindle LV2 at 20 rpm at 25^0C.

Ash content (WHO GUIDE LINE)

Total ash

The ground air-dried fenugreek mucilage powder approximately 3 g was weighed in a previously ignited and

tarred crucible (usually of platinum or silica) and it was ignited by gradually increasing the heat to 500-600°C until it was white which indicate the absence of carbon. It was cooled in a desiccator and weighed. The content of total ash in mg per g of air-dried material was calculated.

Acid-insoluble ash

To the crucible containing 1 g of total ash, 25 ml of hydrochloric acid (~70g/l) was added and it was covered with a watch-glass and boiled for 5 minutes. The watch-glass was rinsed with 5 ml of hot water and this liquid was added to the crucible. The insoluble matter was collected on an ashless filter-paper and washed with hot water until the filtrate was neutral. The filter-paper containing the insoluble matter to the original crucible was dried on a hot-plate and ignited to constant weight. The residues were allowed to cool in a suitable desiccator for 30 minutes and then weighed. The content of acid-insoluble ash in mg per g of air-dried material was calculated.

Water-soluble ash

To the crucible containing 1 g of total ash, 25 ml of water was added and boiled for 5 minutes. Insoluble matter was collected on an ashless filter-paper, washed with hot water and ignited in a crucible for 15 minutes at a temperature not exceeding 450°C. The content of water-soluble ash in mg per g of air-dried material was calculated by subtracting the weight of this residue in mg from the weight of total ash.

Microbial count

The microbial count of the Fenugreek mucilage was performed as outlined in the *Indian pharmacopoeia* for the presence of Bacteria as well as for Fungi. Total count of bacteria and fungi was calculated using plate count method.

Plate count method

For bacteria: Using Petri dishes 9 to 10 cm in diameter and to each dish a mixture of 1 ml of the sample preparation and about 15 ml of liquefied *casein soya bean digest agar* (Pancreatic digest of casein - 15 g, pepsin digest of soya bean meal - 5g, NaCl - 5 g, agar - 15 g, water upto 1000 ml) at not more than 45^0. Sample preparation was sprayed on the surface of the solidified 15 ml of *casein soya bean digest agar* medium in a petri dish of 9 to 10 cm in diameter. Incubate at 30^0 to 35^0 for 5 day. Number of colonies that are formed were counted. Result was calculated using plates with the greatest number of colonies but taking 300 colonies per plates as the maximum consistent with good evaluation.

For fungi: It was conducted as described in the test for bacteria using Sabouraud *dextrose agar medium* (Mixture of equal parts of peptic digest of animal tissue and pancreatic digest – 10 g, agar – 15 g, water up to 1000 ml) in place of liquefied *casein soya bean digest agar* and the plates incubated at 20 to 25 ^{0}C for 5 days. Result was calculated using plates with not more than 100 colonies.

Loss on drying

Weight loss on drying was determined for 1 gm of mucilage at 105^0C by drying for 2 hour.

Drug excipients compatibility studies

I.R. Spectroscopy of Fluoxetine HCl and polymer mixture

IR spectroscopy was conducted using a IR Spectrophotometer (Grams Buck Scientific- 500) and the spectrum was recorded in the wavelength region of 4000–400 cm^{-1}. The procedure consisted of dispersing a sample (drug alone, polymer alone i.e. fenugreek mucilage, HPMC K 100M and mixture of drug and polymer) in KBr to prepare 10% of mixture and compressing into discs by applying a pressure of 5 t for 5 min in a hydraulic press. The pellet was placed in the light path and the spectrum was recorded. All spectra were collected as an average of three scans at a resolution of 2 cm^{-1}.

Differential Scanning Colorimetry (DSC)

DSC was performed using DSC-60 calorimeter (DSC-PYRIS-1, Perkin Elmer instruments, SICART) to study the thermal behavior of Fluoxetine HCl, polymer alone i.e. fenugreek mucilage, HPMC K 100M and mixture of drug and polymer. The instrument comprised of calorimeter (DSC-60), flow controller (FCL-60), thermal analyzer (TA-60) and operating software (TA-60). The samples were heated in hermetically sealed aluminum pans under nitrogen flow (20 ml/min) at a scanning rate of 10^0c/min from 25^0C to 200^0C. Empty aluminum pan was used as reference.

Preliminary trials

Tablets were prepared by direct compression. Fluoxetine HCl, HPMC K 100M, ethyl cellulose, Compritol 888 ATO, fenugreek mucilage were weighed accurately as per quantities given in Table No.3 after screening thorough 100# sieve individually. Fluoxetine was mixed with HPMC K 100M/ ethyl cellulose/ Compritol ATO 888/fenugreek mucilage and then this powder mixture was mixed with MCC. The powder mixture was lubricated with talc and magnesium stearate. Powder mixture was blended for 10 minutes to obtain uniform mixture. Compression was done in Rotary multistation tablet compression machine (Rimek machinery 10 stations, RSB4-1, Ahmedabad, India) using round 12 mm punch. Weight of tablet was adjusted to 500 mg.

Formulation of tablets

Tablets were prepared by direct compression method. Fluoxetine HCl, HPMC K 100M, ethyl cellulose, Compritol

888-ATO, fenugreek mucilage were weighed accurately as per quantities given in Table No.4 and passed from 100# sieve individually. Fluoxetine was first mixed with fenugreek mucilage and then this powder mixture was then mixed with HPMC K 100M/ ethyl cellulose/ Compritol ATO 888 and MCC. The powder mixture was lubricated with talc and magnesium stearate. Powder mixture was blended for 10 minutes to obtain uniform mixture. Compression was done in Rotary multistation tablet compression machine (Rimek machinery 10 station, RSB4-1, Ahmedabad, India) using round 12 mm punch and compression force was adjusted to obtain tablets with hardness in range of 4-5 kg/cm^2. Weight of tablet was adjusted to 500 mg.

Evaluation of powder blend

Powder blend was characterized for its flow property by evaluating angle of repose, carr's index and hausner's ratio. Angle of repose was determined using funnel method.

Enteric coating of tablet[5]

Three different concentrations of cellulose acetate phthalate (CAP) (3%, 5% and 7%) were prepared in 1:1 acetone and isopropyl alcohol. Diethyl phthalate was used as plasticizer (10 %). Coating was done by dip coating method up to 8 % weight gain. 5% cellulose acetate phthalate was selected for coating of tablet based on % drug dissolved at various time interval and capacity of different concentrations of cellulose acetate phthalate to protect Fluoxetine from gastric environment (Data not shown).

Evaluation of formulation[6]

Weight variation

The tablet weight was measured using electronic balance. Twenty tablets were selected at random and average weight was calculated. The test was performed according to the USP 2007.

Hardness

Monsanto hardness tester was recorded for the determination of the hardness. The tablet was placed in contact between the plungers and the handle was pressed, the force of the fracture was recorded. In this work, for each formulation the hardness of 6 tablets was evaluated.

Friability

Friability of the tablets was determined using Roche friabilator (Electrolab, Mumbai). This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets from at a height of 6 inches in each revolution. Preweighed sample of tablets was placed in the friabilator and are subjected to 100 revolutions. Tablets were dedusted using a soft muslin cloth and reweighed. The friability (F) is given by the formula:

$$F = (1- W_0 / W) \times 100$$

Where, W_0 is the weight of the tablets before the test and W is the weight of the tablet after the test.

Disintegration test

Disintegration test was conducted as per USP 2007 using six tablets. The test was performed using simulated gastric fluid maintained at 37±2 ^{0}C for one hour. Then the tablets were immersed in simulated intestinal fluid maintained at 37±2 ^{0}C for six hour. The tablets were observed for the evidence of disintegration, cracking or softening.

Drug content

Five tablets from each formulations were powdered. Powder equivalent to 100 mg of the Fluoxetine HCl was taken and 100 ml of methanol was added and stirred in mechanical stirrer for 24 hour and filtered. The filtrate was then suitably diluted with methanol and analyzed against a blank by spectrophotometrically at 278 nm using a Shimadzu double beam spectrophotometer.

***In-Vitro* release study**

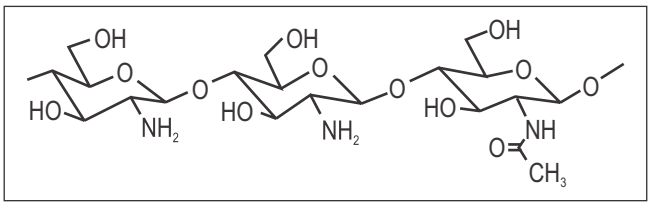
Dissolution study of Fluoxetine delayed release tablet was carried out in 0.1 N HCl for first 2 hour and in phosphate buffer (pH 6.8) for the remaining 22 hours. The delayed release tablet of Fluoxetine HCl was evaluated for their integrity in the physiological environment of stomach and small intestine under conditions mimicking mouth to colon transit. This study was carried out using a USP apparatus - I (50 rpm, 37± 0.5^{0}C). The tablets was tested for drug release for 2 h in 0.1 N HCl as the average gastric emptying time is about 2 h. and then the dissolution medium was replaced with 500 ml of pH 6.8 phosphate-buffered saline. The dissolution study was continued up to 24 hour. At various time interval 5 ml of the dissolution sample was withdrawn and replaced with 5 ml fresh phosphate buffer. The samples were analyzed by UV method at λ_{max} 277 nm.

Elucidation of release mechanism[7,9,11,12,13]

The release parameters and mechanism of release of Fluoxetine HCl from the tablets was investigated by fitting the data to Zero order, First order, Higuchi, Hixson-Crowell and Korsmeyer- Peppas models.

Comparison of Drug Release Data

In order to examine the release mechanism of Fluoxetine from the prepared tablets, the results of the dissolution study was examined according to following equation. Release profiles comparison: the difference factor (*f*1) and similarity factor (*f*2) was used to compare the drug release profiles. The equations are as below:



Where *n* is the sample number, and *Rj* and *Tj* are the percentages of the reference and test drug release, respectively, at different time intervals *j*.

Stability study

The optimized formulation was subjected to the accelerated stability studies according to ICH guidelines (40 ± 2 °C and 75 ± 5% RH) for a period of 3 month in a stability chamber. The optimized formulations were then placed in glass vials and hermetically closed with rubber plugs and sealed with aluminum caps. After 20 days formulation was evaluated for their drug content and in vitro drug release.

RESULTS AND DISCUSSION

Phytochemical, microbial and physicochemical characterization of fenugreek mucilage

The dried mucilage was studied for percentage yield, chemical test, particle size, weight loss on drying, viscosity, pH, swelling ratio, different ash value i.e. total ash value, acid insoluble ash value, water soluble ash value, particle density, and bulk and tapped density, angle of repose compressional properties and microbial content and data are shown in Table No.1 and Table No.2.

Preliminary trials

Polymers like HPMC, Compritol ATO 888, ethyl cellulose and fenugreek mucilage alone were tried for dissolution study. Hydroxypropyl methylcellulose forms firm gel but do not hydrate quickly. On the other hand, fenugreek mucilage hydrates very quickly. Besides this, HPMC matrices exhibited burst release. Additionally when polymer concentration is low, the hydrated matrix would be highly porous rapid diffusion of drug from matrix. Also tablets prepared with alone HPMC had lower crushing strength as compared to fenugreek mucilage alone. So, fenugreek mucilage was selected as controlled release polymer to retard drug release and to impart sufficient strength to tablet and HPMC was used as matrixing agent. Compritol is more lipophilic matrix that hardly allows any water to penetrate into the pores of the matrix structure, resulting in very slow drug release. Besides, the tablets prepared with compritol are also the hardest tablets. Fluoxetine HCl matrix tablets with ethyl cellulose results in very slow drug release during the GIT transit time. To accelerate the release of Fluoxetine from ethylcellulose matrix tablet, the addition of water-swellable polymers, such as fenugreek mucilage has been proposed. Upon contact with aqueous media, this additive hydrates and potentially leaches out of the membranes. Design was prepared for nine batches using fenugreek mucilage at 40%, 50% and 60% concentration; HPMC at 10%, 15% and 20%; compritol ATO 888 at 10%, 15% and 20% concentration and ethyl cellulose at 2%, 3% and 4% concentration.

Drug excipients compatibility study

Differential Scanning Calorimetry (DSC)

The DSC patterns of pure Fluoxetine HCl, HPMC K 100M and fenugreek mucilage and of their physical mixtures shown in Figure No.1. Pure Fluoxetine HCl showed a sharp endotherm at 159.68°C corresponding to its endotherm at 159.68°C corresponding to its melting point (157-162°C as per USP). There was a negligible change in the melting endotherms of the physical mixtures compared to pure drug. Physical mixtures showed sharp endotherm in the range of 151.92°C – 161.2°C, which is corresponding to the melting point of pure Fluoxetine HCl. This result clearly verified that Fluoxetine HCl with all polymers was thermodynamically stable.

IR Spectroscopy

The spectra of all samples showed in Figure No.2 were identical and no any sifting of characteristic absorption bands of Fluoxetine HCl in IR spectra of physical mixtures produced with various polymers.The characteristic IR absorption peak of Fluoxetine HCl for C-F stretching was around 1107 cm−1, C=C stretching was located at 1564 cm−1, N-H stretching was seen at 3010 cm−1,C-H stretching for phenyl group was seen at 1947 cm-1, C-H bending was appeared at 1445 cm−1 and at 1188 cm-1, C-N vibration was present in pure Fluoxetine HCl powder sample, and these were not shifted in the physical mixture of Fluoxetine HCl with polymers. The IR spectra of all the tested samples showed the prominent characterizing peaks of pure Fluoxetine HCl which confirmed that no chemical modification of the drug had been taken place. This indicated that there was no difference between the internal structures and conformation of these samples at the molecular level. Thus it can be concluded that there is no any chemical interaction between drug and polymers. The results of DSC and FTIR study confirmed that there was no chemical interaction between Fluoxetine HCl and other polymer used in study.

Evaluation of powder blend

Flowability of powder blend was evaluated by determining carr's index and angle of repose, hausner's ratio as it is prerequisite to obtain solid dosage form with an acceptable weight variation.

Table No.5 depicts the result of evaluation parameters of powder blend of all formulations. The bulk density and tapped density for all the formulations varied in the range of 0.39 to 0.49 and 0.48 to 0.60 respectively. The obtained values lie within acceptable range. The percent Compressibility for all formulation was found to be in the range of 16.32 to 20.00 and Hausner's ratio for all powder blends was found to be in range of 1.19 to 1.25, also the Angle of repose for powder blend of all formulations ranged in between 27.25 to 28.72. All formulations have revealed good compressibility and good flow properties.

Evaluation of formulated Fluoxetine HCl delayed release tablet

The comparison of physical properties of the matrix tablets is shown in Table No.6. The average % deviation of all tablets and % deviation of individual tablet were found to be within the limit of USP 2007 hence all formulations passed the weight variation test.

The hardness value of the tablet formulations was within the range of 4.90 – 5.9 kg/cm^2. From the hardness value shown in Table No.6 it can be concluded that as the concentration of fenugreek mucilage increases there is increase in hardness value. Another measure of tablet strength is friability. In present study friability of all formulations was below 1% (0.31 to 0.72%) indicating friability was within pharmacopoeial limit. No tablets show the evidence of disintegration cracking or softening in simulated gastric fluid in 1hour. All tablets disintegrate in simulated intestinal fluid.

Drug content uniformity amongst different batches was found to be lie within range of 91.57 to 109.82%. As per USP/NF'07, range of content uniformity of Fluoxetine delayed release formulation is 90 to 110%, so all batch passed content uniformity test.

In vitro drug release study

Drug release data of matrix tablet shows that drug release was significantly affected by polymer content. Less than 10% drug was released in first 2 hour. Formulation X1 containing lowest (40%) concentration of fenugreek mucilage released the drug in 11 hour and as the concentration of fenugreek mucilage as well as concentration of HPMC K 100M was increased, release was retarded upto 24 hour. As the concentration of fenugreek mucilage was increased from 40% to 60% and concentration of ethyl cellulose from 2% to 4% drug release was retarded upto 72% in 24 hour. Similarly as the concentration of compritol ATO 888 was increased from 10% to 20%, drug release was retarded upto 65%. Drug release was more retarded in case of combination of fenugreek mucilage and compritol ATO 888 (X7,X8,X9) than combination of fenugreek mucilage and ethyl cellulose (X4,X5,X6). Compritol contains lower percentage of free fatty acids and hydroxyl numbers but contains higher percentage of fatty esters[14,15]. This factors may account for low dissolution behaviour of this matrix. Finally batches containing combination of fenugreek mucilage and ethyl cellulose (X4,X5,X6) give 79.23% drug release within 24 hour and batches having combination of fenugreek mucilage and compritol ATO 888 (X7, X8, X9) give 69.26% drug release within 24 hour.

Fig.1: DSC thermogram of (A) pure Fluoxetine HCl, (B) pure fenugreek mucilage, (C) pure HPMC K 100M, (D) mixture of Fluoxetine HCl, fenugreek mucilage and HPMC K 100M.

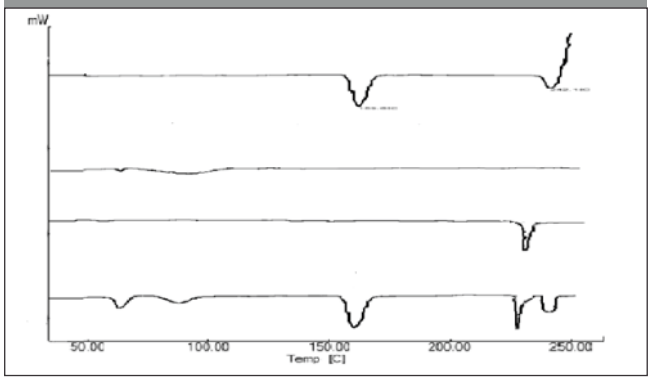


Fig. 2: IR spectra of (A) pure Fluoxetine HCl, (B) pure fenugreek mucilage, (C) pure HPMC K 100M,(D) mixture of Fluoxetine HCl, fenugreek mucilage and HPMC K 100M.

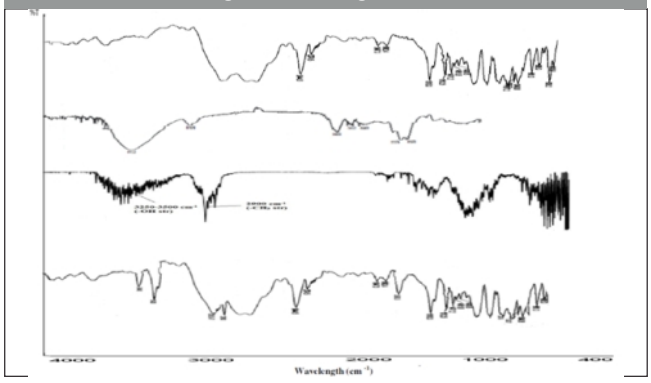


Fig. 3: Comparative dissolution profile of different batches of Fluoxetine delayed release tablet and Marketed formulation

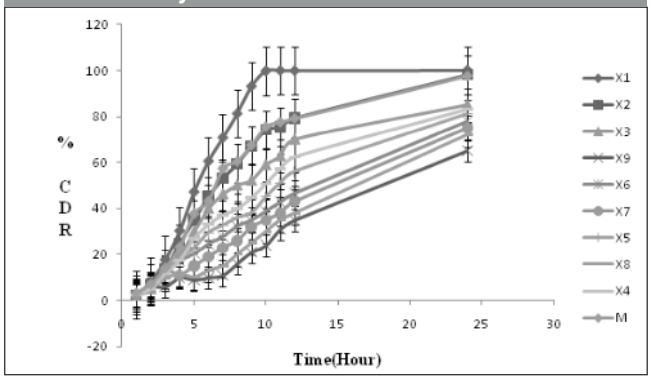


Table 1: Phytochemical and microbial properties of fenugreek mucilage

Properties		Fenugreek mucilage
Chemical test	Reuthenium red	Red color-mucilage present
	Molish red	Violet ring at junction of two liquid-presence of carbohydrate
	Fehling solution	Negative-no reducing sugar present
Other Parametes	Yield of mucilage	35%
	Particle size	47.8 µm
	Viscosity	500 cp
	pH	2
	Swelling ratio	4.5

Table 3: Composition of preformulated Fluoxetine HCl tablet

Batches	Y1	Y2	Y3	Y4
Fluoxetine Hcl	60	60	60	60
Fenugreek mucilage	300	-	-	-
HPMC K 100M	-	100	-	-
Ethyl cellulose	-	-	20	-
Compritol ATO 888	-	-	-	100
MCC	Qs	qs	Qs	qs
Talc	2%	2%	2%	2%
Mg.stearate	2%	2%	2%	2%
Total weight	500	500	500	500

Table 2: Physical properties of fenugreek mucilage

Physical Property	Practically Found Value	Accepted Range	Reference
Carr's index	15%	-	-
Hausner's ratio	1.23	-	-
Total Ash	0.85%	Not more than 15%	Quality standards of Indian Medicinal Plants Vol-III pg no: 304
Water soluble ash	0.35%	Not more than 30%	Quality standards of Indian Medicinal Plants Vol-III pg no: 304
Microbial Count	For bacteria-4 cfu/g For fungi-2 cfu/g	N.M.T. 10000cfu/g N.M.T. 200cfu/g	Quality standards of Indian Medicinal Plants Vol-III pg no: 304
Angle of repose	22.25^0	-	Herbal Pharmacopeia of India
Tapped density	0.66 g/ml	-	-
% LOD	0.47%	Not more than 0.5%	-

Table 4: Composition of Fluoxetine HCl tablet

Batches	Xl	X2	X3	X4	X5	X6	X7	X8	X9
Fluoxetine Hcl	60	60	60	60	60	60	60	60	60
Fenugreek mucilage	200	250	300	200	250	300	200	250	300
HPMC K100M	50	75	100	-	-	-	-	-	-
Ethyl cellulose	-	-	-	10	15	20	-	-	-
Compritol ATO 888	-	-	-	-	-	-	50	75	100
MCC	qs	qs	qs	qs	qs	qs	qs	qs	qs
Talc	2%	2%	2%	2%	2%	2%	2%	2%	2%
Mg.Stearate	1%	1%	1%	1%	1%	1%	1%	1%	1%
Total weight	500	500	500	500	500	500	500	500	500

Table 5: Pre compression parameters of powder blend

Batch	Angle of Repose (θ) n=3, (±S.D)	Bulk Density n=3, (±S.D)	Tapped Density n=3, (±S.D)	% Compressibility n=3, (±S.D)	Hausner's ratio n=3, (±S.D)
X1	27.75±0.12	0.40±0.01	0.48±0.04	16.6±0.22	1.20±0.08
X2	28.23±0.16	0.40±0.02	0.49±0.01	18.3±0.18	1.22±0.09
X3	28.72±0.18	0.39±0.01	0.48±0.02	19.35±0.21	1.23±0.05
X4	27.75±0.12	0.45±0.03	0.54±0.03	16.32±0.25	1.19±0.06
X5	27.75±0.15	0.47±0.02	0.57±0.04	16.90±0.15	1.20±0.08
X6	27.91±0.18	0.49±0.04	0.58±0.02	17.64±0.28	1.21±0.11
X7	27.25±0.22	0.47±0.01	0.57±0.01	17.54±0.31	1.21±0.04
X8	27.75±0.14	0.49±0.02	0.60±0.01	18.36±0.14	1.22±0.07
X9	27.91±0.18	0.48±0.03	0.60±0.04	20.00±0.21	1.25±0.05

Table 6: Post compression parameters of Fluoxetine tablet

Batch	Weight Variation (mg)n=20, (±S.D	Hardness (Kg/cm^2) n=6, (±S.D)	% Friability n=6, (±S.D)	% Drug Content n=3, (±S.D)
X1	495.5±3.65	5.30±0.35	0.55±0.03	91.57±0.23
X2	499.9±2.96	5.36±0.64	0.42±0.04	98.26±0.15
X3	505.2±2.79	5.39±0.26	0.30±0.02	103.25±0.25
X4	496.5±2.66	6.02±0.35	0.72±0.04	98.38±0.34
X5	505.2±2.17	6.05±0.37	0.55±0.04	109.82±0.27
X6	505.2±2.69	6.06±0.37	0.63±0.04	99.32±0.43
X7	498.9±1.91	5.35±0.42	0.55±0.03	98.47±0.09
X8	495.2±2.44	5.41±0.45	0.42±0.05	103.25±0.26
X9	501.8±1.80	5.40±0.35	0.42±0.02	98.46±0.27

Table 7: Difference (f_1) and similarity factor (f_2) of release behaviour between matrix tablets and marketed formulation

Batches	*f1*	*f2*
X1	3.25	58.30
X2	2.69	84.86
X3	3.14	66.85
X4	4.12	69.40
X5	5.36	70.15
X6	4.30	72.20
X7	6.19	59.20
X8	7.78	75.36
X9	6.12	60.32

Comparison of drug release data and elucidation of release mechanism

All the formulations passed the similarity criteria and simultaneously formulation X2 exhibit f2 value 84.86 which give out quite impressible mark about X2 dissolution behaviour. So we can conclude that formulation X2 meeting the criteria with marketed formulation hence it was optimised formulation.

All formulations followed Higuchi square root kinetics which is characteristic of fenugreek mucilage matrix system[5]. To confirm diffusion mechanism, release data were fitted to Korsmeyer-Peppas equation. Formulations X1, X2 and X3 follows Korsmeyer-Peppas model, which appears to indicate

Table 8: Fitting of release kinetic models to drug-release data for Fluoxetine delayed release tablet

Formulation		X1	X2	X3	X4	X5	X6	X7	X8	X9
Zero order	r^2	0.826	0.840	0.831	0.789	0.816	0.789	0.834	0.816	0.868
	Slope	7.235	7.300	7.573	8.052	7.934	8.175	5.383	5.448	5.765
	Intercept	25.25	24.38	22.15	3.954	4.677	3.786	3.496	1.899	0.034
First order	r^2	0.720	0.720	0.714	0.853	0.817	0.804	0.850	0.853	0.865
	Slope	0.062	0.065	0.066	0.082	0.086	0.086	0.081	0.083	0.089
	Intercept	1.415	1.411	1.367	1.131	1.126	1.103	1.024	1.145	1.236
Higuchi	r^2	0.915	0.928	0.924	0.992	0.995	0.995	0.991	0.983	0.979
	Slope	35.22	35.46	36.75	37.22	36.90	37.81	24.81	23.01	26.35
	Intercept	13.27	14.56	14.56	34.38	33.43	35.24	22.00	23.64	26.73
Korsmeyer peppas	r^2	0.976	0.999	0.998	0.879	0.878	0.834	0.786	0.801	0.870
	Slope	0.981	0.657	0.612	1.451	1.148	1.125	1.276	1.065	1.342
	Intercept	0.814	0.840	0.883	0.834	1.101	1.180	0.812	0.801	0.834

a coupling of the diffusion and erosion mechanism -so-called anomalous diffusion— which might be due to swelling and erosion property of HPMC and it may indicate that the drug release is controlled by more than one process. It was found from the Korsmeyer-Peppas model (Table No.8) that in formulation X2 release exponent n was 0.65.

In X2 diffusion coupled with erosion might be the mechanism for drug release from Fluoxetine delayed release tablets (X2).

Stability study:

The results of accelerated stability studies carried out according to ICH guidelines; indicate that optimized Fluoxetine delayed release tablet did not show any changes in physical parameter and the drug content (Data not shown). Furthermore, in vitro release studies carried out on the optimized formulation stored at accelerated test conditions indicated no statistically significant change in the drug release profiles (data not shown). Hence the preparations are sufficiently stable as per the regulatory requirements.

CONCLUSION

In this study, an attempt was made to develop sustained release enteric coated tablet of Fluoxetine HCl. Amongst the polymers tested, fenugreek mucilage and HPMC K 100M (Batch X2) combination could retard release up to 24 hour was selected for the development of formula. All formulations followed Higuchi square root kinetics in respect to drug release. Formulations X1, X2 and X3 containing combination of fenugreek mucilage and HPMC followed/displayed Korsmeyer-Peppas model, which appears to indicate a coupling of the diffusion and erosion mechanism—so-called anomalous diffusion. Analysis of in *vitro* release study showed that Batch X2 had *f2* value 84.86 and *f1* value 2.69. So batch X2 is the optimum batch which has dissolution profile similar to marketed formulation. The optimized formulation was found to be stable at all the stability conditions. Formula containing 50% fenugreek mucilage and 15% HPMC K 100M exhibited drug release profile similar to marketed product FLUTOP-DR.

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