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FORMULATION DEVELOPMENT AND EVALUATION OF PULSATILE DRUG DELIVERY SYSTEMS FOR PRAVASTATIN PRESSCOATED TABLETS

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ABSTRACT
Pravastatin is a cholesterol-lowering agent that belongs to a class of medications known as statins. It was derived from microbial transformation of mevastatin, the first statin discovered. It is a ring-opened dihydroxyacid with a 6'-hydroxyl group that does not require *in vivo* activation. The Aim and objective of this work is to the development and evaluation of press coated tablets using core tablets with superdisntegrants like crospovidone & CCS and polymers like Ethyl cellulose, HPMC K15M. From the reproducible results obtained from the executed trails of core and press coated tablets it can be concluded that P6 of core tablet and P3F5 of coated tablet were maintained lag phase upto 6hrs and brust release was at 7th hr and followed by maximum release at the end of 8th hr, so it is selected as optimized formulations for designing Pulsatile device. Therefore the study proved that coated Pravastatin can be successfully used as a time dependent modified Chronopharmaceutical formulation. Finally from the above results we can conclude that pulsatile drug delivery system of Pravastatin can be formulated using Ethyl cellulose and HPMC K15M.

KEYWORDS: Pravastatin, CCS, Crospovidone, Ethyl cellulose, HPMC K15M.

INTRODUCTION

Controlled drug delivery systems have acquired a centre stage in the arena of pharmaceutical research and development sector. Such systems offer temporal and /or spatial control over the release of drug and grant a new lease of life to a drug molecule in terms of patentability. Oral controlled drug delivery systems represent the most popular form of controlled drug delivery systems for obvious advantages of oral route of drug administration. 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. In such systems the drug release commences as soon as the dosage form is administered as in the case of conventional dosage forms. However, there are certain conditions, which demand release of drug after a lag time. Such a release pattern known as "pulsatile release".[1]

Pravastatin is a cholesterol-lowering agent that belongs to a class of medications known as statins. It was derived from microbial transformation of mevastatin, the first statin discovered. It is a ring-opened dihydroxyacid with a 6'-hydroxyl group that does not require *in vivo* activation. Pravastatin is one of the lower potency statins; however, its increased hydrophilicity is thought to confer advantages such as minimal penetration through lipophilic membranes of peripheral cells, increased selectivity for hepatic tissues, and a reduction in side effects compared with lovastatin and simvastatin.

Structure

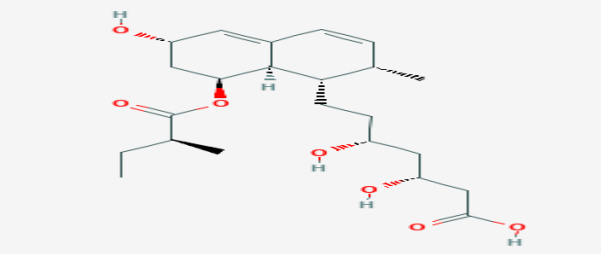

Fig 1.1: Structure of Pravastatin.

Experimental work

Materials

The following materials that were either AR/LR grade or the best possible grade available were used as supplied by the manufacturer without further purification or investigation Pravastatin sample was collected from Luna Chemicals industries Pvt. Ltd, Vadodara, CCS, Crosspovidone B.M.R Chemicals, Hyderabad, MCC, Talc, Magnesium stearate S.D.Fine CHEM, Mumbai , Ethyl cellulose, HPMCK15M from NR CHEM, Mumbai.

METHODOLOGY

PREFORMULATION STUDIES[52-56]

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

Determination of Melting Point

Melting point of Pravastatin was determined by capillary method. Fine powder of Pravastatin was filled in glass capillary tube (previously sealed at one end). The capillary tube was tied to thermo meter and the thermometer was placed in the Thais tube and this tube was placed on fire. The powder at what temperature it melted was noticed.

Solubility

Solubility of Pravastatin was determined in pH 1.2, pH 6.8 and pH 7.4 phosphate buffers. Solubility studies were performed by taking excess amount of Pravastatin in different beakers containing the solvents. The mixtures were shaken for 24 hrs at regular intervals. The solutions were filtered by using whattmann's filter paper grade no. 41. The filtered solutions were analyzed spectrophotometrically at 240 nm.

Preparation of Standard Calibration Curve of Pravastatin in 0.1 N HCL

10mg of Pravastatin was accurately weighed and transferred into 10ml volumetric flask. It was dissolved and diluted to volume with 0.1 N HCL buffer to give stock solution containing 1000µg/ml.

The standard stock solution was then serially diluted with 0.1 N HCL buffer to get 5 to 30µg/ml of Pravastatin. The absorbance of the solution were measured against 0.1 N HCL buffer as blank at 240nm using UV visible spectrophotometer. The absorbance values were plotted against concentration (µg/ml) to obtain the standard calibration curve.

Preparation of Standard Calibration Curve of Pravastatin in 6.8 PH BUFFER

10mg of Pravastatin was accurately weighed and transferred into 10ml volumetric flask. It was dissolved and diluted to volume with 6.8 phosphate buffer to give stock solution containing 1000µg/ml.

The standard stock solution was then serially diluted with 6.8 phosphate buffer to get 5 to 30µg/ml of Pravastatin. The absorbance of the solution were measured against 6.8 phosphate buffer as blank at 240nm using UV visible spectrophotometer. The absorbance values were plotted against concentration (µg/ml) to obtain the standard calibration curve.

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

2. Evaluation of Preformulation parameters[58-63]

i. Angle of repose

The angle of repose of powder blend was determined by the funnel method. The accurately weight powder blend were taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$\tan \theta = h/r$

Where, h and r are the height and radius of the powder cone respectively.

Table: Angle of Repose.

Sr. No.	Angle of repose(θ)	Type of flow
1	<25	Excellent
2	25-30	Good
3	30-40	Passable
4	>40	Very poor

ii. Determination of Bulk Density and Tapped Density

5 g of the granules (W) from each formula were introduced into a 100 ml measuring cylinder, and the initial volume was observed. The cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 Sec intervals. The tapping was continued until no further change in volume was noted. The bulk density, and tapped density were calculated using the following formulae.

- Bulk density = W / V_O
- Tapped density = W / V_F

Where, W = weight of the granules, V_O = initial volume of the granules, V_F = fi Pravastatin volume of the granules.

iii. Hausner's Ratio

- It indicates the flow properties of the granules and is measured by the ratio of tapped density to the bulk density.
- Hausner's Ratio = Tapped density/Bulk density

Table: Hausner's Ratio.

Sr. No.	Hausner's Ratio	Property
1.	0-1.2	Free flowing
2.	1.2-1.6	Cohesive powder

iv. Compressibility index (Carr's Index)42,43

Compressibility index is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. A material having values of less than 20% has good flow property.

$$C_I = \frac{(Tapped\ Density - Bulk\ Density)}{Tapped\ Density} \times 100$$

Table: Carr's index.

Sr. No	Carr's Index	Properties
1	5-12	Free flowing
2	12-16	Good
3	18-21	Fair
4	23-35	Poor
5	33-38	Very poor
6	>40	Extremely poor

Formulation of Compressed Tablets of Pravastatin:[57]

The methodology adopted includes:

1) Preparation of core tablets of Pravastatin.
2) Coating of the core tablets

1. Formulation of core tablets of Pravastatin

The inner core tablets were prepared by using direct compression method as per the developed formulation table which was shown above. Accurately weighed amounts of Pravastatin, MCC, CCS, SSG, and Talc were dry blended for about 15min followed by addition of magnesium stearate. The mixture was then further blended for 10 min. Now the resultant powder blend was manually compressed using punching machine and finally the core tablet was obtained.

Table: Formulation Table Of Pravastatin Core Tablets.

Ingredients(mg)	P1	P2	P3	P4	P5	P6
Pravastatin	40	40	40	40	40	40
Crosspovidone	2	4	6	--	--	--
CCS	--	--	--	2	4	6
MCC	52	50	48	52	50	48
Mg.stearate	4	4	4	4	4	4
Talc	2	2	2	2	2	2
Total wt(mg)	100	100	100	100	100	100

2. Formulation of Coating of the core tablets of Pravastatin

The optimized core tablets were coated with coating ingredients like HPMC K15M and Ethyl Cellulose. Now accurately weighed amount of barrier layer material was transferred into a 10mm 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 10mm flat oval shape punch. The prepared tablet of each batch was evaluated for the tablet properties.

Table: Composition of compression coated tablets of Pranlukast.

Formulation	P3F1	P3F2	P3F3	P3F4	P3F5
Core	100	100	100	100	100
Ethyl cellulose	300	-	150	100	200
HPMC K 15M	-	300	150	200	100
Total weight	400	400	400	400	400

Evaluation of Tablet Properties[44,45]

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.

1. 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 -10.

Table: Weight variation limits.

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

2. 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.

3. 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. Percentage of friability of the tablets of a badge can be find by the following.

Formula

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

Where,

W1 = weight of tablets before testing

W2 = weight of tablets after testing.

4. 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.

5. Content Uniformity

The tablets were tested for their drug content uniformity. At random 20 tablets were weighed and powdered. The powder equivalent to 200 mg was weighed accurately and dissolved in 100ml of buffer used. The solution was shaken thoroughly. The un dissolved 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 236 nm. The concentration of the drug was computed from the standard curve of the Pravastatin in 6.8 phosphate buffer.

6. 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 6.8 phosphate buffer solution at 37°C ± 1°C such that the tablet remains 2.5 cm below the surface of the liquid. The time taken for the complete disintegration of the tablets was noted.

7. Invitro Dissolution time

In-vitro dissolution study of core and coated tablets of Pravastatin was carried out using Lab India DS8000 USP dissolution test apparatus. The details are given as below:

Procedure

Tablet was introduced into the basket of the Lab India DS-8000 USP dissolution test apparatus and the apparatus was set in motion, 5 ml of sample was withdrawn for half a n hour at 5 min intervals. Samples withdrawn were a analyzed by UV spectrophotometer for presence of drug using buffer solution as blank.

Evaluation of Pulsatile Drug Delivery Systems[48]

1. Characteristics of Press coated tablets of Pravastatin

Characteristics of tablets of Pravastatin such as hardness and disintegration test were conducted. 3 tablets were taken and hardness of formulations was determined by using Monsanto hardness tester. Average of three determinations was noted down. 6 tablets were taken in Electrolab USP Disintegration test apparatus and disintegration time of tablets was determined using pH 6.8 buffer.

Thickness of coated Pravastatin tablet formulations was determined by using digital Vernier calipers. 3 tablets of each type of coated formulation were determined for thickness and average thickness of the formulation was determined. Similarly the thickness of the coating on the formulation was determined by deducting the thickness of core tablets from thickness of the coated formulation.

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.

2. *In-vitro* Dissolution methods

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 spectrophometer (PG Instruments T60) 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.

RELEASE KINETIC MODELS

One of the most important and challenging areas in the drug delivery field is to predict the release of the active agent as a function of time using both simple and sophisticated mathematical models. The importance of such models lies in their utility during both the design stage of a pharmaceutical formulation and the experimental verification of a release mechanism. In order to identify a particular release mechanism, experimental data of statistical significance are compared to a solution of the theoretical model. It is therefore clear that only a combination of accurate and precise data with models accurately depicting the physical situation will provide an insight into the actual mechanism of release.

To analyse the mechanism for the drug release and drug release rate kinetics of the dosage form, the data obtained was fitted in to Zero order, First order, Higuchi matrix, Krosmeyers-Peppas and Hixson Crowell model. In this by comparing the R-values obtained, the best-fit model was selected.

The results obtained from in vitro drug release studies were plotted adopting four different mathematical models of data treatment as follows:

- % Cum. Drug Release v/s Time (Zero order rate kinetics).
- Log % Cum. Drug Retained v/s Time (First order rate kinetics).
- % Cum. Drug release was plotted against √T (root time). (Higuchi model)
- Log % Cum. Drug Release v/s Log Time (Korsmeyer-Peppas exponential equation).

RESULTS AND DISCUSSION

Preformulation studies

Determination of Melting Point

Melting point of Pravastatin was found to be in the range of 172° C.

Solubility

Solubility of Pravastatin was determined in pH 1.2, water, & pH 6.8 phosphate buffers.

Table: Data for Solubility Curve for Pravastatin.

Buffers	Solubility (mg/ml)
0.1N HCL	0.568
6.8 buffer	0.254
7.4 buffer	0.198
Methanol	0.935
Ethanol	0.864

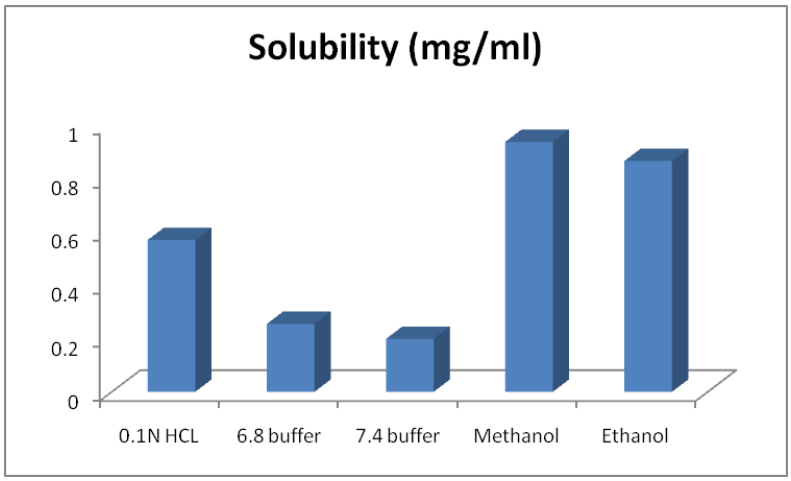

Fig: Solubility studies of Pravastatin.

Discussion: From the above obtained solubility data we can say that 6.8 ph buffer is having more solubility than 1.2 ph buffer.

Uv spectrum of Pravastatin

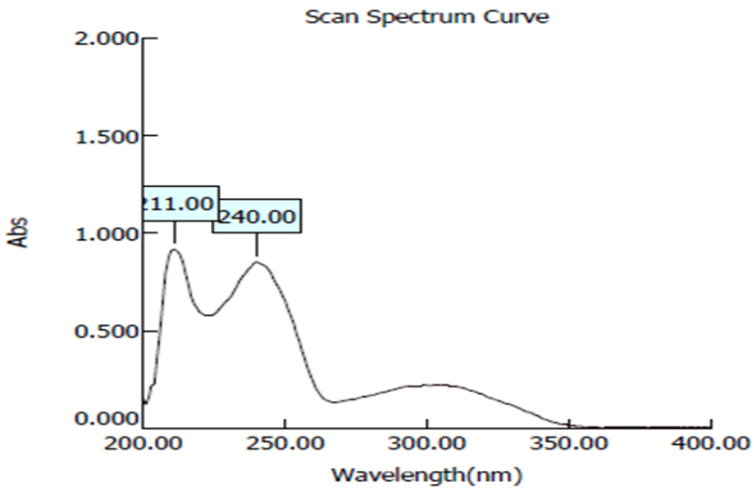

Fig: UV Spectrum of Pravastatin.

Preparation of Standard Calibration Curve of Pravastatin

Table: Standard Calibration Curve of Pravastatin at 239 nm.

Concentartion(µg/ml)	Absorbance
0	0.164
5	0.297
10	0.476
15	0.628
20	0.798
25	0.964
30	0.164

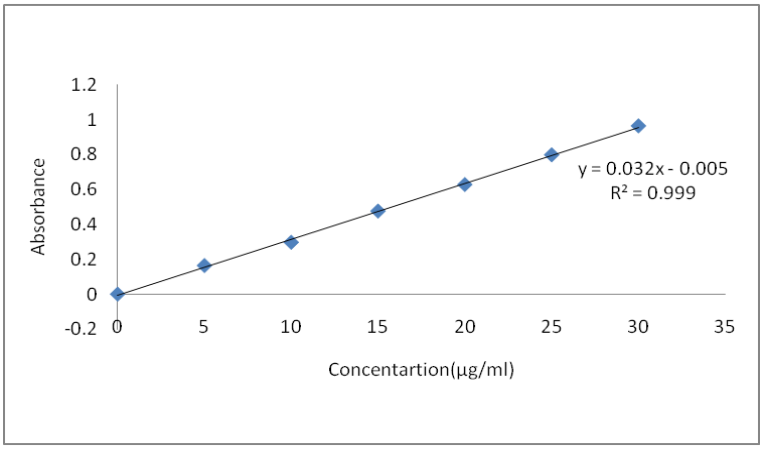

Figure: Calibration curve of pravastatin in 6.8pH buffer.

Compatibility Studies

Compatibility with excipients was confirmed by FTIR studies. The pure drug and polymers were subjected to FTIR studies. In the present study, the potassium bromide disc (pellet) method was employed.

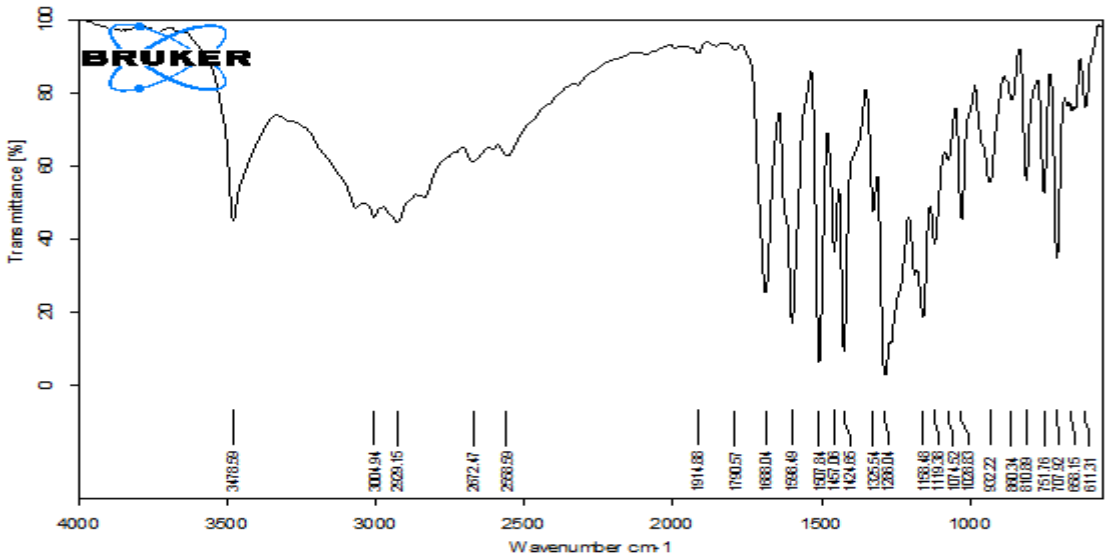

Figure: FTIR Spectrum of Pravastatin pure.

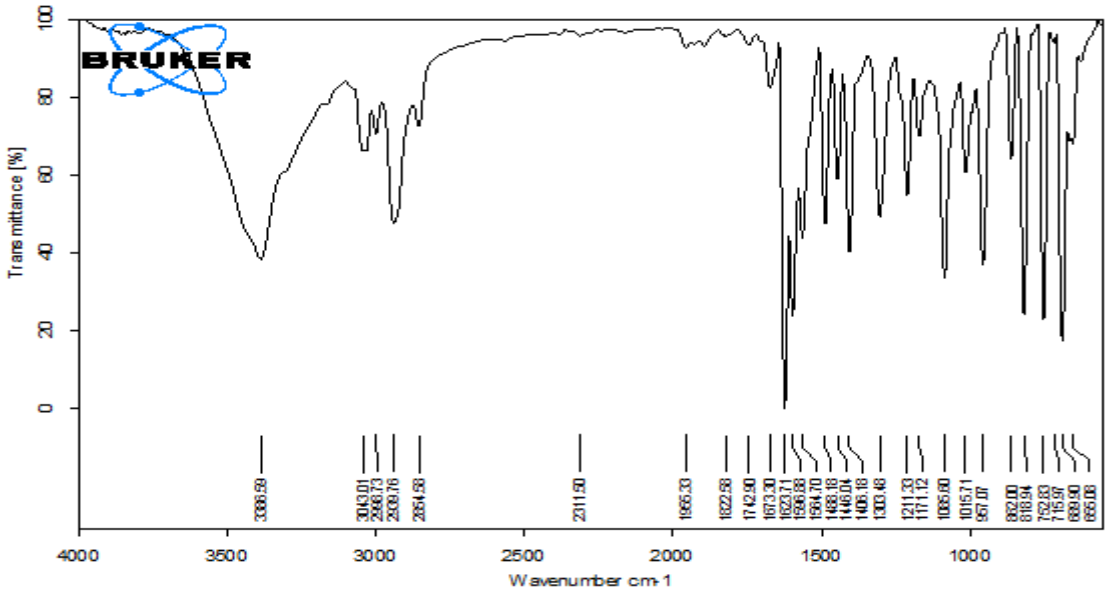

Figure: FTIR Spectrum of Pravastatin and Excipients.

Discussion: Form the drug excipient compatibility studies we observe that there are no interactions between the pure drug (Pravastatin) and optimized formulation (Pravastatin+ excipients) which indicates there are no physical changes.

Table: Micromeretic properties of core tablet of Pravastatin.

FormulationCode	Derived properties		Flow properties		
	Bulkdensity (mean±SD)	Tapped density (mean±SD)	Angle of repose (mean±SD)	Carr's index (mean±SD)	Hausner's ratio (mean±SD)
P1	0.526±0.26	0.598±0.06	26.26±0.02	12.04±0.03	1.14±0.95
P2	0.516±0.41	0.584±0.01	28.21±0.63	11.64±0.26	1.13±0.74
P3	0.482±0.52	0.567±0.23	25.26±0.46	14.99±0.14	1.18±0.25
P4	0.526±0.85	0.593±0.74	28.63±0.41	11.30±0.85	1.13±0.16
P5	0.509±0.41	0.601±0.45	30.14±0.52	15.31±0.36	1.18±0.05
P6	0.498±0.66	0.562±0.26	27.52±0.26	11.39±0.10	1.13±0.03

Discussion

The angle of repose of different formulations was ≤ 30.14 which indicates that material had good flow property. So it was confirmed that the flow property of

blends were free flowing. The bulk density of blend was found between 0.48g/cm^3 to 0.52g/cm^3.Tapped density was found between 0.56g/cm^3 to 0.60g/cm^3. These values indicate that the blends had good flow property. Carr's index for all the formulations was found to be between 11.30-15.31 and Hausner's ratio from 1.13-1.18 which reveals that the blends have good flow character.

Table: Post compression parameters of core tablet.

	Post compression parameters of core tablet					
	Avg.Wt (mg)	Hardness (kg/cm^2)	Thickness (mm)	Drug content (%)	Friability (%)	Disintegration time(secs)
P1	97.02±0.32	3.02±0.16	2.96±0.48	86.36±0.62	0.86±0.02	72±0.19
P2	98.26±0.54	3.26±0.02	3.02±0.16	92.12±0.36	0.52±0.15	55±1.26
P3	98.14±0.26	3.36±0.63	2.93±0.24	95.01±0.25	0.81±0.63	46±0.58
P4	99.52±0.59	3.14±0.14	3.15±0.29	96.63±0.14	0.69±0.14	86±0.91
P5	97.36±0.84	3.52±0.52	2.92±0.17	91.52±0.25	0.52±0.25	67±0.22
P6	98.14±0.12	3.26±0.26	3.36±0.62	93.26±0.36	0.63±0.19	59±0.54

Table: Evaluation of Physical Parameters of compressed tablets of Pravastatin.

Formula	Weight variation (mean ± SD, mg)	Hardness	Friability (%)	Thickness	Drug content
P3F1	398.26±1.02	6.05±0.15	0.84±0.26	4.65±0.02	84.15±0.15
P3F2	397.41±0.26	6.56±0.36	0.75±1.14	4.86±0.21	94.63±0.52
P3F3	399.52±1.25	7.06±0.48	0.26±0.25	4.92±0.14	91.52±0.63
P3F4	396.36±0.63	6.45±0.15	0.45±0.26	4.26±0.85	92.15±0.01
P3F5	397.84±0.74	6.85±0.22	0.31±0.36	4.64±0.39	96.02±0.15

Table: Cumulative percent drug release of Pravastatin core tablets of different formulations (P1 to P6).

Time	P1	P2	P3	P4	P5	P6
0	0	0	0	0	0	0
5	21.06	29.21	45.26	36.18	36.18	39.15
10	32.18	36.06	59.15	46.18	42.26	57.05
15	48.19	52.18	74.52	55.42	59.63	65.24
20	56.47	65.54	86.15	69.48	71.84	79.49
25	66.89	78.19	98.26	80.63	88.26	88.05
30	82.48	93.82		89.48	94.63	99.26

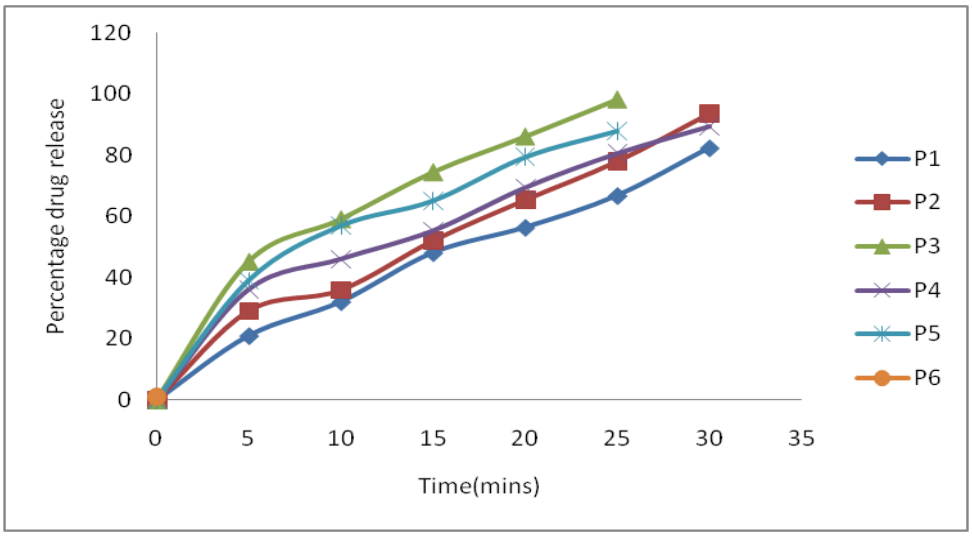

Fig: Cumulative percentage drug release of Pravastatin core tablets P1 – P6.

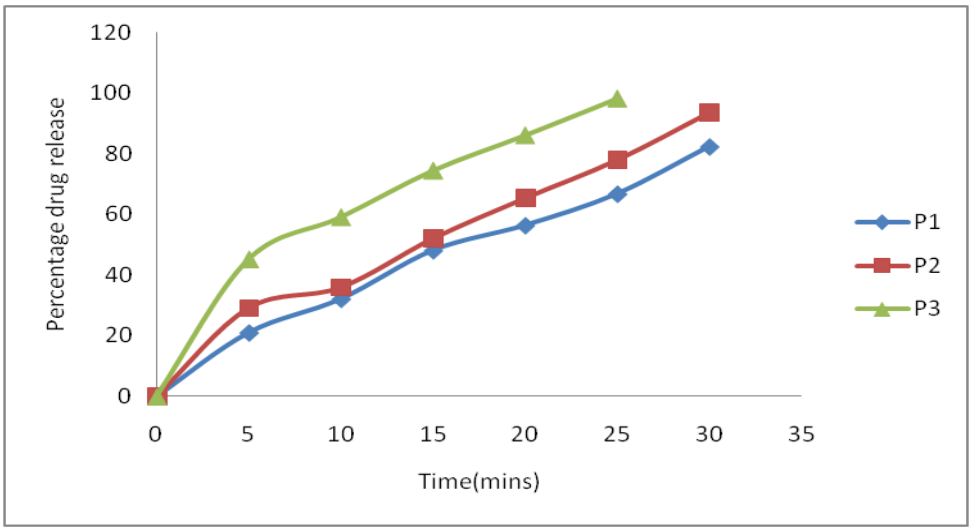

Fig: Cumulative percentage drug release of Pravastatin core tablets P1 – P3.

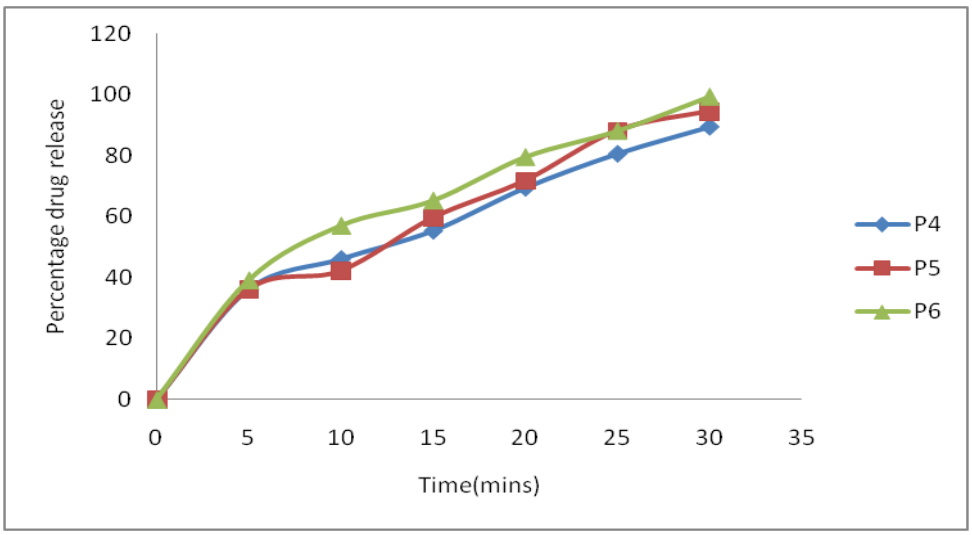

Fig: Cumulative percentage drug release of Pravastatin core tablets P4-P6.

In vitro drug release studies of press coated tablets

Table: Cumulative % drug release of coated different formulation (P3F1 to P3F5)

Time(hrs)	P3F1	P3F2	P3F3	P3F4	P3F5
0	0	0	0	0	0
1	0.96	1.56	0.35	0.12	0.26
2	1.56	6.85	1.56	1.36	0.96
3	3.85	10.63	3.85	4.89	1.52
4	9.56	26.84	9.18	6.15	2.96
5	32.85	42.56	13.85	9.86	3.84
6	46.85	62.15	26.84	46.96	6.82
7	72.96	75.26	62.36	76.85	79.85
8	80.96	82.56	83.65	89.82	97.52
9	92.61	97.85	95.34	96.34	
10	99.85				

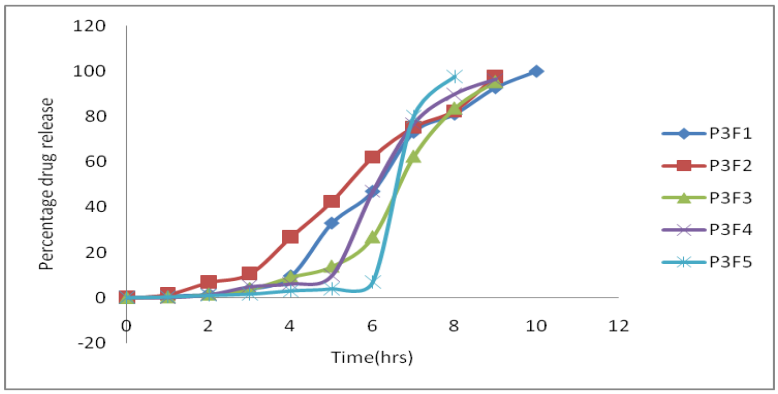

Fig: Cumulative percentage drug release of Pravastatin press coated tablets P3F1-P3F5.

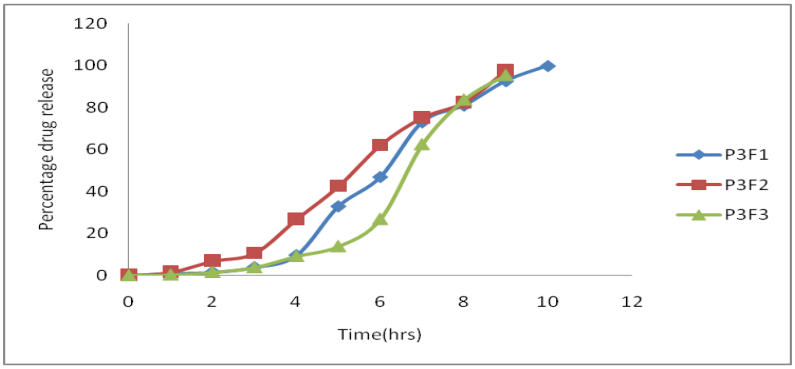

Fig: Cumulative percentage drug release of Pravastatin press coated tablets P1F6-P3F6.

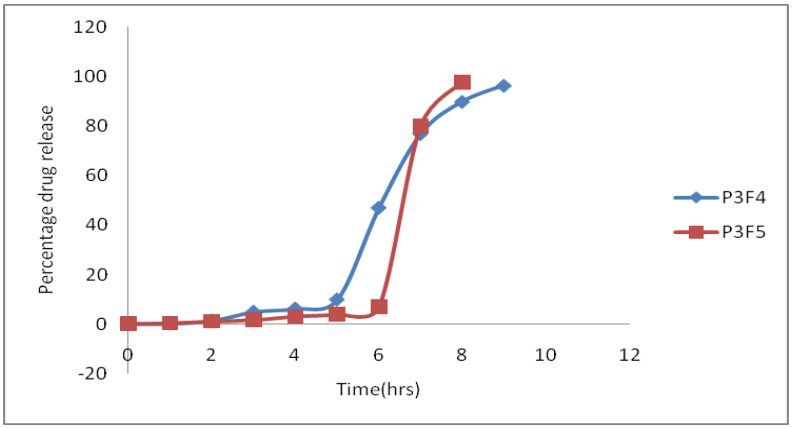

Fig: Cumulative percentage drug release of Pravastatin press coated tablets P4F6-P3F5.

DRUG RELEASE KINETICS OF PRAVASTATIN PRESS COATED TABLETS
ZERO ORDER RELEASE KINETICS

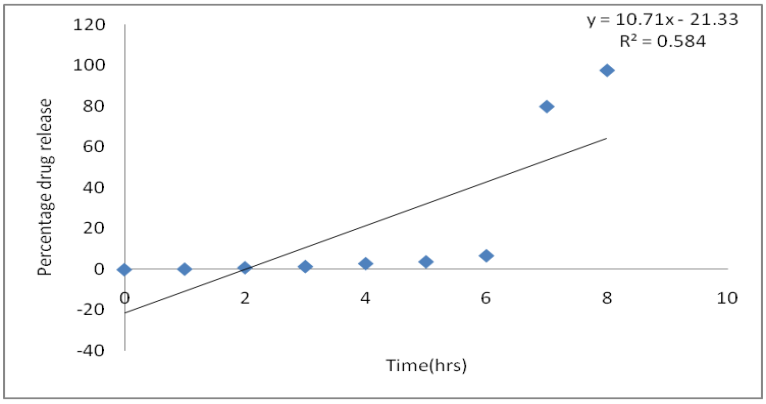

Fig: Zero order release kinetics for best formulation (P3F5).

FIRST ORDER RELEASE KINETICS

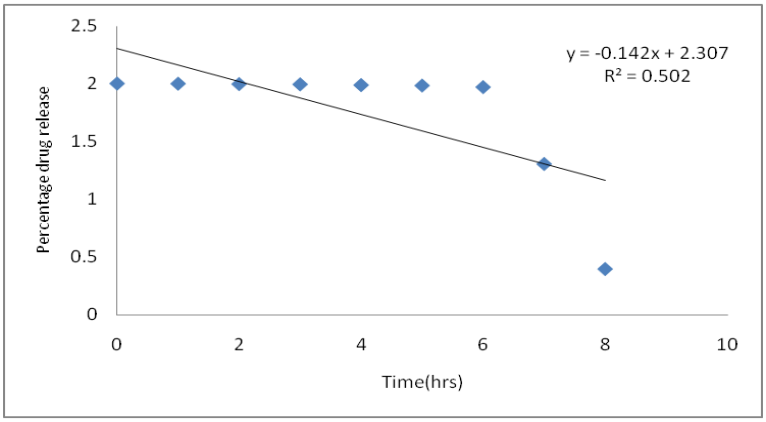

Fig: First order release kinetics for best formulation (P3F5).

HIGUCHI PLOT

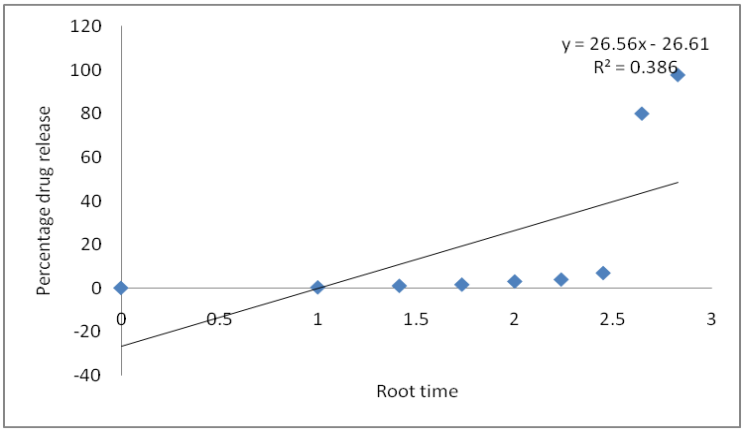

Fig: Higuchi release kinetics for best formulation (P3F5).

PEPPAS

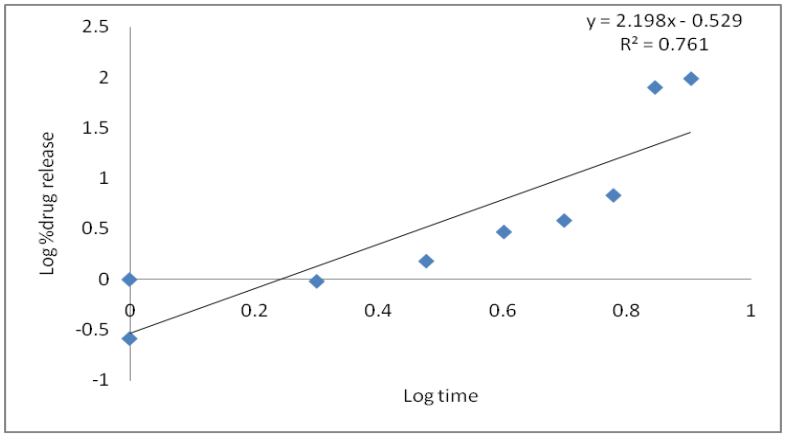

Fig: Peppas release kinetics for best formulation (P3F5).

Table: *in-vitro* drug release mechanism of best formulation.

Batch	Zero Order	First Order	Higuchi	Peppas	Peppas
Code	**r2**	**r2**	**r2**	**r2**	**n**
P3F5	0.584	0.502	0.386	0.761	2.198

SUMMARY

Pravastatin is a cholesterol-lowering agent that belongs to a class of medications known as statins. It was derived from microbial transformation of mevastatin, the first statin discovered. It is a ring-opened dihydroxyacid with a 6'-hydroxyl group that does not require *in vivo* activation. Pravastatin is one of the lower potency statins; however, its increased hydrophilicity is thought to confer advantages such as minimal penetration through lipophilic membranes of peripheral cells,

increased selectivity for hepatic tissues, and a reduction in side effects compared with lovastatin and Pravastatin.

The usual dose of Pravastatin is 40-80mg orally once a day as treatment of HMGCR inhibitor and anti-proliferative agent. So Pravastatin was chosen as a model drug with an aim to develop a pulsatile drug delivery system for reduces levels of "bad" cholesterol (low-density lipoprotein, or LDL) and triglycerides in the blood. In this research work preparation of pulsatile drug delivery system was prepared using superdisintegrants like Crospovidone, CCS were selected in the system. Melting point of Pravastatin was found to be in the range of 172° C. The solubility of the Pravastatin was that 6.8 ph buffer is having more solubility than 1.2 ph buffer. All the prepared formulations were analysed for Pre-compression parameters were conducted for all formulations blend and were found to be satisfactory. The angle of repose of different formulations was ≤ 30.14 which indicates that material had good flow property. So it was confirmed that the flow property of blends were free flowing. The bulk density of blend was found between 0.48g/cm^3 to 0.52g/cm^3. Tapped density was found between 0.56g/cm^3 to 0.60g/cm^3. These values indicate that the blends had good flow property. Carr's index for all the formulations was found to be between 11.30-15.31 and Hausner's ratio from 1.13-1.18 which reveals that the blends have good flow character.

POST COMPRESSION PARAMETERS OF PRAVASTATIN CORE TABLETS

Weight Variation Test: The percentage weight variations for all formulations were given. All the formulated (P1 to P6) 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 3-4 kg/cm2. This ensures good handling characteristics of all batches.

Disintegration test for core tablets: It was found between 46 – 86 seconds ensuring that all the cores of different formulations were rapid disintegrating type.

Friability Test: The % friability was less than 0.77 % in all the formulations ensuring that the tablets were mechanically stable.

The percentage of drug content for P1 to P6 was found to be between 86.36% - 96.26%. It complies with official specifications.

From the Invitro drug release data of the core tablets it was concluded that the formulation P3 of core tablet containing 6mg of shows immediate release while compared with CROSPOVIDONE.

POST COMPRESSION PARAMETERS OF COATED TABLETS

Weight Variation Test: The percentage weight variations for all formulations were given. All the formulated (P3F1 to P3F65) 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 6.05 – 7.06 kg/cm^2. This ensures good handling characteristics of all batches.

Thickness: The measured thickness of tablets of all the formulations ranged between 4.26 - 4.86mm. This ensures good handling characteristics of all batches.

Friability Test: The % friability was less than 1 % in all the formulations ensuring that the tablets were mechanically stable.

The percentage of drug content for P3F1 to P3F5 was found to be between 84.15% - 96.02%. It complies with official specifications.

From the drug release kinetics of the press coated tablet it was concluded that the formulation P3F5 maintains lag phase for 6 hours and the drug release was bursted at the end of 7hours and followed by maximum release at the end of 8hrs. It follows zero order release and follows super caseII transport mechanism.

CONCLUSION

The aim of this study was to explore the feasibility of time dependent pulsatile drug delivery system of Pravastatin for reduces levels of "bad" cholesterol (low-density lipoprotein, or LDL) and triglycerides in the blood. A satisfactory attempt was made to develop pulsatile system of Pravastatin and evaluated it.

From the reproducible results obtained from the executed trails of core and press coated tablets it can be concluded that:

o On the basis of drug content, *in-vitr*o release studies and its kinetic data P3 of core tablet and P3F5 of coated tablet were selected as optimized formulations for designing Pulsatile device.

o Therefore the study proved that coated Pravastatin can be successfully used as a time dependent modified Chronopharmaceutical formulation.

o Finally from the above results we can conclude that pulsatile drug delivery system of Pravastatin can be formulated using Ethyl celluloe and HPMC K15M.

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