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Formulation and Evaluation of Time-Controlled Pulsatile Release Rosuvastatin Press-Coated Tablets

G. S. Sri Lekha[1*], Dr. M. Sunitha Reddy[1], M. Nagarjuna[1]

[1]Department of Pharmaceutics, Centre for Pharmaceutical Sciences, Institute of Science and Technology, Jawaharlal Nehru Technological University Hyderabad, Kukatpally, Hyderabad, 500085, Telangana, India

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***Corresponding author:** G. S. Sri Lekha
Department of Pharmaceutics, Centre for Pharmaceutical Sciences, Institute of Science and Technology, Jawaharlal Nehru Technological University Hyderabad, Kukatpally, Hyderabad, 500085, Telangana, India

Abstract

Rosuvastatin belongs to the HMG-CoA reductase inhibitor class of drugs (statins). The main aim of the present study was to formulate and evaluate time-controlled pulsatile release Rosuvastatin press-coated tablets. The core tablets were formulated by the Direct compression method. Coated tablets were formulated by the Press-coating technique. The drug delivery system was designed to deliver the drug at a specific time for the patient suffering from Hyperlipidemia. The core tablets containing Rosuvastatin, anhydrous lactose, and different ratios of super disintegrants like croscarmellose sodium, and sodium starch glycolate, among six core tablets were formulated, and they were evaluated for post-compression parameters like Weight variation, Thickness, Hardness, Friability, Disintegration, and In-vitro drug release profile, then the core was optimized by using different ratios of polymers such as Eudragit-S100, Eudragit-L100, and HPMC K4M, Ethyl Cellulose (1:2, 2:1 ratios). Totally four coating compositions were fixed and coated to core tablets by press-coating method, then they were evaluated for post-compression parameters like Weight variation, Hardness, Thickness, and In-vitro drug release studies were performed in 0.1 N HCl for 2 hrs, pH 6.8 phosphate buffer for 6 hrs and pH 7.4 phosphate buffer from the dissolution data the coat containing Eudragit-S100, Eudragit-L100 (2:1) combination shown best profile for pulsatile release of Rosuvastatin. The 10 hrs of lag time for the drug release and the drug release were depending on the effects of the composition of the polymers used.

Keywords: Rosuvastatin, Hyperlipidemia, Press-coating technique, Polymers like Eudragit L-100, Eudragit S-100, HPMC K4M, Ethyl Cellulose.

1. INTRODUCTION

Pulsatile release drug delivery system is defined as the timed release of drugs after programmable lag phases. Following the lag phase, drug release may be rapid and quantitative, lasting for a long time. Lag time is defined as the time it takes between placing a dosage form in an aqueous environment and the active ingredient starting to be released from the dosage form [1]. These pulsatile systems are gaining popularity as a means of developing drugs for which conventional controlled drug release systems with continuous release are ineffective. PDDS are gaining popularity because the drug is released fully after a defined lag time [2]. These pulsatile systems are useful for drugs with chrono-pharmacological behaviour where night time dosing is required, as well as for drugs with a high first pass effect and having an absorption site in the GIT. Pulsatile drug delivery systems can be time controlled (or) site-specific controlled [3].

Rosuvastatin is a selective and competitive inhibitor of HMG-CoA reductase (statins), the rate-limiting enzyme in the conversion of 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, a precursor of cholesterol. Rosuvastatin has a high uptake and selectivity for action in the liver, which is the target organ for lowering cholesterol levels. Initially, it increases the number of hepatic LDL receptors on the cell surface, which improves LDL uptake and catabolism. Further, rosuvastatin inhibits hepatic VLDL synthesis, Lowering the total number of VLDL and LDL particles. Generally, it works by slowing the production of cholesterol in the body, reducing the amount of cholesterol that can build up on the artery walls and block blood flow to the heart, brain, and other organs. Asthma, Peptic ulcers, CVS disorders, Arthritis,

and Hypercholesteremia are all diseases that require PDDS. Many circadian-dependent diseases manifest acute symptoms in the early morning hours (or) after waking up in the morning. As a result, drug delivery should be altered to achieve an effective drug level at the required time [4]. The pulsatile drug delivery systems are designed to deliver drugs to the correct site of action at the right time and in the right amount, providing spatial and time-based delivery and improving patient compliance [5].

Hyperlipidemia is a disorder of metabolism of lipids indicated by elevation of plasma concentration of various lipids and lipoproteins which is the key risk factor for cardiovascular diseases. The current anti-hyperlipidemic treatment includes statins, fibrates. Statins correct the altered blood-lipid profile by inhibiting the biosynthesis of cholesterol and the fibrates acts by enhancing the removal of triglyceride rich lipoproteins.

After oral administration, press coated tablets pass from the stomach to the cecum or colon. Despite the widespread use of pH-dependent systems for colon-targeted drug delivery, there has always been discussion about their usefulness for the intended purpose, owing to the high pH variability of the gastrointestinal tract inter and intra individuals, as well as a lack of proper coating materials that would dissolve at the desired pH of the colon. Diet and disease have an impact on it. Colonic pH was found to be significantly lower than normal during the acute stage of inflammatory bowel disease. In ulcerative colitis, pH values ranging from 2.3 to 4.7 have been measured in the proximal colon. This disadvantage was overcome by creating a time-dependent rupturable and erodible type press coated pulsatile colon targeted drug delivery -system with a combination of hydrophilic and hydrophobic polymers [6].

Hydroxypropylmethylcellulose (HPMC) is a well-known water-soluble polymer that has long been used in medication dosage forms as a rate-controlling membrane to regulate drug release. When in contact with water, HPMC swells due to gellification. The gel forms a viscous layer around a core, acting as a protective barrier to both water influx and drug efflux in solution. HPMC K4M has swelling, viscous gelation, and erosion properties, which may cause drug release to be delayed due to the lengthening of the drug diffusion pathway and drug release rate. The outer coat is ruptured due to the hydrophilic polymer. Due to the rapid diffusion of the dissolved drug through the hydrophilic gel layer, the use of a hydrophilic polymer (HPMC K4M) alone helps to control the drug release of highly water-soluble drugs is limited. The use of hydrophobic polymers such as Ethyl cellulose in combination with HPMC K4M will delay drug release. So, in the current study, an attempt was made to create time-controlled pulsatile release tablets of atenolol by combining a hydrophilic polymer (HPMC K4M) with a hydrophobic polymer (EC). Although Ethyl cellulose (EC) is naturally insoluble in water, it has been used as a rate-controlling membrane to regulate drug release. Plastic deformation has been used as the primary consolidation mechanism in the direct compression of EC to form a compact film. Because ethyl cellulose has a porous structure, it controls the diffusion of water inside the coating layer of HPMC K4M, maintains the integrity of the swellable layer of HPMC K4M, and delays drug release. When a barrier layer containing HPMC K4M and ethyl cellulose was exposed to dissolution media, the HPMC K4M particles swell and erode, causing the outer coating to breakdown, a process that was slowed to varying degrees depending on the amount of EC present, demonstrating that manipulation of both components controls the erosion rate [7-9].

The aim of this study was to develop press-coated tablets for pulsatile drug delivery of Rosuvastatin by achieving a pH-independent time-controlled disintegrating or rupturing function with a distinct predetermined lag time. To avoid drug release in gastric and intestinal fluids, the rapidly disintegrating inner core tablets containing rosuvastatin and other excipients were press coated with a barrier layer composed of a mixture of different weight ratios of hydrophobic polymer (ethylcellulose) and hydrophilic polymer (HPMC K4M). Ethyl cellulose was chosen for its rupturable properties, while HPMC K4M was chosen for its swelling and erodible properties.

2. MATERIALS AND METHODS

2.1. Materials

Rosuvastatin calcium was obtained as a gift sample from BLD PharmaTech, Hyderabad, India. Croscarmellose sodium and Sodium starch glycolate were obtained as gift samples from Bio FMC, Hyderabad, India. Anhydrous lactose was obtained as a gift sample from DFE Pharma, Hyderabad, India. Magnesium stearate was obtained as a gift sample from Valtries, Hyderabad, India. Aerosil was obtained as a gift sample from Evonik, Hyderabad, India. Eudragit-L100 and Eudragit -S100 were obtained as gift samples from Sanya Chemicals, Maharashtra, India. HPMC K4M was obtained from Lotte fine Chemicals. Ethyl Cellulose (EC) was obtained as a gift sample from Asha Cellulose, Mumbai, India. Starch was obtained as a gift sample from Colorcon Asia Pvt. Ltd, Hyderabad, India.

2.2. Methods

2.2.1. Identification of the Drug

Rosuvastatin was identified by using Fourier Transfer Infra-Red Spectroscopy (FT-IR)

2.2.2. API Characterization

Organoleptic properties such as colour, odour as well as the drug's powder nature, were observed using visual inspection and general methods.

2.2.3. Solubility

As the drug belongs to BCS Class-II (i.e., low solubility and high permeability), solubility analysis of API was done with solvents and various buffers.

2.2.4. Analytical Method Development

Prior to the development of any product, it is crucial to design an appropriate analytical method that provides accuracy and precision and will be used throughout the development process.

2.2.4.1. UV Absorption maxima (λ_{max}) of the drug sample

100 mg of the drug was dissolved in 100 ml of phosphate buffered saline pH 6.8 as the stock solution, and 1 ml was taken from the stock solution and diluted to 100 ml to get primary stock solution and from this 1 ml of sample is taken and diluted to 10ml in volumetric flask to get 10µg/ml. 10ppm concentration sample was taken and were analysed by using UV Visible Spectrophotometer (Shimadzu) by scanning in UV range 200-400 nm using phosphate buffer pH 6.8.

2.2.4.2. Standard graph of Rosuvastatin calcium using Phosphate buffer pH 6.8

100 mg of the drug was dissolved in 100 ml of phosphate buffered saline pH 6.8 as the stock solution, and 1 ml was taken from the stock solution and diluted to 100 ml to get primary stock solution and from this aliquot of 0.8, 1.0, 1.2, 1.4, 1.6, 1.8, 2.0, 2.2, 2.4 ml is transferred to each 100 ml volumetric flask and diluted up to the mark to get the concentration of 8, 10, 12, 14, 16, 18, 20, 22, 24 µg/ml. From this the sample with 10ppm concentration was taken and was analysed by using UV Visible Spectrophotometer (Shimadzu) by scanning in UV range 200-400 nm using phosphate buffer pH 6.8. The graph was plotted by taking concentrations on the x-axis and respective absorbance on the y-axis. The Linear regression (R^2) was calculated using a straight-line equation (y=mx+c) with the application of the Microsoft EXCEL statistical function program.

2.2.5. Drug- Excipient Compatibility studies

Drug-Excipient compatibility studies was carried out to evaluate the compatibility between the active ingredient and other excipients to produce a stable, safe and therapeutically efficacious product. The KBr pellet technique was used to prepare samples by combining a weighed amount of drug with potassium bromide and similarly, an accurately weighed quantity of drug and other excipients was mixed, and one milligram of the sample was taken and mixed with 10 mg of potassium bromide using mortar and pestle. These quantities are usually sufficient to form a disc of 10-15 mm diameter and a pellet of suitable intensity using a hydraulic press to form a transparent pellet. The pellet was placed in the diffuse reflectance sampler, and the spectrum was recorded by scanning in the wavelength region of IR 4000-400 cm-1 in an FT-IR Spectrophotometer. The IR spectrum of the drug was compared to that of the mixture to check for any drug-excipient interactions.

2.2.6. Preformulation studies

The core powder blend was evaluated for Bulk Density, Tapped Density, Hausner's ratio, Carr's index, and Angle of repose.

3. FORMULATION OF ROSUVASTATIN PRESS-COATED TABLETS

3.1. Preparation of Core Tablets by Direct Compression Method

The core tablets of Rosuvastatin calcium were prepared by direct compression method. An accurately weighed quantities of Rosuvastatin, anhydrous lactose, croscarmellose sodium, sodium starch glycolate were sifted through sieve no. 40 separately and was dry blended for 5 minutes then colloidal silicon dioxide and magnesium stearate which was sifted together through sieve no. 60 and added to the above blend. This mixture was further blended for 5 minutes. Then compress the lubricated blend mixture into 6 mm round concave shaped double punch rotary tablet compression machine (Cadmach machinery, Ahmedabad, India) to produce the desired core tablets (average tablet weight = 150 mg). The hardness of the tablets was adjusted at 1-2 Kg/cm² using Monsanto hardness tester.

Table 1: Core tablets formulation compositions

S. No	Ingredients(mg/unit)	F1	F2	F3	F4	F5	F6
1.	Rosuvastatin calcium	20	20	20	20	20	20
2.	Croscarmellose sodium	8.5	11	13.5	-	-	-
3.	Sodium Starch Glycolate	-	-	-	8.5	11	13.5
4.	Anhydrous lactose	116.5	114.0	111.5	116.5	114.0	111.5
5.	Magnesium stearate	3	3	3	3	3	3
6.	Aerosil	2	2	2	2	2	2
Total weight of tablet (mg)		150	150	150	150	150	150

3.2. Preparation of Press-Coated Tablets by Direct Compression Method:

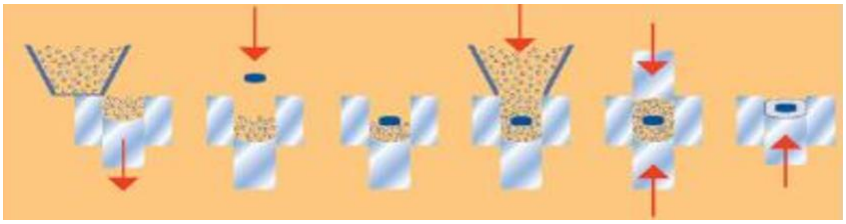

Fig 1: Several Manufacturing steps of Press-Coated Tablets

As mentioned in the table no.2 various formulation compositions containing Eudragit-L100, Eudragit-S100, HPMC K4M, EC, Starch, Magnesium stearate and Colloidal silicon dioxide (Aerosil) were sifted through sieve no. 22 and then the mixture is blended for about 10 minutes. Through direct compression method the press-coated pulsatile tablets were prepared by using the above press-coating material. The die (10 mm in diameter) was prefilled with half amount of coating material then the inner core tablet was placed at the centre on the powder bed and residual half amount of press-coating material was filled into the die. As a result, final compression was done by 9 mm round concave shaped, double punch rotary tablet compression machine (Cadmach Machinery, Ahmedabad, India) and compression force was control to produce 5 ± 0.5 Kg/cm² tablet hardness. The press-coated rosuvastatin tablets were tested for weight variation, thickness, hardness, drug content, friability and invitro-dissolution study.

Table 2: Press-Coating formulation composition ratios (1:2, 2:1)

S. No	Ingredients (mg/unit)	CF1	CF2	CF3	CF4
1.	Eudragit-L100	92	46	-	-
2.	Eudragit-S100	46	92	-	-
3.	HPMC K4M	-	-	92	46
4.	EC	-	-	46	92
5.	Starch	7	7	7	7
6.	Magnesium stearate	3	3	3	3
7.	Aerosil	2	2	2	2
Total weight of tablet (mg)		150	150	150	150

4. EVALUATION OF ROSUVASTATIN CORE AND PRESS-COATED TABLETS

4.1. Evaluation tests for Pre-compression Parameters [10-20]

4.1.1. Bulk Density

The bulk density of a compound varies substantially with the method of crystallization, milling, or formulation. Bulk density was determined by pouring the pre-compression blend into a graduated cylinder via a large funnel and measuring the weight and volume.

Bulk Density = Weight of the Blend / Bulk Volume

4.1.2. Tapped Density

Tapped density was determined by placing a graduated cylinder containing a known mass of blend and by using mechanical tapper apparatus, which was operated for a fixed number of taps until the powder bed volume has been reduced to a minimum. Using the weight of the drug in the cylinder and the minimum volume obtained after a number of taps, the tapped density was measured.

Tapped Density = Weight of the blend / Tapped Volume

4.1.3. Carr's Compressibility Index

Carr's Compressibility Index was measured using the values of bulk density and tapped density. The Following equation was used to find the Carr's Compressibility Index.

Carr's Compressibility Index (%) = Tapped Density – Bulk Density / Tapped Density x 100

4.1.4. Hausner's Ratio

It indicates the flow property of the powder blend and the ratio of Tapped density to the Bulk density of the powder or granules.

Hausner's Ratio = Tapped Density / Bulk Density

4.1.5. Angle of Repose

The "fixed-funnel method" was used to calculate the angle of repose. In this method, the weighed quantity of powder blend was poured through the funnel and thus the ratio of height of the heap of blend to that of radius of the surface of blend was measured and calculated through the following formula.

Tan θ = Height of the heap of blend / Radius of the surface of the blend

The above-mentioned Pre-compression parameters were calculated and mentioned in Table 8.

4.2. Evaluation tests for Post-compression Parameters of Rosuvastatin Core tablets and Press-coated tablets [21-30].

4.2.1. Weight Variation

Twenty tablets were chosen randomly from each batch and weighed individually. The average weight and standard deviation were determined and the results are given in Table 9.

4.2.2. Hardness

The amount of force needed to break a tablet in diametric compression. Monsanto tablet hardness tester was used to determine hardness. The hardness of three tablets in each batch was measured, and the average hardness was measured in Kg/cm². And the results are given in Table 9.

4.2.3. Thickness

Three tablets were collected from each batch of formulation, and their thickness was measured using a Vernier calliper. The thickness of the tablet is determined by the hardness of the tablet and can be used as a primary control parameter. Tablet thickness should be maintained to a limit of ±5%. Furthermore, thickness must be controlled in order to facilitate packaging. Thus, the average thickness was determined, and the results are given in Table 9.

4.2.4. Friability

This test evaluates the ability of tablets to withstand abrasion during packing, handling, and transportation. The tablets friability was determined using a Roche friabilator. A pre-weighed sample of tablets was placed in the friabilator drum and rotated about 100 revolutions at 25rpm for 4 minutes. The tablets were reweighed after being dusted with a soft muslin cloth and the specific limit should be NMT 1.0%. The % friability was calculated by using the formula:

% Friability = (W1-W2 / W1) x 100

Where,

W1 = Initial weight of Tablets

W2 = Final weight of Tablets.

And the results are given in table 9.

4.2.5. Disintegration Test

Disintegration time is regarded as an important criterion in selecting the best formulation. To determine the disintegration time of tablets, one tablet was placed in each tube and the basket rack was placed in a 1 litre beaker at 37°C ±1°C. The time taken for the tablets to completely disintegrate was recorded, and the results were given in Table 9.

4.2.6. In-Vitro Dissolution Test

4.2.6.1. Dissolution procedure for Core tablets

In-vitro dissolution of each formulation was determined by employing the USP dissolution apparatus-II using phosphate buffer pH 6.8 (900mL) at 37±0.5ºC. The Rosuvastatin core tablets were added to dissolution medium. 5ml of sample withdrawn from the dissolution medium at regular intervals (10, 20,30,40,50 and 60mins) and same amount of buffer was replaced to the dissolution medium. The speed rotation of the paddle and run time of the dissolution apparatus was maintained at 75 rpm for 60 minutes. The samples were analysed under the UV spectrophotometer at 241nm and the results are given in Table 10.

4.2.6.2. Dissolution procedure for Press-coated tablets

In-vitro dissolution studies of press-coated tablets was performed by employing the USP dissolution apparatus-II using 0.1N HCl dissolution medium for the initial 2hrs, 6.8 phosphate buffer for 6hrs, and replaced with 7.4 phosphate buffer (900mL) for subsequent hours. The dissolution medium was maintained at a temperature of 37±0.5ºC, the speed rotation of the paddle was maintained at 50rpm and the run time was set for 10 hrs. The 5ml of sample was manually withdrawn at a pre-determined time interval (1,2,3,4,5,6,7,8,9,10 hrs respectively) and was replaced with 5ml of buffer solution maintained at the same temperature. The sample was analysed at 241nm using a UV spectrophotometer. The lag time and percentage release of each formulation were determined, and the results are given in Table 12.

5. RESULT AND DISCUSSION

Table 3: API Characterization

Physical Characterization	Description
Colour	White
Odour	-none-
Appearance	Amorphous

Table 4: Drug Solubility

Solvents/Buffers	Solubility (mg/mL)
Water	0.86mg/mL
Ethanol	1mg/mL
pH 1.2	2.56mg/mL
pH 6.8	2.80mg/mL
pH 7.4	1.52mg/mL

The solubility of drug in water was found to be Sparingly soluble in water (i.e., 0.86mg/ml) as mentioned in Table 4.

Table 5: Concentration v/s Absorbance values for Rosuvastatin calcium

S. No	Concentration(µg/ml)	Absorbance at 241 nm
1	8	0.22
2	10	0.29
3	12	0.366
4	14	0.421
5	16	0.488
6	18	0.544
7	20	0.595
8	22	0.675
9	24	0.733

Table 6: Optical characteristics of Rosuvastatin calcium in 6.8 phosphate buffer

Parameter	Valve
Absorption maxima	241.1nm
Beer's law range	8-24µg/ml
Regression equation	0.0308x-0.0109
Correlation coefficient(R^2)	0.9985

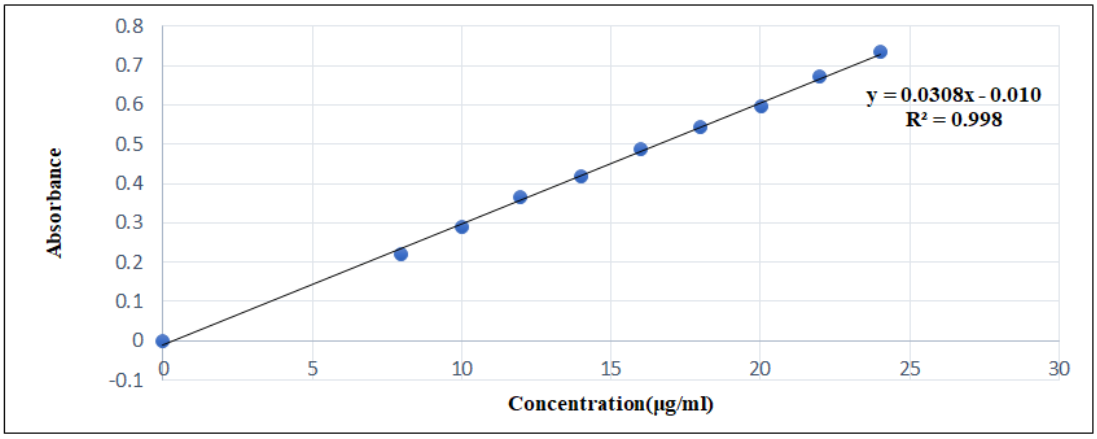

Fig 2: Spectrum of Rosuvastatin calcium Standard solution

Drug-Excipient Compatibility Studies:

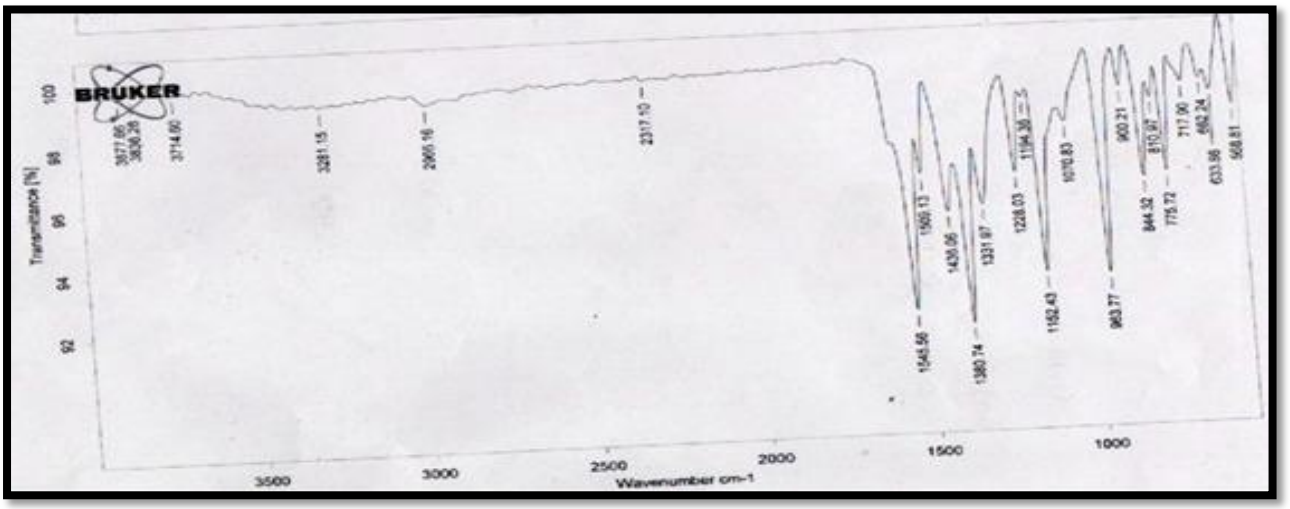

Fig 3: FT-IR Spectra of pure Rosuvastatin calcium

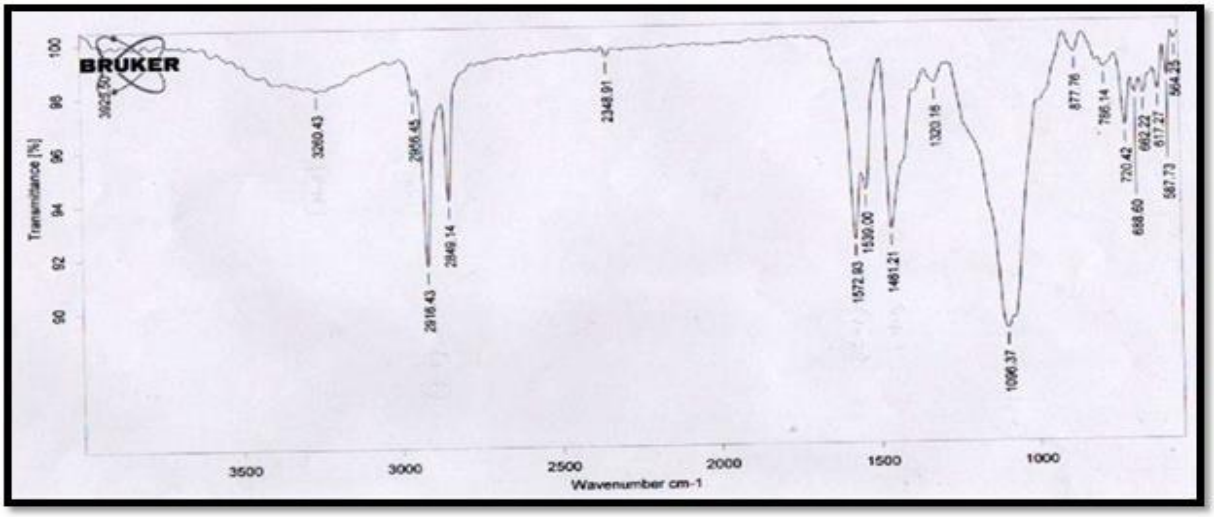

Fig 4: FT-IR Spectra of Drug + All Excipients

Table 7: Interpretation of FT-IR spectrum of Drug and all the Excipients

Wave numbers (cm-1) pure drug	Possible functional groups	Wave numbers (cm-1) mixture	Possible functional groups
3714	O-H Stretching	3300	N-H Stretching
3281	N-H Stretching	2916	C-H Stretching
2966	C-H Stretching	1592	N-H Bending
1152	S=O Stretching	1459	C=C Stretching
1545	C=C Stretching	1092	O-H Bending

Table 8: Evaluation of Pre-compression parameters

S. No	Formulations	Bulk Density (gm/mL) *	Tapped Density (gm/mL) *	Carr's Compressibility Index (%) *	Hausner's Ratio*	Angle of Repose (º)*
1.	F1	0.443±0.05	0.526±0.01	15.77±0.50	1.187±0.2	22.84±1.65
2.	F2	0.427±0.01	0.515±0.07	17.08±0.47	1.206±0.3	22.38±1.45
3.	F3	0.485±0.02	0.518±0.04	25.03±0.61	1.068±0.5	21.05±1.00
4.	F4	0.438±0.05	0.522±0.05	23.05±0.84	1.191±0.3	21.89±1.29
5.	F5	0.439±0.06	0.523±0.17	16.63±0.53	1.192±0.3	19.49±0.98
6.	F6	0.451±0.07	0.510±0.21	11.56±0.43	1.130±0.1	23.32±1.84

* All values were expressed as mean±standard deviation (n=3)

The bulk density of the blend was found between 0.427g/ml to 0.485g/ml. Tapped density was found between 0.510g/ml to 0.526g/ml. From these values, Carr's index and Hausner's ratio were calculated respectively. Carr's index for all the formulations was found to be between 11.56% - 23.06% and Hauser's ratio from 1.06-1.20 which reveals that the blends have good flow character. The angle of repose of different formulations was ≤ 23.32º which indicates that the material had excellent flow properties and thus, the blends were suitable for direct compression method.

Table 9: Post-compression parameters for Core tablets

S. NO	Formulation	Weight Variation (%)* (n=20)	Hardness (kg/cm²)* (n=3)	Thickness (mm)* (n=3)	Friability (%)* (n=3)	Disintegration Time (sec) * (n=6)
1.	F1	2.44±0.76	3.6±0.12	3.2±0.32	0.55±0.46	14±0.56
2.	F2	1.35±0.67	3.4±0.21	3.1±0.29	0.33±0.43	15±0.58
3.	F3	2.03±0.68	3.2±0.32	3.1±0.34	0.53±0.48	18±0.54
4.	F4	1.43±0.81	3.2±0.16	3.2±0.36	0.26±0.47	15±0.58
5.	F5	0.67±0.86	3.5±0.49	3.2±0.36	0.21±0.41	17±0.84
6.	F6	0.64±0.95	3.9±0.84	3.1±0.39	0.16±0.54	16±0.65

*All values were expressed as mean±standard deviation

The data obtained from post-compression of core tablets such as weight variation, thickness, hardness, friability, and disintegration test are shown in Table 9. All the formulations of core tablets passed the weight variation test as the % weight variation was within the pharmacopeial limits of < 7.5% of the tablet weight (150mg/ml). The hardness of the core tablets was acceptable and uniform from batch-to-batch variation and was found to be 3.2 – 3.9kg/cm2. The thickness of the core tablets was found to be 3.1-3.2mm in all the formulations F1 – F6 and considered to be satisfactory ensuring that all the formulations are mechanically stable. Friability values were found to be less than 0.8% in all the formulations F1 – F6 and were considered to be satisfied for all the formulations as mechanically stable. Disintegration values were found to be 14-18sec in all the formulations F1 – F6 and considered to be satisfactory ensuring that all the core formulations were undergoing faster disintegration due to the addition of super disintegrants in the formulation. All values were expressed in mean± standard deviation.

Table 10: In-Vitro dissolution profile of Core tablets in pH 6.8 Phosphate buffer

S. No	Time (min)	% Amount of drug release					
		F1	F2	F3	F4	F5	F6
1	10	48.1±0.42	48.6±0.65	49.5±0.52	25.4±0.40	28.5±0.40	37.6±0.40
2	20	66.6±0.40	55.3±0.64	69.6±0.81	45.6±0.40	42.7±0.42	65.7±0.83
3	30	69.4±0.40	64.8±0.40	72.1±0.40	65.2±0.51	60.3±0.51	82.3±0.40
4	40	71.3±0.51	71.4±0.41	74.3±0.40	70.3±0.83	72.6±0.52	88.5±0.13
5	50	74.8±0.51	75.6±0.42	75.8±0.40	73.9±0.53	74.1±0.51	94.7±0.40
6	60	75.9±0.57	80.3±0.42	76.4±0.56	75.7±0.51	77.3±0.41	102.8±0.51

*All values were expressed as mean±standard deviation (n=6)

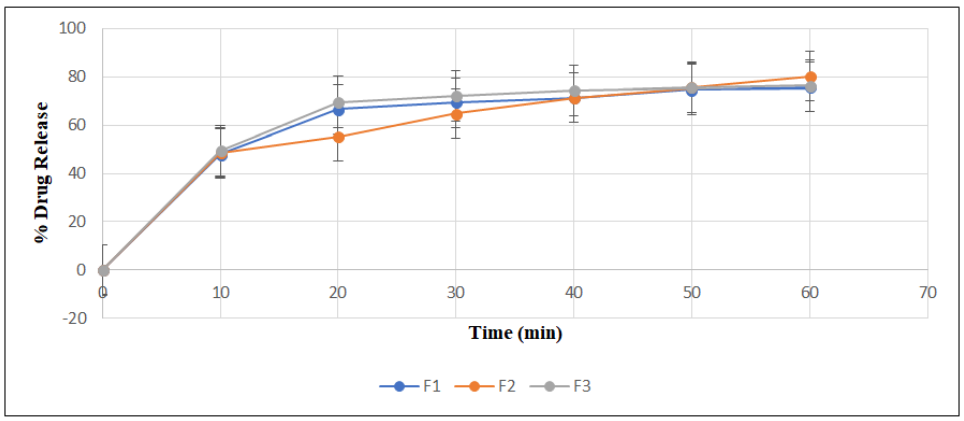

Fig 5: Drug release profile of F1-F3 core tablets

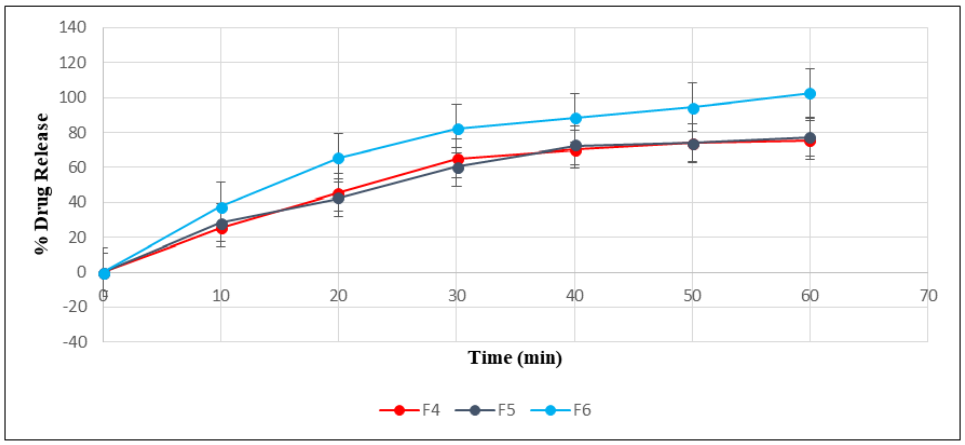

Fig 6: Drug release profile of F4-F6 core tablets

The In-vitro dissolution studies of core tablets indicate that in formulations F1-F3 containing Cross-carmellose sodium and the drug release was found to be 75.9%, 80.3%, and 76.4% as mentioned in Table 10 and Figure 5. Similarly, the dissolution profile of formulations F4-F6 indicates the drug release and was found to be 75.7%, 77.3%, and 102% at 1hr, as mentioned in Table 10 and Figure 6. So, the best

formulation was found to be F6 because the drug release was 88% at 40 minutes. As a result, the formulations F2, F3, F5, and F6 were considered to be the best formulations and were further involved in the compression of final press-coating tablets.

Table 11: Post-compression parameters for Press-coated tablets

S. No	Formulation	Weight variation (%) *	Hardness (kg/cm^2) *	Thickness (mm) *
1	CF1	0.671±0.24	8.2±1.05	5.1±0.64
2	CF2	0.685±0.34	8.7±0.98	5.3±0.43
3	CF3	0.785±0.28	8.4±1.24	5.2±0.56
4	CF4	0.645±0.37	8.5±1.76	5.2±0.67

*All values were expressed as mean±standard deviation (n=3)

The data obtained from post-compression of press-coated tablets such as weight variation, thickness, and hardness are mentioned in Table 11. All the formulations passed the weight variation test as the % weight variation was within the pharmacopeial limits of ±7.5% as the total tablet weight was 300 mg. Hardness of the tablet was acceptable and uniform from batch-to-batch variation, was found to be 8.2– 8.7 kg/cm^2. Thickness values were found to be 5.1-5.2 mm in all the formulations CF1 – CF4 was considered to be constant batch to batch.

Table 12: In-Vitro Drug Release Profile of the Press-coated Tablet Formulations

S. No	Time(hrs)	% Cumulative drug release of press-coated tablets			
		CF1	CF2	CF3	CF4
1	1	7.16±0.56	2.25±0.40	8.54±0.48	9.99±0.46
2	2	16.34±0.40	8.67±0.54	22.76±0.49	24.65±0.51
3	3	30.65±0.59	14.87±0.52	35.34±0.51	38.44±0.54
4	4	38.76±0.56	19.65±0.68	51.32±0.52	49.87±0.56
5	5	49.4 ±0.58	25.98±0.83	62.87±0.81	68.33±0.55
6	6	59.2 ±0.57	54.76±0.56	75.45±0.29	79.88±0.67
7	7	74.6 ±0.89	79.98±0.64	82.34±0.57	88.55±0.65
8	8	88.7 ±1.15	87.88±0.56	98.45±0.57	99.45±0.67
9	9	99.4 ±0.42	92.43±0.57	101.1±0.56	101.65±0.68
10	10		99.53±0.67		

*All values were expressed as mean±standard deviation (n=6)

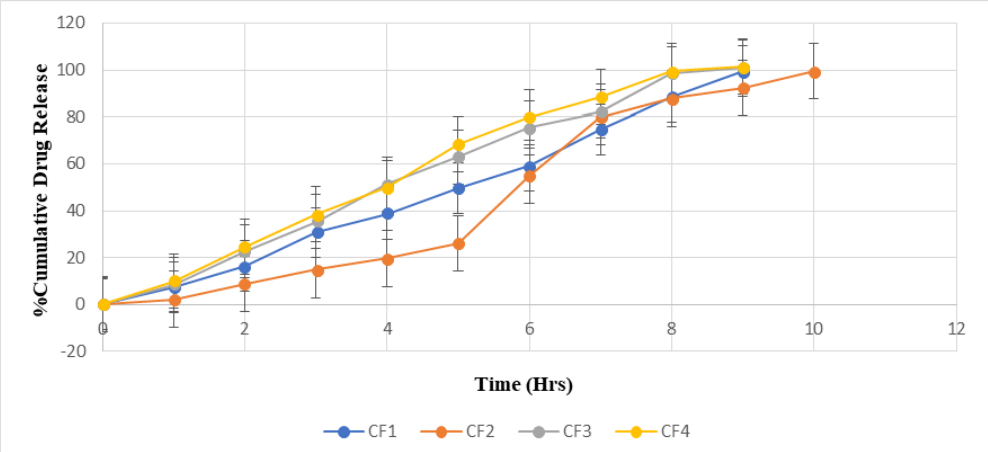

Fig 7: Drug release profile of different formulations of Rosuvastatin calcium press-coated (CF1-CF4)

The in-vitro dissolution studies were carried out for the press-coated formulations CF1-CF4, the drug release was found to be 99.4%, 99.53%, 101.15%, and 101.65% respectively in 10 hrs. The best formulation was found to be CF2, due to the lag was successfully maintained in the first 5 hrs and drug release was 99.53% at 10 hrs. In all other formulations, the lag phase was not maintained, the drug was released during the initial hours also so they failed in dissolution.

6. CONCLUSION

The pulsatile release dosage forms were formulated by the press-coating technique. The lag time

and time-controlled release behaviour of Rosuvastatin from press-coated could be modulated by varying the concentration of polymer in the outer coating layer and the thickness of the compression coating. The in vitro drug release studies of pulsatile release dosage forms showed drug release for 10 hrs. CF1-CF4 formulation showed the required lag time. Hence, the formulated pulsatile release dosage forms were suitable for the chronotherapeutic delivery of Rosuvastatin calcium to treat the hyperlipidemia with desired drug profile.

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