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FORMULATION AND EVALUATION OF PULSATILE DRUG DELIVERY SYSTEM OF PITAVASTATIN

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ABSTRACT

Aim of the present work was to formulate and evaluate an oral pulsatile drug delivery system to achieve time release of Pitavastatin based on chronopharmaceutical approach for the treatment of Pitavastatin a lipid lowering agent that belongs to the statin class of medications for treatment of dyslipidemia Pulsatile delivery system is capable of delivering drug when and where it required most. Time delayed tablets, designed to release drug after a predictable lag time, are intended for oral chronotherapy. The basic design consists of a core tablets prepared by wet granulation method. The tablets were coated with an inner swellable layer containing HPMC and intermediate rupturable layer of EC: HPMC (9:1). The entire device was enteric coated with 3% cellulose acetate phthalate solution, so that the variability in gastric emptying time can be overcome. The prepared pulsatile tablets were evaluated for the drug content, thickness and in-vitro release profile, etc. In-vitro release profiles of pulsatile device during six hours studies were found to have very good sustaining efficacy. During the first five hours it shows minimum drug release and at the end of six hours immediate release was observed.

Key Words: *HPMC, Chronotherapy, pulsatile.*

INTRODUCTION

Chronopharmaceutic is a branch of pharmaceutics devoted to design and evaluation of drug delivery system that release a bioactive agent at a rhythm that ideally matches the biological requirement of a given disease therapy. Ideally chronopharmaceutical drug delivery system should embody time controlled and site specific drug delivery system [1].

Extending patent life among modified release oral dosage forms, increasing interest has currently turned to systems designed to achieve time specific (delayed, pulsatile) and site-specific delivery of drugs. In particular, systems for delayed release are meant to deliver the active principle after a programmed time period following administration. These systems constitute a relatively new class of devices which is having importance connected with the recent advances in chronopharmacology. It is by now well-known that the symptoms of a large number of pathologies as well as the pharmacokinetics and pharmacodynamics of several drugs follow temporal rhythms, often resulting in circadian variations [2].

MATERIALS AND METHODS

Pitavastatin, Lactose Monohydrate, Lactose Monohydrate, Sodium Starch Glycolate, HPMC 50cps, Cellulose acetate phthalate,Ethyl cellulose, Ethyl cellulose, Triacetin,Acetone, Sodium Chloride, Sodium Bicarbonate, Potassium dihydrogen, Sodium hydroxide, Hydrochloric acid,Citric acid, Tartaric acid, Magnesium stearat Talc. Dichloro Methane, Ethyl alcohol, Starch, Chitosan.

It is one of the important pre requisite in development of any drug delivery system. Preformulation studies were performed on the drug, which included melting point determination, solubility and compatibility studies.

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Formulation of granules of Pitavastatin:

For the batch size of 100 tablets, Pitavastatin was taken and mixed with lactose, MCC, and other ingredients in glass mortar and pestle and mixed well. Binder solution was added to that mixture to form a cohesive mass and passed through sieve No. 12 and 22. Wet granules were collected and dried at 60°C for one hour. 3% HPMC 50 cps in Distilled water was found to be suitable to formulate granules and tablets of Pitavastatin since it gave desirable hardness and friability to the formulated tablets [4, 5].

Evaluation of preformulation parameters

Tablets were subjected to evaluation of properties including drug content uniformity, weight variation, tablet hardness, friability, and thickness, and in-vitro drug release with different media.

Granules formulated were weighed for practical yield and the same was recorded. These granules were mixed with 1% magnesium stearate and 1% purified talc mixed with 10% fines and subjected to compression. Compression of tablets was done in rotary compression tablet machine using flat oval shape punch. The prepared tablet of each batch was evaluated for the tablet properties.

RESULT AND DISCUSSION

Shape of the tablet:

Microscopic examitions Pitavastatin of tablets from F1 to F8 were found to be oval in shape with smooth shining surface and free from cracks

Melting Point Determition: 190-192^0

Micromeretic properties of Granules of Pitavastatin:

Carr's Index: Carr's index was carried out and the results were shown in Table-2. It was found to be between 10.80±0.17and 13.50±0.17indicating the granules have the required flow property for compression.

Angle of Repose (θ): The angle of repose for the formulated blend was carried out and the results were shown in Table-2. It can be concluded that all the formulation blends angle of repose was found to be in the range 26.46±0.23 to 29.54±0.23. Hence the entire formulation blends was found to possess good flow property.

Evaluation of Physical Parameters of compressed tablets of Pitavastatin:

Weight Variation Test: The percentage weight variations for all formulations were tabulated in Table-3. All the formulated (F1 to F8) tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits. The weights of all the tablets were found to be uniform with low standard deviation values.

Hardness test:The measured hardness of tablets of all the formulations ranged between 3.5±0.5 to 3.8±0.4 kg/cm^2 (Table-3). This ensures good handling characteristics of all batches.

Friability Test: The values of friability test were tabulated in Table-14S. The % friability was less than 0.6% in all the formulations ensuring that the tablets were mechanically stable

Thickness of core and coated Pitavastatin Tablets:

Thickness of the coated tablet: Thickness of the coated formulation was measured with Digital verniar caliper. The measured thickness of coated tablets of each formulation ranged between **s**2.46±0.06mm to 3.46±0.08mm (Table15).This ensures uniform coating to all batches.

Content uniformity of different formula (F1 to F8):

Drug content uniformity: The percentage of drug content for F1 to F8 was found to be between 96.13±2.10% t o 100.60±2.16%. It complies with official specifications. The results were shown in Table-6.

Cumulative percent drug release of core Pitavastatin tablets of different formulations. (F1 to F8):

In-vitro Dissolution of Core Tablet: All the eight formulations of prepared core tablets of Pitavastatin were subjected to *in vitro* release studies. The values of Dissolution test were tabulated in Table-18. It was found to be between 97.61% and 101.29%. All the formulations gave maximum release within 90 minutes.

Cumulative % drug release of coated different formulation (F1 to F8):

With all the formulations, there was no drug release in pH 1.2, thus indicating the efficiency of 3% CAP for enteric coating. In case of formulation F1, at the end of 6th hour.

The cumulative drug release was found to be 36.24%, because it does not contain Sodium bicarbonate and Sodium chloride. Therefore enough pressure was not created inside to rupture the tablet. It contains chitosan which is rate controlling polymer. So F1 is having lowest cumulative percentage drug release.

In case of formulation F2 & F3, Formulation F2 contains 2.5% Sodiumbicarbonate and 2.5% Sodium chloride and formulation F3 contains 3.5% Sodium bicarbonate pitavastatin and 3.5% Sodium chloride. At the end of 6th hour the cumulative drug release was found to be 71.71% and 75.83%. So as the content of sodium bicarbonate Pitavastatin and sodium chloride increase, drug release is going to be increase which might be due to increase in pressure inside coated layer.

Formulation F4, F6 and F8 contain 5% sodium bicarbonate pitavastatin, 5% tartaric acid and 5% citric acid respectively. Formulation F6 and F8 also contain 2.5% sodium bicarbonate. Here in F4, F6 and F8 cumulative drug release was found to be 77.61%, 82.08% and 84.04% respectively after 6th hour. So as the content of tartaric acid and citric acid increased with sodium bicarbonate pressure inside the coated layer increased which rupture the layer which leads to increase the cumulative percent drug release. Tartaric acid is retarding drug release as compared to citric acid.

Formulation F5 and F7 commonly contain 2.5% sodium bicarbonate and 2.5% tartaric acid and 2.5% citric acid respectively, and formulation F4 contain 5% sodium bicarbonate, Here in F4, F5, and F7 cumulative drug release was found to be 77.61%, 67.82% and 73.55% respectively after 6th hour. So it can be concluded that tartaric acid is most pressure controlling gas producing excipient while citric acid and sodium bicarbonate are followed by tartaric acid [6].

Table No. 1: Different Formulations of Pitavastatin Granules

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Pitavastatin	4	4	4	4	4	4	4	4
Lactose	50	50	40	55	50	25	50	25
MCC	35	35	35	35	35	35	35	35
$NaHCO_3$	20	20	20	20	20	20	20	20
NaCl	-	25	50	-	-	-	-	-
Tartaric acid	-	-	-	-	25	50	-	-
Citric acid	-	-	-	-	-	-	25	50
Sodium starch Glycolate	-	25	25	25	25	25	25	25
HPMC	35	35	35	35	35	35	35	35
Magnesium stearate	3	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3	3
PVP K30LR	30	-	-	-	-	-	-	-
Chitosan	20	-	-	-	-	-	-	-
TOTAL	200	200	200	200	200	200	200	200

Table No. 2: Micromeretic properties of Granules of Pitavastatin

Formula	Micromeretic properties of powder blend				
	Angle of Repose (θ) ±SD	Bulk Density (g/ml) ±SD	Tapped Density (g/ml)±SD	Carr's Index. (%)±SD	Hausner's ratio±SD
F1	27.63±0.38	0.379±0.019	0.421±0.021	10.80±0.17	1.11±0.025
F2	28.68±0.23	0.382±0.025	0.434±0.018	11.12±0.12	1.12±0.037
F3	26.46±0.23	0.363±0.032	0.420±0.025	13.14±0.26	1.14±0.032
F4	27.68±0.58	0.385±0.022	0.432±0.032	11.10±0.21	1.12±0.020
F5	26.54±0.28	0.376±0.017	0.433±0.029	13.50±0.17	1.14±0.018
F6	28.89±0.23	0.376±0.013	0.420±0.024	10.82±0.26	1.12±0.029
F7	29.54±0.23	0.362±0.011	0.420±0.019	13.14±0.12	1.14±0.031
F8	28.48±0.45	0.376±0.032	0.420±0.026	10.82±0.19	1.12±0.039

Table No. 3: Evaluation of Physical Parameters of compressed tablets of Pitavastatin

Formula	Weight variation (mean ± SD, mg) (n = 20)	Hardness (mean ± SD) (n = 3)	Friability (%) (n = 10)
F1	200±1.96	3.5±0.5	0.100
F2	199±1.67	3.8±0.4	0.571
F3	199±1.77	3.5±0.2	0.632
F4	200±1.62	3.8±0.4	0.060
F5	199±1.74	3.5±0.5	0.140
F6	199±1.15	3.8±0.4	0.160
F7	200±1.47	3.8±0.3	0.478
F8	199±1.37	3.6±0.4	0.130

Table No. 4: Thickness of core and coated Pitavastatin Tablets

Formulation code	Thickness(mm)± SD	
	Core tablets	Coated Tablets
F1	2.92±0.06	3.46±0.08
F2	2.12±0.05	2.62±0.09
F3	2.00±0.07	2.48±0.08
F4	2.13±0.08	2.52±0.06
F5	2.10±0.09	2.62±0.07
F6	2.94±0.08	2.47±0.08
F7	2.01±0.07	2.46±0.06
F8	2.14±0.06	2.58±0.07

Table No. 5: Content uniformity

Formulation code	pH 1.2	pH 6.8
F1	97.76±2.93	97.78±1.72
F2	96.13±2.10	98.03±2.76
F3	100.06±2.85	97.81±3.10
F4	100.32±2.42	100.21±2.17
F5	97.36±2.50	97.09±3.11
F6	99.36±1.15	98.06±1.31
F7	98.54±1.66	96.34±1.98
F8	100.59±2.50	100.60±2.16

Table No. 6: Cumulative percent drug release

TIME	Cumulative % drug release							
	F1	F2	F3	F4	F5	F6	F7	F8
5	4.29	22.23	26.78	16.94	10.50	10.89	11.19	11.68
10	10.36	41.16	31.57	29.50	19.11	23.03	18.72	23.37
15	17.81	55.20	34.76	42.65	32.18	42.59	34.37	43.58
20	24.70	73.77	45.56	55.21	41.70	55.35	53.64	57.54
25	30.17	84.36	59.95	66.18	50.45	65.61	64.24	67.82
30	35.63	98.98	74.38	75.75	63.15	76.07	77.07	78.49
40	46.63	99.86	92.93	84.12	71.49	86.54	89.45	91.96
50	50.62	100.26	99.53	95.48	86.63	98.82	95.77	98.02
60	56.85	99.87	101.17	99.27	98.51	97.41	98.62	100.23
75	68.84	99.44	101.52	100.06	98.11	98.82	97.21	101.29
90	78.78	99.86	100.26	98.67	97.61	99.39	99.62	–
105	88.90	–	–	–	–	–	–	–
120	99.42	–	–	–	–	–	–	–

Table No. 7: Cumulative % drug release

Time (Hrs.)	Cumulative % drug release							
	F1	F2	F3	F4	F5	F6	F	F8
		IN pH 1.2						
1	0.84	0.56	0.37	0.69	0.42	0.31	1.03	0.85
2	1.52	2.08	0.82	1.44	0.55	1.14	1.60	1.32
		IN pH 6.8						
3	6.19	7.27	7.30	16.78	5.25	8.93	6.33	9.43
4	14.70	16.09	14.21	21.74	13.82	16.21	17.56	18.37
5	26.91	32.07	27.88	42.17	27.42	31.16	32.51	35.75
6	35.24	71.71	75.83	77.61	67.82	82.08	73.55	84.04
7	48.15	83.12	84.17	98.37	88.15	95.22	97.67	99.27
8	64.95	95.37	96.46	–	99.02	100.53	–	–
9	75.16	–	–	–	–	–	–	–
10	85.84	–	–	–	–	–	–	–
11	97.62	–	–	–	–	–	–	–

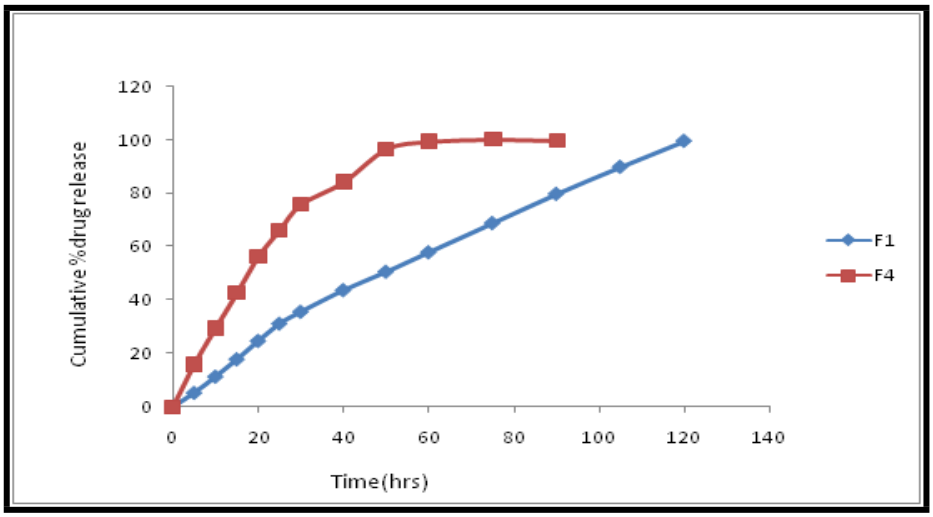

Fig. 1: Cumulative percentage drug release of coated formulation F1 & F4

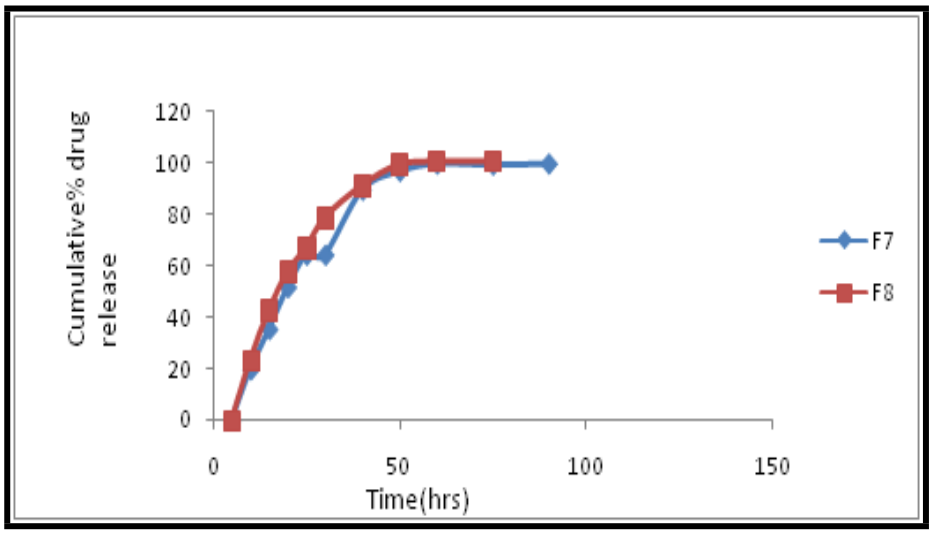

Fig. 2: Cumulative percentage drug release of coated formulation F7 & F8

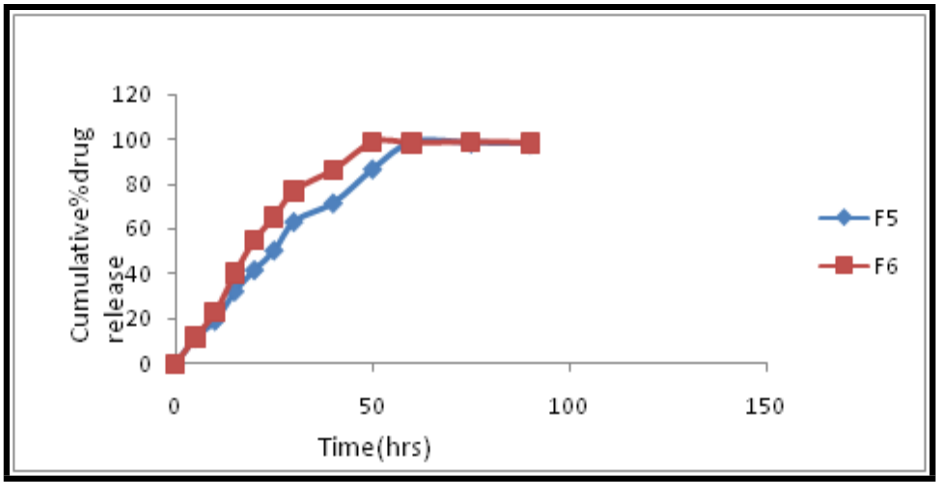

Fig. 3: Cumulative percentage drug release of coated formulation F2 & F3

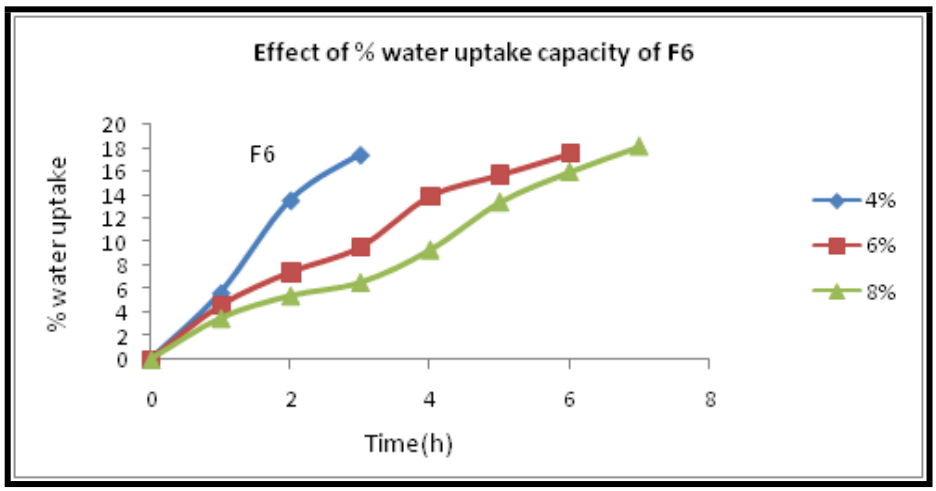

Fig. 4: Cumulative percentage drug release of coated formulation F5 & F6

Table No. 8: Effect of Outer Polymer Concentration on % Water Uptake

TIME (hrs)	F-3			F-6			F-8		
	4%	6%	8%	4%	6%	8%	4%	6%	8%
1	5.9	3.42	4.76	6.67	5.58	6.51	5.87	6.35	2.62
2	12.32	6.28	5.22	15.58	8.42	7.46	13.47	8.38	5.31
3	16.72	9.47	7.35	17.46	9.56	6.55	16.61	9.45	6.47
4	-	12.73	9.11	-	12.89	9.31	-	12.81	8.24
5	-	14.58	12.51	-	16.71	12.39	-	14.65	13.26
6	-	16.34	15.82	-	18.51	14.97	-	18.63	14.90
7	-	-	16.64	-	-	17.15	-	-	18.92

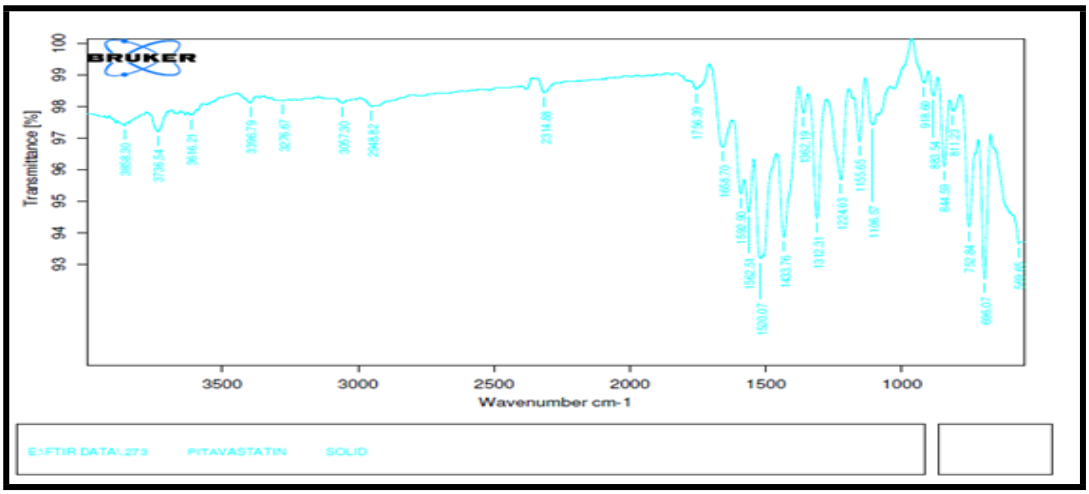

Fig. 5: Effect of % Water Uptake capacity of F6

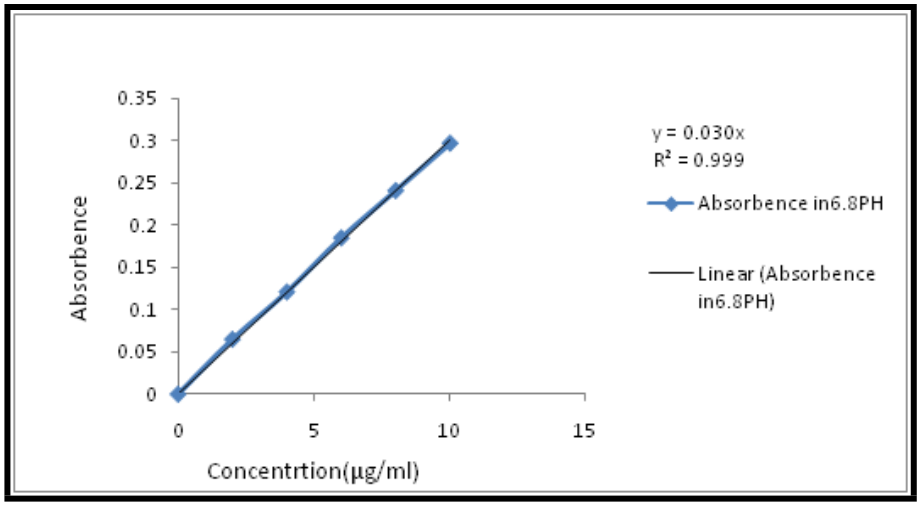

Fig. 6: FTIR Spectrum of Pitavastatin

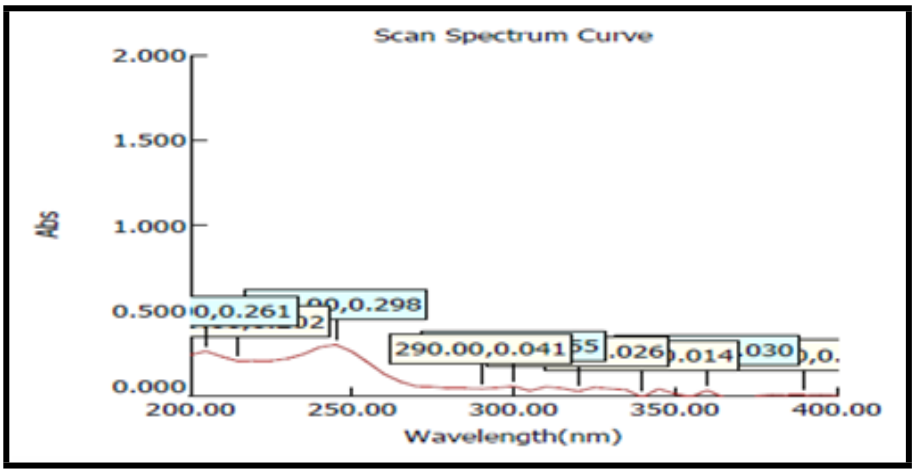

Fig. 7: Calibration curve in Phosphate buffer pH 6.8

Calibration curve:

In preformulation studies, it was found that, the estimation of Pitavastatin by spectrophotometric method at 245 nm in pH 1.2 and pH 6.8 buffers had good reproducibility, at the concentration between 2-10 µg/ml. Correlation between concentration coefficient was found 0.999 for both pH 1.2 and pH 6.8 and slope for ph 1.2 and pH 6.8 was found 0.045 and 0.029 respectively [9].

Stability Study:

Stability studies were carried out in view of the potential utility of the pulsatile device for release of Pitavastatin. The results indicated that the selected formulations showed no change in physical appearance. Drug content was affected to a lesser extent in case of the core tablet. While in case of coated formulations no change was observed.

Stability Studies were carried out at 40^{0}C temp and 75% RH for 30 days. The core tablet and coated tablet of selected formulation were packed in amber-colored bottles tightly plugged with cotton and capped. And %drug content was checked at regular time intervals.

CONCLUSION

The aim of this study was to explore the feasibility of time dependent pulsatile drug delivery system of for the Pitavastatin a lipid-lowering agent A satisfactory attempt was made to develop pulsatile system of Pitavastatin and evaluated it.

From the reproducible results obtained from the executed experiments it can be concluded that:

1. 3% HPMC Coating layer gives better rupture of outer coating.
2. Increases in amount of HPMC coating reduce the rupture time.
3. Coating of Ethyl Cellulose and HPMC in the ratio 9:1 was suitable as intermediate polymeric coating for the tablet having 3% HPMC as inner coating layer.
4. Coating of 3% CAP was suitable as outer most coating layer to retard the drug release in acidic media.
5. Increase in amount of Ethyl cellulose increased the lag-time.
6. Increases in amount of HPMC in intermediate coating layer decreased the lag time, because it swells and form pores through which dissolution medium penetrate and tablet ruptured early.
7. From the dissolution studies, it was observed that, the enteric coat of the cellulose acetate phthalate was intact for 2 hours in pH 1.2 buffer and followed Korsmeyer-peppas equation.
8. On the basis of drug content, particle size and morphology, *in-vitro* release studies and its kinetic data, F3, F6 and F8 were selected as optimized formulations for designing Pulsatile device.
9. Therefore the study proved that coated Pitavastatin can be successfully used as a time dependent modified chronopharmaceutical formulation.
10. Stability studies proved that the formulation is quite stable and drug content was affected to a lesser extent in case of the core tablet, while in case of coated formulations no change was observed. So it can be concluded that coating of tablets seems to decrease the effect of temperature and moisture on the degradation of Pitavastatin. In conclusion, Pulsatile drug release over a period of 5-6 hours was achieved, in which core tablet of Pitavastatin was coated first by 3% HPMC100 cp layer then by EC: HPMC (9:1) and finaelly with CAP coating solution. Thus Pulsatile drug delivery system can be considered as one of the promising formulation technique for chronotherapeutic manaegement of a lipid-lowering.

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