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Research Article

Formulation and evaluation of Rosuvastatin pulsatile drug delivery system by using press coating technique

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ABSTRACT

Pulsatile drug delivery systems are developed to deliver drug according to circadian behavior of diseases. This means that these systems will deliver drug at time when disease display it's most morbid and mortal state within a circadian cycle (24 hrs). The product follow a sigmoidal drug release profile characterized by a time period of no release (lag time) followed by a rapid and complete drug release. Thus drug can be delivered at right time in right amount and at right site of action. By use of such approach, the potential benefits of chronotherapeutics have been investigated and established for number of diseases like asthma, arthritis, cancer, diabetes, epilepsy, hypertension, ulcer, hypercholesterolemia etc. Congestive heart failure is one of such diseases that follow circadian rhythms where increasing of air way resistance and worsening of heart function is observed during the early morning time. So, in this research work press-coated tablet containing rosuvastatin in the inner core was formulated with an outer barrier layer by different compositions of natural polymers like xanthan gum and guar gum. The effect of formulation composition of the barrier layer on the lag time of drug release was investigated.

Keywords: Pulsatile drug delivery system; Press-coated tablet; Circadian rhythms; Lag time.

INTRODUCTION

Controlled drug delivery systems have acquired a centre stage in the area of pharmaceutical R &D 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 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 is known as "Pulsatile" release synchronize drug concentrations to rhythms in disease activity (Parmar R. *et al*., 2009).

Today, a vast amount of literature reports that biological processes are not constant but vary according to time. Although much of drug delivery research has focused on constant drug release rate due to limitations of delivering drug according to disease rhythmicity, clinical studies show that magnitude of rhythmic differences can be to a great extent and a strong determinant of when during 24 hour most morbid and mortal event will occur. For many drugs constant release system is not suitable. Drugs not suitable for constant release are used in disease condition that exhibit rhythmic variation within a circadian cycle.

PULSATILE DRUG DELIVERY SYSTEMS

A Pulsatile drug delivery system delivers drug in rapid and burst manner within a short time period immediately after a programmable lag phase. There are many situations where drug is needed to be released immediately (after bursting the delaying film coat) at specific site (Patel J. D *et al*., 2010).

These situations, therefore, compel designing a delayed fast release systems. These systems are mainly appropriate for drugs that are metabolized to pharmacological active compounds, drugs which have long in vivo half lives showing an inherently prolonged duration of action, drugs with very short in vivo half life which require a prohibitively large amount of active ingredients in dosage form, drugs which are required in large doses for therapeutic effect and drugs which are required in very low dose. Additionally a delayed burst release can also be utilized for enhancing absorption, reducing side effects, increasing and decreasing dose (Kikuchi A *et al*., 2002).

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Table 1: Formulation of Rosuvastatin with different polymers

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Rosuvostatin calcium	10	10	10	10	10	10	10	10	10
Cross povidone	7.5	11.25	15	-	-	-	-	-	-
Cross carmellose	-	-	-	7.5	11.25	15	-	-	-
Sodium starch glycolate	-	-	-	-	-	-	7.5	11.25	15
MCC	126.5	122.75	119	126.5	122.75	119	126.5	122.75	119
Talc	3	3	3	3	3	3	3	3	3
Magnesuim sterate	3	3	3	3	3	3	3	3	3

Table 2: Precompression parameters for the powder blend

Formulation code	Bulk density (g/cc)	Tapped density (g/cc)	Carr's index	Hausner's ratio	Angle of repose (θ)
F1	5.65±0.005	6.15±0.01	10±0.50	1.10±0.2	29.32±6.98
F2	5.28±0.01	5.83±0.01	11±0.47	1.11±0.22	30.21±4.96
F3	5.54±0.02	6.15±0.02	9.9±0.61	1.10±0.2	26.31±3.43
F4	5.69±0.005	6.15±0.03	8.9±0.98	1.09±0.3	29.35±6.46
F5	5.45±0.017	6.01±0.009	9.9±0.43	1.10±0.2	30.51±5.29
F6	5.75±0.015	6.35±0.01	10±0.46	1.21±0.19	35.52±1.94
F7	5.27±0.011	5.97±0.02	12±0.32	1.13±0.23	34.65±1.91
F8	5.94±0.03	6.65±0.03	11±0.2	1.11±0.22	30.86±2.90
F9	5.17±0.02	5.85±0.04	12±0.83	1.13±0.37	31.57±1.85

n = 3 ± S.D (All the values are average of 3 values)

Advantage of pulsatile drug delivery system

There are many advantages of pulsatile dosage form over conventional dosage form (Burnside B *et al*., 2003).

- Increases absorption and bioavailability than conventional immediate release or sustained release drug due to its ability to release drug in a burst manner, at target site of absorption.
- Site targeting allows delivery of poorly bioavailable drugs that would get destroyed in higher GI tract environment e.g. (peptide and protein molecules)
- Reduces dose of drug without decrease in therapeutic effects.
- Decreases side effects.
- Decreases food effect (change occurring in bioavailability of drug when given with food).
- Improved compliance.
- Chronotherapy, programmed delayed release provides optimal treatment of diseases.
- Pulse release allows multiple dosing in a single dosage form.
- Allows site specific release for local treatment of diseases. Drug release is not affected by change in pH of the gastrointestinal tract, viscosity of lumen contents, and agitation rate of GI tract.

Hypercholesterolemia, or high cholesterol, occurs when there is too much cholesterol in the body. Cholesterol is a soft, waxy, fat-like substance that is a natural component of all the cells of the body. Our body makes all the cholesterol it needs. Any added cholesterol, which comes from the foods you eat, can cause harm. High cholesterol raises your risk for heart disease, heart attack, and stroke. When there is too much cholesterol circulating in the blood, it can create sticky deposits (called plaque) along the artery walls. Plaque can eventually narrow or block the flow of blood to the brain, heart, and other organs (Lemmer B *et al*., 33, 1996). Blood cells that get caught on the plaque form clots, which can break loose and completely block blood flow through an artery, causing heart attack or stroke (Francesco P *et al*., 59, 2009).

In the present research rosuvastatin calcium is formulated into pulsatile drug delivery system, by using various polymers which helps in release of drug at predetermined rates.

Materials and Methods

Rosuvostatin calcium- Chandra labs, MCC-Degussa India Pvt. Ltd., Mumbai L.R, Crosspovidone, Sodium starch glycolate, Mannitol, Magnesium stearate, Talc, Cross carmellose S.D. Fine Chem.Ltd.,Mumbai. L.R, Xanthan gum, Guar gum, - L.R. Sisco Research Lab. Pvt. Mumbai.

Formulation of core tablets by direct compression

The inner core tablets were prepared by using direct compression method. Powder mixtures of Rosuvostatin calcium, mannitol, Sodium starch glycolate or crosscarmellonose or crosspovidone, and talc were dry blended for 20 minutes followed by addition of Magnesium Stearate. The mixtures were then further blended for 10 min., 150mg of resultant powder blend was manually compressed using hydraulic press at a

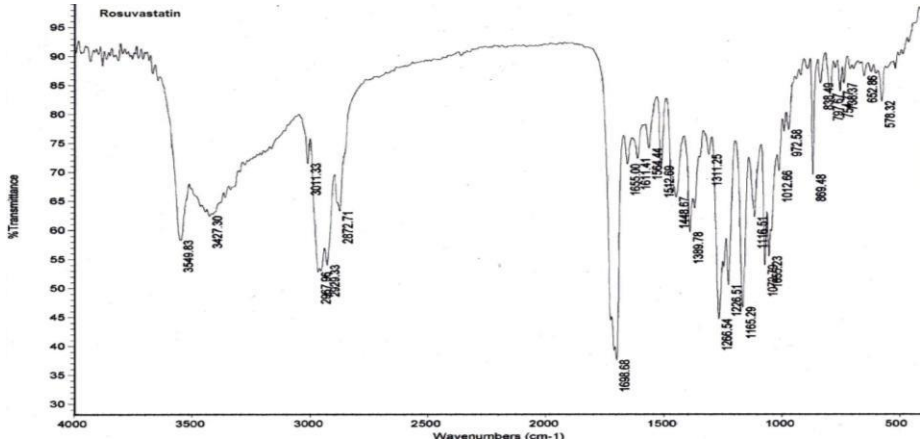

Figure 1: FTIR Spectrum of rosuvastatin

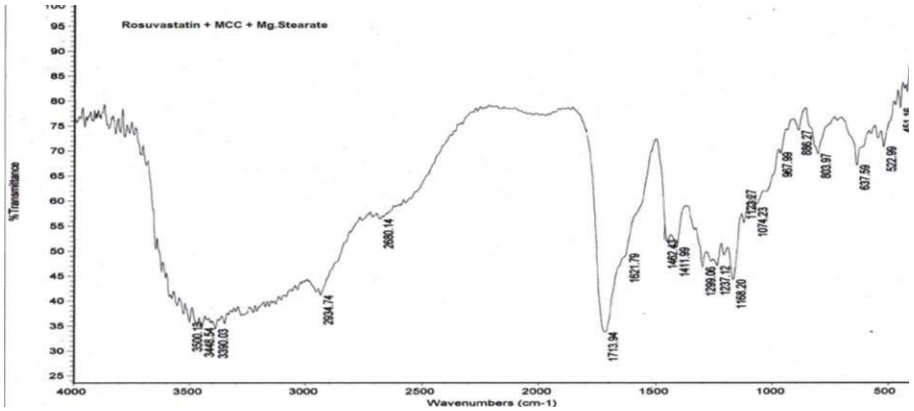

Figure 2: FTIR Spectroscopy of Rosuvastatin with MCC and Mg. stearate

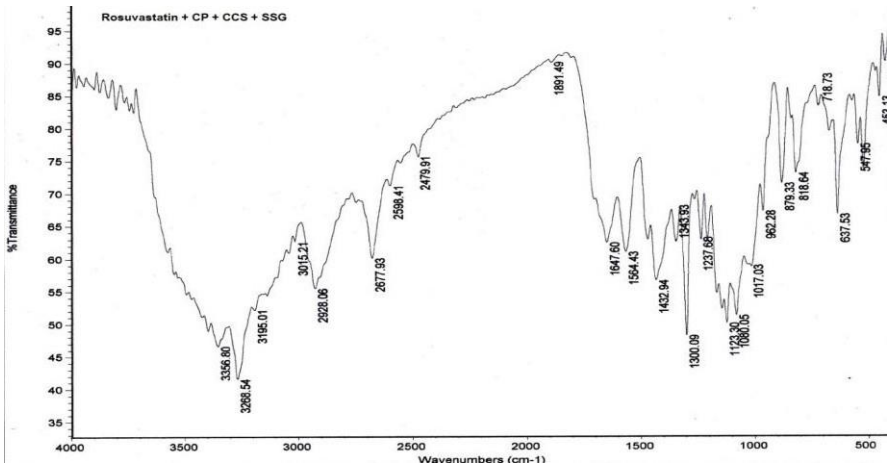

Figure 3: FTIR Spectroscopy of Rosuvastatin with cp + ccs + ssg

pressure of 1 ton, with a 7mm punch and die to obtain the core tablet.

Formulation of mixed blend for barrier layer

The various formulation compositions containing Xanthan gum and Guar gum. Different compositions were weighed dry blended at about 10 min. and used as press-coating material to prepare press-coated pulsatile tablets respectively by direct compression method.

Preparation of press-coated tablets

The core tablets were press-coated with 300mg of mixed blend/granules as 150mg of barrier layer material was weighed and transferred into a 13mm die then the core tablet was placed manually at the center. The remaining 150mg of the barrier layer materiel was added into the die and compressed at a pressure of 5 tons for 3min using KBr hydraulic press.

Evaluation

Pre Compression Parameters

The powder blend is evaluated for various Precomperssion parameters such as bulk density, tapped density, angle of repose, hausner's ratio, compressibility index to determine the flow properties of the powdered blend (Lachman L *et al*., 3, 1987).

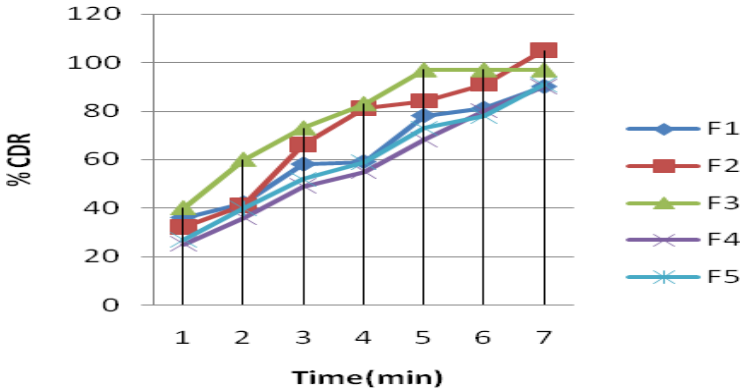

Figure 4: *In vitro* drug release pattern for formulation (F1-F5)

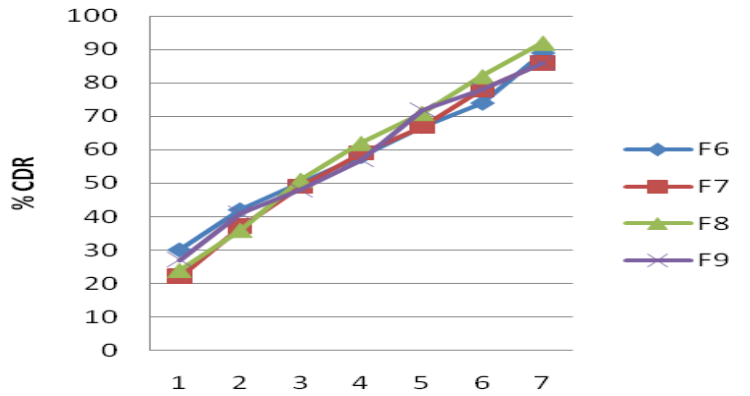

Figure 5: *In vitro* drug release pattern for formulation (F6-F9)

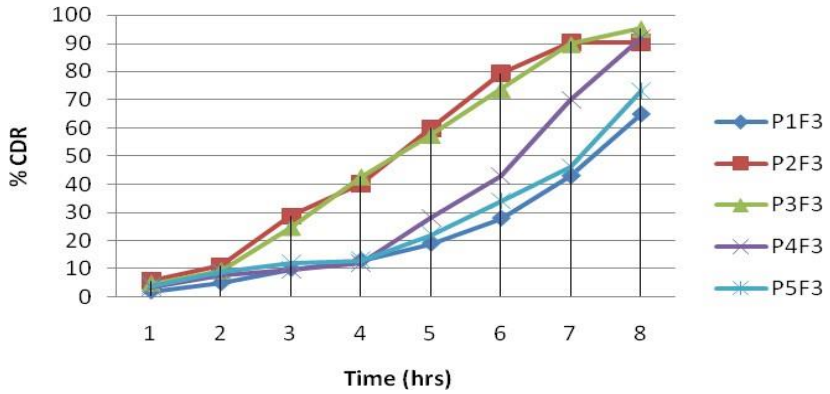

Figure 6: Dissolution profile of press coated of Rosuvastatin calcium tablets

Post compression parameters

Weight variation

Twenty tablets were weighed individually and the average weight was calculated. The individual tablet weights are then compared to the average weight. Not more than two tablets should differ in their average weight by more than percentages stated in USP. No tablet must differ by more than double the relevant percentage.

Thickness

Three tablets from each batch of formulation were collected and the thicknesses of the tablets were measured with the help of Vernier callipers. The average thickness was calculated.

Hardness

Hardness was measured using Monsanto tablet hardness tester. The hardness of five tablets in each batch was measured and the average hardness was calculated in terms of kg/cm^2.

Friability (F)

Friction and shock are the forces that most often cause tablets to chip, cap or break. The friability test is closely related to tablet hardness and designed to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping. It is usually measured by the use of the Roche friabilator.

Drug content uniformity

Accurately weighed quantity of the powder tablet equivalent to 20 mg of the drug was transferred to 100

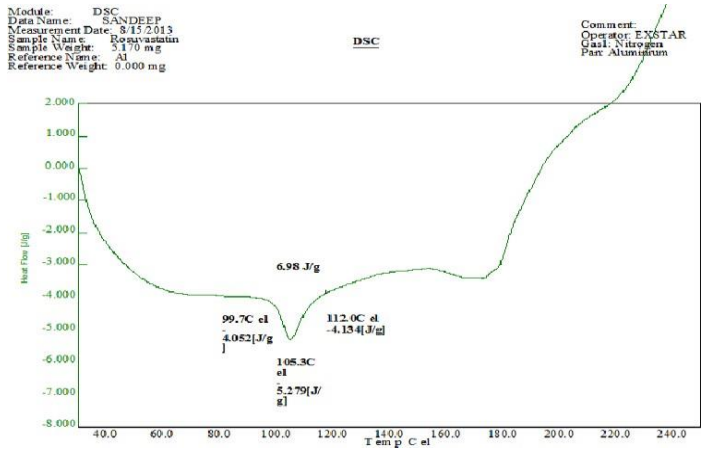

Figure 7: DSC Spectroscopy of rosuvastatin

Table 3: Post compression Parameters for core tablet

Formulation	Weight Variation (%)	Hardness (kg/cm^2)	Thickness (Mm)	Friability (%)	Disintegration Time (sec)
F1	0.91	5.6	2.8	0.75	12
F2	0.95	5.4	2.7	0.8	14
F3	**0.94**	**5.2**	**2.9**	**0.61**	**16**
F4	0.92	4.8	2.8	0.92	21
F5	0.99	5.8	2.7	0.653	12
F6	0.84	5.3	2.9	0.765	11
F7	1.01	4.6	2.6	0.456	14
F8	1.00	4.2	2.6	0.248	14
F9	0.91	4.1	2.8	0.567	14

Table 4: Dissolution for core tablet

Dissolution time (Min)	Core formulation code with % drug release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
5	36	32	**40**	25	27	30	22	24	27
10	42	41	**60**	36	40	42	37	36	41
15	58	66	**73**	49	52	50	49	51	48
20	59	81	**83**	55	59	58	59	62	57
30	78	84	**97**	68	73	67	67	71	72
45	81	91	-	80	78	74	78	82	78
60	90	105	-	90	91	89	86	92	86

ml volumetric flask. 50 ml of buffer solution of pH-1.2 was added. Mixture shaken for 10 min, and then the volume was made up to 100 ml with the same buffer solution, mixed solution was filtered through the membrane filter disc with an average pore diameter Swelling index (%) =M_t– M_0 / M_0 X 100 not greater than 0.45µm. 5 ml of the filtrate was diluted to 100 ml with same buffer solution and examined under U.V Spectrophotometry at 244nm (Punitha S *et al*., 2013).

Disintegration time for RRCT (Rapid release of core tablet)

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 phosphate buffer pH 6.8 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.

Swelling studies: (Timmermans J *et al*., 1994)

The extent of swelling was measured in terms of % of weight gained by the tablet. One tablet from each formulation was weighed and kept in Petri dish containing 50 ml of 0.1N HCl solution. At the end of specified time intervals tablets were withdrawn from Petri dish and excess buffer blotted with tissue paper and weighed. The % of weight gained by the tablet was calculated.

***In vitro* Dissolution methods for press-coated tablets**

In vitro Dissolution studies of Pulsatile delivery systems was done with the conventional paddle method of press coated tablets were performed at 37 ± 0.5°C using ph 6.8 buffer solution in USP II paddle method at 50 rpm. 5 ml of filtered aliquot was manually withdrawn at pre-determined time intervals and replaced with 5 ml of fresh ph 6.8 buffer solution maintained at the

Table 5: Post compression parameters for Rosuvastatin Press coated tablets

Physical parameter/ formulations	Weight variation (%)	Hardness (Kg/cm^2)	Thickness (mm)	Friability %	Swelling index%
P1F3	1.056	7.8	3.5	0.5	280
P2F3	1.235	7.4	3.8	0.48	100
P3F3	1.536	7.6	3.6	0.52	120
P4F3	1.245	8.1	3.3	0.49	150

Table 6: *In vitro* percentage drug release for press coat tablets

Time in hrs	In-vitro percentage drug release				
	P1F3	**P2F3**	**P3F3**	**P4F3**	**P5F3**
1	2.2	5.6	4.8	**3.3**	4.0
2	5.0	11.0	9.3	**7.6**	9.0
3	10.0	28.6	24.7	**9.7**	12.6
4	13.6	40.2	42.6	**11.9**	13.2
5	19.2	59.8	57.4	**28**	22.6
6	28.4	79.2	73.6	**43**	34.1
8	43.4	90.3	89.7	**70**	46.0
10	65.0	-	95.2	**92**	73.1

Table 7: Stability studies of the formulation P4F3 of Rosuvastatin press coated tablets

Sampling Interval	25˚C/60%RH	30˚C/65% RH	40˚C/75% RH
0th Day	92	92	92
15th day	91.5	91.45	91.40
45th day	90.96	90.85	90.82
90th day	90.45	90.42	90.38

same temperature. The samples were analysed at 244nm using a UV spectrophotometer. The lag time and percentage release was determined of the each formulation.

RESULTS AND DISCUSSIONS

FTIR studies conducted on pure drug and mixture of drug and polymers (Figures 1,2,3) showed that there is no marked interaction between drug and selected polymers. The graphs obtained indicate that the drug is compatible with the excipients used.

PRE COMPRESSION STUDIES

The pre compression parameters were determined and listed in the table-2. The formulations showed good flow properties and compressibility index. Angle of repose ranged from 29.32 to 35.52 and the compressibility index (Carr's) ranged from 8.9 to 12. The BD and TD of the prepared granules ranged from 5.17 to 5.94 and 5.83 to 6.65 respectively. The result of angle of repose indicates good flow property of the powder.

POST COMPRESSION PARAMETERS FOR THE ROSUVASTATIN

The results of the post compression parameters for core tablet are given in the tables-3,4. And for the press coated tablets are given in the tables-5, 6, 7.

Dissolution for core tablet

Core tablets were introduced into dissolution test apparatus at 50 rpm for time period of 1 hr, 5 ml of sample was withdrawn for 15min and analyzed by UV for presence of drug using buffer solution as blank. By observing the values, F3 shows maximum drug release.

Based on the drug release within the required time period **F3** was optimized and further formulated for press coating.

From the above core formulations F3 was selected for press coat by using different natural polymers (xanthan and guar gum) in different ratios (1:0, 0:1, 1:1, 3:1, 1:3) among which 3parts of xanthan and 1 part of guar gum was optimized based on the lag time (11% within 4 hours) and percent of drug release and also further evaluated.

DSC

The DSC graph for the formulation **(P4F3)** an obtained formula is given in the figure 7. The dsc graph shows a endothermic peak at 105.3˚c which is near to the melting point range of pure drug Rosuvastatin. This indicates that there is no effect of compression force and temperature and formulation

Stability Studies

Stability studies of the formulation P4F3 of Rosuvastatin press coated were carried out to determine the effect of formulation additives on the stability of the drug and also to determine the physical stability of the formulation. The stability studies were carried out at 25°C/60%RH, 30°C/65% RH and 40°C/75% RH for 90 days. There was no significant change in the physical

property and percent of drug release during 10 hour during the stability period.

CONCLUSION

From the above experimental results it can be concluded that, Formulated tablets gave satisfactory results for various parameters like hardness, friability, thickness, weight variation and content uniformity. Xanthan gum and guar gum (3:1) has predominant effect on the lag time, while also shows significant effect on drug release. Press coated tablet shows a delayed release pattern. The pre compression parameters show good flow properties and compressibility index. The result of angle of repose indicates good flow property of the powder. Among all the core tablet formulations **F3** was selected based on drug release within a given period of time. In-vitro release rate studies showed that the maximum drug release was observed in P3F3 and P4F3formulations.But **P4F3** was optimized based on less amount of drug release during lag time. Formulations P4F3 found to be stable at 40^{o} C and 75% RH for a period of 3 month. FT-IR studies revealed that there was no interaction between Rosuvastatin and the polymers.

DSC Studies indicates that there is no effect of compression force and temperature and formulation. Stability studies of the formulation P4F3 of Rosuvastatin press coated were carried out to determine the physical stability of the formulation. There was no significant change in the physical property and percent of drug release during 10 hour during the stability period

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