Research Article

PREPARATION AND EVALUATION OF FLUVASTATIN EXTENDED RELEASE TABLETS USING NEEM GUM

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ABSTRACT

Extended release dosage forms prolong and control the release of the drug that is dissolved or dispersed in a matrix system is one of the widely used approaches in pharmaceutical dosage forms. Majority of the polymers either from natural or synthetic origin is used as matrix forming agent in pharmaceutical dosage forms. There are many benefits of using natural gums in drug delivery. Recent past has witnessed the application of natural gums and mucilage's as pharmaceutical aids in drug delivery. The present study was planned with an objective to develop fluvastatin extended release tablets by using neem gum as matrix forming agent. The prepared tablets were evaluated for their physicochemical properties, drug content and *in vitro* drug release. The results of the study indicated the usefulness of neem gum as pharmaceutical excipient for the preparation of extended release dosage forms.

Keywords: Fluvastatin, neem gum, extended release, matrix forming agent.

INTRODUCTION

Extended release dosage forms offer therapeutic benefit in drug therapy through maintaining plasma drug level over an extended period of time and thereby minimizing dosage frequency and improve patient compliance¹. Matrix system is widely used for the purpose of extended release². Matrix is a homogeneously dispersed embedded composite of one or more drugs with hydrophilic or hydrophobic polymers³. Majority of the polymers used for the drug delivery is either from natural or synthetic origin⁴. There are many benefits of using natural gums in drug delivery. They are inexpensive and do not cause side effects. They are locally available, renewable resource that can be processed in an environmentally friendly manner. These benefits have provided numerous recent endeavors to evaluate the efficacy of these natural gums and mucilage available from different regions of India for using them as pharmaceutical aids in drug delivery. Neem gum is obtained from the neem trees of family Meliaceae⁵. Gum contains mannose, arabinose, galactose, glucosamine, fructose, xylose and glucose⁶. Studies were being performed on neem gum as binding agent and sustained release agent.

Fluvastatin therapeutically used for lowering cholesterol has been reported, particularly in the treatment of hyperlipo-proteinemia and atherosclerosis⁷. After oral administration it absorbs rapidly and almost completely (> 90%) but exhibits extensive first pass metabolism⁸. Fluvastatin has a short biological half-life of 1.5-2 hours. Fluvastatin is available as immediate and extended release dosage form in market and administered at dose range of 20-80 mg per day⁹. Usually, doses at or below 40 mg are taken once a day at bedtime. Doses of 80 mg are to be taken in divided dosages (40 mg twice a day). Some adverse events such as elevation in transaminase levels, headache, and dyspepsia have been reported¹⁰ for it. In order to increase the tolerability and reduce the occurrences of adverse events, a sustained release (SR)

formulation of fluvastatin has been developed and marketed¹¹. Reports have shown development of few sustained release products such as matrix tablets, microcapsules, GRDDS, pulsatile dosage forms¹² etc. The present work planned with an object to develop an extended release tablet dosage forms of fluvastatin using neem gum as matrix forming natural polymer. The developed formulations were evaluated for their physicochemical properties, drug content and *in vitro* drug release. The optimized formulation was compared with commercial tablets. The results of the study found to be promising indicated the usefulness of neem gum in preparation of fluvastatin extended release tablets.

MATERIALS AND METHODS

Fluvastatin was obtained as gift sample from M/s. Aurobindo Pharma Ltd., Hyderabad, Neem gum was purchased from Madhava Shetty, Botanist, Sri Venkateswara University, Tirupaty. Hydroxy propyl methyl cellulose, lactose mono hydrate, magnesium stearate was procured from M/s. Lobachemie Pvt. Ltd., Mumbai. All other chemicals and reagent used were of analytical grade.

Purification of Neem gum

Neem gum exudates were procured from authenticated vendor, Madhava Shetty, faculty of Botany, SV University, Tirupaty. The neem gum was purified before use. The visible debris and non-gum parts were removed, and the exudates were soaked in purified water over night. The impurities were removed, and soft swollen mass was collected in stainless steel trays and dried in tray dryer at 40-50°C for 10 to 12 hours. The dried gum was collected, powdered and passed through sieve no #80. The powdered gum was stored in airtight container until further use.

Phytochemical and Physicochemical Evaluation Neem Gum

Qualitative analysis of neem gum was performed as per the standard procedure to confirm the phytochemical nature of the mucilage¹³. Physicochemical parameters such as water-soluble ash, water insoluble ash, total ash, acid insoluble ash, swelling index, moisture uptake, specific gravity was studied for neem gum as per standard methods^{14,15}.

Fourier Transform Infrared Spectroscopy (FTIR)

The FTIR Spectra for neem gum, fluvastatin and mixture of neem gum and fluvastatin was carried out by using FTIR spectrophotometer (Spectrum II, Perkin Elmer). Potassium bromide pellet were prepared with each sample and the IR spectrum was recorded in the wave number range of 4000 cm⁻¹ to 400cm⁻¹.

Differential scanning calorimetry

Differential scanning calorimetry (DSC) study for neem gum, fluvastatin and mixture of neem gum and fluvastatin was performed using STA 7300 (HITACHI, Japan) operating with TA 7000 software. Temperature axis and cell constant were calibrated using Indium. Samples were heated at 10°C min⁻¹ over the temperature range 30-300°C under dry nitrogen with nitrogen flow rate set at 50 ml min⁻¹ in pin holed aluminium pans.

Tablet Manufacturing

Fluvastatin tablets were prepared by wet granulation method. The ingredients were weighed according to the formulae shown in Table 2 and mixed in geometric order. The granulation was done by adding small quantity of water. The wet mass was passed through sieve number # 12. The granules were dried at 60 °C in a tray dryer. The dried granules were passed through sieve number #20. These granules were lubricated by blending. The blend was subjected to compression using 9 mm circular standard biconvex punch on an eight-station rotary compression machine (M/s. Karnavati Engg. Ltd., Model: Rimek Mini Press II) at a force of 5 tons.

Evaluation of Blend Properties

The blends of all tablet formulation were evaluated for bulk properties. Flow properties of the blends were determined by the static angle of repose (θ), which was measured according to the fixed funnel and free-standing cone method¹⁶. The bulk and tapped densities of blends were determined by the tap method and the compressibility index was calculated by using the data.

Physical Evaluation of Tablets

The tablets were evaluated for appearance, dimensions, hardness and friability. Hardness was determined by using Monsanto hardness tester. Friability was determined using Roche friability testing apparatus. Weight variation was performed according to the Indian Pharmacopoeia procedures.

Drug Content

Ten tablets were taken, and their average weight was noted. The tablets were powdered and the sample equivalent to one tablet was weighed accurately. The powder was transferred into a 100 ml volumetric flask and 25 ml of methanol was added, mixed well then 50 ml of distilled water was added and sonicated for 15 minutes. After equilibrium the samples were made up to volume with distilled water. The resulted solution was filtered through

0.45 μ m filter paper and suitably diluted and the drug content was estimated spectrophotometrically by measuring the absorbance at 234 nm using UV-Visible spectrophotometer (M/s. Shimadzu, Model: UV-1800)¹⁷.

In vitro Dissolution studies

In vitro dissolution studies of fluvastatin tablets were conducted using USP Dissolution apparatus I¹⁸. The dissolution medium was 1000 ml distilled water and the temperature was maintained at 37 $\pm$ 0.5 °C at 50 rpm. The samples 5 ml of the media were withdrawn from the dissolution apparatus over a period of 8 hours and the samples were replaced with 5 ml fresh buffer. The samples were analyzed for the amount of fluvastatin content at 234 nm.

DISCUSSION

The present study was aimed to explore the possibilities of using natural gum, neem gum as a pharmaceutical excipient for the formulation of extended release tablets. Fluvastatin (FVT) belongs to the statin family and is considered as the first line of defense against hyperlipidemia having short biological half-life. Hence, it was planned to develop extended release tablets of fluvastatin by using neem gum as matrix forming agent.

Neem Gum

Neem gum exudates were procured from an authenticated vendor, purified and conducted confirmative and purity tests. The results of qualitative phytochemical analysis as shown in Table 1 indicated the presence of carbohydrates, mucilage and polysaccharides, terpenoids, steroids, amino acids and glycosides as a characteristic features of neem gum.

The physicochemical parameters such as total ash, water soluble ash, water insoluble ash, acid insoluble ash found to be 3.9%, 0.96%, 0.79% (%) and 0.54% respectively, specific gravity was 1.28, swelling index and moisture uptake was 166 % and 27 % w/w respectively.

FTIR Spectroscopy

FTIR studies have been performed for the pure drug, neem gum and combination of pure drug with neem gum in Figure 1. The FTIR spectra of fluvastatin showed characteristic peaks of alcoholic OH at 3614.22 cm⁻¹, COOH at 3000.04 cm⁻¹, C-O at 1692.08 cm⁻¹, mono substituted benzene at 771.06 cm⁻¹. Neem gum spectra showed characteristic peaks of - alcoholic OH at 3396.38 cm⁻¹, COOH at 2925.94 cm⁻¹, C-O at 1634.07 cm⁻¹, Aromatic C=C at 774.33 cm⁻¹. The FTIR spectra of mixture showed characteristic peaks of alcoholic OH at 3604.22 cm⁻¹, COOH at 2942.08 cm⁻¹, C-O at 1643.21 cm⁻¹, mono substituted benzene at 744.36 cm⁻¹. From the above interpretation it is understood that there is no major shifting in the frequencies of above said functional groups of fluvastatin in mixture. Fluvastatin was identified and which indicates that there is no chemical interaction between fluvastatin and neem gum which were used in the formulations.

Differential scanning calorimetry

DSC thermo gram for neem gum showed an endothermic peak at 96.5 °C to 143.5 °C, fluvastatin showed endothermic peak at 144.6 °C to 161.9 °C and mixture of neem gum and fluvastatin showed broad endothermic peak at 115.6°C to 145.3 °C. The results indicated lack of interaction between neem gum and fluvastatin in Figure 2.

Pre-compression blend properties

The extended release matrix tablets were prepared by wet granulation method by using rotary compression machine. Before compression the blends were evaluated for flow properties such as Angle of repose and Carr's index. The pre-compression properties of formulation FN1 to FN6 are shown in Table 3. The bulk density and tapped density of the formulation was found to be in the range of 0.608 to 0.677 g/ml and 0.721 to 0.764 g/ml respectively. The compressibility index and Hausner ratio values were found to be 14.66-16.44 % and 1.11-1.18. The angles of repose values were found to be 24.45 -28.45°. These results indicated the good bulk properties of the blend and are suitable for tablet compression.

Physicochemical parameters of tablets

Fluvastatin tablets were prepared by using neem gum as a polymer at different drug to polymer ratios by wet granulation technique. The process could result good tablets without any defects. The physical parameters of tablets FN1 to FN6 were shown in Table 4. The average weights of different formulations were found to be in the range of 210 mg to 450 mg. The diameter, thickness was found to be 9 ± 0.1 mm and 3.6 mm to 3.9 mm. The hardness was found to be 4.0 to 5.2 kg/cm². Friability is less than 1%. All these parameters are under the compendia requirements. The drug content of different formulations were found to be in the range of 98.6 ± 0.4 % w/w to 101.2 ± 0.8 % w/w. The low standard deviation values indicate the uniformity of drug content.

In vitro dissolution studies

In vitro dissolution studies of fluvastatin tablets were conducted for 8 hours. The percentage drug release was calculated, and the results are shown in Table 5 and Figure 3. The prepared formulations showed gradual and extended release of drug over a period of 8 hours. It was found as the neem gum concentration increases the drug release was slow and controlled. The drug release from commercial tablet was also extended up to 8 hours. Among all the formulation FN5 containing 300 mg of neem gum and 20 mg of HPMC as binder is considered to be the suitable formulations for extended release tablets of fluvastatin.

The drug release kinetics was studied by calculating zero order¹⁹ and first order kinetics²⁰. The results of correlation coefficient values indicated that the drug release from the fluvastatin tablets FN1 to FN6 follows zero order kinetics Table 6. The mechanism of drug release was studied by plotting the cumulative percent drug release versus square root time (Higuchi)²¹ and log time versus log percent drug release (Korsmeyerpeppas)^{22,23}. The results suggested that the drug release follows diffusion mechanism and non-fickian. The dissolution profiles of all the prepared formulations were compared with commercial product by calculating dissimilarity factor (f_1) and similarity factor (f_2)^{24,25}. Formulation FN5 also showed desired similarity factors of 56 and difference factor of 11, which indicates the comparable release with that of commercial tablets. The results of the present study clearly indicated the usefulness of neem gum as a matrix forming natural polymer for the preparation of extended release tablets of fluvastatin.

Table 1: Phytochemical Analysis of Neem Gum

Phytochemical constituent	Test	Result
Carbohydrates	Molisch's test	Present
Mucilage	Ruthenium test.	Present
Polysaccharides	Iodine test	Present
Enzyme	Enzyme test	Absent
Alkaloids	Dragendroff's test	Absent
Flavonoids	Ferric chloride test for Flavonoids	Absent
Terpenoids	Salkowski test	Present
Tannins	Ferric chloride test for Tannins	Absent
Steroids	Liebermann's-Burchard	Present
Proteins and amino acid	Ninhydrin test	Present
Glycosides	Liebermann's test.	Present
Phenolic compound	Ferric chloride test for Phenols	Absent

Table 2: Formulae for the Preparation of Fluvastatin Tablets

S. No.	Ingredients	Quantity/ tablet (mg)					
		FN1	FN2	FN3	FN4	FN5	FN6
1	Fluvastatin	80	80	80	80	80	80
2	Neem gum	80	160	240	250	300	320
3	Hydroxy Propyl Methyl Cellulose (HPMC E5)	20	20	20	20	20	20
4	Lactose monohydrate	20	20	20	20	20	20
5	Magnesium stearate	10	10	10	10	10	10
	Total Weight	210	290	370	380	430	450

Table 3: Pre Compression Parameters

S. No.	Formulation	Bulk density (gm/ml)	Tapped density (gm/ml)	Compressibility Index (%)	Hausner ratio	Angle of repose (°)
1	FN1	0.645	0.764	15.57	1.18	28.22
2	FN2	0.646	0.721	14.66	1.12	27.68
3	FN3	0.677	0.739	15.28	1.16	28.45
4	FN4	0.635	0.741	16.44	1.14	24.45
5	FN5	0.628	0.735	15.28	1.11	26.67
6	FN6	0.608	0.722	15.45	1.17	27.88

Table 4: Physical Parameters of Tablets

Formulation	Thickness (mm)	Diameter (mm)	Hardness (kg/cm ²)	Friability (%)	Average weight (mg)	Drug Content (%w/w)
FN1	3.7	9.06	4.0	0.652	210	99.3 ± 0.6
FN2	3.9	9.2	5.1	0.614	293	98.6 ± 0.4
FN3	3.6	9.06	4.8	0.565	374	100.1 ± 0.5
FN4	3.8	8.97	4.6	0.657	380	98.9 ± 0.8
FN5	3.7	9.04	4.9	0.598	432	99.5 ± 0.6
FN6	3.8	9.2	5.2	0.563	454	101.2 ± 0.8

Table 5: Dissolution Profiles of Fluvastatin ER Tablets

Time (h)	Cumulative Percent Drug Release (%w/w)						
	FN1	FN2	FN3	FN4	FN5	FN6	Commercial
1	20.1 ± 0.3	20.8 ± 0.4	14.5 ± 0.2	23.5 ± 0.2	20.2 ± 0.1	17.5 ± 0.2	13.5 ± 0.4
2	32.6 ± 0.4	40.8 ± 0.1	34.6 ± 0.4	36.6 ± 0.6	25.7 ± 0.4	22.6 ± 0.4	18.0 ± 0.2
3	38.5 ± 0.2	61.3 ± 0.2	45.3 ± 0.6	50.8 ± 0.5	41.4 ± 0.6	24.7 ± 0.6	32.1 ± 0.6
4	54.5 ± 0.1	65.7 ± 0.5	52.7 ± 0.2	52.1 ± 0.4	57.0 ± 0.5	35.1 ± 0.7	61.8 ± 0.8
5	64.1 ± 0.2	66.8 ± 0.2	64.3 ± 0.3	55.5 ± 0.2	63.3 ± 0.4	43.1 ± 0.5	76.8 ± 0.6
6	90.7 ± 0.3	89.1 ± 0.3	85.6 ± 0.7	66.2 ± 0.1	74.0 ± 0.2	56.7 ± 0.4	77.8 ± 0.5
7	91.1 ± 0.4	100.3 ± 0.1	95.3 ± 0.4	76.8 ± 0.3	84.1 ± 0.2	74.1 ± 0.3	92.0 ± 0.4
8	107 ± 0.6	100.3 ± 0.3	102.6 ± 0.1	96.2 ± 0.1	100.3 ± 0.3	85.3 ± 0.5	103.0 ± 0.3

Table 6: Dissolution Kinetics of Fluvastatin Tablets

Formulation	Correlation coefficient (r)					Zero Order Rate constant (k ₀) (mg/h)	n	f ₁	f ₂
	Zero	First	Higuchi	erosion	Peppas				
FN1	0.9919	0.9279	0.9568	0.8682	0.98739	13.05	0.821	13.7	52.6
FN2	0.9735	0.9445	0.9807	0.8354	0.98303	12.36	0.763	20.1	42.7
FN3	0.9943	0.9167	0.9653	0.8710	0.99235	12.89	0.913	13.5	51.6
FN4	0.9726	0.8556	0.9731	0.8082	0.98085	10.14	0.611	23.5	42.6
FN5	0.9951	0.9810	0.9677	0.8605	0.98673	11.85	0.800	11.8	56.6
FN6	0.9821	0.9318	0.9239	0.8763	0.94808	9.96	0.778	28.0	36.8

Figure 1: FTIR Spectra of (a) Fluvastatin (b) Neem gum and (c) Fluvastatin +Neem gum mixture

Figure 2: DSC Thermo grams of (a) Fluvastatin (b) Neem gum and (c) Fluvastatin + Neem gum mixture

Figure 3: Dissolution Profiles of Fluvastatin Extended Release Tablets

CONCLUSION

Application of natural gums and mucilages as pharmaceutical aids in drug delivery has become an interest of research. The present study was planned to develop fluvastatin extended release tablets by using neem gum as matrix forming agent. The study showed that neem gum can be purified to use it as pharmaceutical excipient. The tablets prepared by using neem gum were found to be good and meet all the compendia requirements. The concentration of neem gum played a major role in drug release. The results of the study indicated that neem gum could be used as a matrix forming agent for the preparation of fluvastatin extended release tablets.

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