World Journal of Pharmaceutical and Life Sciences
WJPLS
www.wjpls.org
SJIF Impact Factor: 6.129

FORMULATION AND IN VITRO EVALUATION OF SUSTAINED RELEASE TABLETS OF FLUVASTATIN

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Article Received on 27/07/2022 **Article Revised on 17/08/2022** **Article Accepted on 07/08/2022**

ABSTRACT

The current study's goal was to create a sustained release formulation of fluvastatin that would keep the drug's therapeutic levels stable for more than 12 hours. Guar gum, sodium CMC, and hydroxypropyl cellulose are just a few examples of natural polymers that have been used as polymers. The dosage of fluvastatin was set at 20 mg. The tablet's 150 mg total weight was taken into account. There were three different concentrations of polymers used: 25, 50, and 100 mg. Various physicochemical evaluation parameters were applied to all of the formulations, and they were all found to be within acceptable bounds. The formulation (F6), however, demonstrated a better and more desired drug release pattern, i.e., 96.10% in 12 hours, as evidenced by the dissolution studies. It used a release kinetics system of zero order.

KEYWORDS: Fluvastatin Guar gum, Hydroxy propylcellulose Sodium CMC and sustained release tablets.

INTRODUCTION

Fluvastatin is Fast and nearly entirely absorbed (> 90%), however considerable first pass metabolism occurs. When a dose of 10 mg is administered, bioavailability is 24% (interval 9–50%). Comparing the extended-release pill to an immediate-release capsule taken when fasting, the mean relative bioavailability is 29% (interval: 9% to 66%). Fluvastatin oral dosage takes less than an hour to reach peak concentrations (Tmax). The aim of this study is To formulate sustained release tablets of Fluvastatin to improve its oral bioavailability and to reduce its dosing frequency.

MATERIALS

Fluvastatin, Guargum, Hydroxyl propylcellulose, Sodium CMC, MCC pH 102, Magnesium stearate, Talc.

Methodology

Table 1: Formulation composition for tablets.

Formulation No.	Fluvastatin	Sodium CMC	Guar Gum	Hydroxy propyl cellulose	Mag. Stearate	Talc	MCC pH 102
F1	20	25			4	4	QS
F2	20	50			4	4	QS
F3	20	100			4	4	QS
F4	20		25		4	4	QS
F5	20		50		4	4	QS
F6	20		100		4	4	QS
F7	20			25	4	4	QS
F8	20			50	4	4	QS
F9	20			100	4	4	QS

All the quantities were in mg

Method of preparation

All components, including fluvastatin, were separately processed through sieve no. 60. By triturating for up to 15 minutes, all the materials were thoroughly combined. Talc was used to lubricate the powder mixture. The direct compression approach was used to create the tablets.

Evaluation of post compression parameters for prepared Tablets

The physicochemical characteristics of the suggested formulation tablets, such as weight variation, hardness, thickness, friability, and drug content, were examined.

Graphs of Fluvastatin was taken in Simulated Gastric fluid (pH 1.2) and in p H 6.8 phosphate buffer at 298 nm and 294 nm respectively.

Table 2: Observations for graph of Fluvastatin in 0.1N HCl (298nm).

Conc [µg/l]	Abs
4	0.104
8	0.205
12	0.302
16	0.411
20	0.503
24	0.608
28	0.710
32	0.808

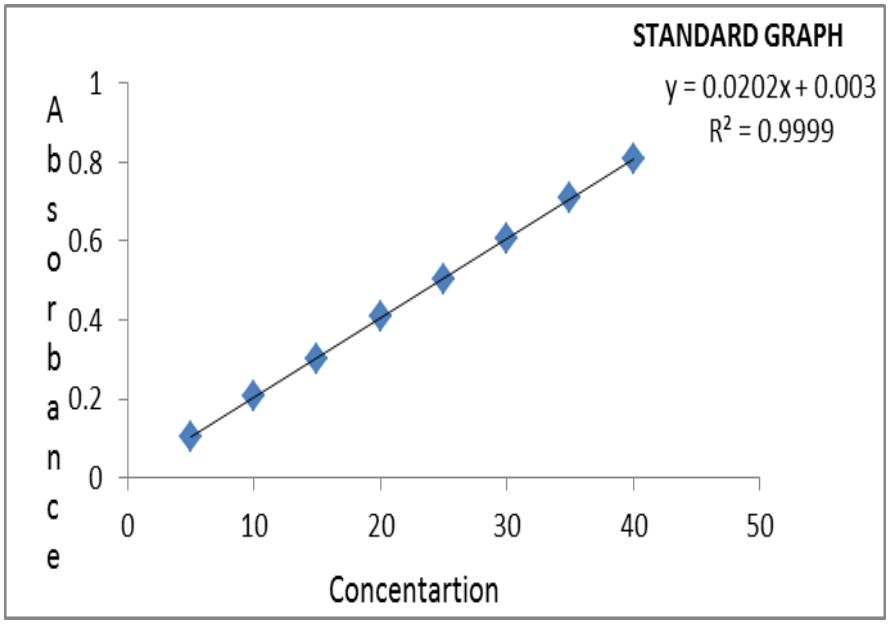

Figure 2: Standard graph of Fluvastatin in 0.1N HCl.

Table 3: Observations for graph of Fluvastatin in p H 6.8 phosphate buffer (294nm).

Conc [µg/l]	Abs
4	0.098
8	0.195
12	0.298
16	0.392
20	0.490
24	0.595
28	0.690
32	0.776

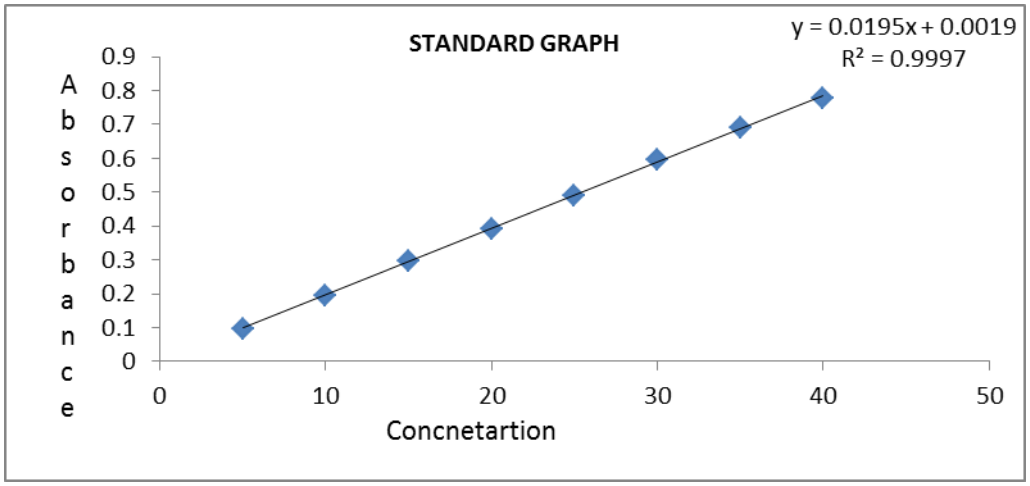

Figure 3: Standard graph of Fluvastatin p H 6.8 phosphate buffer (294nm).

Preformulation parameters

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

Angle of repose

The angle of repose for all formulations were determined to be between 25.11 and 25.12 Demonstrating the powders favourable flow characteristics.

Bulk density

The Bulk density for all formulations were determined to be between 0.49±0.04 and 0.55±0.08 **(gm/ml)** Demonstrating the powders favourable flow characteristics.

Tapped density

The tapped density for all formulations were determined to be between 0.54±0.04and 0.5 2±0.03 **(gm/ml)** Demonstrating the powders favourable flow characteristics.

Hausner's Ratio

Hausner's Ratio ranges from 0.86±0.06 and 1.17±0.0 Demonstrating the powders favourable flow characteristics.

Table 4: Pre-formulation parameters of Core blend.

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	25.11	0.49±0.04	0.54±0.04	16.21±0.06	0.86±0.06
F2	25.67	0.52±0.09	0.52±0.04	16.87±0.05	0.98±0.05
F3	25.54	0.50±0.05	0.58±0.05	17.11±0.01	0.64±0.03
F4	25.43	0.51±0.06	0.54±0.07	17.67±0.08	1.12±0.04
F5	25.34	0.52±0.03	0.57±0.03	16.92±0.04	1.2±0.08
F6	24.22	0.53±0.04	0.56±0.06	17.65±0.09	1.06±0.09
F7	25.18	0.54±0.06	0.59±0.04	16.43±0.05	0.76±0.03
F8	24.22	0.58±0.04	0.67±0.02	17.97±0.02	1.15±0.09
F9	25.12	0.55±0.08	0.5 2±0.03	17.54±0.09	1.17±0.02

Evaluation of post compression parameters for prepared Tablets

a) Hardness (kg/cm2)

A difference in tablet density and porosity will results in difference in tablet hardness .the hardness of the tablet was discovered to be between 4.1 to 4.5.

b) Friability (%loss)

All the formulations was discovered to be between 0.45 to 0.56.this shows that the produced tablets have good handling characteristics.

C) Weight variation (mg)

The maximum percentage varience allowed by the pharmacopoeia is 5%.all of the tablets had weights between 145.4 to 152.5 mg.

d) Drug content (%)

Ranging from 98.42 to 99.76.

e) Thickness (mm)

Specifications for thickness and diameter can be established for each product separately.too much

varience in tablet thickness might cause packaging issues aswell as concerns with consumer acceptence.

Within each formulation, the thickness of the tablets did not differ noticeably. Showing that the powders behaved uniformly throughout the compression process.

All tablet formulations were determined to have a thickness that fell between 4.9 to 6.9mm.

Figure 4: Quality Control Parameters For tablets.

Formulation codes	Weight variation(mg)	Hardness (kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)
F1	152.5	4.5	0.50	6.8	99.76
F2	145.4	4.5	0.51	6.9	99.45
F3	148.6	4.4	0.51	4.9	99.34
F4	150.6	4.5	0.55	6.9	99.87
F5	149.4	4.4	0.56	6.7	99.14
F6	150.7	4.5	0.45	6.5	98.56
F7	152.3	4.1	0.51	6.4	98.42
F8	151.2	4.3	0.49	6.7	99.65
F9	148.3	4.5	0.55	6.6	99.12

***In-Vitro* Drug Release Studies**

In-vitro Drug Release Studies of all formulations are presented in the table. experiments are carried out in 0.1 N HCl, p H 6.8 Phophate buffer for 12 hpors.

Table 5: Dissolution Data of Fluvastatin Tablets Prepared With Sodium CMC In Different Concentrations.

Time (hr)	Cumulative Percent Drug Dissolved (n=3±SD)		
	F1	F2	F3
0.5	25.5	20.1	16.4
1	46.7	39.4	26.7
2	76.5	55.3	34.6
3	98.4	75.3	42.4
4		87.3	55.4
5		99.4	67.4
6			85.4
7			91.5
8			97.3

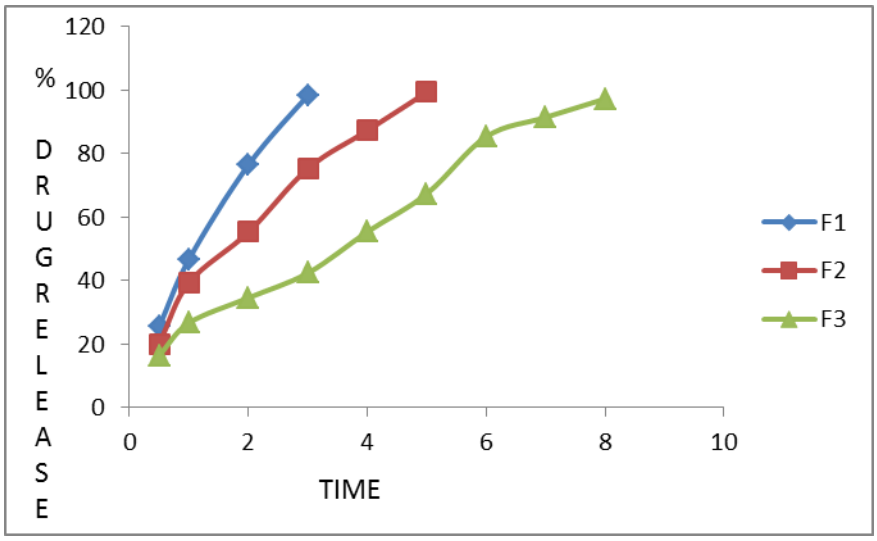

Fig. 7.5: Dissolution profile of Fluvastatin (F1, F2, F3 formulations).

Table 6: Dissolution Data of Fluvastatin Tablets Prepared With Guar gum In Different Concentrations.

Time (hr)	Cumulative Percent Drug Dissolved (n=3±SD)		
	F4	F5	F6
0.5	17.25	16.42	14.62
1	38.26	25.73	19.86
2	54.16	36.63	22.35
3	72.01	45.04	31.45
4	88.26	58.25	39.80
5	97.10	65.33	45.25
6		76.41	58.24
7		84.84	66.73
8		97.80	71.34
9			75.52
10			82.17
11			87.10
12			96.10

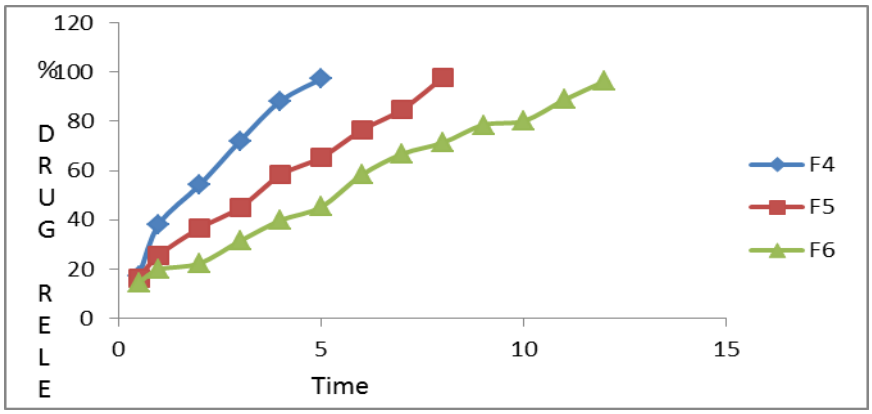

Fig. 6: Dissolution profile of Fluvastatin (F4, F5, F6 formulations).

Table 7: Dissolution Data of Fluvastatin Tablets Prepared With Hydroxy propyl cellulose In Different Concentrations.

Time (hr)	Cumulative Percent Drug Dissolved (n=3±SD)		
	F7	F8	F9
0.5	10.4	9.4	8.5
1	16.5	15.6	14.5
2	28.6	21.4	18.4
3	39.5	36.7	23.4
4	48.5	42.4	28.2
5	59.4	49.6	34.8
6	69.2	55.3	40.2
7	74.5	60.3	44.8
8	82.3	72.8	50.4
9	87.78	83.52	63.34
10	98.78	88.65	69.27
11		96.56	74.86
12			79.97

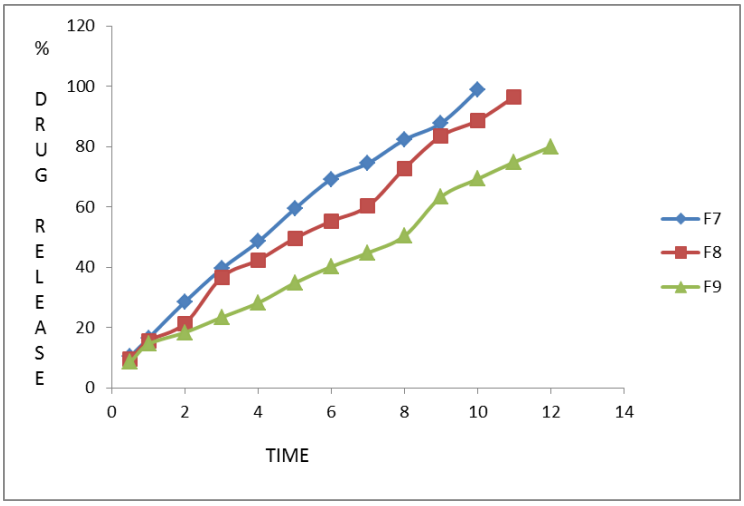

Fig. 7: Dissolution profile of Fluvastatin (F7, F8, F9 formulations).

Release Rate Kinetics

Table 8: Release kinetics data for optimised formulation.

Cumulative (%) Release Q	Time (T)	LOG (%) Release	LOG (%) Remain	Release Rate (Cumulative % Release / t)	1/Cum% Release	Peppas log Q/100	% Drug Remaining
0	0		2.000				100
14.62	0.5	1.165	1.931	29.240	0.0684	-0.835	85.38
19.86	1	1.298	1.904	19.860	0.0504	-0.702	80.14
22.35	2	1.349	1.890	11.175	0.0447	-0.651	77.65
31.45	3	1.498	1.836	10.483	0.0318	-0.502	68.55
39.8	4	1.600	1.780	9.950	0.0251	-0.400	60.2
45.25	5	1.656	1.738	9.050	0.0221	-0.344	54.75
58.24	6	1.765	1.621	9.707	0.0172	-0.235	41.76
66.73	7	1.824	1.522	9.533	0.0150	-0.176	33.27
71.34	8	1.853	1.457	8.918	0.0140	-0.147	28.66
75.52	9	1.878	1.389	8.391	0.0132	-0.122	24.48
82.17	10	1.915	1.251	8.217	0.0122	-0.085	17.83
87.1	11	1.940	1.111	7.918	0.0115	-0.060	12.9
96.1	12	1.983	0.591	8.008	0.0104	-0.017	3.9

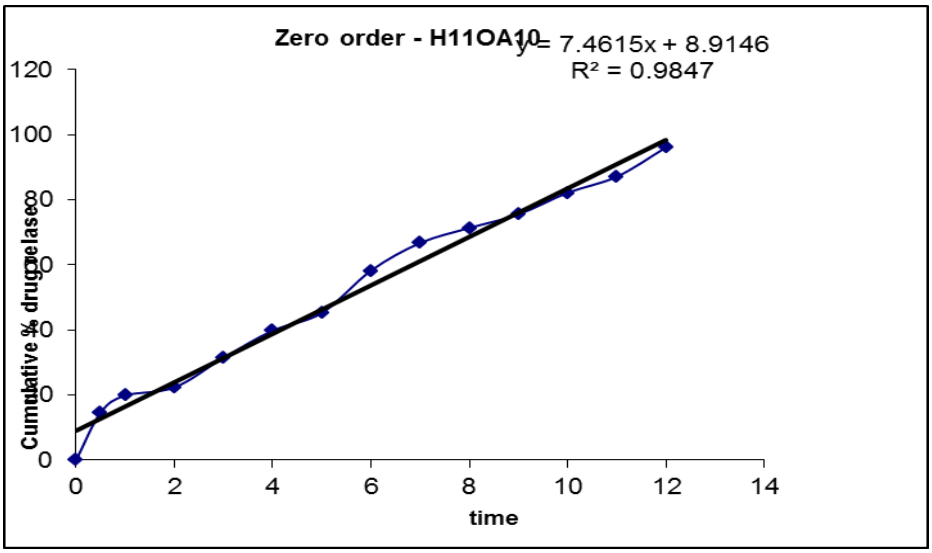

Fig. 8: Zero order release kinetics graph.

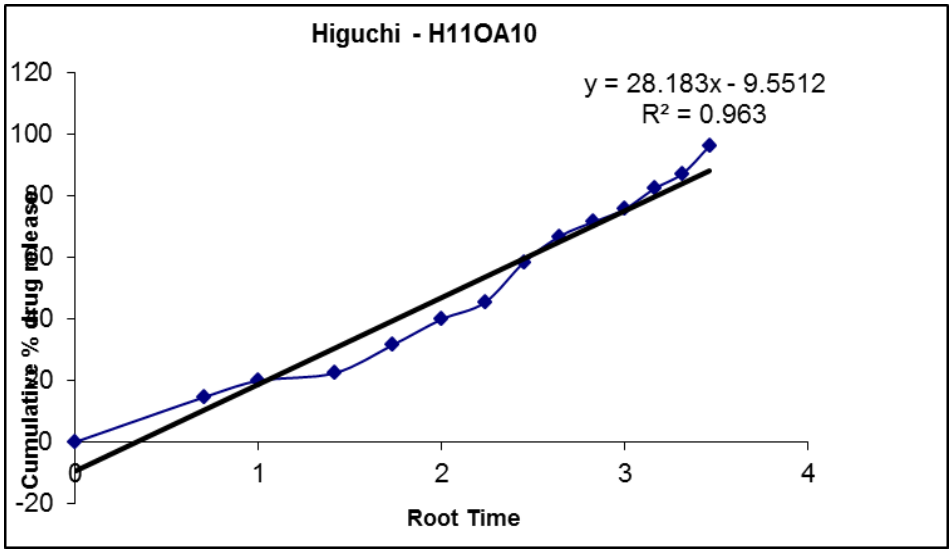

Fig. 8.1: Higuchi release kinetics graph.

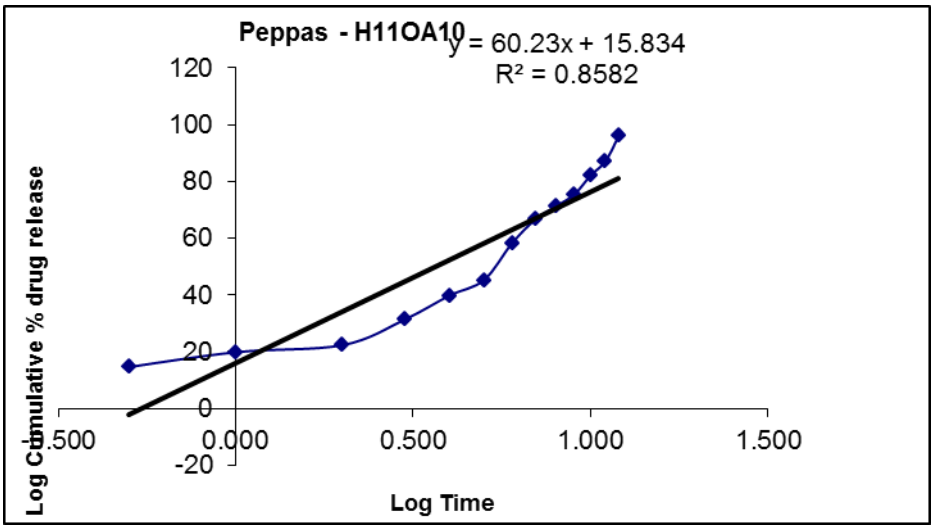

Fig. 8.2: Kars mayer peppas graph.

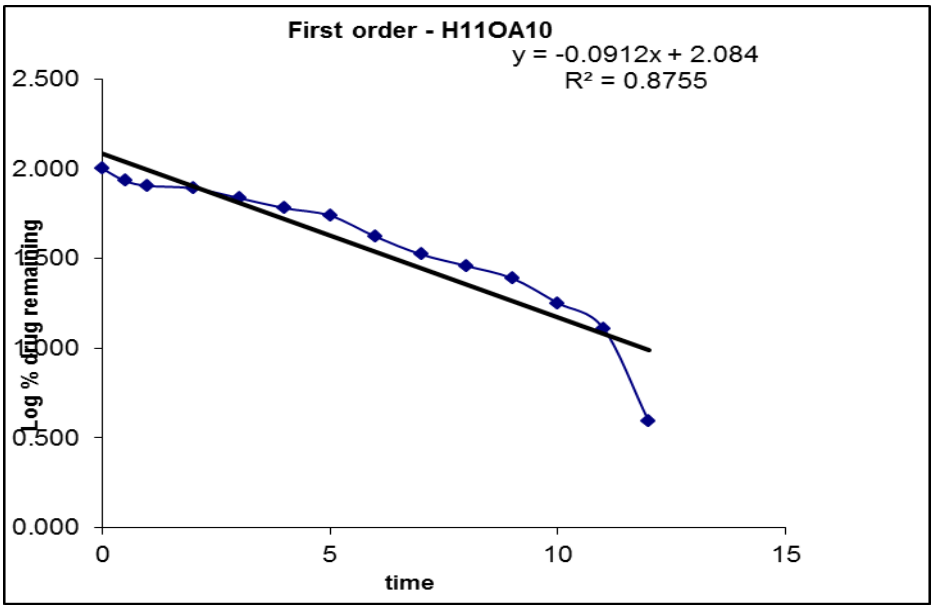

Fig. 8.3: First order release kinetics graph.

CONCLUSION

The aim of the present study was to develop sustained release formulation of Fluvastatin to maintain constant therapeutic levels of the drug for over 12 hrs. Various natural polymers such as Guar gum Sodium CMC and Hydroxy propylcellulose were employed as polymers. Fluvastatin dose was fixed as 20 mg. Total weight of the tablet was considered as 150 mg. Polymers were used in the concentration of 25, 50 and 100 mg concentration. All the formulations were passed various physicochemical evaluation parameters and they were found to be within limits. Whereas from the dissolution studies it was evident that the formulation (F6) showed better and desired drug release pattern i.e.,96.10 % in 12 hours. It followed zero order release kinetics mechanism.

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