Original Research Article

GASTRORETENTIVE SYSTEM OF FLUVASTATIN SODIUM BY USING NATURAL MUCILAGE AND SYNTHETIC POLYMER

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ABSTRACT

Fluvastatin sodium is a novel compound used as cholesterol lowering agent which acts through the inhibition of 3- hydroxyl-3- methyl glutaryl- coenzyme A (HMG-Co A) reductase. It has short biological half life (1-3h) in humans required a dosing frequency of 20 to 40mg twice a day. Due to its short variable biological half life it has been developed to a sustained gastroretentive system with a natural and synthetic polymer and to study how far the natural mucilage improves the sustained activity. Floating tablets were prepared by direct compression method using in combination of natural mucilage and synthetic polymer. Prior to the preparation of tablets the physical mixtures were subjected to FT IR studies and pre compression parameters. After preparation of tablets they were subjected to various tests like swollen index, drug content, *In vitro* dissolution and release kinetics with pcp disso software etc. The tablets prepared by direct compression shown good in thickness, hardness and uniformity in drug content, the prepared tablets floated more than 12h except FS1 and FS2 shows 9 and 11h. Swollen index studies shows with increase in concentration of polymer the swelling increases the diffusion path length by which the drug molecule may have to travel and cause lag time. In vitro results shows that on increasing the amount of hibiscus polymer the sustain activity is increased because of its integrity and forms a thick swollen mass and reduces the erosion property of the HypromelloseK100M, kinetic studies shows that FS 1, FS2, FS3 followed the Korsmeyer peppas model and the rest FS 4, FS 5, FS6 follows the zero order respectively. Based on n value indicating that the drug release followed super case II transport mechanism due to the erosion of the polymer.

***Keywords*:** Natural Mucilage, Synthetic polymer, Release kinetics & HypromelloseK100M.

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INTRODUCTION

The goal of any drug delivery system is to provide a therapeutic amount of the drug at the target site in the body. It aims to achieve and maintain the desired drug concentration. During the last three decade many studies have been performed concerning the sustained release dosage form of drugs, which have aimed at the prolongation of gastric emptying time (GET) The GET has been reported to be from 2 to 6 hours in humans in the fed state.[1] 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. Fluvastatin has an

half life of 1- 3h.[2] The beauty of buoyancy offers to achieve increased residence time in the stomach. The present work is an effort to improve the sustained activity, therapeutic efficacy and to study the prepared tablets in combination of the natural mucilage with synthetic polymer.[3]

MATERIALS AND METHODS

Fluvastatin sodium was purchased from Alibaba chemicals Hypromellose K100M purchased from S.D. fine chemicals Ltd., Mumbai, Hibisicus Mucilage was prepared in own laboratory other chemicals used in the study were procured from local market as AR grade and used as without further purification.

Preparation of dry Hibiscus mucilage

The matured leaves from *hibiscus* species were collected, washed, dried using tray dryer at 37^0 C for 24 h, later the dried leaves crushed and soaked in water and heated up to 80-90^0 C for 30-45 min for complete release of the water soluble mucilage/polysaccharide into the solvents. The mucilage/polysaccharide was then extracted by using multi layer muslin/cheese cloth bag to remove the mare and concentrated viscous solution under reduced pressure at 60-70^0 C. Acetone was added to the concentrated viscous solution with constant stirring. The gel like precipitate was formed and separated by filtration. The precipitate was washed 2-3 times with acetone after complete washing of the precipitate with acetone, creamy with powder was obtained. The powder was dried in an oven at 37^0 C, collected, grounded, passed through a sieve no # 80 and stored in a desiccators till use.[4, 5]

Drug-excipients interaction study

a) FT IR studies

Infrared spectrophotometry is an analytical technique utilized to check the chemical interaction between the drug and other excipients used in the formulation. One milligram of the sample was powdered and intimately mixed with 10mg of dry powdered potassium bromide. The powdered mixture was taken in a diffuse reflectance sampler and the spectrum was recorded by scanning in the wavelength region of 4000-400cm^{-1} in an FTIR spectrophotometer (Jasco 460 plus, Japan). The IR spectrum of the drug was compared with that of the physical mixture to check for any possible drug-excipients interaction. The graphs were shown in Fig no: 7

Precompression parameters

The following tests were performed for polymers as well as for drug substance. The values were shown in table no: 2

a) Bulk density

The powder sample under test was screened through sieve #18 and the sample equivalent to 10g was accurately weighed and filled in a 50ml graduated cylinder and the powder was leveled and the unsettled volume (V_0) was noted. The bulk density was calculated in g/cm^3 by the formula,

Bulk density (ρ_0) = $\frac{M}{V_0}$ Where, M = mass of powder taken, V_0= apparent unstirred volume.[6]

b) Tapped density

The powder sample under test was screened through sieve #18 and the weight of sample equivalent to 10g was filled in 50ml graduated cylinder. The mechanical tapping of the cylinder

was carried out using tapped density tester at a constant rate for 100 times Volume was considered as tapped volume (V_f). The tapped density was calculated in g/cm^3 by the formula,

$$Tapped\ density\ (\rho_t) = \frac{M}{V_f}$$ Where, M = weight of sample powder taken, V_f = tapped volume.

c) Percentage compressibility or Carr's index

Based on the poured density and tapped density, the percentage compressibility of the granules was computed using the Carr's compressibility index by the formula,

$$Carr's\ index\ (\%) = \frac{tapped\ \ density\ -\ poured\ \ density}{tapped\ \ density}\ x\ 100$$

d) Hausner's ratio

Hausner's ratio was calculated using the formula,

$$Hausner's\ ratio = \frac{tapped\ \ density}{poured\ \ density}$$

e) Angle of repose

)Angle of repose of the granules was determined by the height cone method. A funnel was fixed to a desired height and granules were filled in it. They were allowed to flow down on a graph paper fixed on a horizontal surface and angle of repose was calculated using the formula.

$$Tan\ \theta = \frac{2h}{D}$$ Where, *h* and D are height and diameter of the pile respectively.

f) Formulation of floating tablets

Fluvastatin sodium tablets were prepared by direct compression method. Fluvastatin sodium, different proportions of polymers such as Hypromellose K100M, Hibiscus mucilage, Sodium bicarbonate, citric acid and micro crystalline cellulose was mixed well to obtain mass and the mass was passed through sieve no. 60. Other manufacturing excipients such as talc and magnesium sterate were added. The well mixed powder was compressed under 8 mm Rimek tableting machine, Mini press - I 10 station. The compositions of formulations were shown in table no: 1

Table no 1: COMPOSITION OF THE FORMULATIONS

Ingredients (mg)	FS1	FS2	FS3	FS4	FS5	FS6
Fluvastatin Sodium	80	80	80	80	80	80
HypromelloseK100M	20	25	30	30	20	20
Hibiscus Mucilage	20	20	20	30	30	25
Sodium Bicarbonate	50	50	50	50	50	50
Citric Acid	10	10	10	10	10	10
Micro crystalline cellulose	70	65	60	50	60	65

All weights are in mg, 1% of talc and magnesium sterate was added before punching.

Total Weight of prepared tablets was 250 mg.

1. Post compression parameters

All the prepared matrix tablets were evaluated for the following official parameters, results were shown in table no: 3

a) Hardness

The hardness of ten tablets was measured using Monsanto hardness tester. The mean and standard deviation were computed and reported. It is expressed in kg/cm^2.

b) Friability

c) The friability of the tablets was determined using Electrolab Friabilator. It is expressed in percentage (%). Ten tablets were initially weighed and transferred into the Friabilator. The Friabilator was operated at 25rpm for 4min. After 4min the tablets were weighed again. The friability was then calculated using the formula,

$$Friability\ (\%) = \frac{initial\ weight - final\ weight}{initial\ weight} x\,100$$

d) Weight variation test

Ten tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 10 tablets was calculated. The batch passes the test for weight variation test if not more than two of the individual tablet weights deviate from the average weight by more than the percentage shown in table 9 and none deviate by more than twice the percentage shown.

e) Drug content

Ten tablets were weighed and average weight was calculated. All the 10 tablets were crushed in mortar. The powder equivalent to 50mg of Fluvastatin Sodium was dissolved in 250ml of 0.1N HCl and shaken for 20min. Solution was filtered and 5ml of the filtrate was diluted to 100ml using 0.1N HCl. Absorbance of resultant solution was measured at 304.5nm using 0.1N HCl as a blank. The amount of drug present in one tablet was calculated.

f) Swelling index

The swelling of floating tablet were determined by swelling the tablets in 0.1 N HCL (pH 1.2) at the room temperature. Swollen weight of the tablet determined then swelling index was calculated by the following equation. Results were shown in table no: 4 & Fig no: 1, 2.

$$Swelling\ index = \frac{initial\ weight - final\ weight}{initial\ weight} x\,100$$

g) *In vitro* floating study

The time taken by the tablet to emerge onto the surface of the medium after adding to the dissolution medium is called Buoyancy lag time (BLT). Duration of time by which the dosage form constantly emerges on surface of medium called Total floating time (TFT) Both BLT & TFT were determined by placing the tablet in 900ml of simulated gastric fluid without pepsin, at pH 1.2, temperature 37±0.5ºC, paddle rotation at 50rpm using stopwatch.

h) *In vitro* dissolution study

Dissolution of the tablets of each batch was carried out using USP type-II apparatus using paddle. The dissolution medium consisted of 900ml of 0.1N HCL (pH 1.2) for 24h, maintained at 37 $\pm$ 0.5°C. One tablet was placed in each dissolution vessel and the paddle rotation speed was set at 75rpm. 5ml of the sample was withdrawn every half hour for 3h and for every 1h for 5h the same volume of the fresh medium was replaced every time. The samples were analyzed for drug content at a wavelength of 304.5 nm using double beam UV-Visible spectrophotometer. The content of the drug was calculated using the equation generated from the standard curve the percentage cumulative drug released was calculated. Results were shown in table no: 5

i) Stability studies

A study of stability of pharmaceutical product is essential. These studies were designed to increase the rate of chemical or physical degradation of the drug substance or product by using exaggerated storage conditions. Stability studies are important to prevent economic repercussions may lead to considerable financial loss. From the point of view of safety to patient it is important that the patient receives a uniform dose of the drug throughout the shelf life of the product. The formulation stored at elevated temperatures such as 30^0C /± / 2^0C / 65% /±/ 5% RH for 3 months. The samples were withdrawn at end of 3 months checked for BLT, drug content.

j) Kinetic studies

To analyze the mechanism of drug release from the matrix tablets, the data obtained from the drug release studies was analyzed according to the following equations, In all mathematical equations, Q is the amount of drug released at time t, M_t is the drug released at time t, M is the total amount of drug in the dosage form, F is the fraction of the drug released at time t, K_0 is the zero order release rate constant, K_H is the Higuchi square root of time release rate constant, K_m is constant which depends on the geometry of the dosage form and n is the diffusion exponent indicating the mechanism of drug release. The value n = 0.45 indicates Fickian diffusion, the value of n between 0.45 and 0.89 indicates anomalous transport and the value n = 0.89 indicates case-II transport. Results were shown in table no: 6 & 7

11 Zero order model [7]

$$[Q = K_0 t]$$

12 Higuchi model [8]

$$[Q = K_H t^{½}]$$

13 Korsmeyer-Peppa's model [9,10]

$$F = (M_t/M) = K_m t^n$$

RESULTS & DISCUSSION

FT IR studies of pure drug C-F shows stretching at 1045.73 cm^{-1} O-H stretching at 3645.72 cm^{-1} C-O stretching at 1215.76 cm^{-1} and CH_3 deformation at 1444.64 cm^{-1}.On combination with HypromelloseK100M C-F stretching at 1045.31 cm^{-1} O-H stretching at 3649.30 cm^{-1} C-O stretching at 1215.88 cm^{-1} and CH_3 deformation at 1440.95. Pure drug + hibiscus mucilage shows C-F, O-H and C-O stretching at 1045.31, 3643.66, 1217.56 and CH_3 deformation at

1436.57 hence the above results indicate that there is no significant chemical interaction between the drug and polymer. All Precompression parameters & post compression parameters are within limits and the results shows in the table no: 2 & 3

The *in vitro* drug release characteristics were studied in simulated gastric fluid for a 8h using USP XXIII dissolution apparatus, type-II. The gas generating agent come in contact with the acidic medium and evolving the carbon dioxide gas, that is permeated through the matrix and the presence of $NaHCO_3$ also acted as pH regulators in the formulation, increased pH values around the drug.

Table: 2. Preformulation studies

Formulation code	Bulk density (g/cm^3)*	Tapped density (g/cm^3) *	Carr's index (%)*	Hausner's Ratio	Angle of repose(θ)*
FS1	0.287±0.024	0.362±0.026	16.08±0.034	1.22	26.19±0.014
FS2	0.362±0.016	0.434±0.022	15.06±0.028	1.16	23.24±0.017
FS3	0.294±0.018	0.354±0.024	14.54±0.021	1.21	22.15±0.013
FS4	0.285±0.026	0.342±0.032	17.47±0.021	1.22	21.65±0.019
FS5	0.276±0.032	0.336±0.034	16.58±0.038	1.23	19.47±0.016
FS6	0.273±0.022	0.332±0.024	17.44±0.024	1.23	24.85±0.026

*The values represent mean ± SD, n = 3.

Table: 3. Post compression studies

Formulation code	Thickness (mm)*	Hardness Kg/cm^2*	Friability (%)*	Weight Variation*	Drug Content	Buoyancy lag time	Total floating time(h)
FS1	4.58±0.035	5.24±0.08	0.44±0.06	0.514±0.007	98.71	49 sec	9
FS2	4.65±0.035	4.94±0.04	0.52±0.03	0.504±0.003	97.78	57 sec	11
FS3	4.65±0.208	4.62±0.09	0.48±0.08	0.516±0.004	96.86	37 sec	>12
FS4	4.31±0.026	4.54±0.03	0.52±0.05	0.509±0.005	99.17	1:17min	>12
FS5	4.26±0.020	4.86±0.08	0.56±0.09	0.517±0.006	98.71	59 sec	>12
FS6	4.06±0.030	4.82±0.03	0.59±0.04	0.505±0.005	96.38	47 sec	>12

*The values represent mean ± SD, n = 3.

Table no: 4. swelling index report

Hrs	FS1	FS2	FS3	FS4	FS5	FS6
1	34.4	110.8	35.6	124.8	104	106.0
2	68.4	140.5	40.8	173.2	141.6	115.6
3	100.4	186.7	47.6	178.4	166	147.7
4	116.8	200.4	No change	213.2	196.4	163.0
5	148.4	202	No change	224.4	256.8	172.2
6	152.8	206	No change	228	268.8	209.2
7	No change	No change	No change	No change	316	No change
8	No change	No change	No change	No change	No change	No change

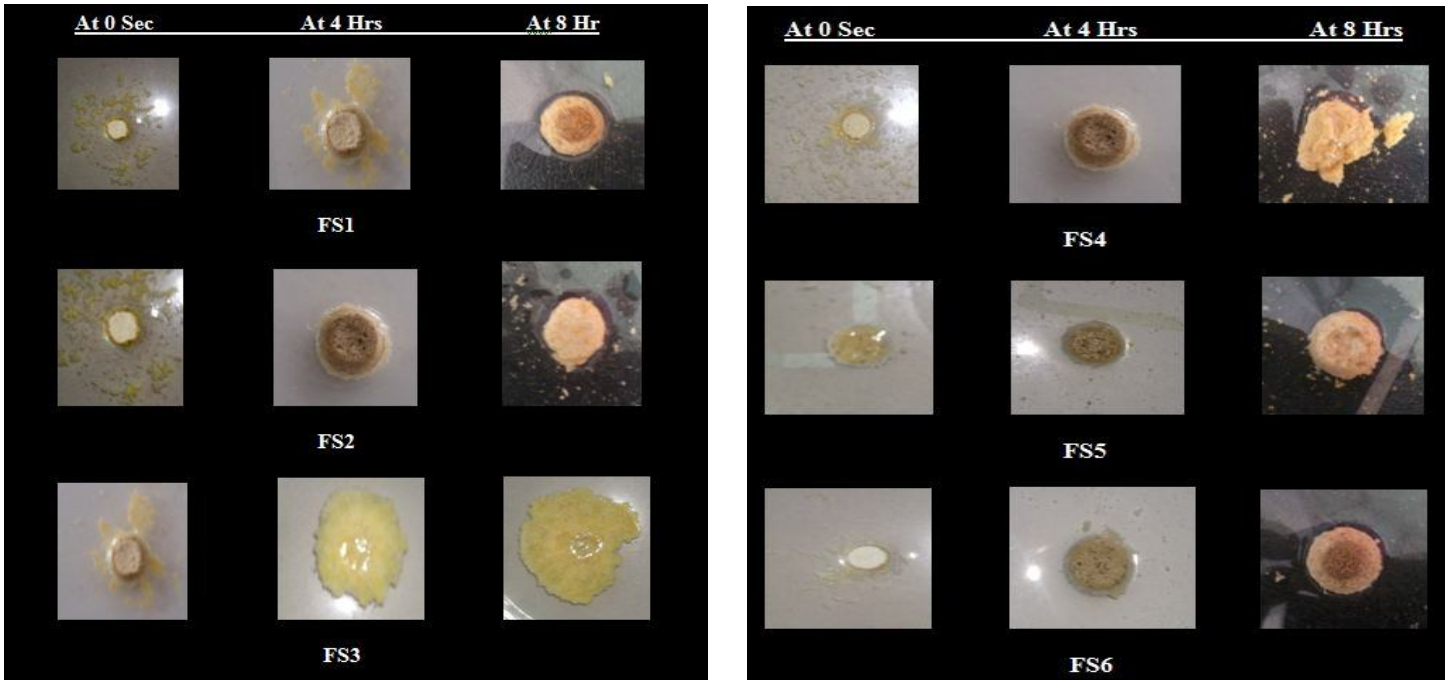


Fig: 1. Tablets showing swelling

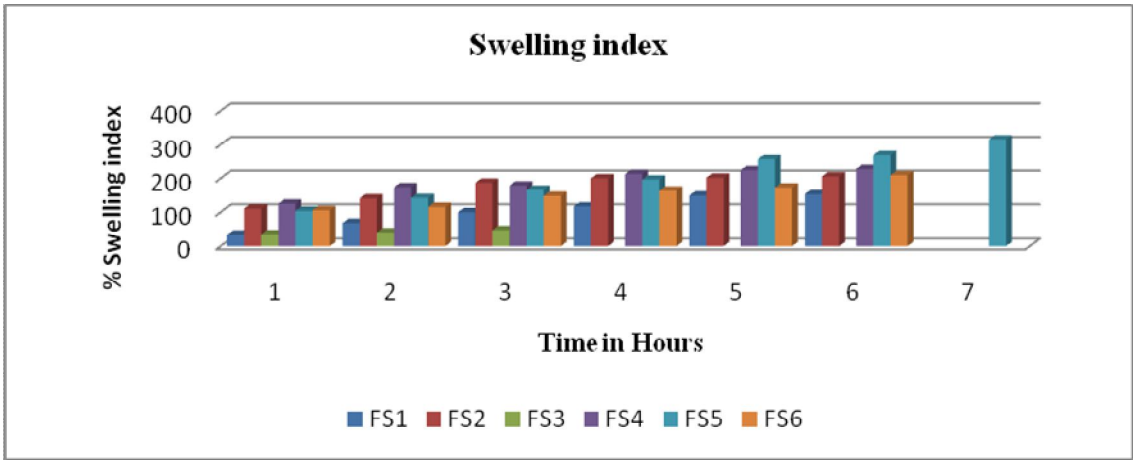


Fig: 2. Swelling Index Report (FS1-FS6)

HPMCK100M was used along with the hibiscus mucilage in preparation of the matrix tablet. The drug release of tablet results that the increase the concentration HPMCK100M increases due to erosion property. On increase of the natural polymer hibiscus mucilage results the drug release decreases due its formation of the thick micro gel formation. Hibiscus mucilage on contact with water forms viscous and tends to bind the mixed polymeric system together resulting in a reduced erosion of floating tablets. It shows that minimum release was found in FS4: 73.96±0.17. The rest of formulations show the cumulative percentage release as follows FS1:90±0.19, FS2: 98±0.18, FS3: 94.56±0.38, FS5: 79.61±0.47, FS6: 85.61±0.36.

Table no: 5. *In vitro* dissolution study

Time (min)	CUMULATIVE PERCENTAGE RELEASE					
	FS1*	FS2*	FS3*	FS4*	FS5*	FS6*
30	6.76±0.31	8.95± 0.23	11.19±0.41	2.52± 0.36	3.38±0.42	5.19± 0.14
60	12.29±0.18	16.25±0.29	18.14±0.40	6.74± 0.40	8.46±0.24	10.41±0.11
90	17.85±0.29	23.17±0.25	25.13±0.17	11.40±0.48	16.12±0.24	16.52±0.17
120	28.51±0.40	29.27±0.35	32.16±0.49	17.77±0.42	22.12±0.52	24.40±0.53
150	36.27±0.29	36.68±0.39	39.66±0.25	21.66±0.19	28.16±0.14	34.49±0.29
180	45.34±0.37	44.56±0.19	47.20±0.35	28.92±0.13	33.81±0.17	41.60±0.52
240	54.47±0.46	55.04±0.23	57.36±0.43	39.18±0.41	42.87±0.54	49.19±0.49
300	62.79±0.35	67.71±0.46	69.30±0.43	48.22±0.36	52.82±0.18	58.11±0.41
360	73.28±0.43	77.89±0.31	80.88±0.29	55.64±0.38	62.83±0.24	66.65±0.24
420	83.82±0.41	85.99±0.71	90.36±0.34	64.77±0.38	70.61±0.11	77.40±0.51
480	90.19±0.19	94.56±0.38	98.60±0.18	73.96±0.17	79.61±0.47	85.61±0.36

*The values represent mean ± SD, n = 3.

Table no: 6. Release kinetics of (FS1-FS6)

Formulation	Zero order		First order		Higuchi		Korsmeyer		Hixson crowell	
	R	K	R	K	R	K	R	K	R	K
FS1	0.9909	0.1972	0.9737	-0.0037	0.9384	3.4407	0.9990	0.1725	0.9909	0.3517
FS2	0.9925	0.2043	0.9646	-0.0041	0.9467	3.5758	0.9990	0.3517	0.9909	-0.0010
FS3	0.9902	0.2118	0.9494	-0.0045	0.9533	3.7193	0.9995	0.5309	0.9866	-0.0011
FS4	0.9963	0.1494	0.9747	-0.0023	0.8997	2.5537	0.9858	0.0151	0.9862	-0.0006
FS5	0.9978	0.1660	0.9742	-0.0027	0.9164	2.8607	0.9872	0.0387	0.9889	-0.0008
FS6	0.9930	0.1778	0.9795	-0.0030	0.9316	3.0908	0.9928	0.0985	0.9928	-0.0008

Table no: 7. Best fit model

Formulation	FS1	FS2	FS3	FS4	FS5	FS6
Model	Korsmeyer peppas	Korsmeyer peppas	Korsmeyer peppas	Zero order	Zero order	Zero order
n - value	0.5031	0.6040	0.8435	0.7423	0.9219	0.8720

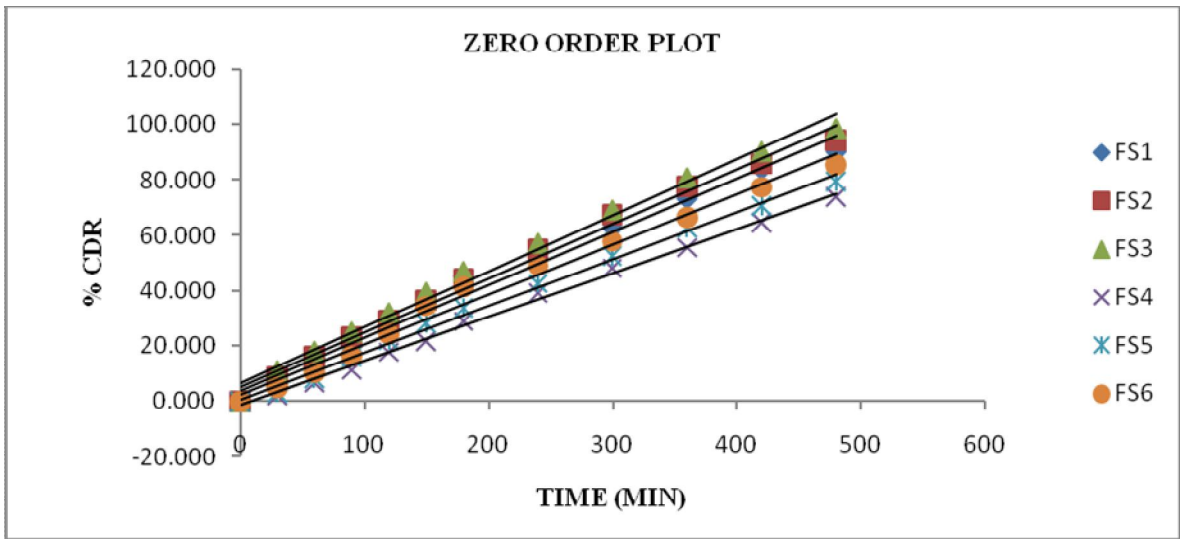


Fig: 3. Zero order plot of Fluvastatin sodium (FS1 - FS6)

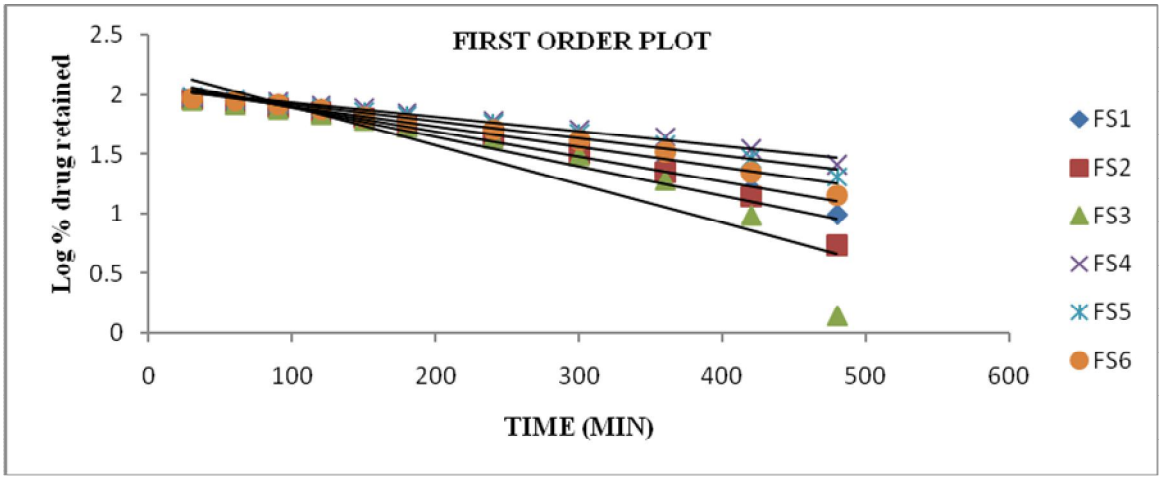


Fig: 4. First order plot of Fluvastatin sodium (FS1 – FS6)

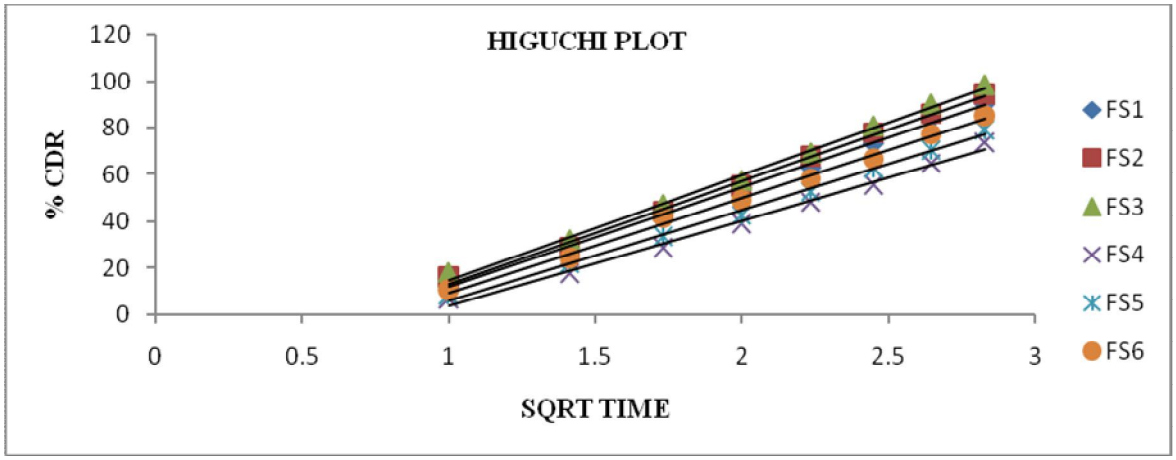


Fig: 5. Higuchi matrix plot of Fluvastatin sodium (FS1- FS6)

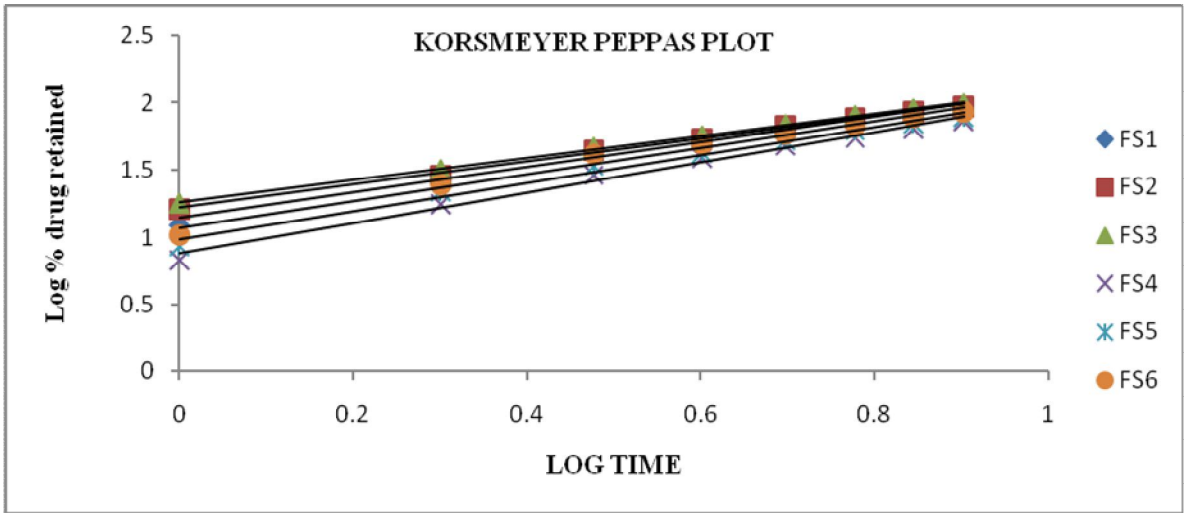
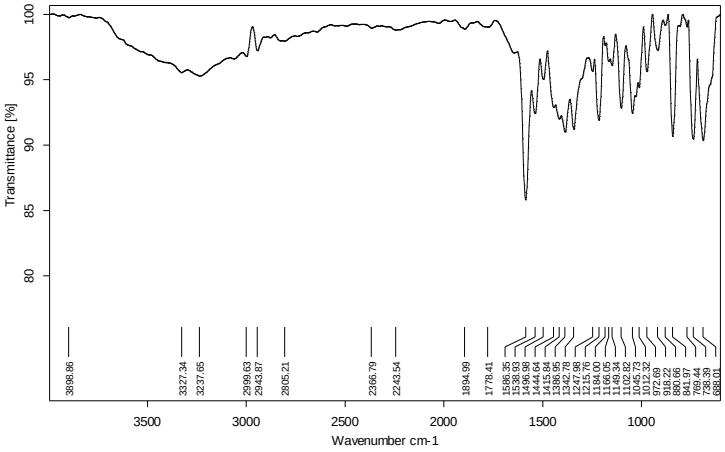
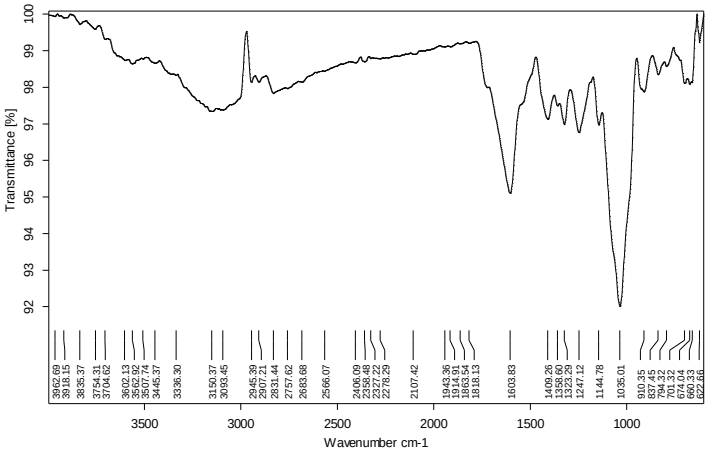


Fig: 6. Korsmeyer peppas plot of Fluvastatin sodium (FS1- FS6)

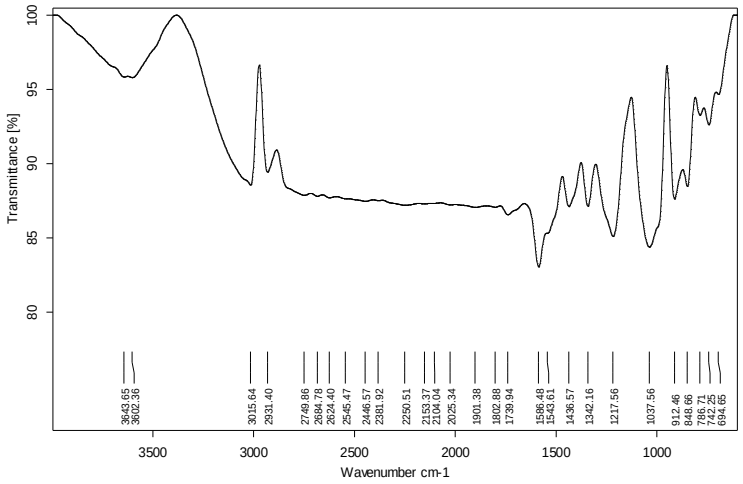


FT IR spectra of Fluvastatin Sodium Polysaccharide

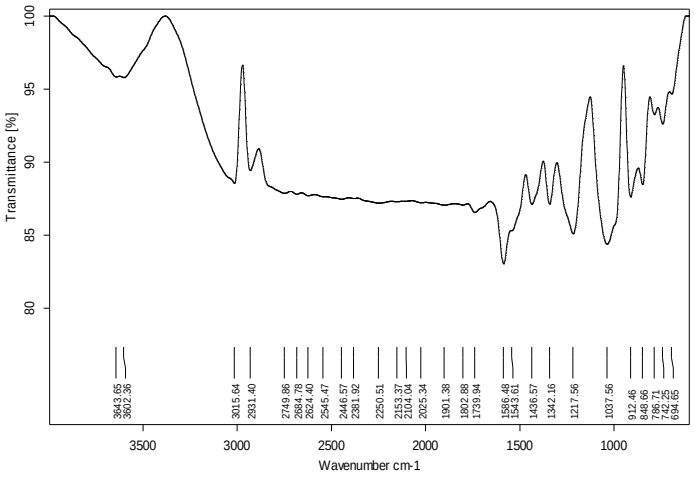


FI IR spectra of Hibiscus

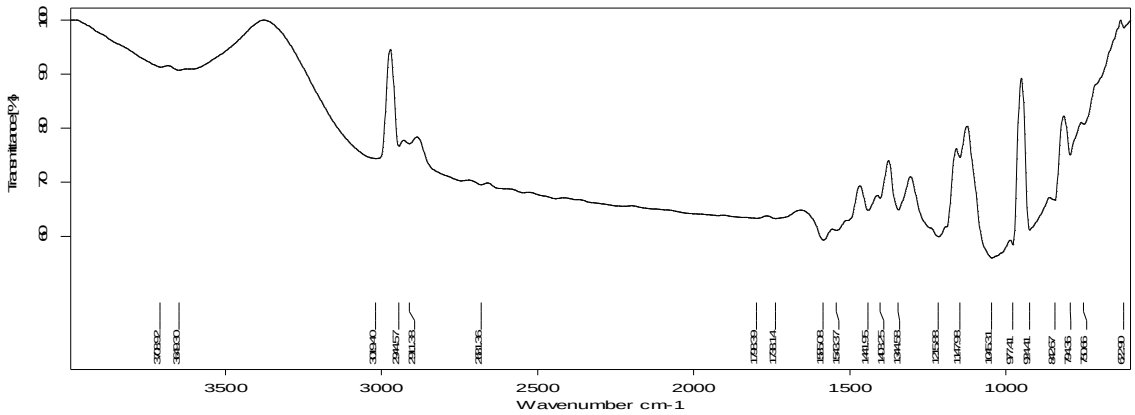
know the mechanism of drug release from these formulations, the data was treated according to First order approximation (log cumulative percent drug remaining to be diffused vs. time), Higuchi's approximation (cumulative percent drug diffused vs. square root of time) and Korsmeyer-Peppas approximation (log cumulative percent drug diffused vs. log time) pattern. release of the drug from a matrix tablet containing hydrophilic polymers generally involves factor of diffusion. Diffusion is related to the transport of drug from the dosage matrix into the *in vitro* study fluid depending on the concentration. As gradient varies, the drug is released and the distance for diffusion increases.



FT IR spectra of Hypromellose K100M polysaccharide



FT IR Spectra of Drug + Hibiscus



FT IR Spectra of Fluvastatin sodium + Hypromellose K100M

Fig no: 7. FT IR Spectra of Drug & Polymers

Table no: 8. Stability studies FS5 at 25^{0}C /± / 2^{0}C / 60% /±/ 5% RH

Formulation FS5	0 Month	1st month	2nd month	3rd month
Hardness(Kg/cm^2)	4.86 ± 0.08	4.86 ± 0.08	4.85 ± 0.02	4.85 ± 0.05
Drug content (%)	98.71	98.68	98.68	98.67
Buoyancy lag time	59 sec	59 sec	59 sec	60 sec
In vitro floating time	>12 h	>12 h	>12 h	>12 h

In respect of physical dimension stability, buoyancy lag time and drug release property the result indicate that drug release decreases with increases the polymer concentration of hibiscus. To The

The *in vitro* release profiles of the drug from the formulations can be expressed by Higuchi's kinetics, as it indicates swelling, Korsmeyer-Peppa's kinetics, as the 'n' value between 0.45 and 0.89 indicates that diffusion is coupled with erosion and hence this mechanism is called anomalous diffusion and Zero order kinetics, as it indicates that the tablets were swollen and the drug release was controlled by swelling. The data for the release kinetics is shown in tables 6 & 7. The formulations containing Fluvastatin sodium with hibiscus mucilage and HPMCK100M kinetic studies shows that FS1, FS2, FS3 follow the Korsmeyer peppas model and the rest FS4, FS5, FS6 follows the zero order. The n values are as follows FS1, FS2, FS3, FS4, and FS6. 0.5031, 0.6040, 0.8435, 0.7423, 0.8219, 0.8720 shows anomalous/non- fickian type transport & FS5 shows 0.9219 indicates indicating that the drug release followed super case II transport mechanism due to the erosion of the polymer. This type of erosion can occur by hydrolysis of water-labile backbone linkages or by enzymatic degradation of backbone linkages.

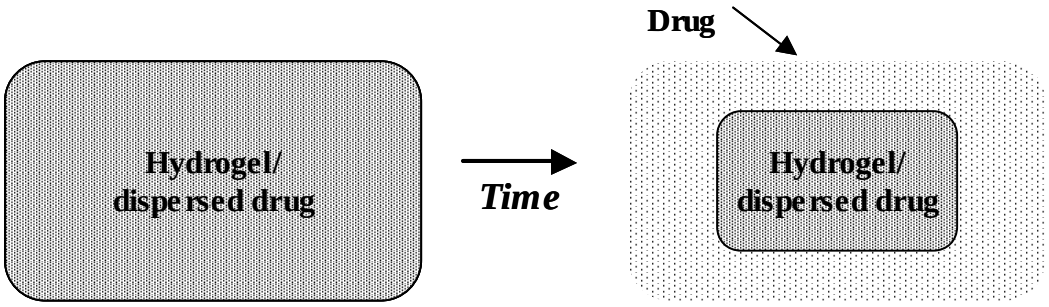


Fig: 8. Schematic diagram of drug release from a hydrogel-based erodible delivery system.

Short term stability studies indicated no appreciable changes in the drug content, total floating, hardness, and buoyancy lag time. The results were shown in the table no: 8.

CONCLUSION

In conclusion the above study shows the plant based mucilage has a good sustained activity over the synthetic moreover this natural based polymer are renewable and non toxic in nature.

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