Research Article

FORMULATION AND EVALUATION OF PULSATILE DRUG DELIVERY SYSTEM FOR HYPERCHOLESTEROLEMIA

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ABSTRACT

Aim of the present work was to formulate and evaluate an oral, pulsatile drug delivery system to achieve timed release of Atorvastatin Calcium, based on chronopharmaceutical approach for the treatment of Hypercholesterolemia. Pulsatile delivery system is capable of delivering drug when and where it is required most. The basic design contains core tablets prepared by wet granulation method. The tablets were coated by using HPMC 15cps with different ratios of CAP or Eudragit RS 100 in inorganic solvents. The prepared pulsatile tablets were evaluated for the *in-vitro* release profile. Coating of the selected core tablets were planned using Design – expert software 11. 2^3 factorial designs was used. *In-vitro* release profiles of pulsatile device were found to have an initial lag time of four hours during which it shows slight or no drug release and at the end of six hours burst release was observed. The lag time of the pulsatile tablets increased with increasing amounts of Eudragit RS 100 in the coating layer. Stability studies proved that there was no change in core tablets as well as coated tablets of Atorvastatin. The programmable pulsatile release has been achieved from a coated tablet over a 6 hr period, consistent with the demands of chronotherapeutic drug delivery.

Keywords: Pulsatile drug delivery; Hypercholesterolemia; Atorvastatin calcium; Eudragit RS100.

INTRODUCTION

Oral modified release dosage form represents the most popular form of controlled drug delivery systems due to its advantages over other routes of drug administration. In such system, the drugs are released with predetermined rates, either constant or variable. Diurnal blood pressure fluctuations are superimposed by a 24 hour rhythm with lower levels during the night and higher in the day[1].

The term "chrono" basically refers to the observation that every metabolic event undergoes rhythmic changes in time. Literature reveals that circadian rhythm occurs during hepatic cholesterol synthesis and this rhythm varies according to individuals[2]. The diurnal synthesis may represent up to 30%– 40% during the night than during daylight of daily cholesterol synthesis. In many individuals the cholesterol is synthesized during the night as well as during daylight; However the maximal production occurs early in the morning, i.e. 12 h after the last meal [3]. Studies with HMG CoA reductase inhibitors have suggested that evening dosing was more effective than morning dosing and the cholesterol synthesis increases during the night. Chronotherapy can be achieved by timing the medication in accordance with circadian rhythm for hypercholesterolemia[4].

Atorvastatin calcium is a known member of the drug class statins which selectively and competitively inhibits the hepatic enzyme hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase[5]. HMG-CoA reductase, the rate determining enzyme which plays an important role in converting HMG-CoA to mevalonate in the cholesterol biosynthesis pathway, it shows a subsequent decrease in hepatic cholesterol levels. Decreased hepatic cholesterol levels stimulate up regulation of hepatic LDL-C receptors which increases hepatic uptake of LDL-C and reduces serum LDL-C concentrations[6]. The activity of HMG-CoA reductase has circadian rhythmicity, as it is highest at night. The free cholesterol levels have been reported to be lowest at 2 p.m, It is recommended that HMG-CoA reductase inhibitors can be administered between the evening meal and bedtime (9 pm) and capable of releasing drug after predetermine time delay (5-6 hours) and can be characterized by proportioning drug concentration in the early morning hours when free cholesterol levels are more prevalent[7].

MATERIALS AND METHODS

Atorvastatin calcium was obtained as a gift sample from Apotex.Research (P) Ltd Bangalore. Cellulose acetate phthalate, Eudragit RS100,HPMC 15 cps and polyvinyl pyrrolidine obtained as a gift sample from Central Drug House (P) Ltd. New Delhi. Microcrystalline cellulose and Sodium starch Glycolate obtained from S D Fine Chem. Pvt. Ltd, Mumbai. Dicalcium phosphate obtained from NICE CHEMICALS Pvt. Ltd, COCHIN. All other chemicals used were of analytical grades.

Methods

1. Preparation of core tablets of Atorvastatin calcium.
2. Coating of the core tablets

1. PREPARATION OF CORE TABLETS OF ATORVASTATIN CALCIUM

- Wet granulation method was used to prepare core tablets of Atorvastatin calcium, all the polymers, drug and excipients were weighed as per formulation composition.
- Weighed quantity of drug, polymer and other excipients were passed through # 44- sieve.
- Sifted ingredients were transferred into polyethylene bag and the blend was mixed for 15 min.
- PVP K30 was used as a binder and dissolved methanol. The solution of PVP K 30(5-7ml) mixture obtained was then added in to the powder blend and mixed properly to get a wet mass in a mortar.
- Then it was passed through # 40 sieve and kept for drying.
- The granules obtained were then lubricated by adding weighed quantities of Talc and Magnesium stearate was passed through # 80 sieve and again mixed for another 2min in poly bag.
- The tablets were compressed using 6.32 mm round concave punches in “Remik mini press-I” tablet punching machine.

2. COATING OF THE CORE TABLETS USING FACTORIAL DESIGN

2^3 full factorial designs were used to find out the effect of coating on the release rate. Tablets were coated by dip coating method. HPMC 15cps and Eudragit RS100 10% polymer solution was prepared with methanol and tablets were dipped in coating solution with simultaneous drying with the help of hot air. The coated tablets were then dried in hot air oven at $40^{O}C$ for 5 minutes until the coat is dry. Then dried tablets were weighed and re-coated in the same procedure until 15% weight gain obtained by dip coating method. Then these tablets were kept in hot air oven for 5-8 minutes for curing of tablets, to avoid the weight variation of coated tablets. Same coating procedure was carried out using combination of HPMC 15 cps and Cellulose acetate phthalate 10% polymer solution prepared with acetone and with the same weight gain of 15 %.In the present study, the coating of the tablets was designed with variable ratios of coating polymers.

3 factors were studied at two levels. Among these factors amount of HPMC 15 cps and amount of rate controlling polymer are the two quantitative factors and type of rate controlling polymer is a qualitative factor. CAP & Eudragit RS 100 were the two different rate controlling polymers studied. Amount of HPMC 15 cps was studied at 100 & 500 mg. Rate controlling polymers were studied at 100 & 500 mg. 2^3 full factorial design were applied to establish the relation between independent variables [polymer ratio] and dependent variables [lag time, in-vitro drug release at 4^{th} hour and time for maximum % drug release] using Design Expert software version11.

Evaluation of Core Tablet Properties[8,9,10]

Tablets were subjected to evaluation for Assay, weight variation, tablet hardness, friability and thickness and *in-vitro* drug release in different media.

Weight variation

The weight of the tablets were routinely determined to ensure that the tablets Contains the proper amount of drug. Weight variation test was done by weighing 20 tablets as per IP specification.

Tablet hardness

The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of tablets was checked by using Monsanto hardness tester. The hardness was measured in terms of kg/cm^2. 3 tablets were chosen randomly and tested for hardness. The average hardness of 3 determinations was recorded.

Friability

Friability generally refers to loss in weight of tablets in the containers due to removal of fines from the tablet surface. Friability generally reflects poor cohesion of tablet ingredients. Compressed tablets should not lose more than 1% of their weight.

$$\% \text{ Friability} = (\text{Loss in weight} / \text{Initial weight}) \times 100$$

Tablet thickness

Thickness of the tablet is important for uniformity of tablet size. Thickness was measured using Vernier Calipers. It was determined by checking the thickness of ten tablets of each formulation.

Assay:

Randomly 5 tablets were selected and powdered. The powder equivalent to weight of 1 tablet was weighed accurately and dissolved in 5 ml of methanol by sonication and made up to 100 ml of phosphate buffer pH 6.8. The solution was shaken thoroughly. The undissolved matter was removed by filtration through Whatman No.41 filter paper. Then from the first stock solution 1 ml diluted with 6.8 buffer solution in a 10 ml volumetric flask, and again the dilutions were carried out to obtain 10 µg/ml solution. Absorbance was measured at 241.7 nm using UV-visible Spectrophotometer.

***In-vitro* dissolution studies**

The USP apparatus type-II paddle type (Electro lab, Mumbai, India) was used. Dissolution was carried out at a rotation speed of 50 rpm using 900 ml of pH 0.1 N HCl buffer as the dissolution medium maintained at a temperature of 37°C ± 0.5°C for first 2 hours and then 0.1 N HCl was decanted and followed by 900 ml of phosphate buffer pH 6.8 with rotation speed of 50 rpm and at a temperature of 37°C ± 0.5°C. Samples were withdrawn at predetermined time intervals and diluted 1ml in 10 ml of buffer solution and analyzed for drug release using Shimadzu UV-visible spectrophotometer at 241.7nm.

RESULTS AND DISCUSSION

Evaluation Of Core Tablets Of Atorvastatin Calcium

The physical parameters for all formulations were tabulated in Table 5.All the formulated (F1-F4) tablets were found within the pharmacopoeial limits. The weights of all tablets were found to be uniform with low standard deviation values. The measured hardness of tablets of all the formulations ranged between 4.2 to 4.8 kg/cm2 (Table-5).This ensures good handling characteristics of all batches. The % friability was less than 1.0% in all the formulations ensuring that the tablets were mechanically stable. The measured thickness of tablets of all the formulations ranged between 5.35 mm to5.65 mm. This ensures good handling characteristics of all batches. The assay for formulations F1 to F4 was found to be 99.62 % to 107.12 % was within the Indian pharmacopeial limits. The assay of all the tablets was found to be uniform with low standard deviation values.

TABLE 1: Composition of Pulsatile Tablets of Atorvastatin calcium

	F 1	F1 A	F1 B	F 2	F2 A	F2 B	F 3	F3 A	F3 B	F 4	F4 A	F4 B
C0RE COMPOSITION	%	%	%	%	%	%	%	%	%	%	%	%
Atorvastatin	40	40	40	40	40	40	40	40	40	40	40	40
SSG	10	10	10	5	5	5	20	20	20	25	25	25
MCC	40	40	40	40	40	40						
PVPK 30	5	5	5	10	10	10	10	10	10	5	5	5
DCP							25	25	25	25	25	25
Methanol	5	5	5	5	5	5	5	5	5	5	5	5
Magnesium Stearate	3	3	3	3	3	3	3	3	3	3	3	3
Talc	2	2	2	2	2	2	2	2	2	2	2	2
Weight of core tablet	100	100	100	100	100	100	100	100	100	100	100	100
C0ATING COMPOSITION												
HPMC 15 CPS	0	400	100	0	400	100	0	400	100	0	400	100
Eudragit RS100	0	100	400	0	100	400	0	100	400	0	100	400
Weight gain in %	0%	10%	10%	0%	10%	10%	0%	10%	10%	0%	15%	15%
Weight of coated tablets	0	110	110	0	110	110	0	110	110	0	115	115

F_1, F2, F3, F4- CORE TABLETS
A- Abbreviation refers to 4:1 HPMCcps 15: Eudragit RS100 in coating composition.
B- Abbreviation refers to 1:4 HPMCcps 15: Eudragit RS100 in coating composition.

Table 2: The 2^3 full factorial design for coating of formulations

		Factor 1	Factor 2	Factor 3
Std	**Run**	**Amount A:HPMC15cps**	**B:Type of rate controlling polymer**	**C:Amount of rate controlling polymer**
		Mg		Mg
4	1	500	Eudragit	100
3	2	100	Eudragit	100
1	3	100	CAP	100
6	4	500	CAP	500
5	5	100	CAP	500
8	6	500	Eudragit	500
7	7	100	Eudragit	500
2	8	500	CAP	100

Table 3: Composition of coating solutions

FORMULATION CODE	HPMC 15 cps	Eudragit RS 100	CAP	Methanol	Acetone	Weight gain in %
F4D1 (mg)	100	100		10		15
F4D2 (mg)	100	500		10		15
F4D3 (mg)	500	100		10		15
F4D4 (mg)	500	500		10		15
F4D5 (mg)	100		100		10	15
F4D6 (mg)	100		500		10	15
F4D7 (mg)	500		100		10	15
F4D8 (mg)	500		500		10	15

TABLE 4: Evaluation of post compression parameters of core tablets of Atorvastatin calcium:

Formulation code	Weight variation (mean±SDmg(n=20)	Thickness (mm) ± SD	Hardness (kg/cm^2) (mean ± SD , (n=3)	Friability (%) (n=10)	Assay(%)
F1	101 ±0.06	5.35 ±0.052	4.2 ±0.28	0.01	104.32 ±0.03
F2	103 ±0.04	5.55 ±0.012	4.5 ±0.5	0.02	99.62 ±0.07
F3	99 ± 0.08	5.65 ±0.042	4.2±0.28	0.01	107.12 ±0.09
F4	102 ± 0.1	5.55 ±0.012	4.8 ±0.58	0.05	102.2 ±0.09

TABLE 5: *In-vitro* Dissolution of core tablets

TIME(h)	F 1	F 2	F 3	F 4
1	32.927±0.8683	13.5029±0.4546	92.214±5.2164	60.8802±0.0739
2	41.638±0.3799++	18.5263±0.7388	100.329±2.0865	114.486±1.1987
3	94.301±0.5519	30.566±0.8405	104.755±3.1298	111.23±1.056
4	103.99±1.8706	39.991±0.4803	105.124±0.5216	110.14±1.354
5	109.679±1.3546	54.807±1.0206	109.665±5.7380	109.171±3.4321
6	106.774±1.9666	61.260±0.9005	113.633±1.5649	103.463±3.1537
8	96.585± 3.2466	84.185±1.0206	95.165±1.0432	94.624±3.6704
10	91.963± 4.113	95.0958±8.045	91.476±3.1298	89.468±4.537
12	86.045±.6866	103.1619±6.604	95.903±2.0865	83.416±5.5537

The values of dissolution test were tabulated in Table-6. All the formulations except F2 gave 100% release within 5 hours. F1 formulation showed 32.92% at 1 st hour and maximum release at 5th hour. F2 gave 13.502 % release at 1 st hour and a maximum release at 12th hour. Formulation F3 gave 92.214 % of drug release at 1 st hour and maximum drug release at 6 th hour. Formulation F 4 showed 60.88 % at 1 st hour and maximum drug release at 2nd hour. So it was considered as the optimum core formulation.

TABLE 6: *In-vitro* Dissolution of coated tablets

TIME(h)	F1A	F1B	F 2 A	F 2 B
0	0	0	0	0
1	3.63±0.0325	1.776±0.037	3.8579±0.0568	2.17±.034
2	4.989±0.431	2.471±0.0325	5.879±0.0511	4.866±0.045
3	14.84±0.72	8.268±0.319	13.86±0.135	10.308±0.123
4	16.988±1.221	8.552±0.491	18.148±0.471	10.855±0.153
5	25.948±0.95	9.16±0.433	24.771±0.591	13.284±0.069
6	33.489±0.72	17.106±0.204	29.86±0.831	14.226±0.525
8	54.448±0.892	45.4±0.319	42.644±0.531	18.514±0.465
10	57.4±0.95	61.823±0.491	58.479±0.711	20.934±0.886
12	74.881±1.695	67.6611±5.192	65.611±0.351	24.67±0.525

TABLE 7: *In-vitro* Dissolution of coated tablets

TIME(h)	F 3 A	F 3 B	F 4 A	F 4 B
0	0	0	0	0
1	0.863±.0369	0.679±0.008	14.422±0.156	4.832±0.365
2	1.046±.0422	0.758±0.015	56.951±0.417	5.127±0.365
3	6.553±0.114	3.774±0.052	95.165±5.216	5.348±0.26
4	6.901±0.126	3.983±0.042	106.231±3.129	6.307±0.26
5	9.289±0.22	4.196±0.089	117.665±3.651	14.090±0.834
6	16.31±0.712	12.41±0.755	123.567±4.694	67.500±4.694
8	74.282±1.214	52.14±0.059	138.321±3.651	107.70±28.168
10	96.983±5.067	70.38±1.231	125.411±6.259	127.624±25.038
12	108.037±9.533	85.22±4.244	110.288±2.608	103.649±17.214

Table 7 & Table 8 showed all 8 formulations which were coated with HPMC 15 cps and Eudragit RS 100. Here all the A formulations were coated with 400 mg of HPMC 15 cps and 100 mg of Eudragit RS 100 B formulations were coated with 100 mg HPMC 15 cps of and 400 mg of Eudragit RS 100.
In all 8 coated formulations, commonly it was found that the B sets of formulations were more controlling the drug release. F4 B showed comparatively good results. All other formulations were more delayed in nature. According to the evaluation tests carried out for the core tablets of, Atorvastatin formulation F4 was found to be the optimum formulation. Further F4 formulation was tried with combinations of HPMC 15cps &CAP and HPMC 15cps & Eudragit RS 100 to obtain pulsatile release tablets.

Time (hrs)	F 4 D1 (Mean ± SD)	F 4 D2 (Mean ± SD)	F 4 D3 (Mean ± SD)	F 4 D4 (Mean ± SD)	F 4 D5 (Mean ± SD)	F 4 D6 (Mean ± SD)	F 4 D7 (Mean ± SD)	F 4 D8 (Mean ± SD)
0	0	0	0	0	0	0	0	0
1	10.43 ± 0.469	4.832 ± 0.365	4.832 ± 0.1883	1.460 ± 0.0312	12.209 ± 0.3651	2.467 ± 0.1512	5.0865 ± 0.3182	1.3684 ± 0.0154
2	24.27 ± 1.877	5.127 ± 0.365	5.031 ± 0.166	2.795 ± 0.198	29.693 ± 0.6781	2.847 ± 0.1043	7 .7091 ± 0.6781	1.5123 ± 0.0625
3	39.94 ± 0.469	5.348 ± 0.2608	8.494 ± 0.641	4.252 ± 0.0678	45.664 ± 0.2086	4.079 ± 0.0625	11.287 ± 0.4173	3.8287 ± 0.0312
4	54.62 ± 1.930	6.307 ± 0.2608	26.225 ± 3.286	4.994 ± 0.2086	56.324 ± 0.4694	10.733 ± 0.2608	30.541 ± 0.7303	5.9644 ± 0.1095
6	75.025 ± 3.442	10.918 ± 0.1043	55.033 ± 1.877	13.647 ± 0.4173	77.054 ± 4.7469	24.421 ± 0.364	76.353 ± 2.608	9.5165 ± 0.3129
8	92.10 ± 13.406	67.50 ± 4.694	73.255 ± 3.025	25.414 ± 2.0344	97.009 ± 4.694	54.369 ± 0.6259	87.050 ± 2.086	21.1355 ± 0.2608
10	108.84 ± 4.746	107.70 ± 28.168	111.116 ± 4.173	65.066 ± 0.9389	112.50 ± 6.7813	100.69 ± 1.564	109.91 ± 3.129	52.1933 ± 0.4694
12	127.62 ± 11.476	127.62 ± 25.038	98.063 ± 7.876	103.28 ± 2.0865	133.15 ± 5.738	114.71 ± 3.6515	102.82 ± 7.824	74.9887 ± 1.7214
24	113.60 ± 9.389	103.64 ± 17.214	92.325 ± 4.225	128.32 ± 4.225	126.14 ± 7.303	125.41 ± 3.129	102.38 ± 4.694	117.296 ± 1.0432

Table 8: *In-vitro* drug release profile of Atorvastatin calcium pulsatile release tablet for F4D1-F4D8

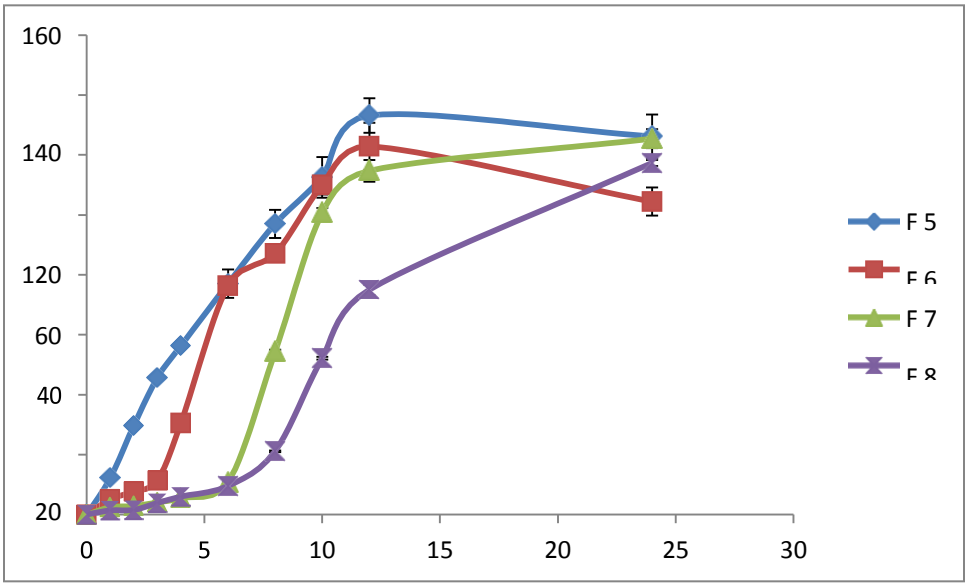

Fig. 2: standard deviation profile of coated formulations F4D5-F4D8

All the eight formulations of prepared coated tablets of Atorvastatin calcium were subjected to *in-vitro* release studies. These studies were carried out using USP dissolution apparatus type-II in pH 6.8 phosphate buffer as the dissolution media. Up to 10% release was accepted as the minimum % release allowed during lag time and after the lag time a rapid release of drug within 8-10 hours[11]. (Table 9)

Formulation F4D1, was coated with HPMC 15 Cps 100 mg and Eudragit RS 100 100 mg and the weight gain was 15% . It showed a 1 hour of lag time [10% release]. Percentage cumulative drug release was found to be 108.849 at the 10th hour. This formulation was not found to be suitable in terms of pulsatile release.

Formulation F4D2, was coated with HPMC 15 Cps 100 mg and Eudragit RS 100 500 mg and the weight gain was 15%. It shows a 6 hours of lag time 67.5009 % drug release showed at 8 h. Percentage cumulative drug release was found to be 107.706 % at the 10th hour.

Formulation F4D3, was coated with HPMC 15 Cps and Eudragit RS 100 with change in 500:100 polymer amount and the weight gain was 15%. This formulation was not found to be good in terms of pulsatile release because it showed a less lag time of 3 hours.

Formulation F4D4, was coated with HPMC 15 Cps and Eudragit RS 100 with change in polymer amount (500:500) and the weight gain was 15%. It showed 4 hours of lag time. Percentage cumulative drug release was maximum of 103.2802 % at 12 hours. This formulation was not found to be suitable in terms of pulsatile release as it showed less lag time and extended the release till 12 h.

Formulation F4D5, was coated with HPMC 15 Cps and CAP with 100mg:100mg and the weight gain was 15%. This formulation could not be considered as pulsatile release as it started releasing the drug at the very first hours i.e, the lag time was not maintained.

Formulation F4D6, was coated with HPMC 15 Cps and CAP with100mg:500mg and the weight gain was 15%. It showed a lag time of 4 hours. It showed maximum drug release of 100.698% at 10th hour. This formulation was not found to be good in terms of pulsatile release as it showed lag time of 4 hours and maximum drug release within 10 hours.

Formulation F4D7, was coated with HPMC 15 Cps and CAP with 500 mg:100 mg and the weight gain was 15%. It showed a lag time of 2 hours only and this formulation showed burst release at 10th hr the release is 109.929%. So this formulation could not be considered as the optimum formulation.

Formulation F4D8, was coated HPMC 15 Cps and CAP with highest of 500 mg:500 mg and the weight gain was 15%..This formulation was not found to be suitable in terms of pulsatile release as it showed lag time of 6 hrs and the release after 12th hr. It cannot be considered as a good pulsatile release formulation.

Data Analysis

Optimization: Responses obtained from all 8 formulations were evaluated using Design-Expert software version 11. Evaluated responses are lag time, %drug release at 4th hour and time for maximum drug release. A numerical optimization technique was used to produce the formulations with the anticipated responses, in which a minimum and a maximum level must be provided for each dependent variables. The p value of lag-time, release at 4 h and maximum% drug release were found to be less than 0.0500 , indicating that the models are significant. The polynomial equations(A: HPMC15cps in mg,B : Rate controlling polymer), response plots for 3 responses are shown.

Lag time

In case of lag time the Coefficients were found to be same and showed a difference in the constant i.e, CAP(+0.50000) showed increased effect on lag time than Eudragit (+0.25000).

For Eudragit

+0.250000-0.000625*HPMC 15CPS+0.010625*Rate controlling polymer

For Cellulose Acetate Phthalate

+0.500000-0.000625*HPMC 15CPS+0.10625* Rate controlling polymer

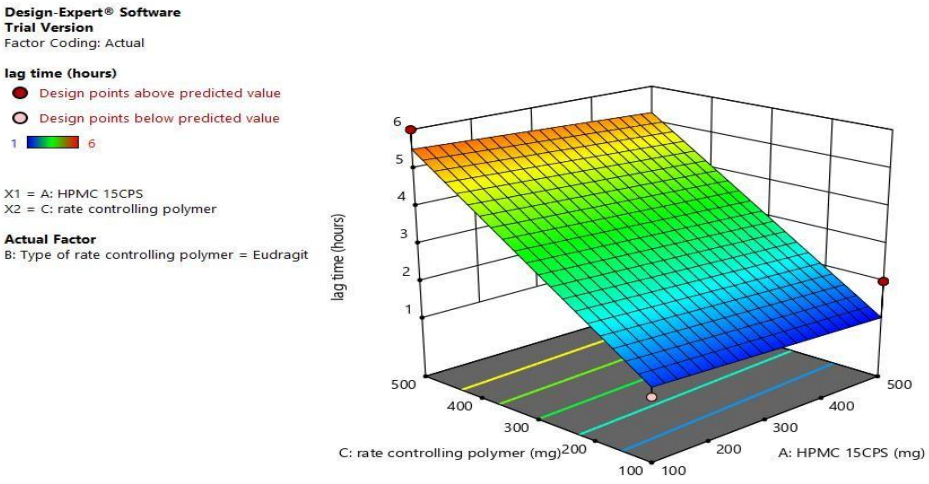

Fig. 3: Response surface plot showing the influence of HPMC 15cps and rate Controlling polymer on the % drug release at lag time

Figure 3 showed the response surface plot for lag time, Here X_1-A: HPMC 15 cps and X_2-C: rate controlling polymer. B type of rate controlling polymer (Eudragit) was considered as actual factors. It was observed that the increase in polymer showed an increase in lag time.

% Drug release at 4thhour

In case of % drug release at 4th hour the coefficients are almost same and the constant terms varied. CAP (+77.35228) showing a more controlling effect than Eudragit (+75.25351).

For Eudragit

+75.25351-0.087109*HPMC 15CPS-0.136905*Rate controlling polymer +0.000167* (HPMC 15CPS* rate controlling polymer)

For Cellulose Acetate Phthalate

+77.35228-0.144167*HPMC 15CPS-0.081664*Rate controlling polymer +0.000167* (HPMC 15CPS* rate controlling polymer)

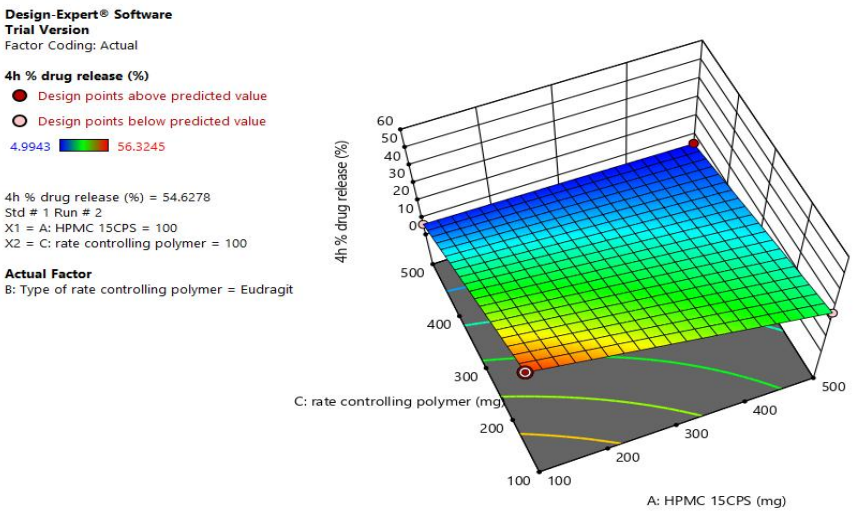

Fig. 4: Response surface plot showing the influence of HPMC 15cps and rate Controlling polymer on the % drug release at the end of 4th hour

Figure 4 Shown a minimum release at maximum concentration of polymers. Less polymer concentration leads to more release.

Maximum % drug release

In case of maximum % drug release the coefficients are same and constant is differed. CAP (+8.25000) showed an increased control over Eudragit (+7.75000).

For Eudragit

+7.75000+0.001250*HPMC 15CPS+0.031250*Rate controlling polymer

For Cellulose Acetate phthalate

+8.25000+0.001250*HPMC 15CPS+0.031250*Rate controlling polymer

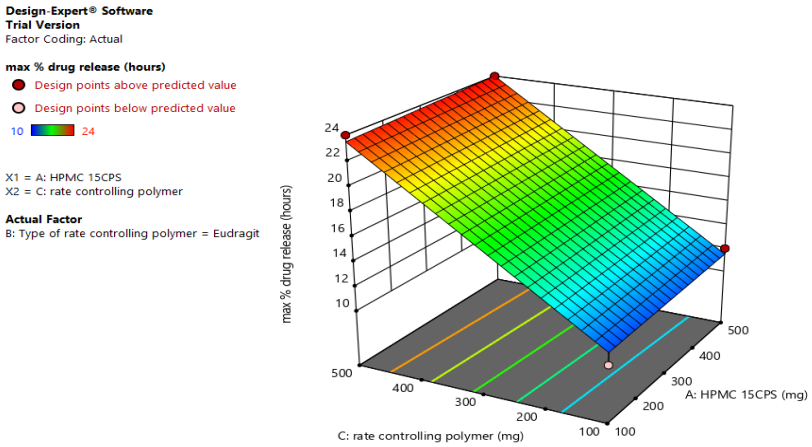

Fig. 5: Response surface plot showing the influence of HPMC 15cps and rate Controlling polymer on the % drug release at the maximum % drug release

In Figure 5, it was observed that the increased polymer concentration gave a more time for the maximum % drug release. The decreased polymer concentration showed a fast maximum % drug release compared to more polymer concentration.

CONCLUSION

The aim of this study was to explore the feasibility of time dependent pulsatile drug delivery system of Atorvastatin calcium for the treatment of hypercholesterolemia. A satisfactory attempt was made to develop pulsatile system of Atorvastatin calcium and evaluate it.

As the formulation F4D2 showed a complete release at 10th hour and the lag time of 6 hours , it can be considered as an optimum formulation for pulsatile drug release. Pulsatile drug release over a period of 8-10 hours were achieved, in which core tablet of Atorvastatin calcium was coated by HPMC 15cps and Eudragit RS 100 with weight gain of 15% and showed a lag time of 6 hours. Thus pulsatile drug delivery system can be considered as one of the promising formulation technique for chronotherapeutics management of hypercholesterolemia.

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