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DESIGN AND EVALUATION OF CONTROLLED RELEASE FLUVASTATIN TABLETS OF LIPID LOWERING AGENT FOR HYPERLIPIDEMIA

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Abstract:

In the present research, an attempt has been made to formulate controlled release matrix tablets of Fluvastatin (FS).Different formulations were prepared by wet granulation method by using different polymers like HPMC K-4M, HPMC E-15, guar gum, eudragit S100, PVP etc. with different ratios were used in the development of formulations. HPMC K-4M, HPMC E-15 and guargum are used as rate conyrolling polymer, PVP used as binder eudragit S100 used as enteric polymer, lactose used as filler, and microcrystalline cellulose as disintegrant. The prepared tablets were evaluated for pre compression and post compression parameters with different ratios. The effect of polymer loading in in-vitro drug release and the mechanism of release was studied by different mathematical models. It can be concluded that among all the formulations the combiFStions of HPMC K-4M and Eudragit S100 was considered as the optimized formulations in the present research work. The optimized formulations show non-fickian diffusion mechanism of release and other all evaluation.

Key words: *Fluvastatin, HPMC, Eudragit S100, guar gum, PVP*

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INTRODUCTION:

Fluvastatin is an antilipemic agent that competitively inhibits hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase. HMG-CoA reductase catalyzes the conversion of HMG-CoA to mevalonic acid, the rate-limiting step in cholesterol biosynthesis. Fluvastatin belongs to a class of medications called statins and is used to reduce plasma cholesterol levels and prevent cardiovascular disease. It is also the first entirely synthetic HMG-CoA reductase inhibitor and is structurally distinct. Fluvastatin, a lipid lowering agent used in the treatment of Hyperlipidemia was used as a model drug to develop a controlled release formulation. Fluvastatin has a short biological half life of 1-2 hour and rapid first pass metabolism which necessitates multiple daily dosing hence the present study was aimed to develop a controlled release formulation of fluvastatin. Rapidly and almost completely absorbed (> 90%), but undergoes extensive first pass metabolism. Bioavailability is 24% (range 9-50%) when a 10 mg dose is given. The mean relative bioavailability of the extended-release tablet is 29% (range: 9% to 66%) compared to an immediate-release capsule administered under fasting conditions. When given orally, fluvastatin reaches peak concentrations (Tmax) in less than one hour. Taking the extended release tablet with a high-fat meal will delay absorption (Tmax = 6 hours) and increase bioavailability by approximately 50%. However, the maximum concentration of fluvastatin sodium extended-release tablets seen after a high fat meal is less than the peak concentration. Long term treatment with controlled-release fluvastatin once daily is generally safe in patients and is well tolerated. The present research project relates to a controlied release oral formulation of anti hyperlipidemic drugs like fluvastatin, the present research comprising FS useful for the treatment of HPL; polymers like guar gums, chitosan, and hydroxypropyl methylcellulose are used for controlling the drug release, and the polymers are mixed in a predetermined ratio. To develop suitable no. analytical method for the estimation of the drug. To evaluate the powder mix for pre compression characteristic and tableting characteristics, to compress the formulation according to compatibility study then evaluate post compression parameters like density, hardness, friability and content uniformity[1,2,3] etc.Optimization of formulation parameters and drug-carrier system using appropriate methods and study of dissolution, percentage of drug content, and degradation of active constituents.

MATERIALS AND METHOD

Fluvastatin was obtained from Spectrum pharma lab, Hyderabad, HPMC K-4-M and HPMC E15 from Strides arcolab, Bangalore. Eudragit S100 from KAPL Bangalore and other chemicals from SD Fine chemicals Ltd. Mumbai.

Preparation of Fluvastatin Matrix Tablets

Controlled release tablets of fluvastatin were prepared by wet granulation technique using variable concentrations of different polymers like HPMC K4M, Eudragit S100, guargum, and Polyvinylpyrollidine-K-30. Wet granulation method is widely employed method for production of compressed tablets.

Table 1: Tablet composition of different formulations of FS matrix tablets containing HPMC K4M as controlled release polymer

Ingredins in (mg)	Formulation Code					
	F1	F2	F3	F4	F5	F6
Fluvastati	40	40	40	40	40	40
Eudragit	20	27.5	30	30	30	30
HPMC	40	40	40	52	6	68
PVP K30	15	15	15	15	15	15
Micro.	76	72.5	70	63	58	53
Lactose	51	47	47	42	39	36
Mg.stearate	6	6	6	6	6	6
talc	2	2	2	2	2	2

Table 2: Tablet composition of different formulations of FS matrix tablets containing HPMC E15 as controlled release polymer

Ingredients (mg)	Formulation Code			
	F7	F8	F9	F10
Fluvastatin	40	40	40	40
Eudragit S100	30	30	30	30
HPMC E15	40	52	60	68
PVP K30	15	15	15	15
Micro cellulose	70	63	58	53
Lactose	47	42	39	36
Mg stearate	6	6	6	6
talc	2	2	2	2

Table 3: Tablet composition of different formulations of FS matrix tablets containing Guar gum as controlled release polymer

Ingredients (mg)	Formulation Code		
	F11	F12	F13
Fluvastatin	40	40	40
Eudragit S100	20	30	30
Guar gum	40	52	60
PVP K30	15	15	15
Micro cellulose	76	63	58
Lactose	51	42	39
Mg stearate	6	6	6
talc	2	2	2

Pre Compressional Parameters[4,5]

Angle of Repose

While there is some variation in the qualitative description of powder flow using the angle of repose, much of the pharmaceutical literature appears to be consistent with the classification by Carr'sin the table below. There are examples in the literature of formulations with an angle of repose in the range of 40-50^0 that manufactured satisfactorily. When the angle of repose exceeds50^o, the flow is rarely acceptable for manufacturing purposes.

The angle of repose (θ) was calculated using the following formula.

tan θ = h/r or θ = tan -1 (h/r)

Bulk Density and Tapped Density

Bulk density is the ratio between a given mass of powder or granules and its bulk volume. Tapped density is the ratio between a given mass of powder or granules and the constant or fixed volume of the powder or granules after tapping. An accurately weighed quantity of powder (W) (which was previously passed through sieve no. 40) was carefully transferred into 250 ml measuring cylinder and initial volume (Vo) was measured. The cylinder is then allowed to tap on to a wooden surface from the height of 2.5 cm at 2-second intervals. The tapping was continued until no further change in volume (until a constant volume) was obtained (Vf). The bulk density and tapped density are calculated by using the following formula.

Bulk Density = W/ Vo

Tapped Density = W/ Vf

Compressibility Index

In recent years, the compressibility index and the closely related Hausner's ratio have become the simple, fast, and popular methods of predicting powder flow characteristics. The compressibility index has been proposed as an indirect measure of bulk density, size and shape, surface area, moisture content, and cohesiveness of materials, because all of these can influence the observed compressibility index. The compressibility index determined by measuring both the bulk volume and tapped volume of a powder.

Basic methods for the determination of compressibility Index

While there are some variations in the method of determining the compressibility index the basic procedure is to measure the unsettled apparent volume, (*V0*), and the final tapped volume, (*Vf*), of the powder after tapping the material until no further volume changes occur. The compressibility index and the Hausner's ratio are
calculated as follows:

$$\text{Compressibility Index} = \left(\frac{V_0 - V_f}{V_0}\right) x100$$

Drug-Excipient compatibility studie

In this FTIR (model – Perkin Elmer) instrument was used. FTIR spectra for the drug of optimized tablets were obtained. One part of Potassium Bromide was mixed with 100 parts of the optimized tablet powder and used for the FTIR spectrum. Pure drug was also mixed with 100 parts of Potassium Bromide and spectrum was obtained.

Both the spectra were compared for the possible deviations.

Post Compressional Evaluation

Hardness / Crushing Strength[6,7]

Hardness (diametric crushing strength) is a force required to break a tablet across the diameter. The hardness of a tablet is an indication of its strength. Oral tablets normally have a hardness of 4 to 6 kg/cm2. The tablet was placed horizontally in contact with the lower plunger of the Monsanto hardness tester and zero reading was adjusted. The tablet was then compressed by forcing the upper plunger until the tablets breaks.This force was noted

Friability test

Friability is the loss of weight of tablet in the container/package, due to removal of fine particles from the surface. This in-process quality control test is performed to ensure the ability of tablets to withstand the shocks during processing, handling, transportation, and shipment. It is usually measured by the use of the Roche friabilator.

The percent friability was determined using the following formula.

$$\text{Friability} = \left(\frac{W_1 - W_2}{W_1}\right) x100$$

Where,

W_1 = weight of ten tablets before test

W_2 = weight of ten tablets after test

Uniformity of weight or Weight variation test[8]

Twenty tablets of each formulation were selected at random and weighed individually. The weight of individual tablets was noted. Average weight was calculated from the total weight of all tablets. The individual weights were compared with the average weight. Not more than two of the tablets must differ from the average weight by not more than the percentages stated in table below. The percentage deviation was calculated by using the following formula:

$$\%\text{Deviation} = \frac{\text{Individual weight} - \text{Average weight}}{\text{Average weight}} x100$$

Estimation of drug content[9,10]

To ensure the consistency of dosage units, each unit in a batch should have active substance content within a narrow range around the label claim. Dosage units are defined as dosage forms containing a single dose or a part of a dose of an active substance in each dosage unit. Five tablets were taken and crushed in motor and powdered.10mg of blend was weighed and transferred in 10mlvoumetric flask .The blend was dissolved in Distilled water. The solution was filtered, suitable diluted and the drug content was analyzed by UV.

Each sample was analyzed in triplicate. Generally, the drug content in any formulation should fall within the limit of 92 – 102%.

Dissolution rate studies

***In vitro* drug release**

The release rate of FS from tablets was determined using The United States Pharmacopoeia (USP) XXIV dissolution testing apparatus II (paddle type). The dissolution test was performed using 900 ml of pH 1.2, for first 2 hours then in phosphate buffer pH 7.2 for rest of the hours at 37 0.5 C and 50 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus hourly for 12 hours, and the samples were replaced with fresh dissolution medium. The samples diluted to a suitable concentration with respected dissolution medium. Absorbance of these solutions was measured using a UV-Visible Spectrophotometer (UV-1800). Cumulative percentage of drug release was calculated.

Kinetics and Mechanism of drug release:

First order constant:

First order rate constant obtained by plotting log %Dissolved versus Time, the plot will be straight line and slope of the line (m) will be –K / 2.303.

The slope of the line and the corresponding value of k can be calculated which is indicative of the release rate profile.

$$\mathbf{In\ Q\text{-}InQo = Kt}$$

Where Q is the amount of drug release at time t. Qo is quantity of drug present initially in the dosage form, and K is the first order release constant.

Higuchi constant:

To investigate the mechanism of drug release the in vitro data were plotted as cumulative drug release versus square root of time as described by Higuchi, when the linearity was observed in the graph that indicates the diffusion controlled release.

$$\mathbf{Q = K_H t^{1/2}}$$

Where Q is amount of drug release at time t, K_H is Higuchi square root of time release rate constant.

Korsemeyer ─ Peppas constant:

To under stand the mechanism of drug release and to compare the differences among release profile of these matrix formulations, the percent drug release versus time profiles were fitted into the equation proposed by Peppas.

$$\mathbf{Mt / M\text{œ} = Kt^n}$$

Where Mt is drug release at time t, Mœ is the total amount of drug in the dosage form, Mt / Mœ is the fraction of drug release up to time t, K is the kinetic constant and n is the release exponent indicative of the release mechanism. Where n = 0.45 indicates Fickian diffusion, when between 0.45 - 0.89 indicates anomalous Non Fickian transport and 0.89 indicates Case- II transport, n=1 for zero-order release.

RESULTS AND DISCUSSIONS

Pre-compressional Parameters: A flow property plays an important role in pharmaceuticals especially in tablet formulation because improper flow may cause more weight variation. The Carr's Index (Compressibility) of the powders was in the range of 8.0 to 18.0. The angles of repose of the powders were in the range of 23^0 to 28^0, which indicate a good flow property of the powders. Here the angle of repose was found to be below40^o this shows that the reasonable flow property of powders. The results are given in the Table No.4,5 and 6.

Post Compressional Parameters (Shape,Hardness & Friability):

The punches used to compress the tablets were 9mm, spherical shaped. The shape and size of the tablets were found to be within the limit. The hardness of the tablets was found to be in the range of 5.24 $\pm$ 0.08 to 4.82 $\pm$ 0.03 Kg/cm^2. It was within the range of monograph specification.Thicknesses of the tablets were found to be in the range of 4.58 $\pm$ 0.035 to 4.06 $\pm$ 0.030 mm. The friability of the tablets was found to be less than 1% and it was within the range of standard specification. The results are given in the Table No.7, 8 and 9.

Weight Variation and Drug Content:

Weight variation test helps to check whether the tablet contain proper quantity of the drug. From each of the formulations ten tablets were randomly selected and weighed. The results are given in table 10 and 11. The average weights of the tablets were found to be within the prescribed official limits (IP). Drug content for each of the formulations were estimated. The drug content for all the batches were found to be in the range of 97.56 to 100.04%. The results are given in table 12.

***In-Vitro* Release Study:**

All the 13 formulation of prepared tablets of FS were subjected to *in vitro* release studies, these studies were carried out using dissolution medium, (pH 1.2 and Phosphate buffer pH 7.2). by using USP-2 (paddle type) dissolution apparatus. The results were evaluated for 12 hours. As per the results of dissolution study formulations F-1, F-2, F-3, F-4, F-5, F-6, F-7, F-8, F-9, F-10, F-11, F-12, and F-13, showed 86.66%, 75%, 72.04%, 91%, 97.23%, 79.88%, 68.03%, 66.13%,70.87%, 75% , 85.11%, 83.57%, 79.03%, release respectively over a period of 12 hours. Formulations except F-4, and F-5, all the formulations failed to sustain release beyond 10 hours. . Among all the formulation, F-4, and F-5, showed 91%, and 97.23%, release respectively at the end of 12 hours. The formulation F5 its release at the end of 12^{th} hr is 97.23% also all other parameters like hardness, thickness, friability, and drug content and weight variation for this formulations were within the range. So, a formulation F-5 was selected as the optimized

formulation results were shown in tables13&14 and figures 7&8..

Release Kinetics: Different models like Zero order, First order, Higuchi's, and Korsmeyer-peppas plots were drawn. The regression coefficient (R^2) value for Zero order, First order, Higuchi's, and Korsmeyer-peppas plots (figure 7.9a-7.9d and table 7.9a-7.9b) for formulation F-4 were found to be 0.978, 0.683, 0.862, 0.976, 0.981(n value) for formulation F-5 were found to be 0.948, 0.598, 0.833, 0.959, 0.986(n value) . The optimized formulations F-5 follow Zero order and Korsmeyer-peppas. The regression coefficient (R^2) of Higuchi plot of optimized formula F-5 is 0.833 that shows the drug releases through the matrix was diffusion and slope (n) value of peppas plot is 0.986 this confirms that non-Fickian diffusion (anomalous transport) was the main mechanism. The regression coefficient (R^2) value of zero order is 0.948 in. Thus, the drug release follows zero order release kinetics results were shown in table 15.

FT IR Spectroscopy:
Drug polymer interaction was checked by comparing the IR spectra of the formulations with the IR spectra of the pure drug. There was no significant change in the functional groups between the IR spectrums of the pure drug and also no additional peaks were seen in the selected formulations (figures 1-6). This confirms that no interaction between drug and excipients.

Stability Study:
Stability studies were carried out on selected formulations (F-5) as per ICH guidelines. There was not much variation in matrix integrity of the tablets at all the temperature conditions. There was no significant changes in drug content , physical stability, hardness, friability and drug release (tables 1 6 & 1 7) for the selected formulation F-5 after 90 days at $25^{o}C\pm 2^{0}C$ / 60% ± 5% RH, $30^{0}C \pm 2^{0}C$ / 65% ±5% RH and $40^{0}C \pm 2^{0}$ / 75% ± 5% RH.

CONCLUSION:
In this study matrix tablet of Fluvastatin were prepared by wet granulation technique, using HPMC K-4M, HPMC E-15 and guar gum polymers as retardant. The formulations F-4, and F-5 showed good drug release with good matrix integrity but the formulation F-4 showed the release up to 11hr (i.e.97.74% release at the end of11hr) while the formulation F-5 showed the release of 97.23% at the end of 12hr so the formulation F-5 selected as the optimized formula . The enteric coated polymer Eudragit S100 was used to avoid the drug release in stomach because the drug is quiet unstable in stomach and the aim of the work is to release the drug in intestine. The formulation F-5 showed good drug release with good matrix integrity. Different parameters like hardness, friability, weight variation, drug content uniformity, *in-vitro* drug release were evaluated. Based on these results formulation F-5was found to be the most promising formulations. The regression coefficient (R^2) of Higuchi plot of optimized formula F-5 shows that the drug releases through the matrix was diffusion and slope (n) value of peppas plot confirms that non-Fickian diffusion (anomalous transport) was the main mechanism. The regression coefficient (R^2) values of zero order of the optimized formulation F-5 was greater than the R^2 values of first order. Thus, the drug release follows zero order release kinetics.

Stability studies were conducted for the optimized formulations as per ICH guidelines for a period of 90 days which revealed the stability of the formulations. The results suggest that the developed controlled-release matrix tablets of F S could perform better than conventional dosage forms, leading to improve efficacy and better patient compliance. Thus the aim of this study was achieved. Further preclinical and clinical studies are required to evaluate the efficacy of these formulations of FS in the management of Hyperlipidemia.

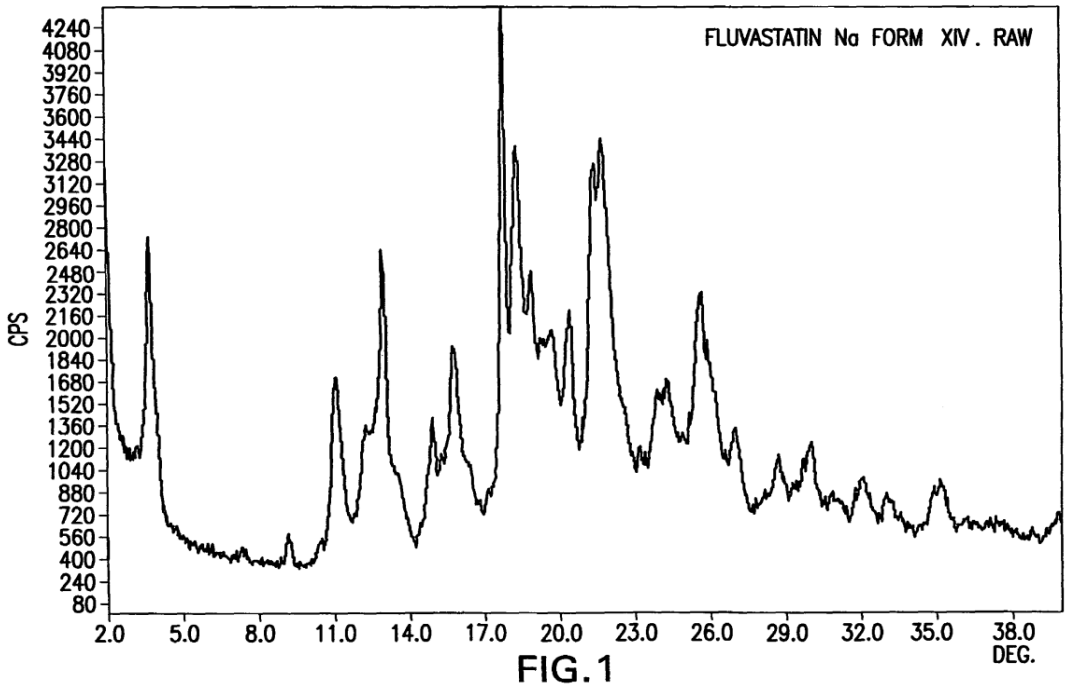

Fig 1: FTIR spectrum of pure FS Table no.

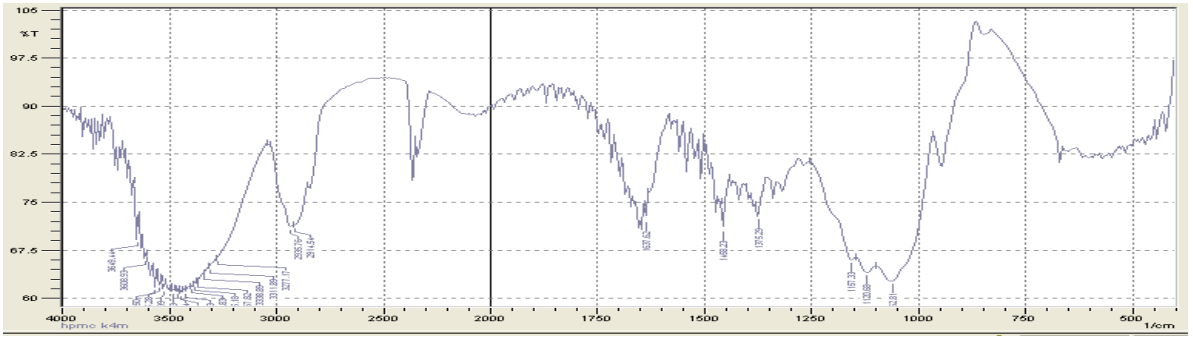

Fig 2: FTIR spectrum of pure HPMC K4M

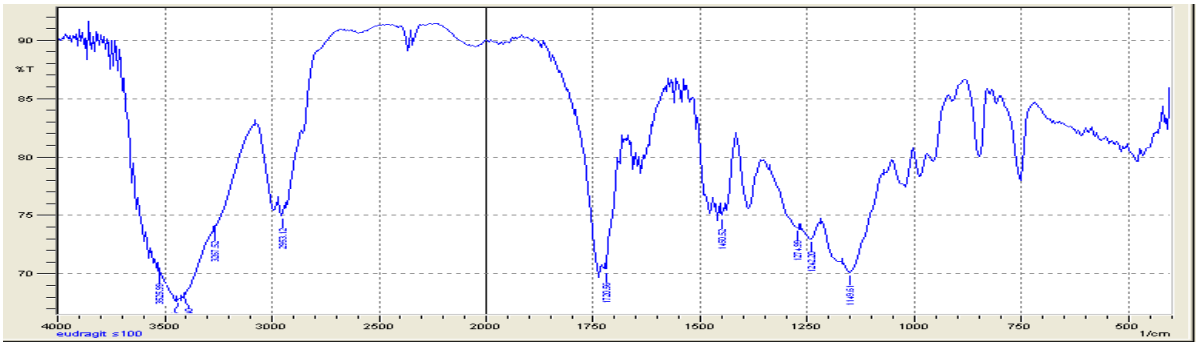

Fig 3: FTIR spectrum of pure Eudragit S100

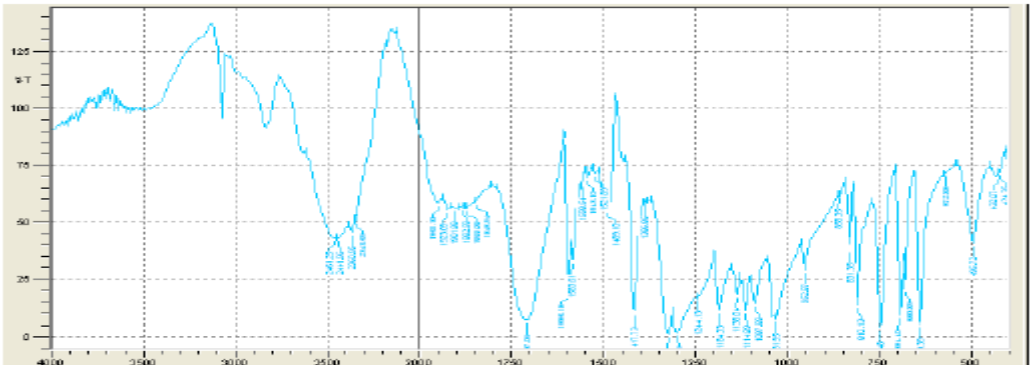

Fig 4: Spectrum of mixture of Eudragit S100 and FS

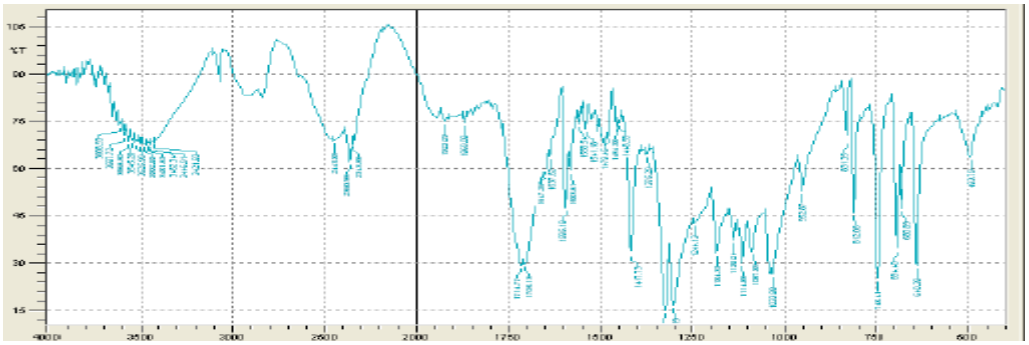

Fig 5: Spectrum of mixture of Eudragit S100, FS and HPMC K4M

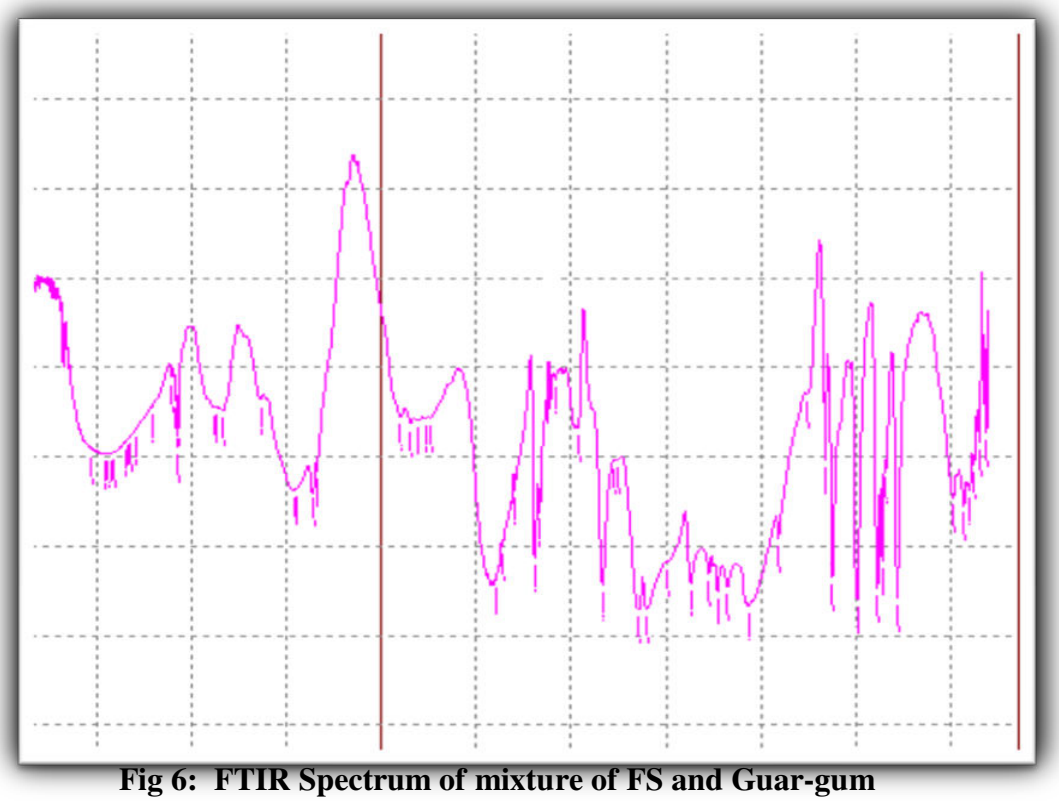

Fig 6: FTIR Spectrum of mixture of FS and Guar-gum

Table 4: Data for blend evaluation of formulation (F-1 to F-6)

Parameters	Formulation Code					
	F1	F2	F3	F4	F5	F6
Angle of repose	24.22 ± 1.25	25.15 ± 1.31	27.22 ± 1.59	28.39 ± 1.52	29.74 ± 1.67	28.56 ± 0.492
Loose bulk density(LBD) (g/ml)	0.238 ±0.008	0.242 ±0.009	0.028 ±0.009	0.236± 0.007	0.237 ± 0.006	0.2150 ± 0.005
Tapped bulk density (TBD) (g/ml)	0.263± 0.010	0.277 ±0.018	0.259 ± 0.014	0.267± 0.012	0.265 ± 0.011	0.2484 ± 0.018
Compressibility index (%)	9.54 ± 0.71	12.63± 1.78	11.71 ± 1.56	11.20 ± 1.23	10.56 ± 0.78	13.46 ± 0.45
Hausner's ratio	1.21±0.01	1.19±0.01	1.23±0.02	1.22±0.01	1.17±0.02	1.18±0.01

Table 5: Data for blend evaluation of formulation (F-7 to F-10)

Parameters	Formulation Code			
	F7	F8	F9	F10
Angle of repose	25.20 ±0.261	24.44 ±0.380	27.76 ±0.311	26.42 ±0.144
Loose bulk density(LBD) (g/ml)	0.36±0.02	0.35±0.02	0.39±0.00	0.34±0.01
Tapped bulk density (TBD) (g/ml)	0.43±0.02	0.40±0.04	0.49±0.01	0.41±0.01
Compressibility index (%)	17.04 ± 0.78	14.00 ± 0.70	14.29 ± 1.24	16.83 ± 0.64
Hausner's ratio	1.23±0.01	1.22±0.01	1.18±0.01	1.21±0.01

Table 6: Data for blend evaluation of formulation (F-11 to F-13)

Parameters	Formulation Code		
	F11	F12	F13
Angle of repose	25.46 ± 1.58	24.69 ± 1.54	27.14 ± 1.35
Loose bulk density(LBD) (g/ml)	0.3464 ± 0.03	0.3702 ± 0.05	0.3655 ± 0.01
Tapped bulk density (TBD) (g/ml)	0.4276 ± 0.007	0.4081 ± 0.005	0.4396 ± 0.004
Compressibility index %	15.11 ± 0.16	13.63 ± 0.20	16.85 ± 0.44
Hausner's ratio	1.21±0.01	1.22±0.00	1.23±0.01

Table 7: Physical properties of tablet formulation (F-1 to F-6)

Parameters	Formulation code					
	F1	F2	F3	F4	F5	F6
Thickness (mm)	4.0 ± 0.011	4.05 ±0.012	4.08 ± 0.008	4.12 ± 0.013	4.21 ± 0.019	4.31±0.016
Hardness (kg/cm^2)	5.24 ± 0.10	4.6 ± 0.52	4.1 ± 0.12	4.5 ± 0.00	4.8 ± 0.35	4.6±0.10
Friability (%)	0.062 ± 0.029	0.081± 0	0.02±0.028	0.076±0.054	0.055 ±0.026	0.089±0.025

The values represent mean ± S.D; n=5.

Table 8: Physical properties of tablet formulation (F-7 to F-10):

Parameters	Formulation code			
	F7	F8	F9	F10
Thickness (mm)	4.06±0.013	4.12± 0.018	4.40 ± 0.016	4.64 ± 0.013
Hardness (kg/cm^2)	4.6 ± 0.02	4.9 ± 0.10	4 ± 0.00	4.5 ± 0.12
Fraibility (%)	0.02±0.028	0.056±0.026	0.107±0	0.034±0.0014

The values represent mean ± S.D; n=5.

Table 9: Physical properties of tablet formulation (F-11 to F-13):

Parameters	Formulation code		
	F11	F12	F13
Thickness (mm)	4.0 ± 0.019	4.08 ± 0.013	4.14 ± 0.025
Hardness (kg/cm^2)	4.8 ± 0.15	4.0 ± 0.20	4.2 ± 0.30
Friability (%)	0.105±0.029	0.059±0.028	0.092±0.024

The values represent mean ± S.D; n=5.

Table 10: Weight variation for tablet formulations (F-1 to F-6):

Sr. No	F-1	F-2	F-3	F-4	F-5	F-6
1	205	214	231	267	200	233
2	203	213	235	263	200	234
3	203	215	230	264	203	234
4	205	215	230	265	202	235
5	201	216	233	264	298	236
6	200	217	231	265	201	235
7	200	215	232	266	203	237
8	298	217	234	265	204	233
9	203	216	230	267	202	236
10	204	215	231	266	200	235
Average Weight	202.2	215.3	231.7	865.2	901.3	234.8
Standard deviation	2.347576	1.251666	1.766981	1.316561	1.828782	1.316561

Table 11: Weight variation for tablet formulations (F-7 to F-13):

Sr. No	F-7	F-8	F-9	F-10	F-11	F-12	F-13
1	232	282	230	281	290	240	283
2	230	280	230	280	298	238	285
3	228	281	228	279	293	240	285
4	230	278	231	278	291	262	284
5	231	281	233	280	289	239	287
6	229	279	299	283	291	243	286
7	233	280	230	293	294	241	286
8	230	282	234	284	292	241	283
9	229	283	233	281	290	243	285
10	232	281	228	288	290	241	287
Average Weight	230.4	280.7	230.6	280.7	290.8	240.8	285.1
Standard deviation	1.57762	1.494434	2.1187	2.110819	1.813529	1.619328	1.449138

Table 12: Drug content uniformity of formulations F1-F13:

Tablet formulation	Calculated value (mg)	Estimated value (mg)	% 0f drug content
F1	250	237.8	97.56
F2	250	242.6	98.52
F3	250	242.2	98.45
F4	250	245.5	99.11
F5	250	249.45	99.89
F6	250	250.2	100.04
F7	250	248.25	99.65
F8	250	244.3	98.86
F9	250	246.05	99.21
F10	250	245.55	99.11
F11	250	243	98.60
F12	250	244.5	98.91
F13	250	240.5	98.11

Table 13: Percentage drug release of formulations F1-F6

Sr. No.	Time (hrs)	FORMULATION CODE					
		F1	F2	F3	F4	F5	F6
In acidic buffer pH 1.2							
1	0	0.0	0.0	0.0	0.0	0.0	0.0
2	1	11.1	9.02	7.11	7.89		7.49
3	2	17.37	14.11	9.8	10.65	9.89	10.1
In phosphate buffer pH 7.2							
4	3	23.75	21.47	20.86	21.33	23.56	17.11
5	4	28.58	30.03	25.11	24.89	28.31	22.13
6	5	38.73	36.33	31.03	31.63	31.88	28.34
7	6	50.01	41.09	38.15	40.14	35.04	34.78
8	7	60.23	56.32	47.01	49.23	40.05	40.94
9	8	73.5	69.95	60.08	61.73	46.89	46.15
10	9	85.95	80.05	71.12	72.01	52.05	52.47
11	10	97.3	94.3	88.03	82.12	65.03	57.23
12	11	94.11	86.13	81	97.74	77	66.05
13	12	86.66	75	72.04	91	97.23	79.88

Table 14: Percentage drug release of formulations F7-F13

S.No.	Time (hrs)	FORMULATION CODE						
		F7	F8	F9	F10	F11	F12	F13
In acidic buffer pH 1.2								
1	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2	1	7.56	8.77	8.63	7.93	9.8	8.54	7.71
3	2	10.87	11.19	10.6	9.97	14.23	10.2	9.89
In phosphate buffer pH 7.2								
4	3	31.88	30.87	25.83	28.81	21.55	19.02	16.78
5	4	44.21	37.29	31.74	35.33	27.52	25.66	18.33
6	5	54.9	52.97	44.44	41.78	33.63	29.57	25.67
7	6	76.47	77.24	55	51.4	42.12	35.87	29.91
8	7	99.4	93.34	79.5	63.17	54.27	41.31	35.84
9	8	95.4	85.11	97.3	78.18	69.5	52.11	42.33
10	9	77.89	83.02	94.03	97.73	82.92	57.89	49.24
11	10	80.03	79.18	86.17	91.11	87.11	67.04	65.41
12	11	73.18	75	78.43	84.89	86.76	75	71.02
13	12	68.03	66.13	70.87	75	85.11	83.57	79.03

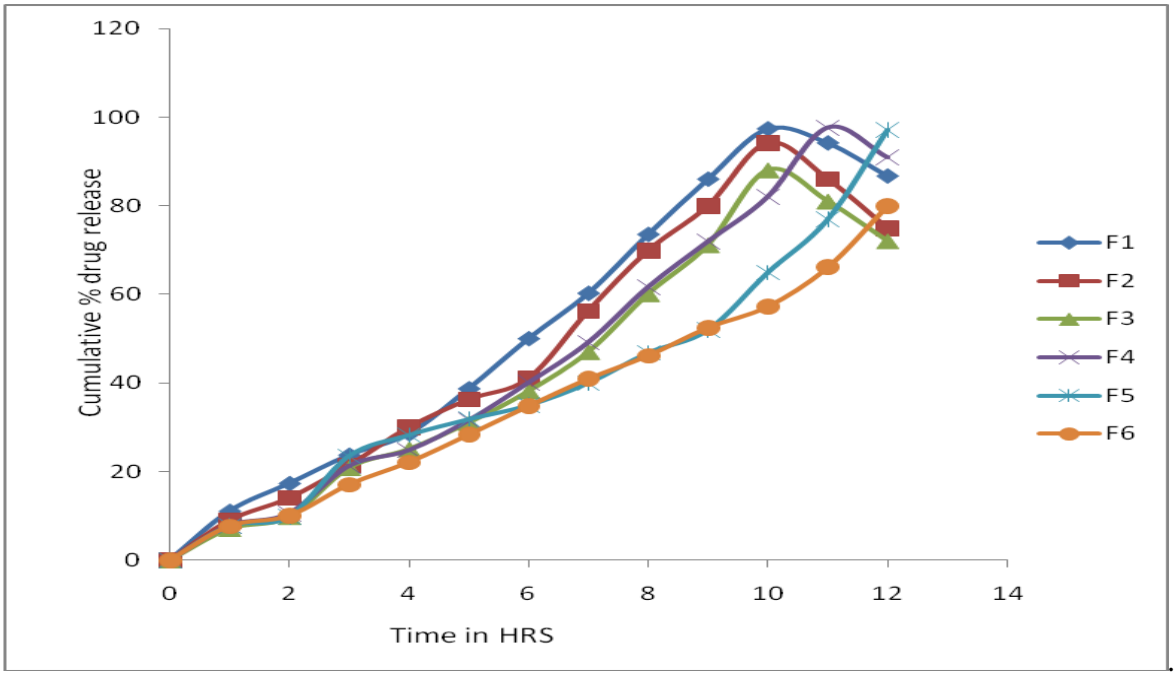

Figure 7: In-vitro dissolution profile of F1 to F6 formulations.

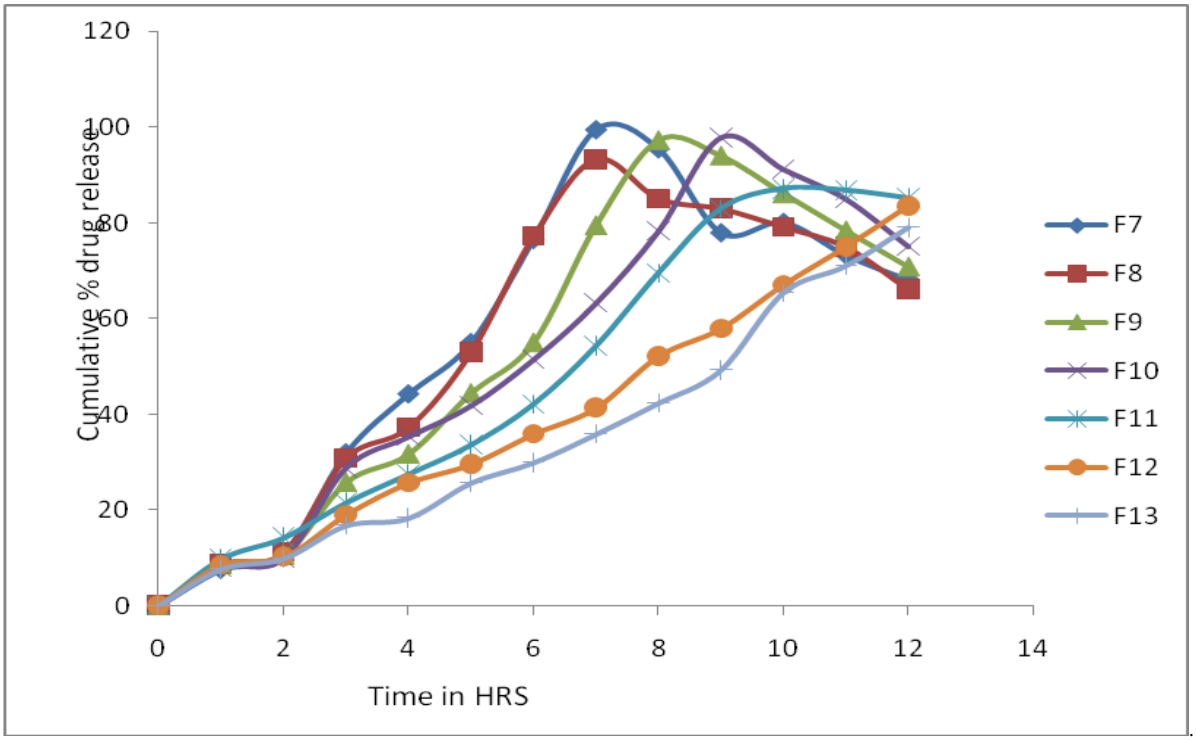

Figure 8: In-vitro dissolution profile of F-7 to F-13 formulations.

Table 15: Correlation coefficients of different mathematical models for formulations F-1 to F-13

Formulations	Zero order R^2	First order R^2	Higuchi's R^2	Korsmeyer-peppas	
				R^2	n value
F1	0.959	0.582	0.888	0.972	0.949
F2	0.932	0.714	0.869	0.972	0.995
F3	0.944	0.798	0.860	0.971	0.967
F4	0.978	0.683	0.862	0.976	0.981
F5	0.948	0.598	0.833	0.959	0.986
F6	0.988	0.890	0.886	0.983	0.978
F7	0.681	0.287	0.760	0.861	0.963
F8	0.720	0.491	0.789	0.871	0.993
F9	0.807	0.469	0.813	0.917	0.951
F10	0.892	0.543	0.867	0.941	0.974
F11	0.966	0.899	0.882	0.972	0.987
F12	0.991	0.896	0.884	0.973	0.979
F13	0.969	0.869	0.839	0.959	0.985

Table 16: Physical appearance of optimized formulation after stability studies:

Temp. and relative humidity	Days				Parameters
	0	30	60	90	
$25^0C \pm 2^0C$ / 60% ± 5% RH	No change				Physical appearance
$30^0C \pm 2^0C$ / 65% ± 5% RH					
$40^0C \pm 2^0C$ / 75% ± 5% RH					

Table 17: physical parameters of optimized formulation after stability studies:

No.of days	Physical parameters								
	Hardness (Kg/cm^2)			Friability (%)			Drug content (%)		
	25±2°C 60±5% RH	30±2°C 65±5% RH	40±2°C 75±5% RH	25±2°C 60±5% RH	30±2°C 65±5% RH	40±2°C 75±5% RH	25±2°C 60±5% RH	30±2°C 65±5% RH	40±2°C 75±5% RH
Initial	5.24± 0.08	4.94± 0.04	4.86 ± 0.32	0.11	0.14	0.11	99.30	9 9	99.30
30	4.54 ± 0.35	4.86 ± 0.25	4.8 ± 0.3	0.07	0.11	0.074	99.30	98.88	99.45
60	4.62 ± 0.31	4.86 ± 0.28	4.94 ± 0.35	0.14	0.11	0.037	99.11	99.05	99.08
90	4.86 ± 0.38	4.9± 03	4.82 ± 0.03	0.074	0.074	0.037	99.18	98.91	99.21

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