ISSN–2230-7346
Journal of Global Trends in Pharmaceutical Sciences

IN - VITRO DESIGNING OF ROSUVASTATIN CHRONO FORMULATION

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ARTICLE INFO

Key Words
Chrono therapeutics, Rosuvastatin, ludiflash, lycoat, HPMC K200M and Ethyl cellulose.

Access this article online
Website: https://www.jgtps.com/
Quick Response Code:

ABSTRACT

The objective was to improve Rosuvastatin prescribed pulsatile release formulation in order to get the disintegrative and ruptured lag-time mechanism with a fixed time delay which matches the chronotherapeutics (hyper cholesteroidal disorder). Pre formulation studies UV, FTIR (Drug excipient compatibility), solubility studies and flow properties were evaluated for blend and drug. All the values were within the limit. 12 core tablets were prepared with two novel disintegrants i.e. ludiflash, lycoat in different concentrations after doing the post compression parameters &drug release F8 was optimized & then coated with PH sensitive polymers HPMC K200M & Ethyl cellulose in different concentrations. Evaluation was carried out for all 6 formulations and all the values were within the limit. Based on In-vitro dissolution studies, swelling index and rupture test C5F8 is optimized and compared with marketed product for 10 hours. As per the ICH guidelines optimized formulation (C5F8) stability tests were conducted for 3 months and was found to be stable. Optimized formulation (C5F8) contains 3:2 polymers (HPM K200M: Ethyl cellulose) demonstrates an outstanding pulsatile drug delivery relative to the branded version (Zentiva) compared to all other formulations

INTRODUCTION

Oral controlled drug delivery system is found to be advantageous and convenient to the patients. In Pulsatile drug delivery the medication is released from these devices at a fixed or adjustable speed. In Chrono formulation , the drug is released after pre determined lag time based on Circadian rhythm and Chronological behavior of the patient. [1-2] There are many conditions that demand pulsatile release like, Body works with the rhythm of the circadian. For examples. Hormone isolation, stomach acid secretion and gastric emptying. The time lag is necessary for medicines which are weakened by the medium of gastric acids (for example, peptide).

The pharmaceutical substances that are metabolized in the first place, resulting in lower bioavailability, a shift in substance and metabolite status and in the probability of food drug interactions, require postponement of the medication as much as practicable. [3-6] Time-controlled drug delivery systems are basically pulsative devices, which are based on physiological conditions such as pH, metabolites, GI motility. Basically these are designed as pellets or mini tablets with different coating techniques to release the drug in Pulsetile model. In present work compression coating (without solvent) is selected to design pulsetile release of Rosuvastatin. Rosuvastatin is an anti-

hyperlipidemic agent, which is a reductase (statin) antagonist of hydroxyl methylglutaryl-CoA (HMG-CoA). Rosuvastatin reduces blood lipid levels and prevents cardiovascular disease. [6] Rosuvastatin is a BCS-Class II therapeutic agent which lowers LDL, triglycerides and improves HDL concentrations.[3-7]

Materials and methods

Materials: Rosuvastatin, Ludiflash & Lycoat were purchased from BMR chemicals, polymers and other excipients were laboratory chemicals of HITS College of pharmacy.

Solubility test:

Solubility was determined by shake-flask method. The excess quantity of Rosuvastatin was mixed with various solvents. The samples were placed in a mechanical shaker at 37 °C and 100 rpm for 24 Hours. The upper layer was separated and filtered through Whatman filter paper and filtrate was diluted and Spectrophotometrically assayed at 292 nm and values were tabulated below in Table no-3. [8]

UV spectrum of Rosuvastatin

Rosuvastatin crude powder analyzed with UV spectroscopic at the range of 200-400 cm-1 and maximum absorption **(λmax)** was determined .results was shown in fig no1[9]

FTIR

FTIR was performed for physical mixture of Rosuvastatin and formulation to check the compatibility of Rosuvastatin and polymers. And results were shown in fig no 2 &3. [9]

Pre-compression of core tablets of Rosuvastatin:Pre-compression parameters like Bulk Density, tapped density, Compressibility Index, Hausner's Ratio and Angle of Repose were performed for all the formulations (blend) and the values was found to be within the limits. Results were discussed. [10-12]

Formulation of core tablets: As per table no - 1, all drug & excipients are blended and punched with 6mm punch.

Coating of the core tablet by Compression coating method: From polymer blend half quantity of Polymer was measured and placed in Die cavity and in the middle core tablet was place and remaining polymer was poured over the core tablet and punched. [13]

Evaluation of tablets (coated &uncoated) [All the evaluation test (Hardness Test, Thickness Of Coated Tablet, Weight Variation, Friability, Disintegration Test) for core and coated tablets as per the standard procedures from book. Three measurements were taken and reported on average. The result was shown in Table no.4. [12-16]:

Drug Content: From each formulation 10 tablets were selected and powdered. From this powder equivalent to 100mg was weighed accurately and dissolved by sonication for 5 minutes with 5ml methanol in 100ml volumetric flask and Volume made up to 100ml by using phosphate buffer 7.4 and absorbance was measured at 292 nm and values are tabulated in Table no 4. [14]

***In-vitro* Dissolution Studies Of Compressed Coated Tablets**: Compressed coated Rosuvastatin tablets dissolution carried out through using pH1.2, Phosphate 6.8 and Phosphate 7.4 buffers till 10 Hours, 2hrs, 3 hrs, and 5 hrs respectively at 37^0C and 50 rpm by using USP dissolution apparatus. Every one hour sample of 1ml was collected and diluted up to 10ml with pH medium, and sample is analyzed for absorbance through ultra visible Spectroscopy at 292 nm. % drug release vs t (time) plotted on graph and results are shown in Table No- 5 & Fig No-4. [15]

Swelling Index: In containers loaded by 10 ml of 1.2 buffer and Phosphate 7.4 buffers, the percentage swelling strength of tablets was determined. Tablets have been withdrawn from containers, weighted and again weighed in the medium at fixed intervals, lined with tissue paper, until the external surface of the tablet has begun to break. The Percentage of swelling was determined and results were tabulated in table no 6. [16-17]

Percentage swelling = **((Wet tablet weight at time –dry tablet weight) / dry tablet weight) × 100**

Rupture Test: The breakage test was performed with USP paddle 2 systems on closed tablets. The other criteria here were similar with the in-vitro process of dissolution by using pH 1.2, Phosphate 6.8 and Phosphate 7.4 buffers. Noted the time where the outer layer started to rupture. The results are shown in table - 7[18]

Drug release Kinetics: Drug release kinetics found to be good for all formulations out of 6 formulation data of formulation **C5F8**was best explained by Higuchi equation, as the plot

showed highest linearity (*r2* = 0.656), followed by zero order equation (*r2* = 0.862). As the drug release was best fitted in Higuchi kinetics, indicating that the rate of drug release is diffusion. The result was shown in Fig No 5.

Comparative Study between optimized formulation and marketed product[x19]

Dissolution tests were separately carried out for Optimized formulation (C5F8) and marketed product (LEXCOL-XL) for 10 hrs with dissolution USP type 2 apparatus in 900 ml of 0.1N HCL at 37±0.5°C & 50 RPM for 2 hr followed by 3 hrs in Phosphate 6.8 and Phosphate 7.4 buffer. Every one hour 1ml samples are collected from each vessel on hourly basis and diluted to 10ml with media and absorbance was measured spectroscopically at 292nm. The retired specimen was replaced immediately with a fresh buffer counterpart. The data obtained for dissolution was compared to time in a percentage of medicines released. The result was shown in figure no 6.[19]

Stability Studies: As for the ICH guidelines for optimized formulation of Rosuvastatin compressed coated tablets sealed in an aluminum foiled cover stored for 3 months and on monthly basis physic -chemical properties were evaluated. The result was shown in Table no-8. [20]

Results and Discussions

Flow Properties of Rosuvastatin:

From the flow properties of pure Rosuvastatin it was observed that Rosuvastatin have good flow property.

Formulation of core tablets: As per table no -1, all drug & excipients are blended and punched with 6mm punch.

Table No-1 Formulation Of Core Tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Rosuvastatin	80	80	80	80	80	80	80	80	80	80	80	80
Lycoat	3	6	9	12	--	--	--	--	--	--	--	--
SSG	--	--	--		3	6	9	12	--	--	--	--
Ludiflash	--	--	--	--	--	--	--	--	3	6	9	12
MCC	61	58	55	52	61	58	55	52	61	58	55	52
Mg.stearate	3	3	3	3	3	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3	3	3	3	3	3
Total wt(mg)	150	150	150	150	150	150	150	150	150	150	150	150

Table: 2 Composition of compression coated tablets

Formulation	C1F8	C2F8	C3F8	C4F8	C5F8	C6F8
Core	150	150	150	150	150	150
HPMC K200M	250	--	175	100	150	75
Ethyl cellulose	--	250	75	150	100	175
Total weight	400	400	400	400	400	400

Table no-3: Solubility studies of Rosuvastatin:

Solvents	Solubility(mg/ml)
0.1N HCL	0.102±0.36
6.8pH Buffer	0.275±0.04
4.5pH Buffer	0.168±0.01
7.4pH Buffer	0.147±0.10

From the above results Rosuvastatin have higher solubility in 6.8pH buffer than the other buffers.

UV spectrum of Rosuvastatin: Wavelength of Rosuvastatin maximum absorption (λmax) was 292 nm.

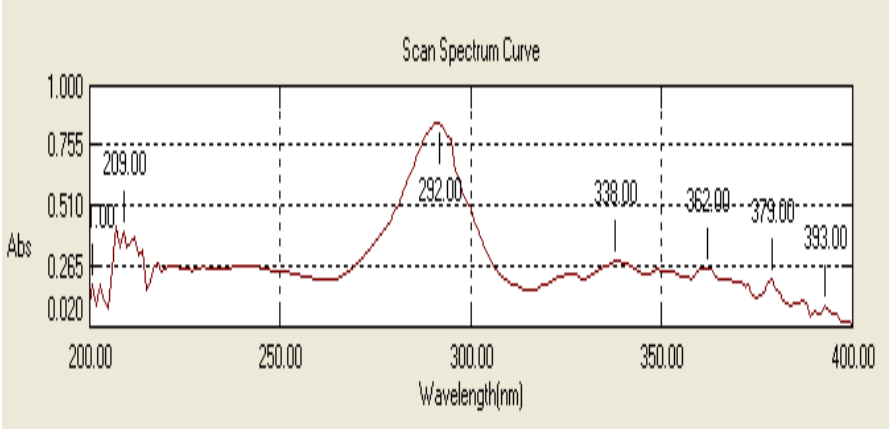

Fig no1: UV spectra of Rosuvastatin at 292nm

FTIR STUDIES (Drug –Excipients Compatibility)

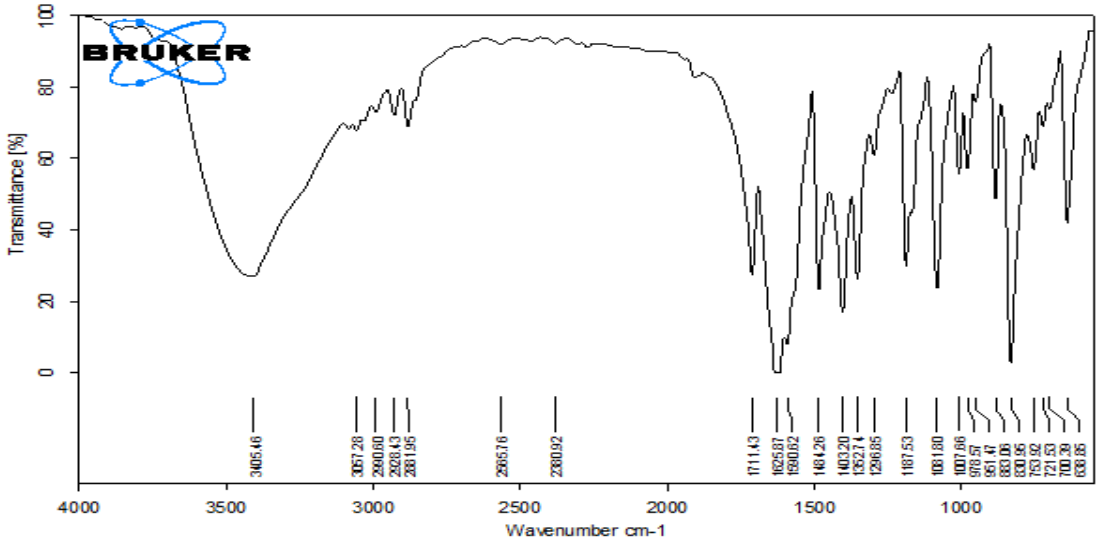

Fig No- 2 FTIR Of Pure Drug (Rosuvastatin)

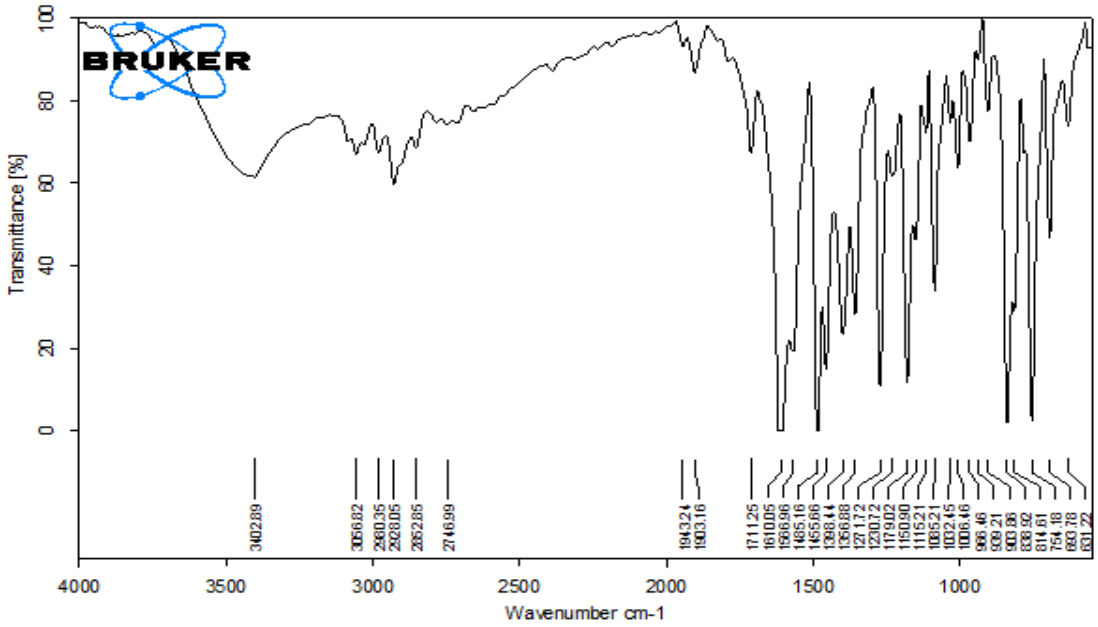

Fig No-3 FTIR Of Rosuvastatin Formulation

Based on the above FTIR spectrums there is no incompatibility between the drug and excipients. In the above spectrum Rosuvastatin has shown peaks at 3403.89 cm^{-1} due to O–H stretching); 2960 and 2877 cm^{-1} due to C–H stretching; and 1711.25 cm^{-1} due to stretching of ester and lactone carbonyl functional groups; 1230,1115.9 and 1006.4cm^{-1}(C-O stretching of esters and anhydrides) . These peaks were commonly observed in both formulation and Rosuvastatin. There is no incompatibility problem.

Pre-compression evaluation of core tablet of Rosuvastatin: Pre-compression studies, bulk density, Hauser ratio, Carr's index, tapped density, and Angle of Repose were evaluated. The value of bulk density and tapped density was within a limit from 0.3-0.4gm/ml. The value of hausner ratio was found to be in the range of 1.14-1.17. The value of carr's index was found to be 11.36 to 14.63 % and the angle of repose for all the formulations was found to be in the range of 25.41°-31.15° which ensure good flow Property

Evaluation of core tablet: Weight variation, Thickness, Hardness, Friability, Drug content, Disintegration, *Percentage drug release*, swelling index, rupture time, acid uptake studies etc. Weight variation was found to be uniform, Hardness ranged between 3.20 to 3.78 kg/cm^2. Friability ranges 0.04-0.52%. The values of drug content were found to be 86.29-97.39%. The values of disintegration were found to be 22- 112 sec.

Cumulative percent drug release of core Rosuvastatin tablets

All 12 formulations were shown good post compression parameters which are suitable for coating out if 12 formulationsF8 is having a good drug release with in 20 min of time with excellent drug content i.e. 98.22±0.06.

Based on invitro dissolution studies of core tablets out of all formulations F8 is showing good dissolution i.e. 99.63±0.28 at 20 min.

Evaluation of compressed tablets of Rosuvastatin

All 6 formulations were evaluated for percentage drug release in PH 1.2,6.8&7.4 buffers the values were tabulated . After 5 hrs of lag time drug release is stated for all 6 formulations in PH 7.4 Phosphate buffer based on data **C5F8**shown good release i.e **97.27±0.80**at 8 th hour**.**

The swelling studies of pulsatile tablet during 9hrs studies were found to have very good sustaining efficacy. The percentage swelling at the end of 5^{th} hour of **C5F8** formulation, was found to be 161±0.33.So increase in the concentration of polymer will decrease the % water uptake capacity and increase the Lag-time.

All 6 formulations are subjected to rupture test, the rupture test was carried out using USP paddle 2 apparatus at 37°c, the time at which the outer polymer coating starts to rupture is called as rupture time. The rupture time of formulations was found to be in a range between 1 to 6.2hr

Drug release Kinetics data:

Drug release kinetics found to be good for all formulations out of 6 formulation data of formulation **C5F8** was best explained by Higuchi equation, as the plot showed highest linearity (*r2* = 0.656), followed by zero order equation (*r2* = 0.862). As the drug release was best fitted in Higuchi kinetics, indicating that the rate of drug release is diffusion. The result was shown in Fig No 5

Table no -4 Evaluation of compressed tablets of Rosuvastatin

Formula	Avg.wt (mean± SD,mg)	Hardness (mean± SD)	Friability (%)	Thickness	Drug content(%)
C1F8	400.26±0.52	7.56±0.62	0.26±0.02	6.85±0.21	89.56±0.02
C2F8	399.85±0.36	7.15±0.52	0.25±0.14	7.42±0.30	90.15±0.26
C3F8	399.74±0.20	8.01±0.41	0.54±0.64	7.10±0.52	95.25±0.05
C4F8	398.45±0.02	7.65±0.26	0.61±0.65	6.48±0.10	97.56±0.20
C5F8	399.12±0.30	7.49±0.63	0.26±0.32	6.95±0.02	97.12±0.32
C6F8	397.56±0.26	7.26±0.25	0.31±0.25	6.47±0.06	95.16±0.52

Table No 5: *In-Vitro* Dissolution Studies Of Coated Tablets

Time(hrs)	C1F8	C2F8	C3F8	C4F8	C5F8	C6F8
0	0	0	0	0	**0**	0
1	6.45±0.21	8.56±0.26	1.58±0.21	0.59±0.48	**0.26±0.48**	0.79±0.26
2	15.86±0.02	17.59±0.32	4.78±0.32	1. 97±0.26	**1.48±0.82**	2.56±0.47
3	25.27±0.52	26.62±0.52	13.15±0.45	4.26±0.49	**3.26±0.15**	5.74±0.52
4	34.68±0.62	35.65±0.14	24.59±0.45	10.65±0.10	**7.49±0.28**	9.65±0.48
5	44.09±0.12	44.68±0.15	36.78±0.26	22.48±0.25	**12.15±0.39**	30.26±0.52
6	53.50±.23	53.71±0.25	48.97±0.56	40.56±0.96	**39.74±0.26**	48.75±0.48
7	62.91±0.20	62.74±0.56	61.16±0.25	58.64±0.23	**72.26±0.47**	67.24±0.36
8	72.32±0.32	71.77±0.62	73.35±0.21	76.72±0.14	**97.27±0.80**	85.73±0.15
9	81.73±0.02	85.8±0.78	85.54±0.36	94.82±0.02		97.85±0.26
10	91.14±0.06	96.83±0.02	97.73±0.15			

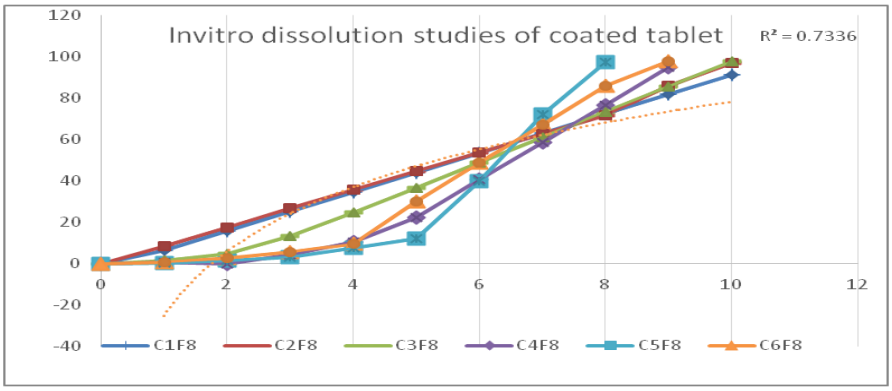

Fig no 4 *In vitro* dissolution studies

Table no-6 Swelling Index

Time(hr)	C1F8	C2F8	C3F8	C4F8	C5F8	C6F8
0	0	0	0	0	0	0
1	76±0.32	84±0.32	72±0.26	79±0.23	68±0.26	74±0.65
2	84±0.21	96±0.52	88±0.32	86±0.65	86±0.03	86±0.56
3	89±0.26	106±0.74	102±0.15	99±0.26	102±0.02	94±0.21
4	96±0.28	124±0.850	126±0.24	104±0.21	138±0.21	114±0.25
5	99±0.65	134±0.59	139±0.1	126±0.02	161±0.33	126±0.56
6	114±0.54	102±0.52	102±0.25	101±0.36	124±0.36	104±0.36
7	106±0.58	94±0.65	91±0.29	94±0.02	102±0.21	82±0.26
8	91±0.63	69±0.31	56±0.28	76±0.32	86±0.09	62±0.03
9	66±0.21	32±0.26	24±0.65	50±0.26	54±0.01	39±0.25

Table no-7 Rupture test

Formulation	Time(hrs)
C1F8	1.2±0.26
C2F8	1.0±0.53
C3F8	3.1±0.45
C4F8	5.0±0.74
C5F8	6.2±0.85
C6F8	5.2±0.23

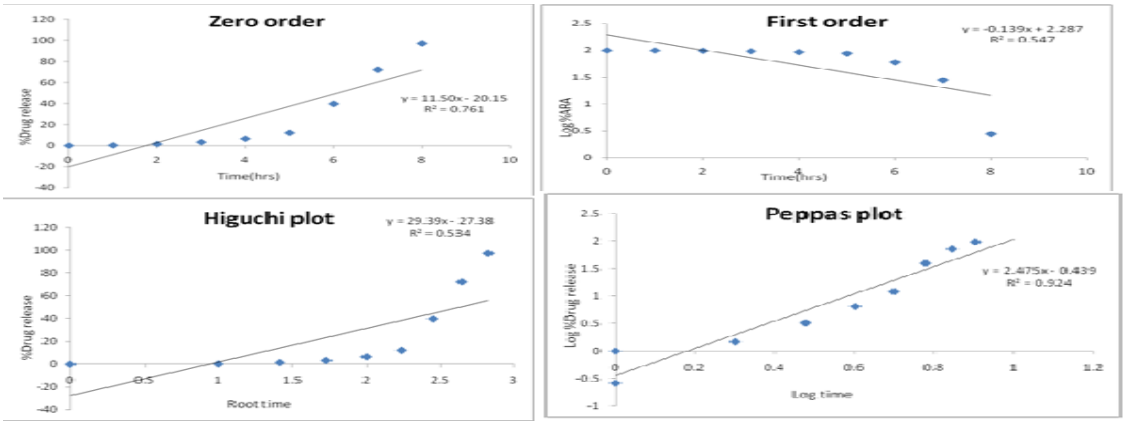

Fig no -5 Drug Release Kinetics

Comparison of optimized formulation of Rosuvastatin& marketed formulation:

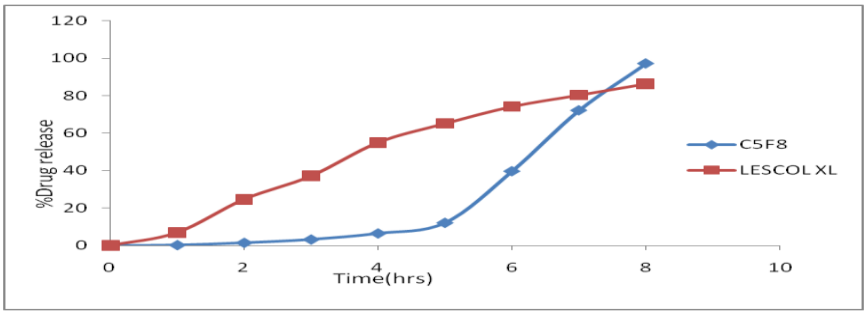

Fig no – 6 Comparison of optimized batch

` **Accelerated stability studies for optimized formulation (C5F8)**

Table no-8 Accelerated stability studies for C5F8 formulation

Evaluation parameters	After 30 days	After 60 days	After 90 days
Colour and appearance	No change	No change	No change
Hardness	7.49±0.13	7.49±0.15	7.49±0.14
% Drug content	97.12±0.32	97.12±0.17	97.12±0.12
% Drug release	97.27±0.80	97±0.80	96.9±0.01

Conclusion: According to my work I am concluding that Rosuvastatin. Chrono formulation can be considered and be evaluated further as it is found to be better compared to conventional formulations, as the drug release is at peak after the lag time, mimicking the Circadian rhythm.

Conflict of Interest - "The authors declare that they have no conflict of interest".

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