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FORMULATION AND EVALUATION OF PULSATILE DRUG DELIVERY SYSTEM OF LOVASTATIN

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ABSTRACT

The aim and objective of the present study was to prepare and evaluate a press coated pulsatile drug delivery system of Lovastatin in order to attain a time controlled release, which is used to lower the risk of cardiovascular disease and manage abnormal lipid levels by inhibiting the endogenous production of cholesterol in the liver. The core was prepared by direct compression, while press coating technique was used in coating the outer layer there by preparing a press coated tablet. The immediate release core formulations comprised of Lovastatin and disintegrants like Crosspovidone, lycoat in different ratios with the drug. The outer coat formulations were prepared using a hydrophilic (HPMC) and hydrophobic (EC) polymer of different ratios. All the core and press coated tablets were evaluated for various preformulation and post compression parameters along with the dissolution study that was performed using USP paddle method at 50 rpm in 0.1 N HCl and phosphate buffer pH 6.8. The optimized formulation F9 containing 200 mg of EC and 200 mg of HPMC K15 may be regarded as the minimum quantity required in outer press coat so as to attain a predetermined lag time of 6 h and the drug release was bursted at the end of 7th hour and showed maximum release at the end of 8th hour. It follows first order release and follows fickian diffusion transport mechanism.

Keywords: ethyl cellulose, hydroxypropyl methylcellulose, press coat, lovastatin, time-controlled release

INTRODUCTION

Oral controlled drug delivery systems represent the most popular form of controlled drug delivery systems. These dosage forms offer many advantages, such as nearly constant drug level at the site of action, prevention of peak-valley fluctuation, reduction in dose of drug, reduced dosage frequency, avoidance of side effects and improved patient compliance. However, there are certain conditions, which demand release of drug after a lag time. Such a release pattern is known as "pulsatile release" **[1]**.

Due to advances in chronobiology, chronopharmacology and global market constraints, the traditional goal of pharmaceutics (eg. design drug delivery system with a constant release rate) is becoming obsolete. So there is a continuous need for developing new delivery systems that can provide increased therapeutic benefits to the patients by delivering drug at the right time, right place & in right amounts to coincide with circadian rhythm of body **[2]**. Chronotherapeutics refer to a clinical practice of synchronizing drug delivery in a manner consistent with the body's circadian rhythm including disease states to produce maximum health benefit and minimum harm **[3]**. However, the major bottleneck in the development of drug delivery systems that match circadian rhythms (Chronopharmaceutical drug delivery systems: ChrDDS) may be the availability of appropriate technology. A major objective of chronotherapy in the treatment of several diseases is to deliver the drug in higher concentrations during the time of greatest need according to the circadian onset of the disease or syndrome.

A pulsatile dosage form, taken at bed time with a programmed start of drug release in the early morning hours, can prevent this. By timing drug administration, plasma peak is obtained, at an optimal time. Number of doses per day can be reduced **[4]**. When there are no symptoms there is no need of drugs. Saturable first pass metabolism and tolerance development can also be avoided. Drug targeting to colon would prove useful where intentional delayed drug absorption is desired from therapeutic point of view in the treatment of disease that have peak symptoms in the early morning such as nocturnal asthma, angina, arthritis **[5]**. Some marketed preparations like Lescol, Mevacor, Prachol and Zocor showed that evening dosing frequency of these medications is more effective than morning dosing.

Lovastatin belongs to the statin class of medications, which are used to lower the risk of cardiovascular disease and manage abnormal lipid levels by inhibiting the endogenous production of cholesterol in the liver.

The pulsatile drug delivery systems for Lovastatin has been developed and evaluated that they can be used to target to colon for treating hyperlipidemia and delivering the drug at a time when it is required to maintain the drug levels in accordance with the circardian rhythm of cholesterol synthesis in reducing the dosing frequency and thereby enhancing drug compliance **[6]**. The pulsatile drug delivery of lovastatin was taken before bed time and that and drug will be released during early morning after a lag period of 6hrs was designed, as in the early morning free cholesterol levels were more. The timely release of drug was achieved by using delayed release polymers.

The Aim and objective of this work is the development and evaluation of pulsatile drug delivery systems of Lovastatin. A successful Pulsatile drug delivery system is one that remains intact in the physiological environment of stomach and small intestine for up to six hours, releasing no or minimum amount of drug, but completely releases the drug after six hours.

MATERIALS AND METHODS

Lovastatin was a gift sample obtained from Ranbaxy Lab. Ltd. (India). Lycoat, Cross povidone, HPMC K15M, Ethyl cellulose purchased from Yarrow chem. Products, Mumbai. All materials used were of pharmacopoeial grade.

Determination of UV spectrum of Lovastatin:

10mg of Lovastatin was dissolved in 2-3ml of methanol then makeupto10ml with 6.8pH buffer so as to get a stock solution of 1000 µg/ml concentration. From the above stock solution subsequent dilutions were made using 6.8pH buffer to get the concentration of 10µg/ml concentration and was scanned under UV Spectroscopy between 200-400nm ranges.

Construction of Standard Curve of Lovastatin in 0.1N HCl and in pH 6.8 phosphate buffer:

10mg of Lovastatin was accurately weighed and transferred into 10ml volumetric flask. It was dissolved and diluted to volume with 0.1N HCl to give stock solution containing 1000µg/ml. The standard stock solution was then serially diluted with 0.1N HCl to get 2 to 12µg/ml of Lovastatin and the absorbance of the solution was measured against 0.1N

HCl as blank at 245nm using UV visible spectrophotometer. The above process was repeated using **pH 6.8 phosphate buffer** in place of 0.1N HCl and the absorbance values were measured at 245nm using UV visible spectrophotometer. The absorbance values were plotted against concentration (µg/ml) to obtain the standard calibration curve.

3. Solubility studies:

Solubility of Lovastatin was determined in Methanol, Ethanol, pH 1.2, pH 6.8 and pH 7.4 phosphate buffers. Solubility studies were performed by taking excess amount of Lovastatin in different beakers containing the solvents. The mixtures were shaken for 24 hr and filtered by using whattmann's filter paper grade no. 41 and were analyzed spectrophotometrically at 245 nm.

COMPATIBILITY STUDIES:

FTIR analysis:

The drug-polymer interactions were studied by FTIR spectrometer, Shimadzu 8400 S. 2% (w/w) of the sample, with respect to a potassium bromide (KBr; SD Fine Chem. Ltd., Mumbai, India) was mixed with dry KBr. The mixture was ground into a fine powder using mortar and then compressed into a KBr discs in a hydraulic press at a pressure of 10000 PSI. Each KBr disc was scanned 10 times at a resolution of 2 cm–1 using Happ-Genzel apodization. The characteristic peaks were recorded.

FORMULATION OF COMPRESSED TABLETS OF LOVASTATIN:

a) Formulation of core tablets of Lovastatin:

The inner core tablets were prepared by using direct compression method. Accurately weighed amounts of Lovastatin, MCC, Crospovidone, Lycoat, and Talc were dry blended for about 15min followed by addition of magnesium stearate. The mixture was then further blended for 10 min and the resultant powder blend was manually compressed using punching machine and finally the core tablet was obtained given in **Table 1**.

Table 1: Formulation of Lovastatin Core Tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6
Lovastatin	20	20	20	20	20	20
Lycoat	3	6	9	--	--	--
Cross povidone	--	--	--	3	6	9
MCC	122	119	116	122	119	116
Mg. stearate	3	3	3	3	3	3
Talc	2	2	2	2	2	2
Total(mg)	150	150	150	150	150	150

b) Formulation of Lovastatin press coated tablets:

The optimized core tablets were coated with coating ingredients like HPMC K15M (water soluble polymer) and Ethyl cellulose (water insoluble polymer) given in **Table 5**. HPMC

was selected because of its erodible behavior and Ethyl cellulose was selected for it's because of its swelling and rupturable behavior. Now accurately weighed amount of barrier layer material was transferred into a 12mm die then the core tablet was placed manually at the center. The remaining amount of the barrier layer material was added into the die and compressed. Compression of tablets was done in rotary compression tablet machine using 12mm flat oval shape punch. The prepared tablet of each batch was evaluated for the tablet properties given in **Table 2**.

Table 2: Formulation of press coated tablets of Lovastatin

Formulation	F7	F8	F9
Core (mg)	150	150	150
HPMC K15M (mg)	150	100	200
Ethyl cellulose (mg)	150	200	100
Total weight (mg)	450	450	450

EVALUATION OF TABLET PROPERTIES:

a) Pre compression studies:

All the pre compression parameters were evaluated for both core and press coated tablet according to the official methods. The evaluated pre compression parameters were angle of repose, bulk and tapped density, compressibility index (Carr's index) and Hausner's ratio.

b) Post compression parameters of Lovastatin core and press coated tablet:

Weight variation: The USP weight variation test is done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average.

Tablet 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. Three tablets were chosen randomly and tested for hardness. The average hardness of 3 determinations was recorded.

Friability: 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. Percentage of friability of the tablets of a badge can be found by the following formula.

Percentage Friability $= W1 - W2/W1 \times 100$

Where, W1 = weight of tablets before testing, W2 = weight of tablets after testing.

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 and reported.

Content Uniformity:

At random 20 tablets were weighed and powdered. The powder equivalent to 20 mg was weighed accurately and dissolved in 100ml of buffer used. The solution was shaken thoroughly and then filtered through Whattmann's filter paper No.41. The absorbance of the diluted solutions was measured at 245 nm. The concentration of the drug was computed from the standard curve of the Lovastatin in 6.8 phosphate buffer.

Disintegration time:

The test for disintegration was carried out in Electrolab USP disintegration test apparatus. The time taken for the complete disintegration of the tablets was noted.

***In- vitro* Dissolution study of core tablets**:

Drug release from tablets was studied using 8 station dissolution rate test apparatus (Lab India, Disso 8000) employing a paddle stirrer at 50 rpm and at 37±1°C. Phosphate buffer of pH 6.8 (900 ml) was used as dissolution fluid and absorbance was measured at 245nm using a Shimadzu UV-150 double beam UV-spectrophotometer. The drug release experiments were conducted in triplicate reported.

STABILITY STUDIES [7]:

Stability studies of the optimized formulation were carried out at 2-8 °C, room temperature and stability chambers maintained at 40°C ± 2°C/ 75 %, RH ± 5 % condition. The samples were withdrawn initially followed by 15 days and 1 month intervals and evaluated for physical stability, drug content and any other instability

EVALUATION OF PULSATILE DRUG DELIVERY SYSTEMS:

a) Characteristics of Press coated tablets of Lovastatin:

The optimized core tablet was taken and press coated tablets were prepared with varied polymers and concentrations considered as F7, F8, F9 were taken and evaluated for hardness, disintegration, thickness of coated Lovastatin tablet formulations. The thickness of the coating on the formulation was determined by deducting the thickness of core tablets from thickness of the coated formulation.

b) *In-vitro* Dissolution study of Press coated tablets of Lovastatin:

Dissolution testing of pulsatile delivery systems with the conventional paddle method at 50 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 0.1N HCL 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 spectrophotometer (PG Instruments T60) for the presence of the drug. Dissolution tests were performed in triplicate.

DATA ANALYSIS:

Mathematical models were often used to predict the release mechanism of the active pharmaceutical ingredient from a delivery system which is a function of time. The acquired in *vitro* data was analyzed using various kinetic models such as zero order, first order, Higuchi **[8]**, Peppas **[9]**, and Hixson Crowell's for describing the drug release parameters. The model that best fits the release data was selected based upon the correlation coefficient value.

RESULTS & DISCUSSION

The pulsatile drug delivery systems for Lovastatin has been developed and evaluated that they can be used to target to colon for treating hyperlipidemia and delivering the drug at a time when it is required to maintain the drug levels in accordance with the circardian rhythm of cholesterol synthesis in reducing the dosing frequency and thereby enhancing drug compliance.

The pulsatile drug delivery of lovastatin has to be taken before bed time and that and drug will be released during early morning after a lag period of 6hrs was designed, as in the early morning free cholesterol levels were more. The timely release of drug was achieved by using delayed release polymers.

UV analysis: The prepared solution was scanned under UV Spectroscopy using 200-400nm given in Fig1 and that the absorption peak was found at 245nm **(Figure 1)**.

Estimation of Lovastatin: The calibration curves were plotted using 0.1N HCL and 6.8 pH buffer and the method was validated for linearity, accuracy and precision. The method obeyed Beer's law in the concentration range of 0-12 μg/ml. When a standard drug solution was assayed repeatedly (n=6).

Solubility: Solubility studies were determined by using 0.1N HCL, 6.8pH buffer, 7.4 pH buffer , methanol, ethanol. The results reported that highest solubility was found in methanol basing on polarity,

when compared to other solvents given in **Figure 2**.

Drug excipient compatibility: FTIR of Lovastatin pure drug and with other excipients were reported in **Figure 3 & 4**. As all spectra are within the marked range. It was concluded that drug was in its normal form before and after its formulation as characteristic peaks at wave numbers C=O stretching at 1721 cm^{-1} and OH stretching at 3542 cm^{-1}, C-H asymmetric stretching at 2947 cm^{-1} respectively.

Pre compression parameters of core tablets: The angle of repose of differentformulations was found to be ≤ 29.63, which indicates that material had good flow property.

The bulk density of blend was found between 0.405g/cm^3 to 0.485g/cm^3. Tapped density was found between 0.474g/cm^3 to 0.579g/cm^3. Carr's index for all the formula-tions was found to be between 11.98- 17.32 and Hausner's ratio from 1.14-1.21 which reveals that the blends have good flow characteristics given in **Table 3**.

Post compression parameters of core tablets (F1-F6): All the formulated (F1 to F6) 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. The measured hardness of tablets of all the formulations ranged, 3-4 kg/cm^2. The % friability was less than 1 % in all the formulations ensuring that the tablets were mechanically stable. Disintegration time was found between 32 – 78 seconds ensuring that all the cores of different formulations were rapid disintegrating type. The percentage of drug content for F1 to F6 was found to be between 89.63% - 98.35%. The percent drug release from all the prepared core tablets was determined and it was found that F3 formulation was selected for press coated formulation as it has good release i.e., 96.53±0.06% after 30min when compared to other formulations. The rapid release of Lovastatin core tablet with an increase in lycoat may be reported due to the rapid disintegration of the tablet. The results were given in **Table 4 & 5** and **Figure 5** respectively.

EVALUATION OF PRESS COATED TABLETS:

The optimized core tablet F3 was taken and press coated tablets were prepared with varied polymers and concentrations considered as F7, F8, F9 were taken and various physical parameters has been determined like weight variation, hardness, friability, thickness, diameter, percent drug content. All obtained results are within the limits except the percent drug content was

found to be more in F9 compared to F7 and F8 given in **Table 6**.

From the *In vitro* drug release studies given in **Table 7** all prepared press coated tablets of lovastatin had shown marked lag time given in **Figure 6**. When core tablet comes in contact with the dissolution medium after erosion of the coating layer rapid drug release was reported. It was observed that the formulation F7 containing HPMCK15M : Ethyl cellulose (1:1) releases maximum drug at the end of 9 hrs and doesn't maintain the lag phase. Whereas the formulation F8 containing HPMC K15M : Ethyl cellulose (1:2) releases maximum drug at the end of 7 hours due to the higher ethyl cellulose concentration and doesn't maintain the lag phase. Whereas F9 containing HPMC K15M : Ethyl cellulose (2:1) maximum drug release was at the end of 8^{th} hour. By comparing the drug release profiles of the formulations F7-F8 the drug release was not lagged up to 5-6 hours. Among all the formulations F9 containing HPMC K15M : Ethyl cellulose (2:1) shows lag time for 6 hours and complete drug was released at the end of 7hours. So F9 was considered as the optimized formulation, So the drug release kinetic studies were performed for the optimized F9 formulation.

Drug release kinetics: Drug release kinetics was assessed by various models like zero order, first order, higuchi, peppas, Hixson Crowell's. The drug release kinetics of the optimized formulation F9 has been studied. In zero order graph the r^2 value was found to be 0.401 and first order r^2 value was found to be 0.963 indicating the relationship between drug release rate with concentration and n value 0.498 of peppas ($n< 5$) indicate that it follows fickian diffusion and it occurs by molecular diffusion due to concentration gradient. Hixson Crowell's model r^2 value 0.963 indicates that due to dissolution of matrix there is change in surface area with respect to time and results given in **Table 8**.

Stability studies: The stability data of the optimized formulation (F9) indicate that the product remained stable at accelerated storage conditions. No changes occurred indicating that the formulation was stable without any physical degradation during storage period given in **Table 9**.

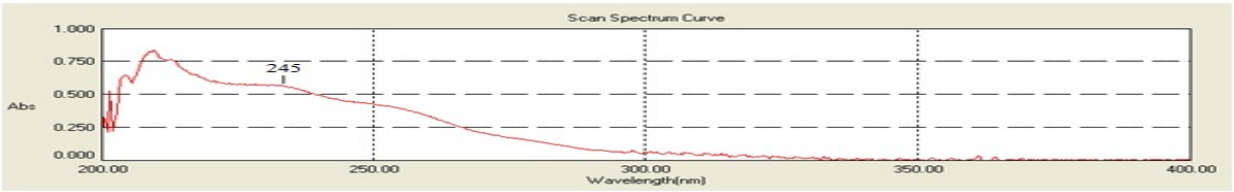

Figure 1: UV Spectrum of Lovastatin

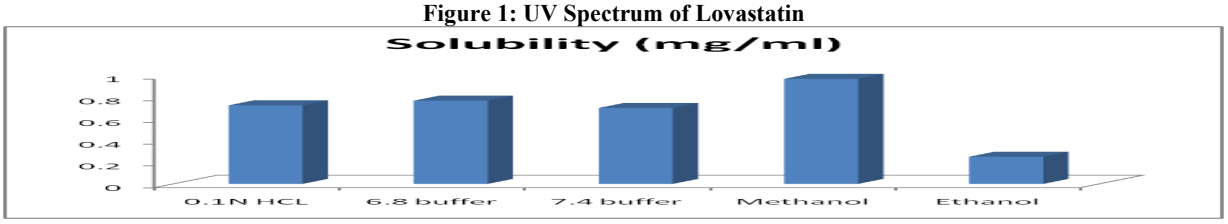

Figure 2: Solubility studies of Lovastatin

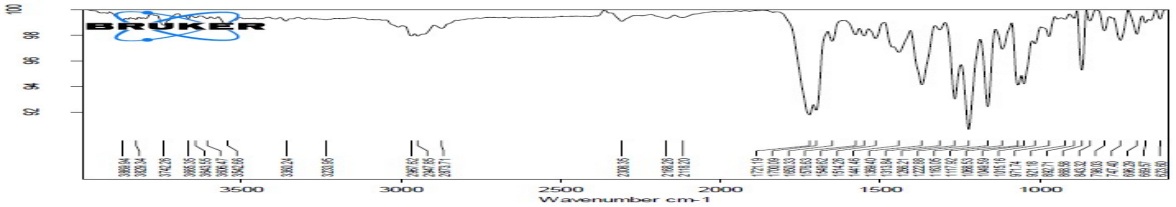

Figure 3: FTIR Spectrum of Lovastatin pure

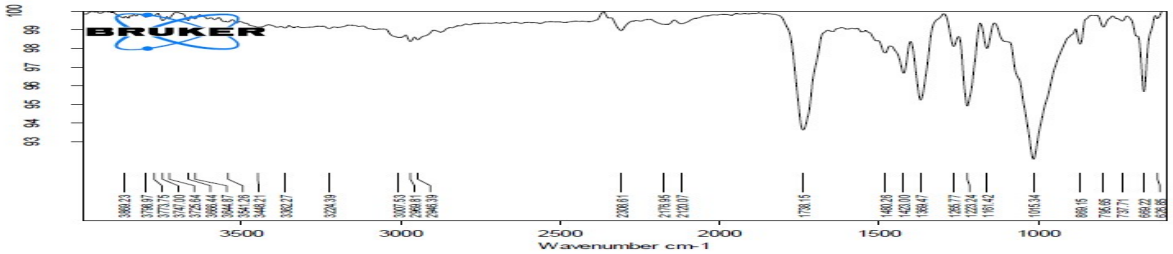

Figure 4: FTIR Spectrum of Lovastatin and Excipients

Table 3: Precompression parameters of core tablet of Lovastatin

Formulation Code	Angle of Repose(ɵ)	Bulk Density (g/cc)	Tapped Density (g/cc)	Carr's Index. (%)	Hausner's ratio
F1	27.15±0.09	0.425±0.011	0.514±0.03	17.32±0.056	1.21±0.024
F2	29.42±0.01	0.415±0.032	0.498±0.007	16.67±0.01	1.20±0.034
F3	28.75±0.03	0.405±0.023	0.474±0.019	14.56±0.024	1.17±0.007
F4	29.63±0.01	0.426±0.001	0.497±0.09	14.29±0.0016	1.17±0.008
F5	27.18±0.03	0.463±0.02	0.526±0.02	11.98±0.01	1.14±0.012
F6	25.45±0.05	0.485±0.01	0.579±0.01	16.23±	1.19±0.05

Table 4: Post compression parameters of Lovastatin core tablet

Formulation Code	Avg.Wt (mg)	Hardness (kg/cm^2)	Thickness (mm)	Diameter (mm)	Drug content (%)	Friability (%)	Disintegration time (secs)
F1	148.12±0.01	3.01±0.01	2.63±0.003	8.01±0.01	89.63±0.06	0.15±0.02	62±0.011
F2	149.26±0.009	3.26±0.006	2.54±0.01	8.03±0.05	96.75±0.01	0.52±0.02	48±0.0167
F3	147.94±0.05	3.37±0.03	2.01±0.006	8.01±0.01	98.35±0.07	0.46±0.05	32±0.025
F4	146.42±0.02	3.18±0.019	2.69±0.008	8.06±0.003	92.28±0.06	0.35±0.04	78±0.015
F5	149.66±0.031	3.56±0.002	2.14±0.009	8.09±0.001	90.14±0.006	0.18±0.01	51±0.011
F6	147.14±0.023	3.29±0.005	2.35±0.012	8.02±0.01	97.15±0.05	0.75±0.03	44±0.006

Table 5: Percent drug release of Lovastatin core tablets of different formulations (F1 to F6)

Time(mins)	F1	F2	F3	F4	F5	F6
5	42.61±0.02	49.61±0.02	53.64±0.01	36.42±0.001	39.64±0.06	56.34±0.02
10	49.35±0.013	59.14±0.016	62.39±0.02	39.46±0.02	46.07±0.034	59.42±0.031
15	55.34±0.021	66.34±0.022	76.42±0.03	47.15±0.01	59.35±0.012	67.19±0.023
20	59.43±0.029	76.59±0.001	83.64±0.01	52.69±0.05	66.19±0.02	74.06±0.021
25	65.96±0.033	82.45±0.021	92.67±0.03	57.06±0.07	70.63±0.05	82.36±0.056
30	70.64±0.03	90.46±0.033	96.53±0.06	63.49±0.02	76.49±0.09	86.49±0.02
45	76.45±0.012	97.14±0.007	---	70.09±0.09	82.56±0.01	90.45±0.01
60	83.45±0.019	---	---	79.62±0.07	86.42±0.02	92.65±0.03

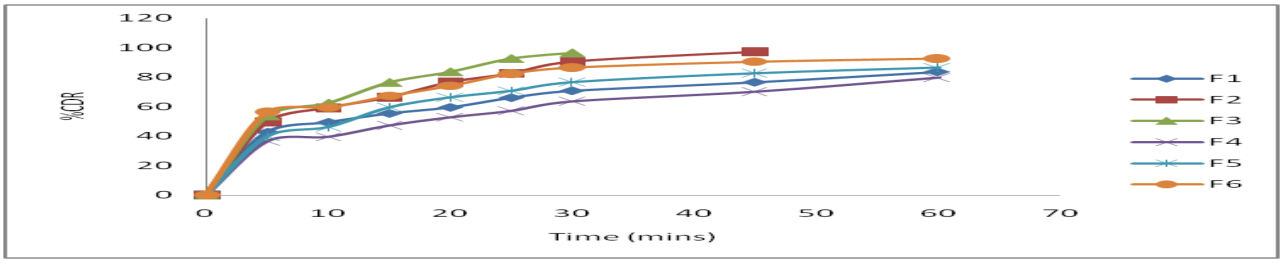

Figure 5: Cumulative percentage drug release of Lovastatin core tablets F1 – F6

Table 6: Evaluation of Physical Parameters of press coated tablets of Lovastatin (F7-F9)

Formula code	Weight variation (%)	Hardness (kg/cm^2)	Friability (%)	Thickness (mm)	Diameter(mm)	Drug content (%)
F7	1.49±0.01	6.24±0.067	0.65±0.01	4.31±0.017	12.83±0.03	96.17±0.067
F8	2.57±0.012	6.19±0.018	0.41±0.017	4.49±0.019	12.72±0.009	97.46±0.078
F9	2.03±0.07	6.87±0.019	0.18±0.015	4.92±0.02	12.34±0.014	98.05±0.097

Table 7: Cumulative % Drug release of Press coated tablets of Lovastatin (F7-F9)

Time (h)	F7	F8	F9
0	0	0	0
1	2.31±0.09	0.68±0.087	0.91±0.05
2	6.49±0.045	1.34±0.023	1.26±0.034
3	10.75±0.043	3.49±0.024	1.97±0.01
4	26.48±0.032	9.75±0.002	2.05±0.032
5	39.42±0.021	14.09±0.01	2.64±0.008
6	68.16±0.011	73.46±0.042	3.48±0.09
7	81.46±0.01	96.09±0.006	83.46±0.01
8	96.21±0.02	---	97.06±0.013
9	98.75±0.04	----	---

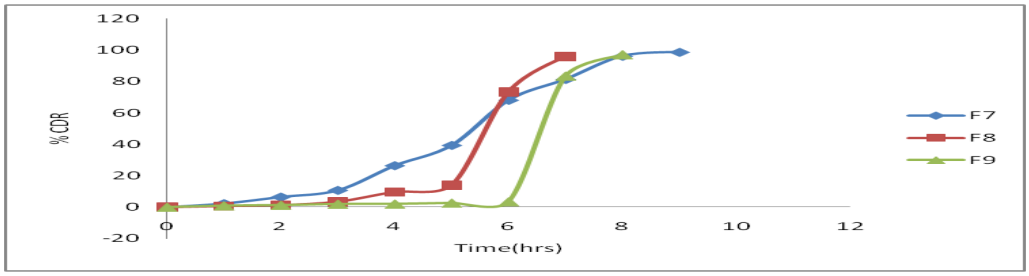

Figure 6: Cumulative percentage drug release of Lovastatin press coated tablets F7-F9

Table 8: *In-vitro* drug release mechanism of best formulation (F9)

Batch	Zero Order	First Order	Higuchi	Hixscon crowell	Peppas	Peppas
Code	r^2	r^2	r^2	r^2	r^2	n
F9	0.401	0.963	0.892	0.963	0.949	0.498

Table 9: stability data in terms of drug content at various storage conditions

Code	Initial drug content	2-8˚ C		Room Temperature		40±2 ˚C/ 75% RH	
		Drug content after 15 days	Drug content after 1 month	Drug content after 15 days	Drug content after 1 month	Drug content after 15 days	Drug content after 1 month
F9	104.72±0.21	100.51±0.41	102.4±0.32	101.31±0.23	103.66±0.1	102.9±0.4	101.12±0.2

CONCLUSION:

The aim of the study was to explore the feasibility of time dependent pulsatile drug delivery system of Lovastatin to treat high blood cholesterol and reduce the risk of cardiovascular disease.

From the reproducible results obtained from the executed trails of core and press coated tablets it can be concluded that the lovastatin press coated tablets were found to be satisfactory in both pre and post compression properties. Among F1-F6 core tablets prepared F3 was optimized. Among formulations F7-F9 of coated tablets F9 was selected as optimized formulations for designing Pulsatile devices. Acquired reports claimed the suitability of the system for a Chrono modulated therapy and delaying the drug release for a programmable period of time. The dosage form can be taken at bed time and will release the contents in the early morning hours when cholesterol synthesis is more prevalent.

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