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Formulation and *In-vitro* evaluation of press coated tablets of Pravastatin for pulsatile drug delivery

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ABSTRACT

The aim of present study is to formulate and evaluate Pravastatin pulsatile drug delivery system by press coated method to mimic the circadian rhythm of the disease by releasing the drug with a distinct predetermined lag time of 6 hrs. The basic design of the system consists of a rapid release core and controlled release coat. Core blend was evaluated for flow properties, hardness, thickness, friability and *invitro* drug release. *Invitro* drug release studies of press coated tablets for various formulations *i.e.,* P1F6-P5F6 was conducted. From the results obtained by executed trails P5F6 of coated tablet containing 50% of ethyl cellulose and 20% of HPMC K15M concentration shows lag time up to 6hr and followed by complete drug release at the end of 8hr. Among these, P5F6 was considered as optimized formulation based on the lag time and percent of drug release (98.96% of drug release in 6 hrs). So, it is selected as optimized formulations for designing pulsatile device.

Keywords: Pravastatin, SSG, lycoat, ethyl cellulose, HPMC K15M, pulsatile drug delivery, Press coated method.

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INTRODUCTION

Delivery systems with a pulsatile pattern are receiving increasing interest for the development of dosage forms, because conventional systems with a continuous release are not ideal. Most conventional oral controlled release drug delivery systems release the drug with constant or variable release rates. A pulsatile release profile is characterized by a time period of no release (lag time) followed by a rapid and complete release. These dosage forms offer many advantages such as: constant drug levels at the site of action, avoidance of undesirable side effects, reduced dose and improved patient compliance, useful for drugs with a chronopharmacological behaviour, a high first pass effects, the requirement of night time dosing and site -specific absorption in GIT[1].

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, etc. Recent studies have revealed that diseases have predictable cyclic rhythms and that the timing of medication regimens can improve outcome in selected chronic conditions[2]. Pulsatile system gaining a lot of interest as it is increasing patient compliance by means of providing time- and site-specific drug delivery system, thus providing special and temporal delivery. Pulsed or pulsatile drug release is defined as the rapid and transient release of a certain amount of drug molecules within a short time-period immediately after a predetermined off-release period. Recent studies show that diseased have predictable cyclic rhythms and the timing of medication regimens can improve outcome in selected chronic conditions [3,4].

MATERIALS & METHODS

Pravastatin purchased from Spectrum pharma labs, Hyderabad, SLS, LYCOAT, HMPC, HMPC K15M, ethyl cellulose, talc, magnesium stearate, Microcrystalline cellulose were used. All the reagents used are of LR grade.

Formulation

Preparation 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, lycoat, 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.

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.

Evaluation Studies

Tablets were subjected to evaluation of properties including drug content uniformity, weight variation, tablet hardness, friability, and thickness, and *invitro* drug release.

1. 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 formula:

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 = final volume of the granules.

2. 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

3. 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.

4. 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.

5. 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.

6. Weight Variation

20 tablets were selected randomly from the lot and weighed individually to check for weight variation.

7. Friability (F)[5]

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. Friability generally reflects poor cohesion of tablet ingredients.

Percentage of friability of the tablets of a badge can be determined by the following

Formula

$$\% \text{ Friability} = W1 - W2 / W1 \times 100$$

Where,

W1 = weight of tablets before testing

W2 = weight of tablets after testing.

8. Drug uniformity[6]

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 Whatman filter paper No.41. Then the serial dilutions were carried out. The absorbance of the diluted solutions was measured spectrophotometrically at 236 nm. The concentration of the drug was computed from the standard curve of the Pravastatin in 6.8 phosphate buffer.

9. Disintegration studies[7]

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.

10. *In-vitro* dissolution studies of Pravastatin[8]

Invitro dissolution study of core and coated tablets of Pravastatin was carried out using Lab India DS8000 USP dissolution test apparatus. 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.

11. Release kinetic models [9. 10]

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. 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 *invitro* 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).

Table 1: Composition of Pravastatin core tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6
Pravastatin	40	40	40	40	40	40
SSG	2	4	6	--	--	--
Lycoat	--	--	--	2	4	6
MCC	52	50	48	52	50	48
Magnesium stearate	4	4	4	4	4	4
Talc	2	2	2	2	2	2
Total wt (mg)	100	100	100	100	100	100

Table 2: Composition of compression coated tablets of Pravastatin

Formulation	P1F6	P2F6	P3F6	P4F6	P5F6
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

UV spectrum of Pravastatin

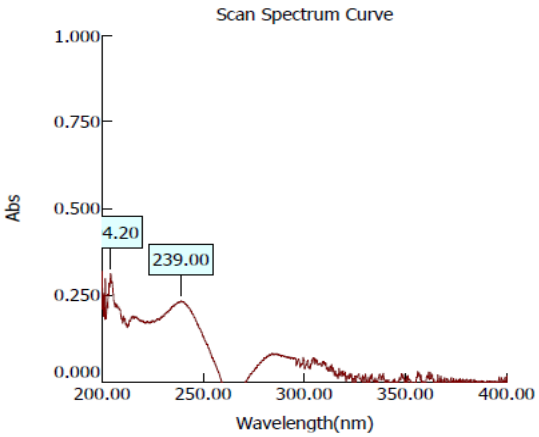

Figure 1: UV Spectrum of Pravastatin

Preparation of Standard Calibration Curve of Pravastatin

Table 3: Standard calibration curve of Pravastatin at 239 nm

Concentartion (µg/ml)	Absorbance
0	0
5	0.119
10	0.242
15	0.394
20	0.529
25	0.667
30	0.791

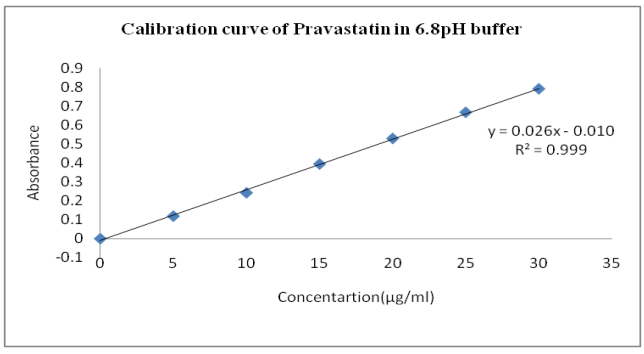

Figure 2: Calibration curve of Pravastatin in 6.8 pH buffer

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. The results were shown in Fig: 3 & 4.

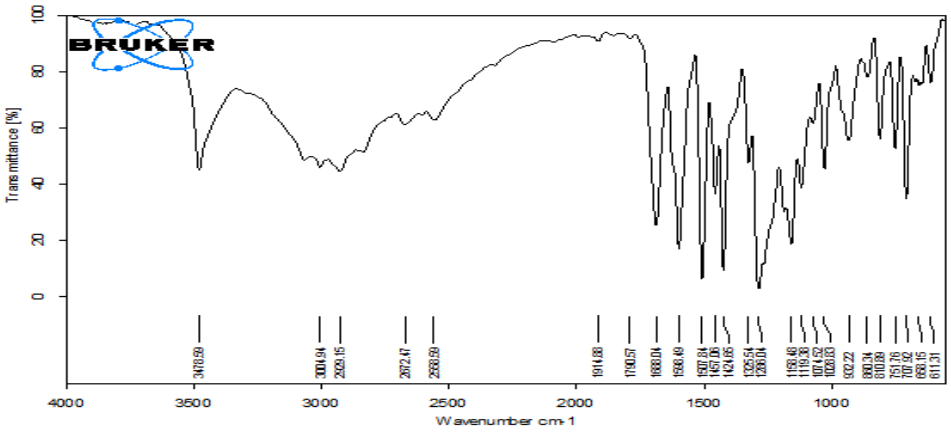

Figure 3: FTIR spectrum of Pravastatin pure

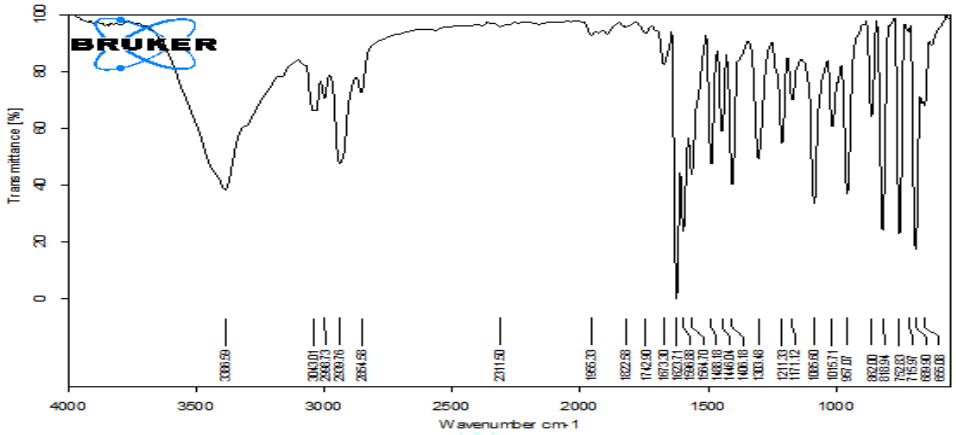

Figure 4: FTIR spectrum of Pravastatin and excipients

Table 4: Post compression parameters of core tablet

	Post compression parameters of core tablet					
	Avg.wt (mg)	Hardness (Kg/cm²)	Thickness (mm)	Drug content (%)	Friability (%)	Disintegration time (secs)
F1	97.02±0.32	3.02±0.16	2.96±0.48	86.36±0.62	0.86±0.02	86±0.19
F2	98.26±0.54	3.26±0.02	3.02±0.16	92.12±0.36	0.52±0.15	67±1.26
F3	96.14±0.26	3.36±0.63	2.93±0.24	89.01±0.25	0.81±0.63	59±0.58
F4	99.52±0.59	3.14±0.14	3.15±0.29	96.63±0.14	0.69±0.14	72±0.91
F5	97.36±0.84	3.52±0.52	2.92±0.17	91.52±0.25	0.52±0.25	55±0.22
F6	98.14±0.12	3.26±0.26	3.36±0.62	96.26±0.36	0.63±0.19	46±0.54

Table 5: Physical parameters of compressed tablets of Pravastatin

Formula	Weight variation (mean ± SD, mg)	Hardness (Kg/cm²)	Friability (%)	Thickness	Drug content
P1F6	398.26±1.02	6.05±0.15	0.84±0.26	4.65±0.02	84.15±0.15
P2F6	397.41±0.26	6.56±0.36	0.75±1.14	4.86±0.21	94.63±0.52
P3F6	399.52±1.25	7.06±0.48	0.26±0.25	4.92±0.14	91.52±0.63
P4F6	396.36±0.63	6.45±0.15	0.45±0.26	4.26±0.85	92.15±0.01
P5F6	397.84±0.74	6.85±0.22	0.31±0.36	4.64±0.39	96.02±0.15

Table 6: Cumulative percent drug release of Pravastatin core tablets of different formulations (F1 to F6)

Time (mins)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
5	21.06±0.48	29.21±0.26	36.18±0.23	36.18±0.26	39.15±0.26	45.26±0.63
10	32.18±0.96	36.06±0.53	42.26±0.96	46.18±0.31	57.05±0.31	59.15±0.62
15	48.19±0.58	52.18±0.51	59.63±0.58	55.42±0.52	65.24±0.52	74.52±0.15
20	56.47±0.63	65.54±0.48	71.84±0.36	69.48±0.4	79.49±0.36	86.15±0.20
25	66.89±0.15	78.19±0.26	88.26±0.26	80.63±0.85	88.05±0.25	98.26±0.23
30	79.48±0.02	88.82±0.96	94.63±0.15	92.48±0.92	99.26±0.41	-

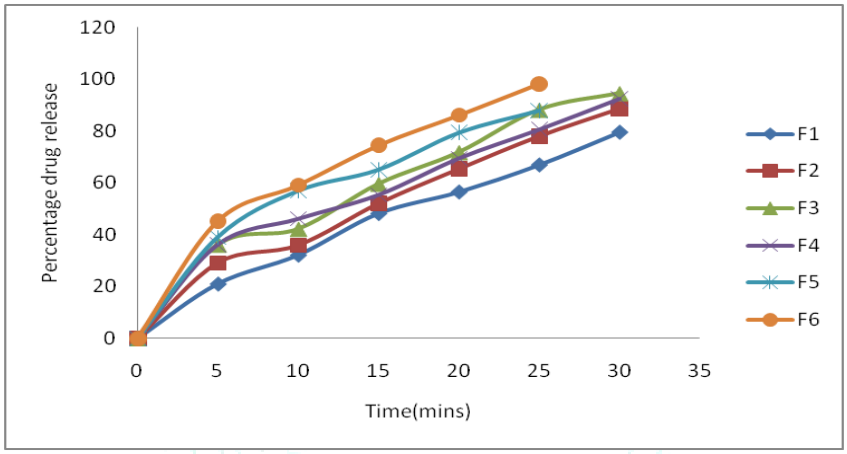

Figure 5: Cumulative percentage drug release of Pravastatin core tablets F1 – F6

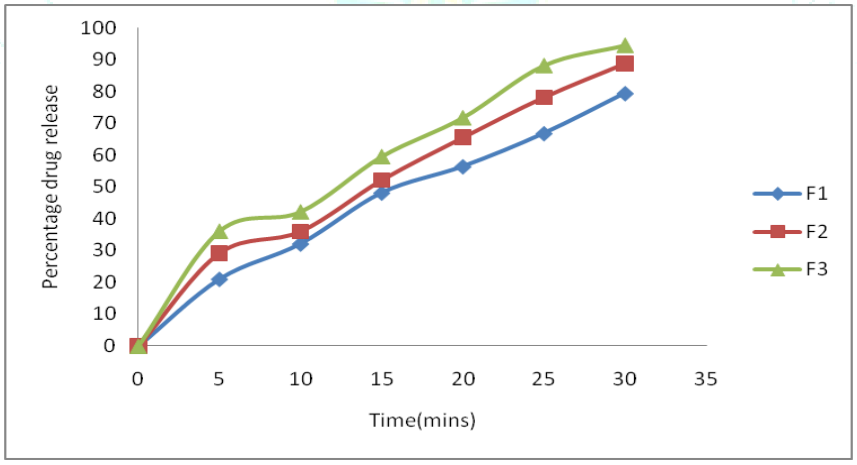

Figure 6: Cumulative percentage drug release of Pravastatin core tablets F1 – F3

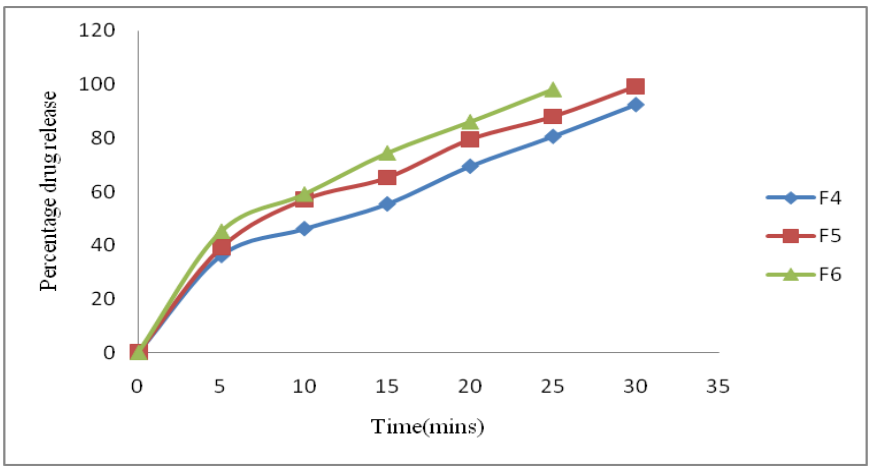

Figure 7: Cumulative percentage drug release of Pravastatin core tablets F4-F6

***In-vitro* Drug Release Studies of Press Coated Tablets**

Table 7: Cumulative % drug release of coated different formulation (P1F6 to P5F6)

Time (hrs)	P1F6	P2F6	P3F6	P4F6	P5F6
0	0	0	0	0	0
1	0.96±0.26	1.56±0.51	0.35±0.23	0.12±0.02	0.26±0.10
2	1.56±0.54	6.85±0.52	1.56±0.36	1.36±0.15	0.96±0.20
3	3.85±0.85	10.63±0.40	3.85±0.50	4.89±0.86	1.52±0.15
4	9.56±0.96	26.84±0.51	9.18±0.51	6.15±0.95	2.96±0.32
5	32.85±0.23	42.56±0.32	13.85±0.62	9.86±0.32	3.84±0.56
6	46.85±0.10	62.15±0.96	26.84±0.63	46.96±0.61	6.82±0.48
7	72.96±0.20	75.26±0.85	62.36±0.48	76.85±0.10	79.85±0.15
8	80.96±0.23	82.56±0.54	89.15±0.15	89.82±0.26	98.96±0.02
9	92.61±0.03	98.05±0.16	98.75±0.02	97.28±0.01	-
10	98.82±0.49	-	-	-	-

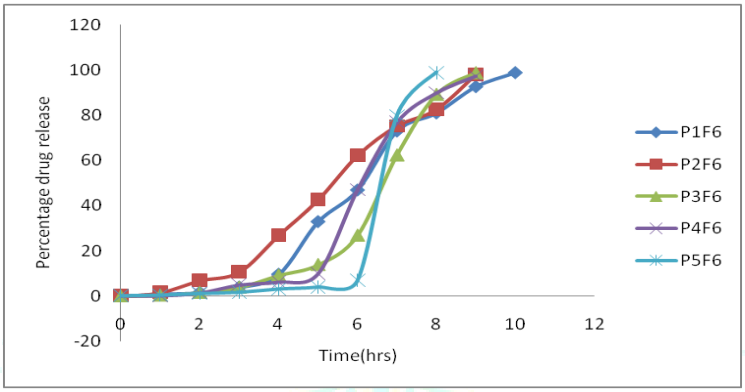

Figure 8: Cumulative percentage drug release of Pravastatin press coated tablets P1F6-P5F6

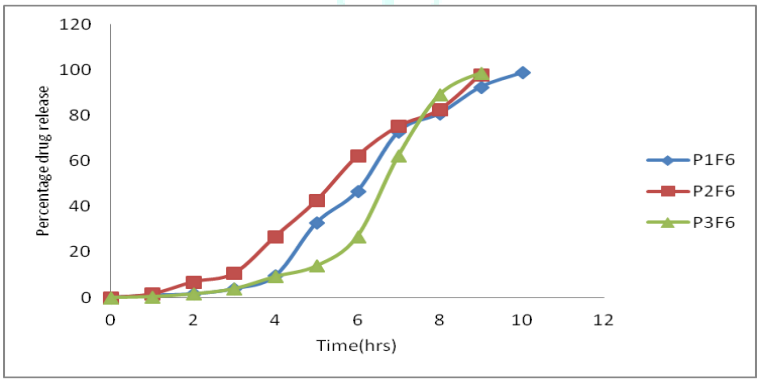

Figure 9: Cumulative percentage drug release of Pravastatin press coated tablets P1F6-P3F6

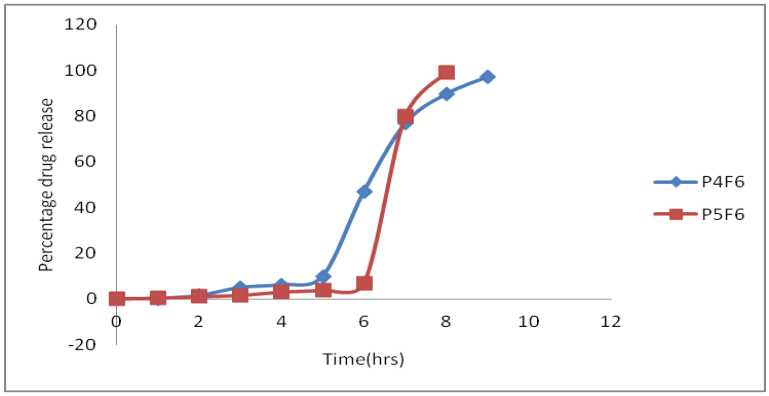

Figure 10: Cumulative percentage drug release of Pravastatin press coated tablets P4F6-P5F6

Drug Release Kinetics of Pravastatin Press Coated Tablets:

Zero order release kinetics

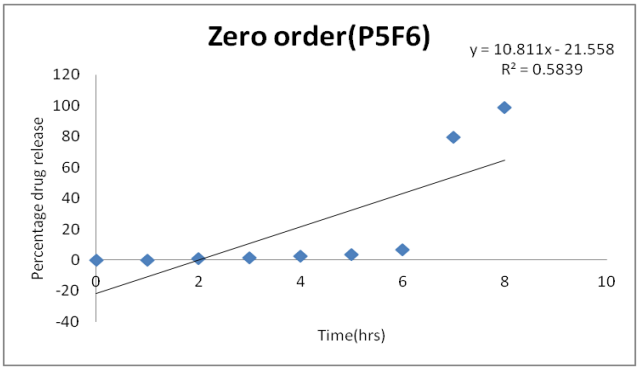

Figure 11: Zero order release kinetics for best formulation (P5F6)

First order release kinetics

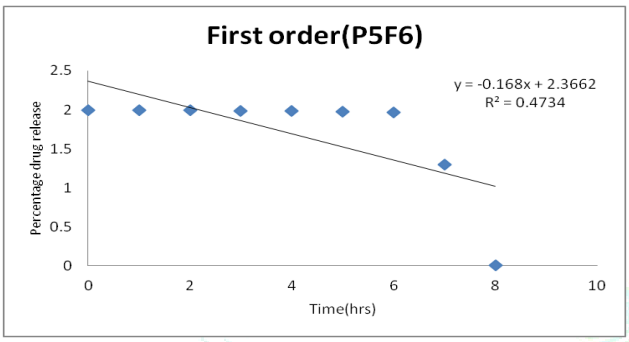

Figure 12: First order release kinetics for best formulation (P5F6)

Higuchi Plot:

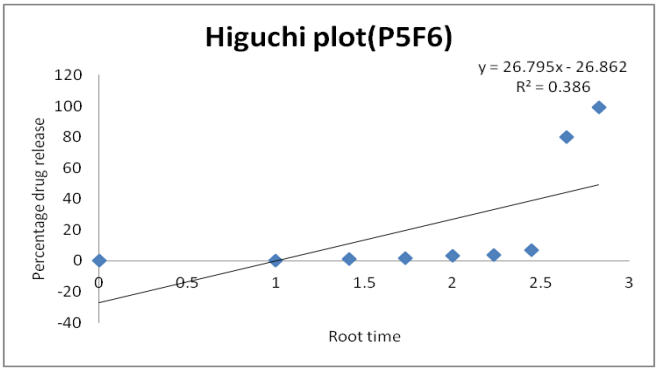

Figure 13: Higuchi release kinetics for best formulation (P5F6)

Peppas plot:

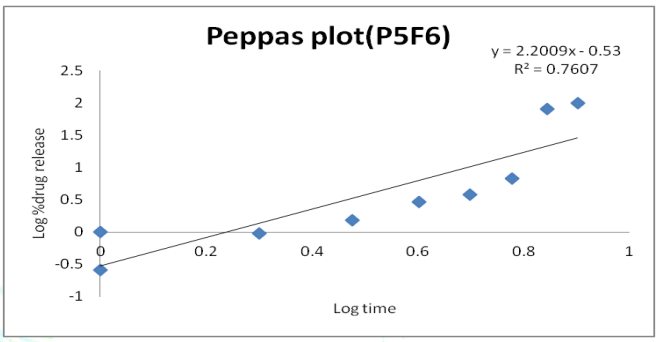

Figure 14: Peppas release kinetics for best formulation (P5F6)

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

Batch	Zero Order	First Order	Higuchi	Peppas	Peppas
Code	r^2	r^2	r^2	r^2	n
P5F6	0.583	0.473	0.386	0.760	2.200

From the drug release kinetics of the press coated tablet it was concluded that the formulation P5F6 maintains lag phase for 6 hours and the drug release was bursted at the end of 7th hour and showed maximum release at the end of 8th hour. It follows zero order release and follows super case II transport mechanism.

RESULTS AND DISCUSSION

Post Compression Parameters of Pravastatin Core Tablets

Weight Variation Test: The percentage weight variations for all formulations were given. 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.

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.

Drug content: The percentage of drug content for F1 to F6 was found to be between 86.36% - 96.26%. It complies with official specifications.

***Invitro* drug release**: From the data obtained the core tablets F6 containing 6mg of shows immediate release while compared with Lycoat.

Post Compression Parameters Oof Coated Tablets

Weight Variation Test: The percentage weight variations for all formulations were given. All the formulated (P1F6 to P5F6) 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/cm2. 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.

Drug content: The percentage of drug content for P1F6 to P5F6 was found to be between 84.15% - 96.02%. It complies with official specifications.

Drug releases kinetics: From the drug release kinetics of the press coated tablet it was concluded that the formulation P5F6 maintains lag phase for 6 hrs and the drug release was bursted at the end of 7hrs and followed by maximum release at the end of 8hrs. It follows zero order release and follows super caseII transport mechanism

CONCLUSION

The characteristic peak stretches of the drug was present in the physical mixture of the drug with the polymers-excipients with no other relevant effects. Hence there are no drug-excipient interactions. Micromeritic properties like bulk density, tapped density, hausner's ratio and angle of repose were inacceptable range. The tablets were evaluated for quality control tests including thichness, weight variation, hardness, friability, drug content uniformity and concluded to be within limits. From the drug release kinetics of the press coated tablet it was concluded that the formulation P5F6 maintains lag phase for 6hrs and the drug release was bursted at the end of 7hrs and followed by maximum release at the end of 8hrs. So, P5F6 formulation was considered to be optimized formulation.

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