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FORMULATION AND EVALUATION OF FLUVASTATIN SUSTAINED RELEASE TABLETS

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ABSTRACT

The objective of the present study was to formulate sustained release matrix tablets of Fluvastatin, for treatment of hypertension. The matrix tablets were prepared by wet granulation method using hydroxyl propyl methylcellulose K4M, sodium alginate in various concentrations. The powder showed satisfactory flow properties and compressibility. All the formulations showed acceptable Pharmacopoeial standards. The result of formulation F7. Model fitting analysis for formulation F7 fitted in the zero order model and Korsemeyer- peppas model. The 'n' values obtained from the peppas-Korsemeyer equation suggested that, drug release was non-Fickian diffusion mechanism. Successful formulation was found stable after evaluation for physicochemical parameters when kept for 90 days at room temperature, 40^0c and 2-8 ^{0}C. It concluded that sustained release matrix tablets of Fluvastatin containing 25% of HPMC K4M and sodium alginate provide a better option for Sustained release of drug.

KEYWORDS: Fluvastatin, Sustained release Matrix Tablets, Polymers, Wet Granulation Technique, In vitro drug release studies.

INTRODUCTION

All the pharmaceutical products formulated for systemic delivery via the oral route of administration irrespective of the mode of delivery (immediate, sustained or controlled release) and the design of dosage forms (either solid dispersion or liquid), must be developed within the intrinsic characteristics of GI physiology.[1,2] Oral drug delivery system is one of the most useful and preferred route of drug delivery for the successful treatment of number of diseases. Sustained release preparations are helpful to reduce the dosage frequency and side effects of drugs and improve patient's convenience. Sustained release matrix tablet is relatively easy to fabricate by incorporating the drug in slowly dissolving or inert porous polymer materials.[3] Hydrophilic polymer like HPMC controls drug release by its rapid hydration, gelation, cross-linking, and swelling properties.[4,5] Fluvastatin is the drug used in cardiovascular diseases. It is an anti-hyperlipidemic agent that competitively inhibits Hydroxy methyl glutaryl co-enzyme A (HMG CO-A). It is used in patients with cardiovascular problems by reducing cholesterol in plasma for a chronic period.[6] This current research focused on sustained the release of Fluvastatin tablets by incorporating different types of polymers and their combinations by using wet granulation technique and evaluated.

MATERIALS

Fluvastatin was obtained from Hetero labs, HYD. HPMC and Sodium alginate procured from SD fine chemicals Mumbai. Other chemicals and the reagents used were of analytical grade.

METHODOLOGY

Preparation of Fluvastatin Tablets[8,9]

Preparation of Sustain release Layer of Fluvastatin by Wet Granulation Method

All the tablets, each containing 200 mg of Fluvastatin were prepared by wet granulation method. Drugs, and excipients were sifted through 40 mesh sieve.1 Binder preparation Granulation 2. Dry mixing: The drug and diluents after stage 1 were mixed well to ensure the uniformity of premix blend. Several drug – diluents premixes were then mixed with the selected ratio of super disintegrating agents(s) previously sifted through sieve no 60 for 5min. 3.

Granulation: Granules were prepared by adding step 2 in step 3a and the wet mass pass through sieve no.18. 4. Drying: The produced granules were dried at 55°C ± 5°C for 1 hour in a hot-air oven. 5. Sizing: Dried granules of Fluvastatin were passed through 20 mesh sieve.6. Lubrication: These granules were blended with lubrication mixture for 5min in polythene bag. 7. Compression: after the lubrication granules were compressed using 16 station rotary tabletting machine, equipped with flat-faced, round punches of 8 mm diameter.

Table 1: Formulation Table.

S.No.	INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8
1	Fluvastatin	40	40	40	40	40	40	40	40
2	Sodium Alginate	100	50	-	-	-	-	50	-
3	HPMC K15	-	-	100	50	-	-	50	50
4	Carbopol934	-	-	-	-	100	50		50
4	Lactose	55	105	55	105	55	105	55	105
6	Iso Propyl Alcohol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
7	Magnesium Stearate	3	3	3	3	3	3	3	3
8	Talc	2	2	2	2	2	2	2	2
9	Total Weight	200	200	200	200	200	200	200	200

EVALUATION PARAMETERS

Weight Variation[10]

Twenty tablets were randomly selected form each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation test if not more than two of the individual tablet weight deviate from the average weight by more than the percentage shown in Table No 1 and none deviate by more than twice the percentage shown.

Thickness[11]

Twenty tablets were randomly selected form each batch and there thickness was measured by using Vernier caliper. Thickness of three tablets from each batch was measured and mean was calculated.

Hardness[12]

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm^2. Three tablets were randomly picked and hardness of the tablets was determined.

Friability[13]

Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche Friabilator was used for the purpose. This device subjects a number of tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at distance of 6 inches with each revolution. Twenty tablets were weighed and placed in the Roche Friabilator, which was then operated for 25 rpm for 4 min. After revolution Tablets were dedusted and reweighed. Compressed tablets should not lose more than 1% of their weight.

The percentage friability was measured using the formula,

$$\% F = \{1-(Wo/W)\} \times 100$$

Where,
% F = friability in Percentage
Wo = Initial weight of tablet
W = weight of tablets after revolution

Content Uniformity[14]

Twenty tablets from each batch were powdered and weighed accurately equivalent to 100 mg Fluvastatin. Dissolve the weighed quantity of powder into 100 ml of 0.1 N NaOH solution by stirring it for 15 min. 01 ml of solution was pipette out into 10 ml volumetric flask and make up the volume with distilled water. Immediately analyze the drug by taking absorbance at nm using reagent blank.

Disintegration time[15]

The disintegration time of tablets was determined by using Disintegration test apparatus (scientific). Tablets were placed in disintegration test assembly and disc was placed on tablets in each glass tube of assembly. The assembly was dipped in a vessel containing 900 ml distilled water at 37°C. The time for disappearance of tablet residue above mesh was noted as disintegration time.

In- Vitro Release study[16]

In-Vitro drug release studies were carried out using Tablet dissolution test apparatus USP II at 100 rpm. The dissolution medium consisted of 900 ml of Standard buffer pH 1.2 for the first 2 hrs, followed by pH 6.8 for remaining period of time. Temperature maintained at 37±5.The sample of 5ml was withdrawn at predetermined time intervals and an equivalent amount of fresh dissolution fluid equilibrated at the same temperature was replaced. From that 5 ml sample, 1 ml sample was withdrawn and placed in a 10 ml volumetric flask and make the volume with distilled water. The diluted samples were assayed at 260 nm against reagent blank.

Kinetic Modelling of Drug Release[17]

All the nine formulation of prepared matrix tablets of Fluvastatin were subjected to in vitro release studies these studies were carried out using dissolution apparatus.

The results obtaining in vitro release studies were plotted in different model of data treatment as follows:

1. Cumulative percent drug released vs. time (zero order rate kinetics)
2. Log cumulative percent drug retained vs. time (First Order rate Kinetics)
3. Cumulative percent drug released vs. square root of time (Higuchi's Classical Diffusion Equation)
4. Log of cumulative % release Vs log time (Peppas Exponential Equation)

Stability Studies[18]

The success of an effective formulation can be evaluated only through stability studies. The purpose of stability testing is to obtain a stable product which assures its safety and efficacy up to the end of shelf life at defined storage conditions and peak profile.

The prepared Matrix tablets of Fluvastatin were placed on plastic tubes containing desiccant and stored at ambient conditions, such as at room temperature, 40±2°c and refrigerator 2-8°c for a period of 90 days**.**

RESULTS AND DISCUSSION

FT-IR Spectrum of Fluvastatin

The compatibility between the drug and the selected Drug and other excipients was evaluated using FTIR peak matching method. There was no appearance or disappearance of peaks in the drug-excipients mixture, which confirmed the absence of any chemical interaction between the drug, polymers and other chemicals.

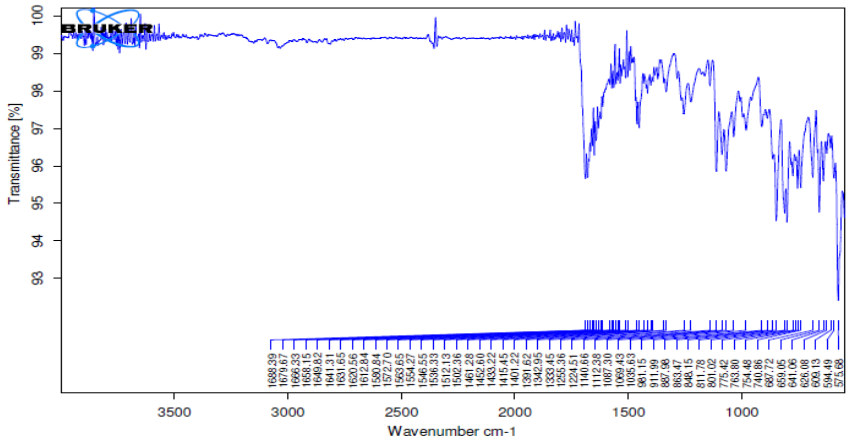

Fig. 1: FTIR Studies of Pure Drug.

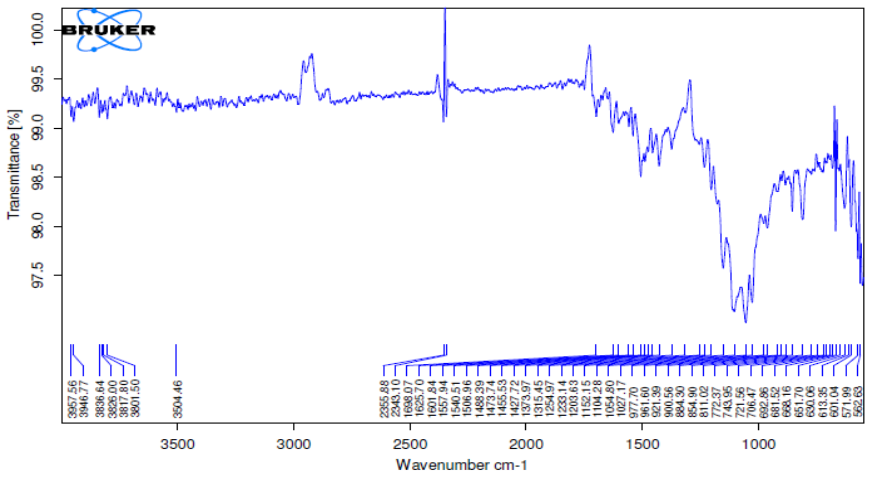

Fig. 2: FTIR Studies of Physical Mixture of Drug and Excipients.

EVALUATION STUDIES

Weight Variation

All the formulated (F1 to F8) tablets passed weight variation test as the % weight variation was within the Pharmacopoeial limits of ±7.5% of the weight. The weights of all the tablets were found to be uniform with low standard deviation values.

Thickness
Tablets mean thickness were uniform in F1 to F8 formulations and were found to be in the range of 2.1 mm to 2.4 mm.

Hardness
The measured hardness of tablets of each batch ranged between 3.15to 3.35 kg/cm^2. This ensures good handling characteristics of all batches.

Friability
The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

Content Uniformity
The percentage of drug content for F1 to F8 was found to be between 93.25% to 96.42% of Fluvastatin, it complies with official specifications.

Disintegration Time
In the presented studies, three different types of in vitro methods of tablet disintegration were used: those where the only factor leading to the disintegration was water wicking into the matrix of the tablet, the tests with water agitation or stirring, and the methods where direct destructive forces were put on the tested tablet, such as grinding or pressing with additional weight. Therefore, disintegration tests showed great variability in the data measured with different methods.

Table 2: Evaluation Parameters of Fluvastatin Tablets.

F. No.	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug Content (%)	Disintegration Time
F1		2	2.5	0.25	90.28	12
F2		1.5	2.7	0.28	93.46	10
F3		1.8	2.5	0.30	88.24	13
F4		2.1	2.3	0.27	89.35	9
F5		1.9	3.1	0.31	97.25	14
F6		2.0	2.8	0.27	96.38	12
F7		1.7	2.9	0.29	98.26	11
F8		2.2	2.6	0.30	96.89	8

Dissolution Studies
All the 8 formulation of Fluvastatin tablets were subjected to in vitro release studies these studies were carried out using dissolution apparatus. The dissolution medium consisted of 900 ml of Standard buffer pH 6.8 for period of time.

Table 3: Drug Release Studies of all Formulations.

Time	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
1	21.16	21.54	19.20	22.30	18.15	20.29	22.52	19.50
2	44.25	46.52	34.85	35.45	32.23	38.40	36.97	32.15
3	51.30	54.63	49.70	48.53	42.96	53.51	58.84	49.63
4	60.22	59.75	59.85	50.43	58.17	54.82	60.96	58.15
5	68.29	65.23	64.36	63.28	65.32	64.19	66.93	67.40
6	75.63	73.26	78.32	77.15	74.95	72.40	79.42	73.34
7	89.56	85.29	82.96	85.69	83.70	81.48	89.53	82.83
8	93.51	92.32	92.42	90.28	94.52	95.50	98.93	93.70

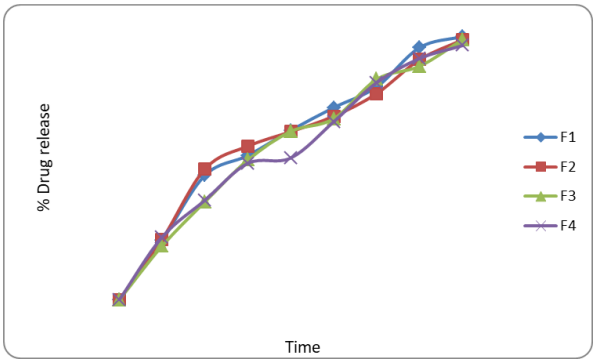

Fig. 3: Dissolution Profile of F1 to F4 Formulations.

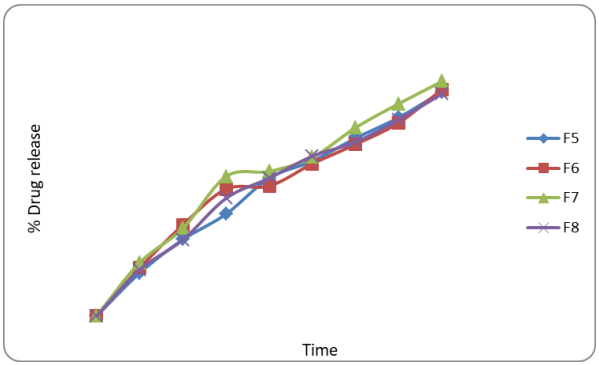

Table 4: Dissolution Profile of F5 to F8 Formulations.

Kinetic Modeling of Drug Release

All the 8 formulation of prepared matrix tablets of Fluvastatin were subjected to in vitro release studies these studies were carried out using dissolution apparatus.

The results obtaining in vitro release studies were plotted in different model of data treatment as follows:

1. Cumulative percent drug released vs. time (zero order rate kinetics)
2. Log cumulative percent drug retained vs. time (First Order rate Kinetics)
3. Cumulative percent drug released vs. square root of time (Higuchi's Classical Diffusion Equation)
4. Log of cumulative % release Vs log time (Peppas Exponential Equation)

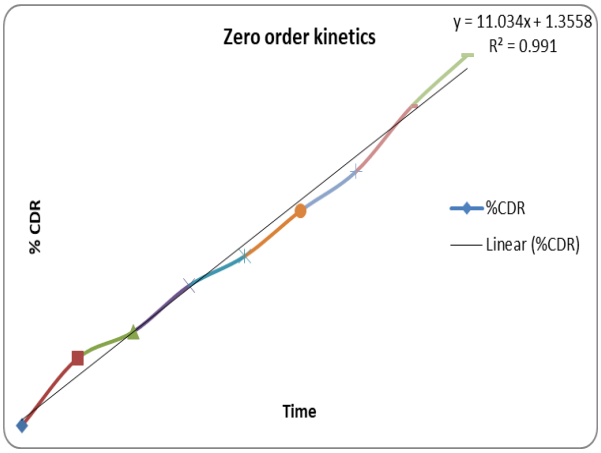

Fig. 5: Zero Order Kinetics of Optimized Formulation.

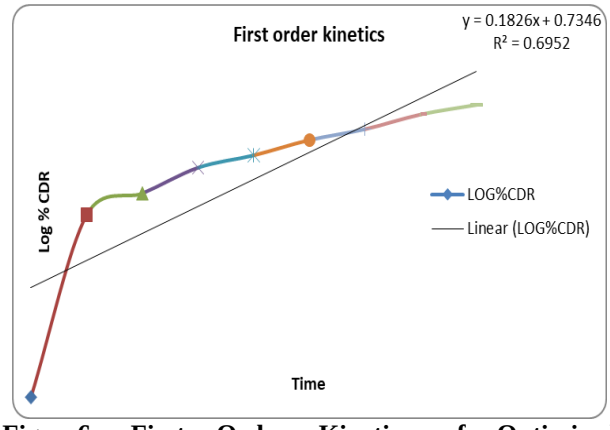

Fig. 6: First Order Kinetics of Optimized Formulation.

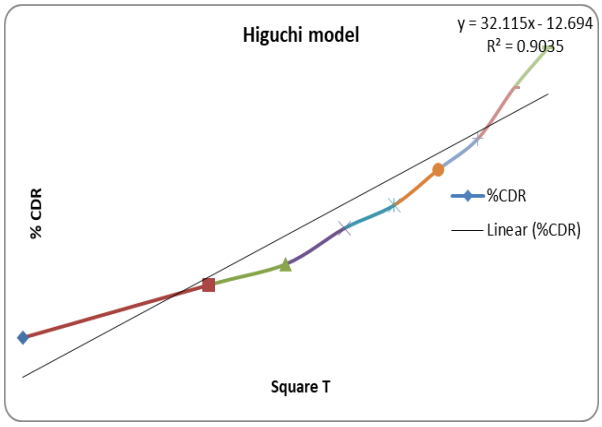

Fig. 7: Higuchi Model of Optimized Formulation.

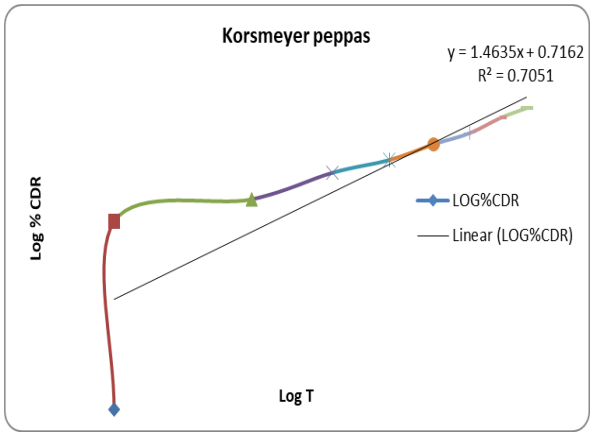

Fig. 8: Korsmeyer Pepps of Optimized Formulation.

The values of in vitro release were attempted to fit into various mathematical models. Plots of zero order, first order, Higuchi matrix, Peppas and Hixson-Crowell.

Regression values are higher with Zero order release kinetics. Therefore all the Fluvastatin Tablets follow Zero order release kinetics.

The table indicates that r^2 values are higher for Higuchi's model compared for all the tablets. Hence Fluvastatin release from all the Tablets followed diffusion rate controlled mechanism.

Stability Study

There was no significant change in physical and chemical properties of the tablets of formulation F-7 after 90 days. Parameters quantified at various time intervals were shown.

Table 4: Stability Studies of all Formulations.

Formulation Code	Parameters	Initial	1st Month	2nd Month	3rd Month	Limits as Per Specifications
F-7	25^0C/60%RH % Release	98.93	98.85	97.95	97.65	Not less than 85 %
F-7	30^0C/75% RH % Release	98.93	98.76	97.88	97.48	Not less than 85 %
F-7	40^0C/75% RH % Release	98.93	98.12	97.75	96.99	Not less than 85 %

CONCLUSION

The present study was undertaken with an aim to formulate and evaluate Fluvastatin sustained release tablets using different polymers as release retarding agents. The tablets were evaluated for physical parameters, *in vitro* release study and stability studies. All formulations were found to be with in the specifications of official pharmacopoeias and/or standard references. In-vitro release indicated that the formulation F7 had better dissolution profile along with sustained action as compare to other formulations. Formulation F7 was subjected to the various pharmacokinetic studies. The result indicated that the formulation F7 follows Higuchi matrix suggesting diffusion controlled release. Stability study was conducted on tablets of Batch F7 stored at room temperature, 40^0C, and 2-8^0C for one month. Tablets were evaluated for hardness, friability, in-vitro release profile and drug content. No significant changes were observed in any of the studied parameters during the study period (3 months), thus it could be concluded that formulation was stable.

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