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Invitro Designing of Fluvastatin Chrono Formulation

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ABSTRACT

The objective was to improve fluvastatin prescribed pulsatile release formulation to get the disintegrative and ruptured lag-time mechanism with a fixed time delay which matches the chronotherapeutics (hypercholesteroidal 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 & Ethylcellulose in different concentrations. An evaluation was carried out for all six 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 the marketed product for 10 hours. As per the ICH guidelines optimized formulation (C5F8), stability tests were conducted for three months and was found to be stable. Optimized formulation (C5F8) contains 3:2 polymers (HPM K200M: Ethylcellulose) demonstrates an outstanding pulsatile drug delivery relative to the branded version (Lexcol XL) compared to all other formulations.

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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 a predetermined lag time based on Circadian rhythm and Chronological behavior of the patient. (De Geest *et al.*, 2006; Smolensky and D'Alonzo, 1988)

Many conditions demand pulsatile release like,

1. Body works with the rhythm of the circadian. For examples. Hormone isolation, stomach acid secretion and gastric emptying.
2. The time lag is necessary for medicines which are weakened by the medium of gastric acids (for example, peptide).
3. The pharmaceutical substances that are metabolized in the first place, resulting in lower bio availability, a shift in substance and metabolite status and the probability of food drug interactions, require postponement of the medication as much as practicable. (Amit and Sonam, 2012; Gothoskar *et al.*, 2004; RavikumarReedy *et al.*, 2009)

Time-controlled drug delivery systems are pulsative devices, which are based on physiological conditions such as pH, metabolites, GI motility. These are designed as pellets or mini-tablets with different coating techniques to release the drug in the pulsatile model. In present work compression coating (without solvent) is selected to design pulsatile release of fluvastatin. Fluvastatin is an antihyperlipidemic agent, which is a reductase (statin) antagonist of hydroxyl methylglutaryl-CoA (HMG-CoA). Fluvastatin reduces blood lipid levels and prevents cardiovascular disease. (Garg *et al.*, 2012) Fluvastatin is a BCS-Class II therapeutic agent which lowers LDL, triglycerides and improves HDL concentrations. (Parag *et al.*, 2010)

MATERIALS AND METHODS

Materials

Fluvastatin, 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 the shake-flask method. The excess quantity of fluvastatin 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 the filtrate was diluted, and Spectrophotometrically assayed at 292 nm, and values were tabulated below in Table 3. (Schachter, 2005)

UV spectrum of fluvastatin

Fluvastatin crude powder analyzed with UV spectroscopic at the range of 200-400 cm-1, and maximum absorption (λ max) was determined, results were shown in Figure 1, (Mutalik *et al.*, 2008)

FTIR

FTIR was performed for the physical mixture of fluvastatin and formulation to check the compatibility of fluvastatin and polymers. And results were shown in Figure 2 & Figure 3. (Mutalik *et al.*, 2008)

Pre-compression o f core tablets of fluvastatin

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 were found to be within limits. Results were discussed. (Keerthi *et al.*, 2014; Mukhopadhyay *et al.*, 2014; Tejaskumar *et al.*, 2013)

Formulation of core tablets

As per Table 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 a die cavity, and the middle core tablet was placed, and the remaining polymer was poured over the core tablet and punched. Table 2, (Krishnaveni *et al.*, 2013)

Evaluation of tablets (coated & uncoated)

All the evaluation tests (Hardness Test, Thickness Of Coated Tablet, Weight Variation, Friability, Disintegration Test) for core and coated tablets as per the standard procedures from the book. Three measurements were taken and reported on average. The result was shown in Table 4. (Anand *et al.*, 2014).

Drug Content

From each formulation, ten 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 4. (Patil *et al.*, 2012)

In- Vitro Dissolution Studies of Compressed Coated Tablets

Compressed coated Fluvastatin tablets dissolution carried out through using pH 1.2, Phosphate 6.8 and Phosphate 7.4 buffers till 10 Hours, 2 hrs, 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 10 ml with pH medium, and the sample is analyzed for absorbance through ultra visible Spectroscopy at 292 nm. % drug release vs t (time) plotted on the graph and results are shown in Table 5 & Figure 4. (Yang *et al.*, 2012)

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 6. (Anand *et al.*, 2014; Karavas *et al.*, 2006)

Percentage swelling = [(Wet tablet weight at time – dry tablet weight) / dry tablet weight] $\times$ 100

Rupture Test

The breakage test was performed with USP paddle two systems on closed tablets. The other criteria here were similar to 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, (Sungthongjeen *et al.*, 2004)

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 Figure 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 an 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 the time in a percentage of medicines released. The result was shown in Figure 6. (Chaudhari *et al.*, 2007)

Stability Studies

As for the ICH guidelines for the optimized formulation of fluvastatin compressed coated tablets sealed in an aluminium foiled cover stored for three months and monthly, physic-chemical properties were evaluated. The result was shown in Table 8. (Patil *et al.*, 2013)

RESULTS AND DISCUSSION

Flow Properties of Fluvastatin

From the flow properties of pure fluvastatin, it was observed that fluvastatin has good flow property.

Solubility studies

From the Table 3, fluvastatin has a higher solubility in 6.8 pH buffer than the other buffers.

UV spectrum of Fluvastatin

Wavelength of Fluvastatin maximum absorption (λ max) was 292 nm.

FTIR Studies (Drug - Excipients Compatibility)

Based on the above FTIR spectrums, there is no incompatibility between the drug and excipients. In the above spectrum fluvastatin 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 fluvastatin. There is no incompatibility problem.

Pre-compression evaluation of core tablet of Fluvastatin

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 0.3-0.4 gm/ml. The value of the 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, and Hardness ranged between 3.20 to 3.78 kg/cm^2. Friability ranges from 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 per cent drug release of core Fluvastatin tablets

All 12 formulations have shown good post compression parameters which are suitable for coating out if 12 formulations F8 has a good drug release within 20 min with excellent drug content, i.e. 98.22±0.06.

Based on in-vitro 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 fluvastatin

All six 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 six formulations in PH 7.4 Phosphate buffer based on data C5F8 shown good release, i.e. 97.27±0.80 at 8th hour.

Swelling Index

The swelling studies of the pulsatile tablet during

Table 1: Formulation of Core Tablets

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Fluvastatin	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
Ethylcellulose	–	250	75	150	100	175
Total weight	400	400	400	400	400	400

Table 3: Solubilitystudies of fluvastatin

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

Table 4: Evaluation of compressed tablets of fluvastatin

Formula	Avg. wt (mean± D, mg)	Hardness (mean± D)	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

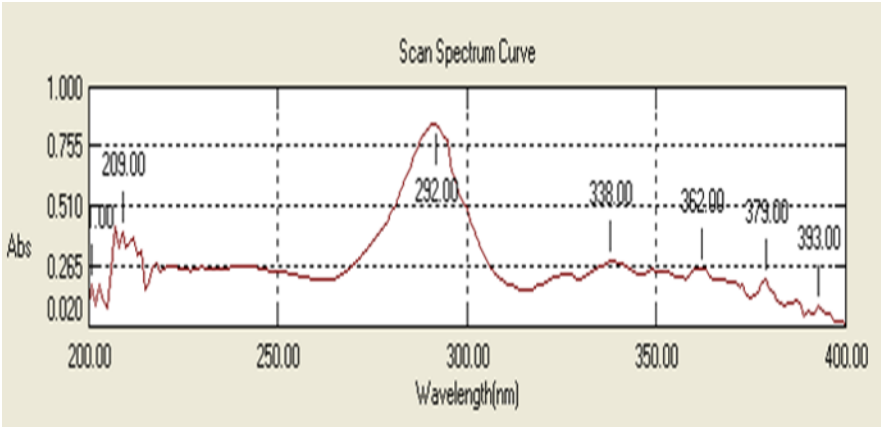

Figure 1: UV spectra of fluvastatin at 292 nm

Table 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			

Table 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 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

Table 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

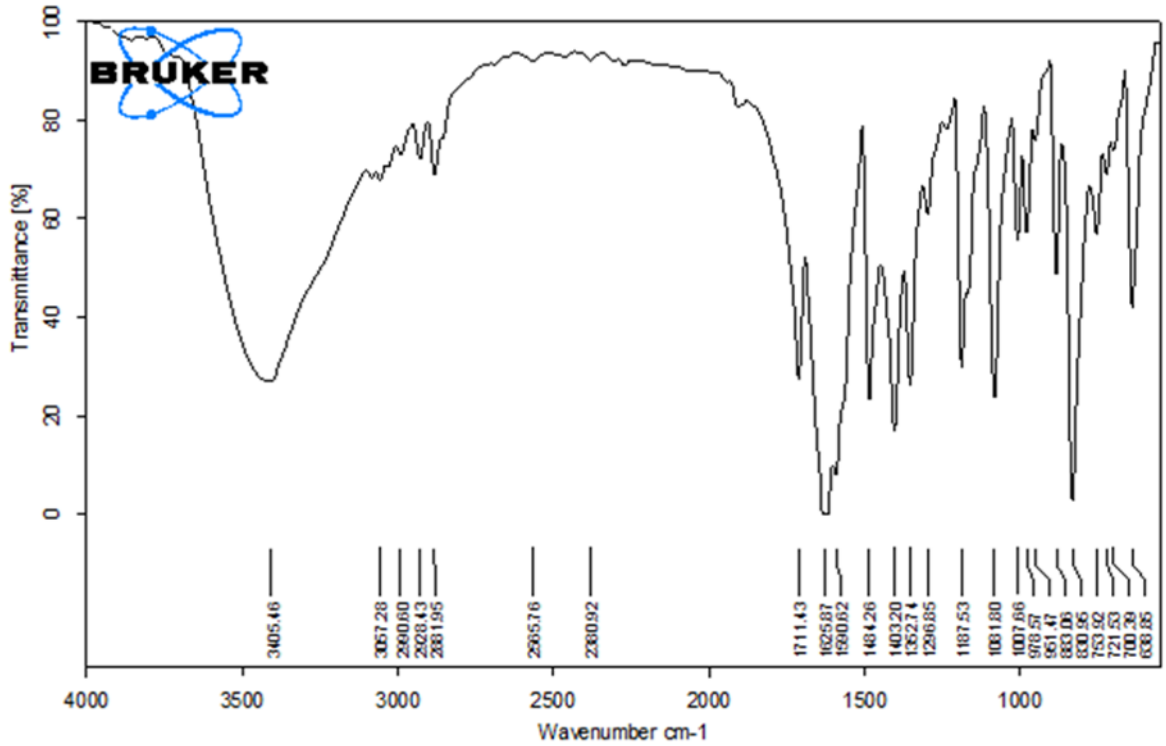

Figure 2: FTIR of Pure Drug (Fluvastatin)

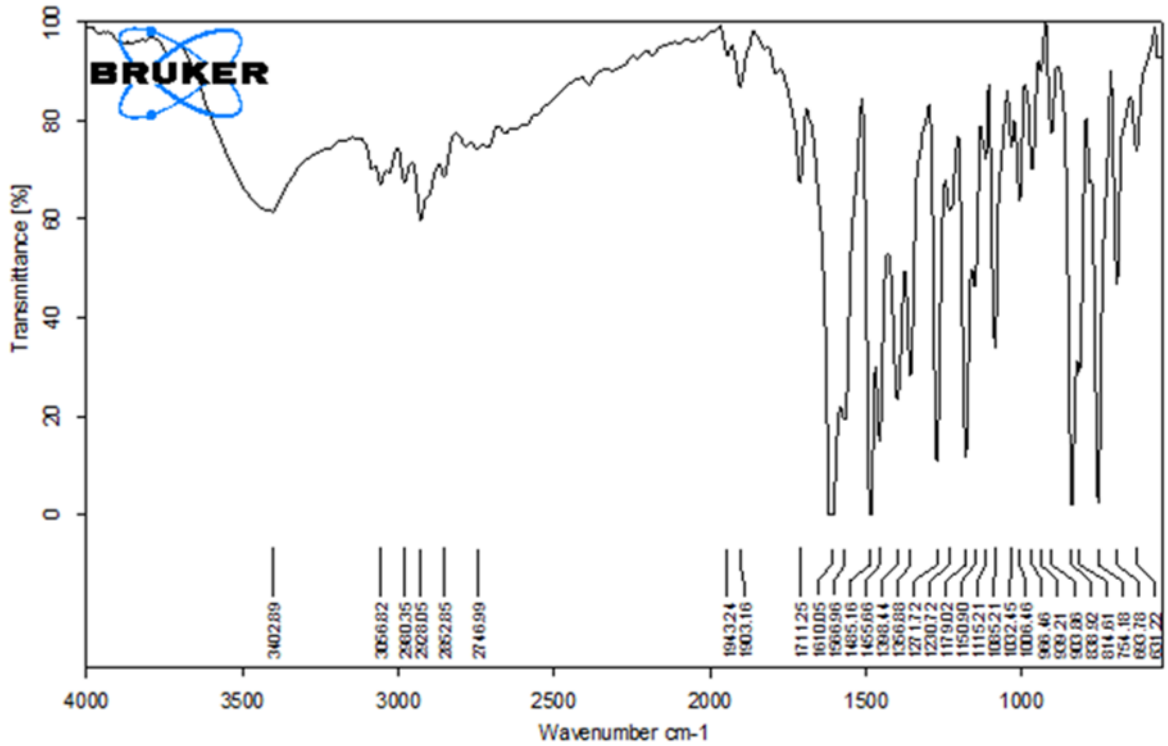

Figure 3: FTIR of Fluvastatine Formulation

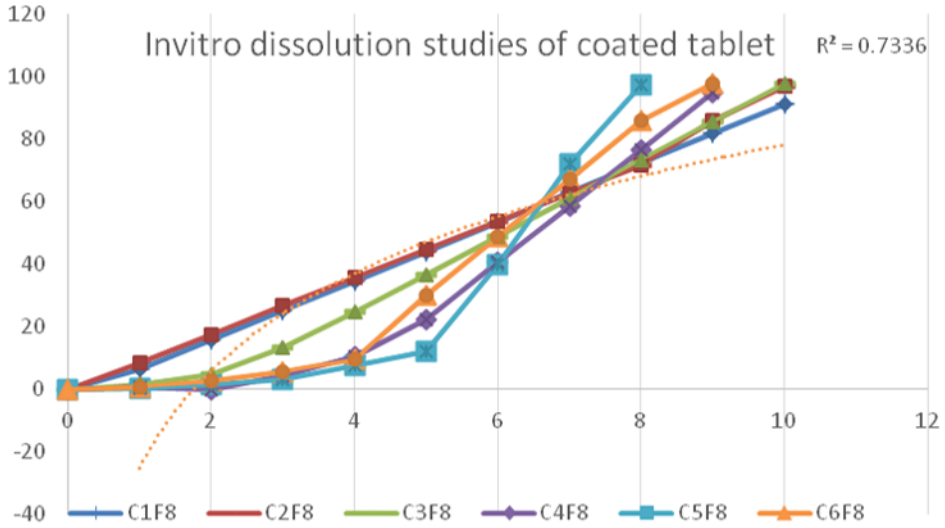

Figure 4: In vitro dissolution studies

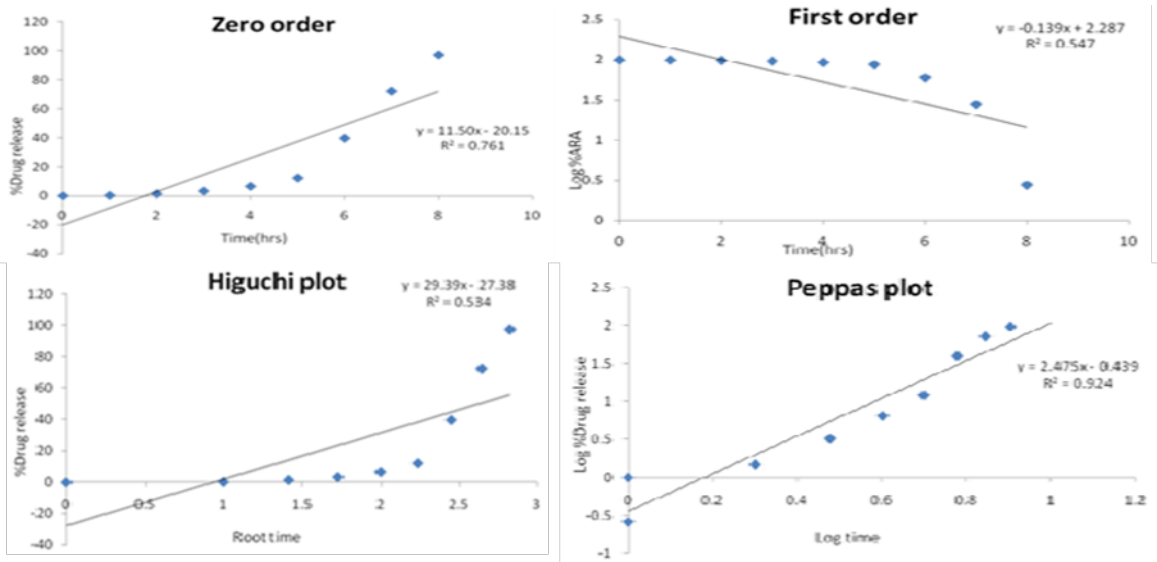

Figure 5: Drug Release Kinetics

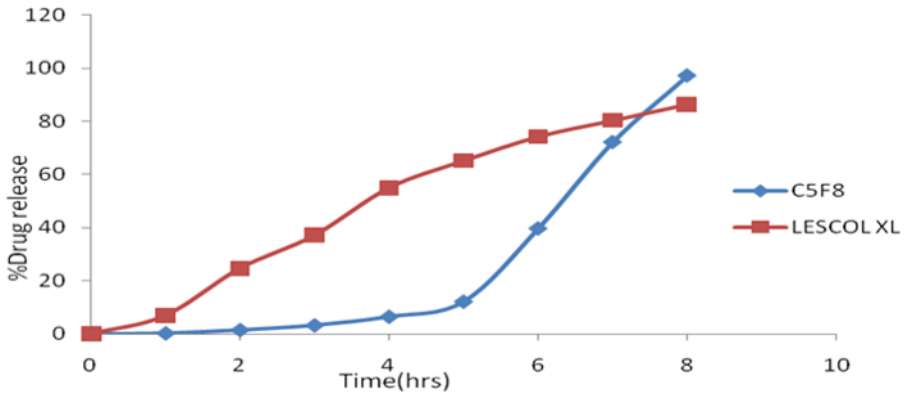

Figure 6: Comparison of optimized batch

9 hrs 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 an increase in the concentration of polymer will decrease the % water uptake capacity and increase the Lag-time.

Rupture test

All six formulations are subjected to rupture test, and the rupture test was carried out using USP paddle two 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 and 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 Figure 5

CONCLUSION

According to my work I am concluding that Fluvastatin 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 a peak after the lag time, mimicking the Circadian rhythm.

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Conflict of Interest

The authors declare that they have no conflict of interest for this study.

REFERENCES

Amit, K., Sonam, R. 2012. Pulsatile Drug Delivery System: Method and Technology Review. *International Journal of Drug Development and Research*, 4:95–107.

Anand, D. S., NeelofarSultana, S., Sultana, S. S., Ramana, B. V., Nagarajan, G. 2014. Formulation and evaluation of bilayer floating tablets of simvastatin and lovastatin. *Journal of Chemical and Pharmaceutical Research*, 6(12):186–197.

Chaudhari, S. P., Chaudhari, P. D., Mistry, C. J., Patil, M. J., Barhate, N. S. 2007. The effect of core and coating composition on drug release from directly compressed time-controlled release tablets. *Pharm Tech*, 31:132–144.

De Geest, B. G., Mehuys, E., Laekeman, G., Demeester, J., De Smedt, S. C. 2006. Pulsed drug delivery. *Expert Opinion on Drug Delivery*, 3(4):459–462.

Garg, B. K., Gnanarajan, P., Kothiyal 2012. Formulation and evaluation of pulsatile drug delivery system of rosuvastatin calcium using different swelling polymers. *The pharma innovation*, 1(7):61–67.

Gothoskar, A. V., Joshi, A. M., Joshi, N. H. 2004. Pulsatile drug delivery systems: a review. *Drug Delivery Technology*, 4(5):1–11.

Karavas, E., Georgarakis, E., Bikiaris, D. 2006. Felodipine nanodispersions as active core for predictable pulsatile chronotherapeutics using PVP/HPMC blends as coating layer. *International Journal of Pharmaceutics*, 313(1-2):189–197.

Keerthi, S., Reddy, V. B., Muralidharan, L. V. G., Nargund 2014. Formulation and evaluation of pulsatile drug delivery system of the anti-asthmatic drug. *Am. J. Pharmtech res*, 4(1):797–809.

Krishnaveni, G., Muthukumaran, M., Krishnamoorthy, B. 2013. Development and evaluation of the pulsatile drug delivery system containing montelukast sodium by press coated tablet using natural polysaccharides. *Int j adv pharm genres*, 1(2):41–51.

Mukhopadhyay, S., Pant, R., Goswami, L. 2014. Formulation and evaluation of pulsatile drug delivery system for sequential release of atorvastatin. *International journal of pharmaceutical and chemical sciences*, 3(2):123–136.

Mutalik, S., Anju, P., Manoj, K., Usha, A. N. 2008. Enhancement of dissolution rate and bioavailability of aceclofenac: A chitosan-based solvent change approach. *International Journal of Pharmaceutics*, 350(1-2):279–290.

Parag, A., Kulkarni, M., Jaaiswal, Santosh, B., Jawale, Satish, V., Shirolkar, Pramod, V., Kasture 2010. Development and evaluation of press coated tablets for Chrono pharmaceutical drug delivery using gellable and permeable polymers. *Scholars research library*, 2(4):482–497.

Patil, B., Abhishek, M., Motegi, U., Kulkarni, Hariprasanna, R. C., Shivanand, A. 2012. Development and evaluation of time-controlled pulsatile release lisinopril tablets. *Journal of Pharmaceutical Science and Bio scientific Research*, 2(1):30–35.

Patil, V., Chandrasekhara, S., Nagesh, C., Praveen, K., Rekha, S. 2013. Pulsatile Drug Delivery System of Terbutaline Sulphate, Using pH-Sensitive polymer. *American Journal of Advanced Drug Delivery*,

1(4):635–650.

RavikumarReedy, J., VeeraJyotsna, M., Mohamed-Saleem, T. S., Praveen, K., Rekha, S. 2009. Pulsatile drug delivery systems. *American Journal of Advanced Drug Delivery*, 1(4):109–111.

Schachter, M. 2005. Chemical, pharmacokinetic and pharmacodynamic properties of statins: an update. *Fundamental & Clinical Pharmacology*, 19(1):117–125.

Smolensky, M. H., D'Alonzo, G. E. 1988. Biologic rhythms and medicine. *The American Journal of Medicine*, 85(1):34–46.

Sungthongjeen, S., Puttipipatkhachorn, S., Paeratakul, O., Dashevsky, A., Bodmeier, R. 2004. Development of pulsatile release tablets with swelling and rupturable layers. *Journal of Controlled Release*, 95(2):147–159.

Tejaskumar, P., Ananthapur, M., Sabitha, J. S., Trivedi, S. 2013. Rinku Mathappan, Prasanth V.V. Formulation and evaluation of erodible pulsatile drug delivery system of salbutamol sulphate for nocturnal asthma. *International Journal of Pharmaceutical Innovations. (IJPI)*, 3(3):24–35.

Yang, W., Donald, E. O., Robert, O. W. 2012. Pharmaceutical Cryogenic Technologies, in Formulating Poorly Water-Soluble Drugs. *Springer*, 3:443–500.