Research Article

FORMULATION AND EVALUATION OF PULSATILE DRUG DELIVERY SYSTEM FOR SEQUENTIAL RELEASE OF ATORVASTATIN

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ABSTRACT

The aim of the present research was to formulate and evaluate pulsatile drug delivery system for sequential release of Atorvastatin that suits with the biological requirement [circadian rhythm] of the disease by releasing the drug with a distinct predetermined lag time of 6-8 hours, in which a core tablet of Atorvastatin were formulated by incorporating sodium starch glycolate and was coated with CAP, HPC etc. in different ratio as a release modifier. All prepared multilayered tablets were subjected for various evaluation studies like disintegration time, water uptake, rupture study etc. Result of in vitro dissolution study of the prepared tablet was suggested that, the release of drug from multilayered pulsatile unit match with chrono-biological requirement of disease.

Keywords: Circadian rhythm, Pulsatile drug delivery system, Eudragit S100, Eudragit RS100.

INTRODUCTION

For many disease states the ideal dosage regimen is that by which an acceptable therapeutic concentration of drug at the site(s) of action is attained immediately and is then maintained constant for the desired duration of the treatment[1]. The differences in patterns of illness between day and night for cardiovascular disorders such as hypertension, angina, heart attack, sudden cardiac death and stroke have been documented. Medications have been formulated, and dosing schedules established, in an attempt to provide appropriate concentration of a drug in the target area of the body when the drug is most needed. It has been recognized that many symptoms and onset of disease occur during specific time periods of the 24 h day, e.g., asthma and angina pectoris attacks are most frequently in the morning hours.

Chronobiology is the study of biological rhythms and their mechanisms[2,3]. The term "chrono" basically refers to the observation that every metabolic event undergoes rhythmic changes in time. Researchers have concluded that all living organisms are composites of rhythms with varying frequencies that may range from seconds to seasons[4]. Chronotherapeutics refers to a treatment method in which in vivo drug availability is timed to match rhythms of disease in order to optimize therapeutic outcomes and minimize side effects[5]. A circadian rhythm takes place during cholesterol synthesis. Cholesterol synthesis is generally higher during night time than day light. Sometimes it varies according to individuals. The maximal production occurs early in the morning, i.e., 12 h after last meal. Studies with 3-hydroxy-3-methylglutaryl-CoenzymeA (HMG-CoA) reductase inhibitors have suggested that evening dosing was more effective than morning dosing. The activity of rate limiting enzyme HMG-CoA is higher in the night time. But the diurnal variations occur due to periodicity or degradation of this regulatory enzyme.

Atorvastatin is a member of the drug class known as statins. It is used for lowering cholesterol. Atorvastatin inhibits the rate-determining enzyme located in hepatic tissue that produces mevalonate, a small molecule used in the synthesis of cholesterol and other mevalonate derivatives. This lowers the amount of cholesterol produced which in turn lowers the total amount of LDL cholesterol. Atorvastatin is a competitive inhibitor of HMG-CoA reducates[6,7].

A pulsatile drug delivery system that can be administered at night (before sleep) but that

release drug in early morning would be a promising chronopharmaceutic system[8]. Pulsatile systems are basically time-controlled drug delivery systems in which the system controls the lag time independent of environmental factors like pH, enzymes, gastrointestinal motility, etc9. Food has been shown to reduce the rate and extent of Atorvastatin absorption. Administration of Atorvastatin with food produces a 25% reduction in Cmax (rate of absorption) and a 9% reduction in AUC (extent of absorption). However, food does not affect the plasma LDL-C lowering efficacy of Atorvastatin. Evening Atorvastatin dose administration is known to reduce the Cmax (rate of absorption) and AUC (extent of absorption) by 30% each. Atorvastatin undergoes high intestinal clearance and first-pass metabolism, which is the main cause for the low systemic availability. So in present study Atorvastatin has been found to be suitable drug candidate for the development of chronomodulated drug delivery[10].

MATERIALS AND METHODS

Materials

Atorvastatin was obtained as a gift sample from Sheron pharmaceutical, Dehradun. Cellulose acetate phthalate, Eudragit S 100 and Eudragit RS 100 obtained as a gift sample from Yarrow chem. Products, Mumbai.All other chemicals used were of analytical grade.

Method

Preparation and fabrication of Atorvastatin loaded pulsatile tablet

The methodology adopted include[11,12] :

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

Preparation of core tablets of Atorvastatin

Tablets of Atorvastatin were formulated by incorporating sodium starch glycolate and other excipients like microcrystalline cellulose, magnesium stearate and Talc etc. Weighed accurate quantity of these excipient and than mixed with magnesium stearate, purified talc and subjected to compression. Compression of tablets was done in rotary compression tablet machine using 16.4x8mm flat oval shape punch.

Coating of the core tablets

Compression coating

It's a novel approach to producing coating layer over the core tablet. For this accurate quantity of pH depended polymer was taken. Half quantity of weighted polymer was placed in the die cavity. Than the core tablet was placed. Over this remaining half part of coating polymer was poured. Than at optimum speed the tablet was compressed.

Dip coating

Prepared core tablet was coated by using dip coating technique. In this method selected polymers dissolve in organic solvent like methanol, ethanol, acetone, at a concentration of 10% w/v. Core tablet were coated using coating pan . Coating procedure repeated until 10% over all weight gain was observed.

Evaluation Parameters[13,14,15]:

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

Weight variation

The weight of the tablet being made was routinely determined to ensure that a tablet contains the proper amount of drug. The USP weight variation test is done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average. The tablets met the USP specification that not more than 2 tablets are outside the percentage limits and no tablet differs by more than 2 times the percentage limit. USP official limits of percentage deviation of tablet are presented in the Table 3.

Table 1: Weight variation limits

S.No.	Average weight of Tablet (mg)	Maximum % difference allowed
1	130 or less	10
2	130-324	7.5
3	324<	5

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 each batch of tablet 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.

Method
20 tablets were weighed and the initial weight of these tablets was recorded and placed in Roche friabilator and rotated at the speed of 25 rpm for 100 revolutions. Then tablets were removed from the friabilator, dusted off the fines and again weighed and the weight was recorded.

$$\%\text{Friability} = \frac{\text{initial weight of tablet} - \text{final weight of tablet}}{\text{initial weight of tablet}} \times 100$$

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.

Content Uniformity
The tablets were tested for their drug content uniformity. At random 20 tablets were weighed and powdered. The powder equivalent to 500 mg was weighed accurately and dissolved in 100ml of phosphate buffer of pH 6.8. The solution was shaken thoroughly. The undissolved matter was removed by filtration through Whattman's filter paper No.41. Then the serial dilutions were carried out. The absorbance of the diluted solutions was measured at 246 nm. The concentration of the drug was computed from the standard curve of the Atorvastatin in phosphate buffer of pH 6.8.

Disintegration time
Tablet disintegration is an important step in drug absorption. The test for disintegration was carried out in Electrolab USP disintegration test apparatus. It consists of 6 glass tubes which are 3 inches long, open at the top, and held against a 10 mesh screen, at the bottom end of the basket rack assembly. To test the disintegration time of tablets, one tablet was placed in each tube and the basket rack was positioned in a 1 litre beaker containing pH 1.2 Buffer solution at 37°C ± 1°C such that the tablet remains 2.5cm below the surface of the liquid. The time taken for the complete disintegration of the tablets was noted.

Effect of outer polymer concentration and water uptake performance
To study the effect of outer polymeric layer concentration on lag time, core tablets were coated with different levels of selected polymer i.e. 4%, 6% and 8% w/w coating (inner swelling layer remained the same). The % water uptake capacity of tablets was determined in the containers filled with 100 ml of pH 1.2 buffer placed in a biological shaker at 37°C. Speed of shaker was adjusted to 75 rpm. Tablets were removed from containers at predetermined regular intervals, blotted with tissue paper, weighed and again placed in medium till the outer coating of tablet started to rupture. The % water uptake was calculated using the formula,
% Water uptake = ((Wt -Wo)/Wo) ×100
Where, Wt is weight of wet tablet at time t and Wo is weight of dry tablet.

Rupture Test
The Rupture test on coated tablets was carried out using USP paddle apparatus at 75 rpm and 37±0.5°C, pH 1.2 and pH 6.8 phosphate buffers were used as the dissolution medium. Initially tablets were subjected to dissolution in pH 1.2 buffer for 2 h and after that media is changed to phosphate buffer (pH 6.8). The time at which the outer coating layer starts to rupture was noted.

In-vitro Dissolution methods
Dissolution testing of Pulsatile delivery systems with the conventional paddle method at 75 rpm and 37±0.5°C has usually been conducted in different buffers for different periods of time to simulate the GI tract pH and transit time that the Pulsatile delivery system might encounter *in-vivo.* The ability of the coats/carriers to remain intact in the physiological environment of the stomach and small intestine is generally assessed by conducting drug release studies in pH 1.2 buffer for 2 hours (mean gastric emptying time) and in pH 6.8 phosphate buffer for remaining hours (mean small intestinal transit time) using USP dissolution rate test apparatus. The samples were withdrawn at regular by conducting drug release studies in pH 1.2 buffer for 2 hours (mean gastric emptying time) and in pH 6.8 phosphate buffer for remaining hours (mean small intestinal transit time) using USP dissolution rate test apparatus. The samples were withdrawn at regular intervals and analyzed by UV spectrophometer (Shimadzu UV/Vis 1800) for the presence of

the drug. Dissolution tests were performed in triplicate.

Despite the simplicity and convenience, conventional dissolution testing primarily provides essential information on the processing specifications of a Pulsatile drug delivery system rather than on the validity of the system design.

Table 2: Composition table of Atorvastatin loaded multiunit pulsatile tablet Formulation F1-F8

S.No	Ingredients	Quantity (mg)							
		F1	F2	F3	F4	F5	F6	F7	F8
1	Atorvastatin	40	40	40	40	40	40	40	40
2	Sodium starch glycolate	20	20	20	20	20	20	20	20
3	Microcrystalline cellulose	40	40	40	40	40	40	40	40
4	Magnesiun stearate	3	3	3	3	3	3	3	3
5	Talc	2	2	2	2	2	2	2	2
6	Eudragit RS 100	100	200	300	400	-	-	-	-
7	Eudragit S 100	-	-	-	-	100	200	300	400
8	Ethyl cellulose	-	-	-	-	-	-	-	-
9	CAP	-	-	-	-	-	-	-	-
10	HPC	400	300	200	100	400	300	200	100

Table 3: Composition table of Atorvastatin loaded multiunit pulsatile tablet Formulation F9-F12

S.No	Ingredients	Quantity (mg)							
		F9	F10	F11	F12	F13	F14	F15	F16
1	Atorvastatin	40	40	40	40	40	40	40	40
2	Sodium starch glycolate	20	20	20	20	20	20	20	20
3	Microcrystalline cellulose	40	40	40	40	40	40	40	40
4	Magnesiun stearate	3	3	3	3	3	3	3	3
5	Talc	2	2	2	2	2	2	2	2
6	Eudragit RS 100	-	-	-	-	-	-	-	-
7	Eudragit S 100	-	-	-	-	-	-	-	-
8	Ethyl cellulose	100	200	300	400	-	-	-	-
9	CAP	-	-	-	-	100	200	300	400
10	HPC	400	300	200	100	400	300	200	100

RESULT AND DISCUSSION

Drug-Excipient compatibility study

From the I.R. Spectrum, it was observed that there were no changes in these main peaks in IR spectra of mixture of drug and polymers, which show there were no physical interactions because of some bond formation between drug and polymers.

The peaks obtained in the spectra of drug and polymers mixtures correlates with the peaks of drug spectrum. This indicates that the drug was compatible with the formulation components. IR studies indicated no interaction between drug and polymers (Fig. 2-5).

Evaluation of physical parameters of compressed tablet of Atorvastatin

The physical parameters for all formulations were tabulated in Table 4. All the formulated (F1 to F8) tablets were found within the pharmacopoeial limits. The weights of all the tablets were found to be uniform with low standard deviation values. The measured hardness of tablets of all the formulations ranged between 5.16±0.28 to 5.66±0.28 kg/cm^2. The % friability was less than 0.6% in all the formulations. The measured thickness of coated tablets of each formulation ranged between 5.36±0.023mm to 5.46±0.015mm which ensures uniform coating to all batches. The percentage of drug content was found to be between 99.07±1.31% and 100.45±2.16%. It complies with official specifications.

Disintegration test

The values of Disintegration test for coated tablets were tabulated in Fig. 6. It was found to be between 174.5±4.94 to 231.5±4.94 minutes. It ensures that all the formulations remained intact for 2 hours in pH 1.2 buffers and later in 6.8 pH buffer.

In-vitro Dissolution of Coated Tablet

All the sixteen formulations of prepared coated tablets of Atorvastatin were subjected to in-vitro release studies. These studies were carried out using USP dissolution apparatus type-II, and pH 1.2 buffer and pH 6.8 phosphate buffer as dissolution media (Fig. 7-10).

In-vitro release profiles of pulsatile device during 8 hrs studies were found to have very good sustaining efficacy. During dissolution studies, it was observed that, the enteric coat of the cellulose acetate phthalate was intact for 2 hours in pH 1.2 buffers, but dissolved in intestinal pH, with all the formulations, there was no drug release in pH 1.2, thus indicating the efficiency of CAP, Eudragit RS 100, Eudragit S 100, and ethyl cellulose for enteric coating.

In case of formulation F1 to F15, at the end of 6.30 th hour the cumulative drug release was found to be 62.23% to 95.23%, which having lower cumulative percentage drug release. While F16 formulation in which CAP with Hydrophilic polymer HPC in the ratio 4:1 is showing 100 % release of active Atorvastatin in phosphate buffer 6.8 pH, meeting the requirement of pulsatile drug delivery system.

Water uptake studies

All the sixteen formulations of prepared coated tablets of Atorvastatin were subjected to water uptake studies. These studies were carried out using ultrsonic bath sonicator (Fig. 11-14).

Water uptake studies of pulsatile device during 8 hrs studies were found to have very good sustaining efficacy. The cumulative drug release at the end of 6.30 th hour of formulation F1 to F16 was found to be 8.91% to 30.12%.

In the F16 formulation in which CAP with Hydrophilic polymer HPC in the ratio 4:1 is showing sufficient Water uptake in 8th hour, meeting the requirement of pulsatile drug delivery system. So increasing outer coating decreased % water uptake capacity and increased Lag-time.

Rupture Test

The values of Rupture test were tabulated in Fig. 15. These were found between 4:35 to 9:10 hours.

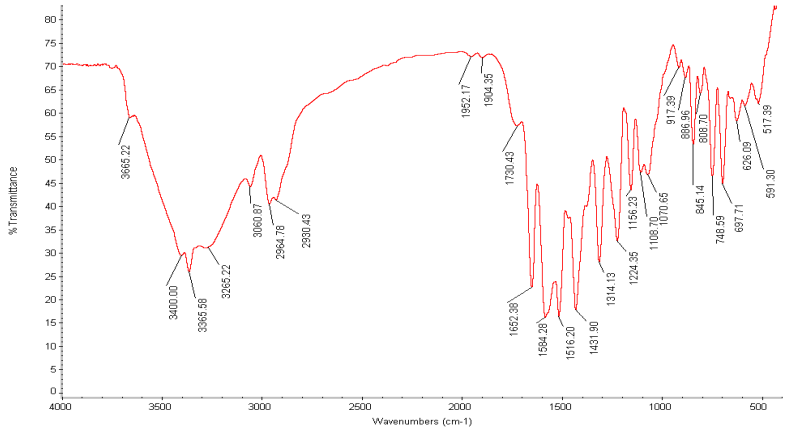

Fig. 2: FTIR Spectrum of Atorvastatin

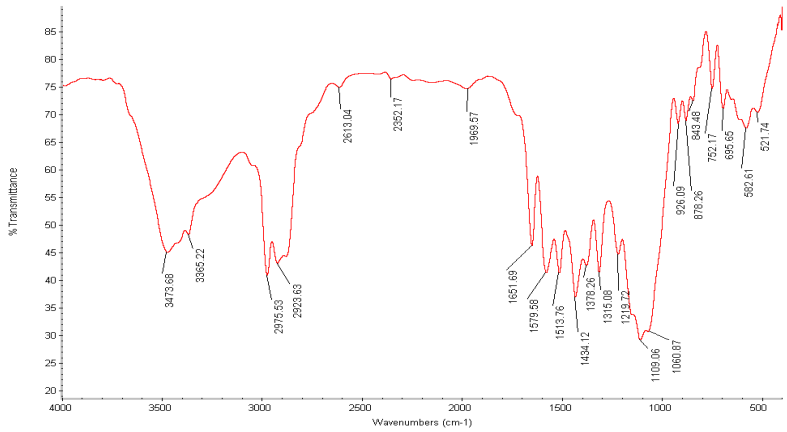

Fig. 3: FTIR Spectrum of Atorvastatin + Ethyl Cellulose

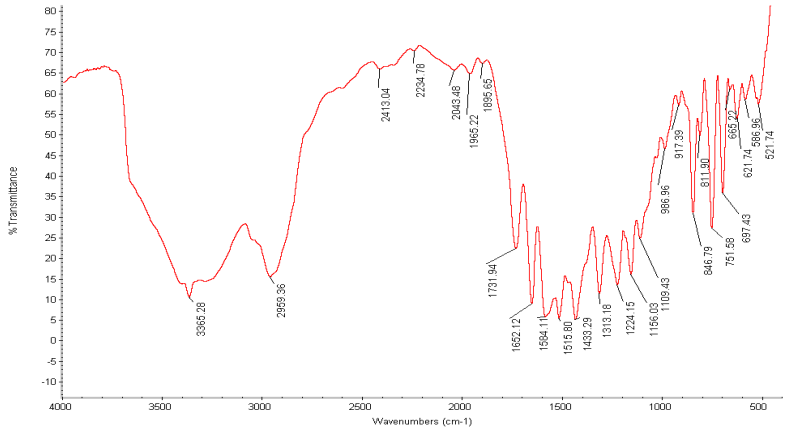

Fig. 4: FTIR Spectrum of Atorvastatin + Eudragit RS 100

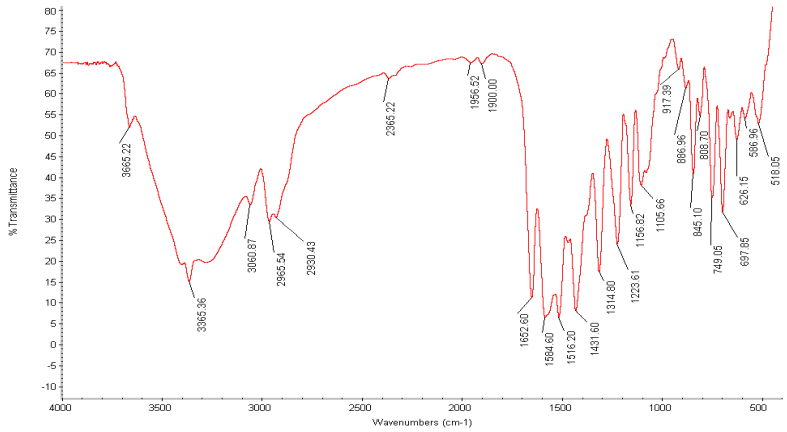

Fig. 5: FTIR Spectrum of Atorvastatin +CAP

Table 4: Evaluation of physical parameters of compressed tablet of Atorvastatin

Formulation Code	Weight variation (mean ± SD, mg) (n = 20)	Hardness (mean ± SD) (n = 3)	Friability (%) (n = 10)	Thickness(mm)±SD
F1	487±7.43	5.83±0.28	0.01	5.35±0.052
F2	493±8.10	5.13±0.5	0.02	5.55±0.012
F3	485±9.23	5.63±0.28	0.01	5.65±0.042
F4	487±7.56	5.23±0.5	0.01	5.65±0.052
F5	490±9.78	5.63±0.38	0.02	5.35±0.032
F6	491±7.68	5.63±0.21	0.06	5.45±0.022
F7	488±9.45	5.43±0.58	0.05	5.55±0.012
F8	485±8.23	5.83±0.68	0.04	5.65±0.062
F9	482±8.10	5.33±0.38	0.03	5.35±0.072
F10	495±7.23	5.63±0.58	0.06	5.75±0.042
F11	483±9.56	5.63±0.21	0.01	5.45±0.062
F12	487±7.67	5.53±0.26	0.02	5.65±0.022
F13	490±7.89	5.73±0.29	0.04	5.75±0.072
F14	492±8.67	5.33±0.21	0.03	5.75±0.032
F15	492±8.10	5.63±0.28	0.05	5.45±0.052
F16	495±7.45	5.83±0.23	0.01	5.65±0.022

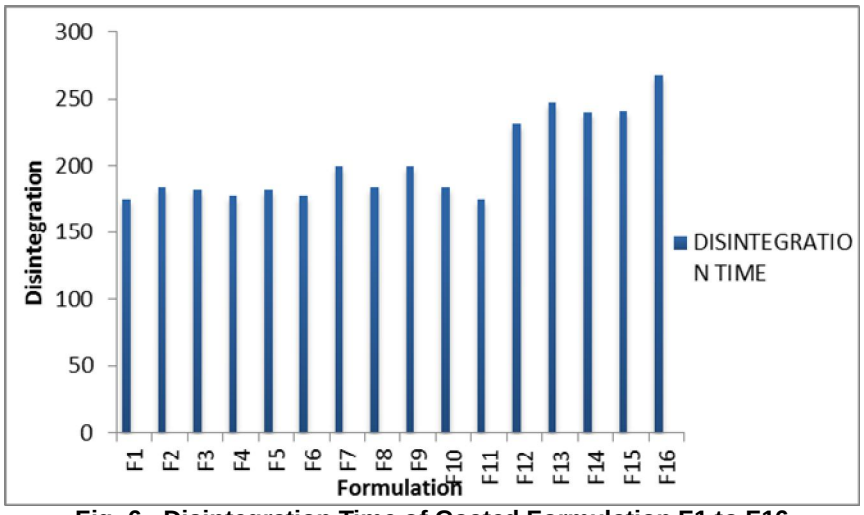

Fig. 6: Disintegration Time of Coated Formulation F1 to F16

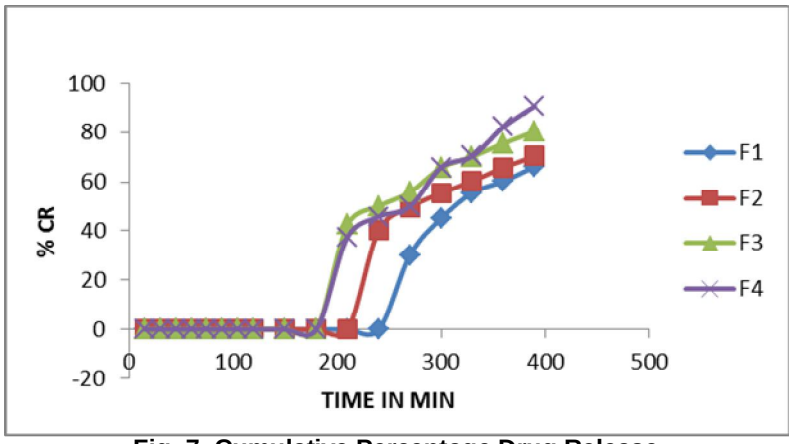

Fig. 7: Cumulative Percentage Drug Release of Coated Formulation F1 to F4

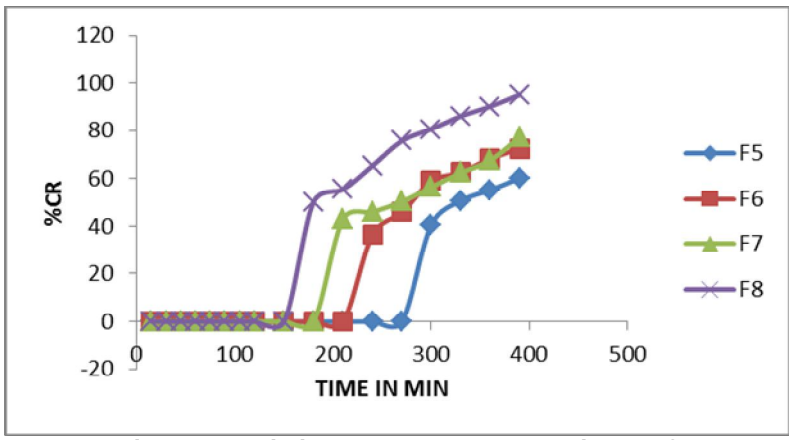

Fig. 8: Cumulative Percentage Drug Release of Coated Formulation F5 to F8

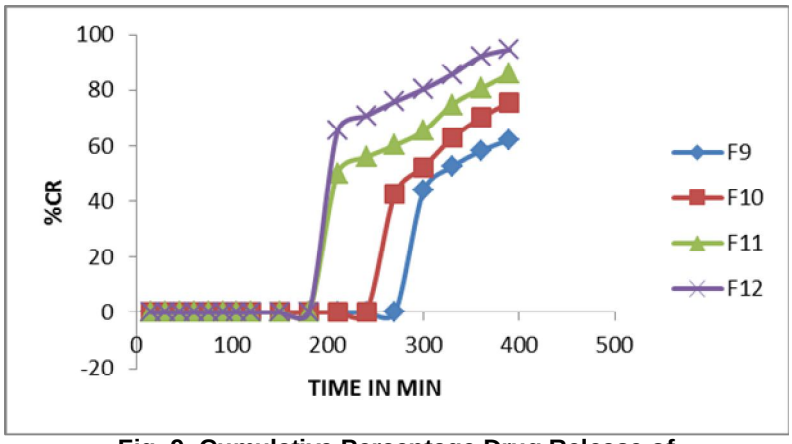

Fig. 9: Cumulative Percentage Drug Release of Coated Formulation F9 to F12

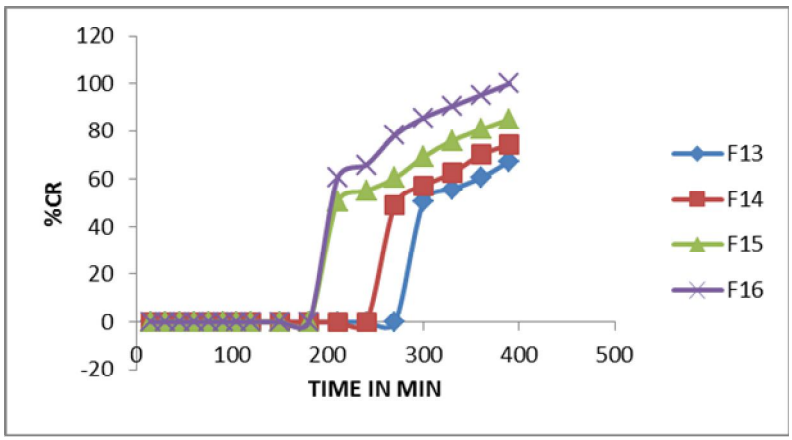

Fig. 10: Cumulative Percentage Drug Release of Coated Formulation F13 to F16

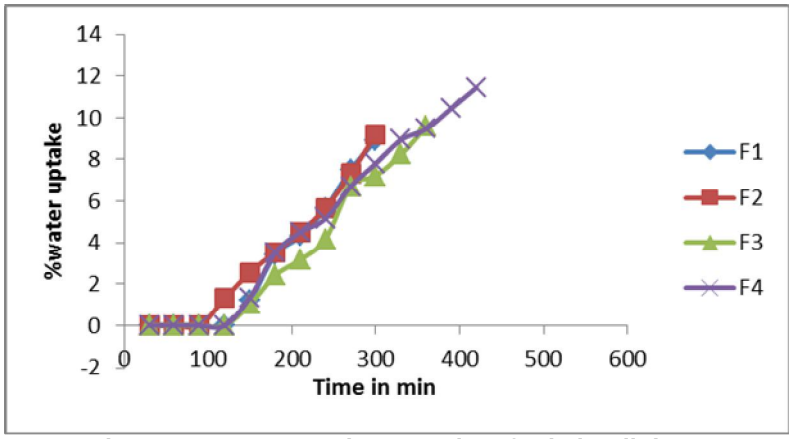

Fig. 11: % Water Uptake Capacity of Ethyl Cellulose

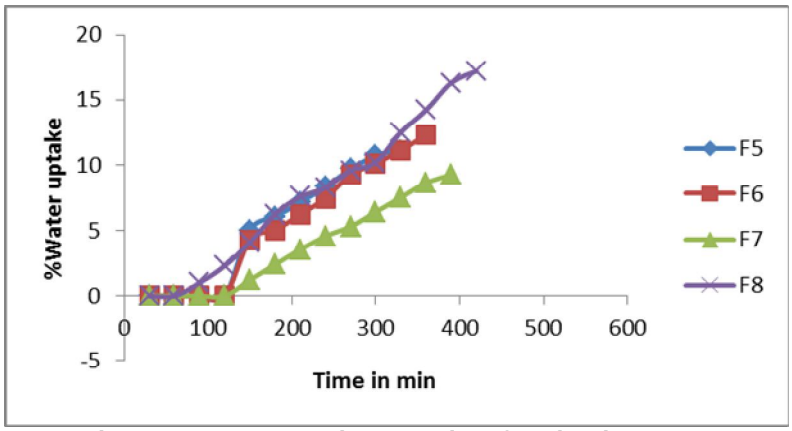

Fig. 12: % Water Uptake Capacity of Eudragit RS-100

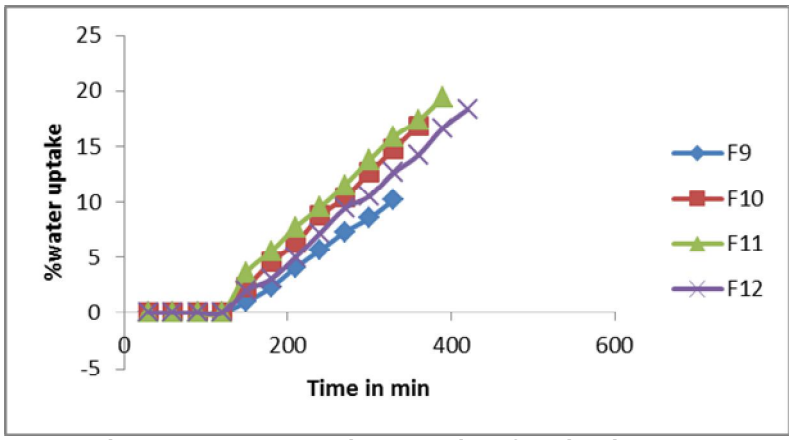

Fig. 13: % Water Uptake Capacity of Eudragit S-100

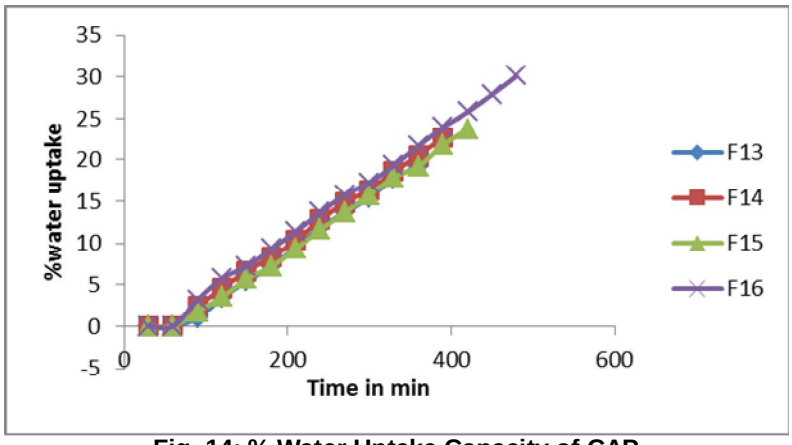

Fig. 14: % Water Uptake Capacity of CAP

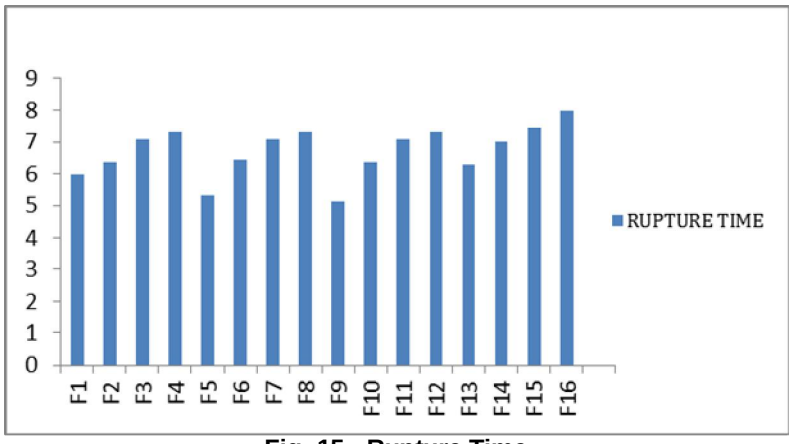

Fig. 15: Rupture Time

CONCLUSION

The aim of this study was to explore the feasibility of time dependent pulsatile drug delivery system of Atorvastatin for the treatment of Hyperlipidemia. A satisfactory attempt was made to develop pulsatile system of Atorvastatin and evaluated it. As per the finding from current research work, it was concluded that coating of CAP and HPC at the ratio of 4:1 provide better lag time with no release of drug during average gastric emptying time. As per the experimental result revealed, formulations F13, F14, F15 and F16 were selected as optimized formulations as they were meet the demand of chronobiology of disease. Hence, it can be concluded that multilayered pulsatile unit of Atorvastatin may be providing a better pharmacological effect, thus can be effectively used in management of hyperlipidemia.

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