ijlpr 2020; doi 10.22376/ijpbs/lpr.2021.11.1.P110-117

International Journal of Life science and Pharma Research

Research Article

Pharmaceutics for Effective Drug Dosage

Formulation and *In Vitro* Evaluation of Compressed Coated Tablets of Simvastatin for Pulsatile Drug Delivery

P.V. Kamala Kumari*[1], V. Mounica[2] and Y. Srinivasa Rao[3]

*[1]*Associate Professor, Department of Pharmaceutics, Vignan Institute of Pharmaceutical Technology, Visakhapatnam, Andhra Pradesh, India.*

[2]*PG student, Department of Pharmaceutics, Vignan Institute of Pharmaceutical Technology, Visakhapatnam, Andhra Pradesh, India.*

[3]*Professor and Principal, Vignan Institute of Pharmaceutical Technology, Visakhapatnam, Andhra Pradesh, India.*

Abstract: Pulsatile drug delivery system is one type of drug delivery system, where the delivery device is capable of releasing drugs after a predetermined time-delay (i.e. lag time). This system has a peculiar mechanism of delivering the drug rapidly and completely after a "lag time," i.e., a period of "no drug release." These systems are beneficial for drugs having high first-pass effect drugs administered for diseases that follow chrono pharmacological behavior such as drugs having specific absorption sites in GIT, targeting to colon; and cases where nighttime dosing is required. The objective of the present study was to formulate and evaluate a press coated pulsatile drug delivery system of simvastatin in order to attain a time controlled release to lower the blood cholesterol level by releasing the drug with a distinct predetermined lag time of five hrs. Simvastatin is a water insoluble drug and its absorption is dissolution rate limited. The core formulations were composed of simvastatin and disintegrants like lycoat, SSG, ludiflash in different ratios and was coated with xanthan gum, guar gum, HPMC K4M, HPMC K15M as a release modifier. Press coated tablets were evaluated for hardness, friability, drug content, and *in vitro* drug release. Result of *in vitro* dissolution study of the prepared tablet suggested that, the release of drug from press coated tablets match with chrono-biological requirement of disease.

Keywords: Chronotherapeutics; Pulsatile drug delivery; Ludiflash; Drug release kinetics

***Corresponding Author**

P.V.Kamala Kumari , Associate Professor, Department of Pharmaceutics, Vignan Institute of Pharmaceutical Technology, Visakhapatnam, Andhra Pradesh, India.

Recieved On 16 July 2020
Revised On 18 September 2020
Accepted On 15 October 2020
Published On 04 January 2021

Funding This research did not receive any specific grant from any funding agencies in the public, commercial or not for profit sectors.

Citation P.V.Kamala Kumari, V.Mounica, Y.Srinivasa Rao , Formulation and In Vitro Evaluation of Compressed Coated Tablets of Simvastatin for Pulsatile Drug Delivery.(2021).Int. J. Life Sci. Pharma Res.11(1), P110-117 http://dx.doi.org/10.22376/ijpbs/lpr.2021.11.1.P110-117

4.1 INTRODUCTION

Medications have been formulated, and dosing schedules are established, in an attempt to provide an appropriate concentration of a drug in the target area of the body when the drug is most needed.[1] The differences in patterns of illness between day and night for cardiovascular disorders such as hypertension, angina, heart attack, sudden cardiac death and stroke have been documented. It has been recognized that many symptoms and onset of the disease occur during specific time periods of the 24 h, e.g., asthma and angina pectoris attacks are most frequently in the morning hours. Chronobiology is the study of biological rhythms and their mechanisms. The term "chrono" basically refers to the observation that every metabolic event undergoes rhythmic changes in time. Researchers have concluded that all living organisms are composites of rhythms with varying frequencies that may range from seconds to seasons[2]. Chronotherapeutics refers to a treatment method in which *in vivo* drug availability is timed to match rhythms of disease in order to optimize therapeutic outcomes and minimize side effects. A circadian rhythm takes place during cholesterol synthesis. Cholesterol synthesis is generally higher during night time than daylight. Sometimes it varies according to individuals. The maximal production occurs early in the morning, i.e., 12 h after the last meal. Studies with 3-hydroxy-3-methylglutarylCoenzymeA (HMG-CoA) reductase inhibitors have suggested that evening dosing was more effective than morning dosing. The activity of rate-limiting enzyme HMG-CoA is higher in the night time[3]. But the diurnal variations occur due to periodicity or degradation of this regulatory enzyme. Simvastatin is a member of the drug class known as statins. It is used for lowering cholesterol. Simvastatin inhibits the rate determining enzyme located in hepatic tissue that produces mevalonate, a small molecule used in the synthesis of cholesterol and other mevalonate derivatives. This lowers the amount of cholesterol produced which in turn lowers the total amount of LDL cholesterol. Simvastatin is a competitive inhibitor of HMGCoAreductase[4]. A pulsatile drug delivery system that can be administered at night (before sleep) but that releases drugs in early morning would be a promising chronopharmaceutical system. 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. However, no effort has been made to develop a system for HMG Co reductase inhibitor that deliver drug at a specified time and shows maximum effect at time when needed most. Hence, an attempt was made to formulate pulsatile drug delivery system of Simvastatin which can deliver the drug after lag time of 5 h. So in the present study Simvastatin has been found to be a suitable drug for the development of chronomodulated drug delivery[5].

4.2 MATERIALS AND METHODS

Simvastatin was obtained as a gift sample and lycoat, SSG, ludiflash, magnesium stearate, talc Xanthan gum, Guar gum, HPMC K4M, HPMCK15M were obtained from Narmada Chemicals.

2.1 Formulation of core tablets [6]

The inner core tablets (F1 to F9) were prepared by using direct compression method as per the developed formulation table which is shown in (Table 1). Accurately weighed amounts of Simvastatin, MCC, lycoat, SSG, ludiflash, 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 a punching machine and finally the core tablet was obtained.

2.2 Coating of core tablets[7]

The optimized core tablets were coated with coating ingredients like Xanthan gum, Guar gum. Accurately weighed amount of barrier layer material was transferred into a 16mm die then the core tablet was placed manually at the center[7]. 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 using16.4x8mm flat oval shape punch. The prepared tablets of each batch were evaluated for the Tablet properties as shown in Table 2.

Table 1: Formula of core tablet

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Simvastatin	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg
Lycoat	5 mg	7.5 mg	12.5 mg	--	--	--	--	--	--
SSG	--	--	--	5 mg	7.5 mg	12.5 mg	--	--	--
Ludiflash	--	--	--	--	--	--	5 mg	7.5 mg	12.5 mg
MCC	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Magnesium stearate	4 mg	4 mg	4 mg	4 mg	4 mg	4 mg	4 mg	4 mg	4 mg
Talc	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg
Total weight	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg

Table 2: Composition of compression coated tablets

Formulation	S1F9	S2F9	S3F9	S4F9	S5F9	S6F9
Core	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg
Guar gum	200 mg	150 mg	250 mg	-	-	-
Tamarind gum	200 mg	250 mg	150 mg	-	-	-
HPMC K 4M	-	-	-	200 mg	150 mg	250 mg
HPMC K 15M	-	-	-	200 mg	250 mg	150 mg
Guar gum:Tamarind gum ratio	1:1	0.75:1.25	1.25:0.75	1:1	0.75:1.25	1.25:0.75
Total weight	500 mg	500 mg	500 mg	500 mg	500 mg	500 mg

2.3 Evaluation of Core tablets

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

2.3.1 Weight variation [8]

The weight of the tablet being made was routinely determined to ensure that a tablet contains the proper amount of drug. The USP weight variation test is done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average [8]. The tablets met the USP specification that not more than 2 tablets are outside the percentage limits and no tablet differs by more than two times the percentage limit.

2.3.2. Tablet hardness [8]

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. The average hardness of three determinations was recorded.

2.3.3. Friability [8]

This was measured using an Roche Friability apparatus where the tablets were subjected to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets from a distance of 6 inches with each revolution. Preweighed samples of 20 tablets were placed in the friabilator, which is then operated for 100 revolutions. The tablets are then dusted and reweighed. Conventional compressed tablets that lose less than 0.5- 1.0% of their weight are generally considered acceptable

2.3.4. Tablet thickness [8]

The thickness of the tablets was determined using Vernier Calipers. Five tablets were used for the above test from each batch. Thickness of the core tablets was noted prior to compression of the cup. Finally the thickness of core-in-cup tablets was determined.

2.3.5. Content Uniformity [9]

The tablets were tested for their drug content uniformity. At random 20tablets were weighed and powdered. The powder equivalent to 200mg was weighed accurately and dissolved in100ml of Phosphate buffer pH 6.8 used. The solution was shaken thoroughly [9]. The undissolved matter was removed by filtration through Whattman's filter paperNo.41. Then the serial dilutions were carried out. The absorbance of the diluted solutions was measured at 238 nm. The concentration of the drug was computed from the standard curve of the Simvastatin in 6.8 phosphate buffer.

2.3.6. Disintegration time [9]

The process of breakdown of a tablet into smaller particles is known as disintegration. It is tested by using digital tablet disintegration apparatus. Place One tablet was placed in each 6 tubes of the basket. A disc was added to each tube and ran the apparatus using 7.8 pH phosphate buffer maintained at 37 °C as the immersion liquid.

2.3.7. In vitro dissolution time [10]

In vitro dissolution study of core and coated tablets of Simvastatin was carried out using Lab India DS8000 USP dissolution test apparatus[10]. Tablet was introduced into the basket of the Lab India DS8000 USP dissolution test apparatus and the apparatus was set in motion. Sample of 5ml was withdrawn for half an hour at 5min intervals. Samples withdrawn were analyzed by UV spectrophotometer for the presence of drug using buffer solution as blank.

2.4 Evaluation of Press coated tablets

2.4.1 Weight variation[8]

The weight of the tablet being made was routinely determined to ensure that a tablet contains the proper amount of drug. The USP weight variation test is done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average [8]. The tablets met the USP specification that not more than 2 tablets are outside the percentage limits and no tablet differs by more than two times the percentage limit.

2.4.2 Characteristics of coated tablets of Simvastatin[11]

Characteristics of tablets of Simvastatin such as hardness and disintegration test were conducted. Three tablets were taken and hardness of formulations was determined by using Monsanto hardness tester[11]. Average of three determinations was noted down. Six tablets were taken in Electrolab USP disintegration test apparatus and disintegration time of tablets was determined using pH 6.8 buffer.

2.4.3 Thickness[11]

Thickness was determined by using Vernier calipers and the values were recorded. Thickness of coated Simvastatin tablet formulations was determined by using digital Vernier calipers by deducting the thickness of core tablets from the thickness of the coated formulation. A successful pulsatile drug delivery system is one that remains intact in the physiological environment of the stomach and small intestine for up to six hours, releasing no or minimum amount of drug, but completely releases the drug after six hours.

2.4.4 In vitro dissolution methods [12]

Dissolution testing was done using USP dissolution rate test apparatus [12] in0.1 N HCl using pH 6.8 Phosphate buffer where the samples were withdrawn at regular intervals and analyzed by UV spectrophotometer (PG Instruments T60). Dissolution tests were performed in triplicate.

4.3 STATISTICAL ANALYSIS

The data obtained were analyzed using Minitab Statistical Software (Version 19.2.0). Student's paired "t" test was

used for analysis of comparison. The data were presented as mean ± standard deviation (SD). Probability value (P) of <0.05 was considered as statistically significant.

4.4 RESULTS

4.1 Evaluation of Core tablets

4.1.1 Weight Variation[8]

Weight variation for all the tablets (F1 to F9) is reported in the (Table 3). All the tablets passed weight variation test as the Percentage weight variation, which was within the Pharmacopoeial limits of ± 5% of the weight. The weights of all the tablets were found to be almost uniform.

4.1.2 Hardness test [8]

Monsanto hardness tester was used to determine hardness of all the tablet formulations. The hardness was maintained to be within 3.12-4.02 kg/cm^2, no variation in the hardness was found which clearly indicates that the blending was uniform (Table 3).

4.1.3 Disintegration test [9]

The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in apparatus was measured and recorded and found to be 30-86 seconds of different formulations.

4.1.4 Friability test[8]

Friability for all tablets is reported in (Table 3). Friability was determined using Roche friabilator. The friability of the formulations was found to be between 0.19-0.77 percent and was within the official requirement (i.e. less than 1%).

4.1.5 Content uniformity[9]

The drug content values are reported in (Table 4). Assay of tablets (F1 to F9) was done with the help of UV-Visible spectrophotometer and the drug content was estimated. The percentage drug content of all tablets was found to be between 90.23%- 98.54% which was within acceptable limits.

Table 3 : Evaluation of core tablets

Formula	Post compression parameters of core tablet				
	Average weight (mg)	Hardness (kg/cm2)	Thickness (mm)	Friability (Percentage)	Disintegration Time (secs)
F1	99.12±0.11	3.34±0.24	3.41±0.02	0.23±0.01	86±0.01
F2	98.97±0.01	3.12±0.22	3.69±0.03	0.41±0.02	63±0.02
F3	97.56±0.08	3.30±0.08	3.97±0.02	0.77±0.01	47±0.02
F4	98.56±0.06	3.20±0.26	3.55±0.01	0.54±0.21	79±0.25
F5	99.23±0.12	3.33±0.37	3.36±0.05	0.63±0.23	58±0.02
F6	99.78±0.014	3.45±0.03	3.64±0.25	0.70±0.21	39±0.05
F7	98.89±0.02	3.36±0.05	3.40±0.21	0.19±0.21	71±0.04
F8	98.55±0.01	3.55±0.25	3.39±0.02	0.35±0.24	53±0.04
F9	99.41±0.02	4.02±0.23	3.77±0.03	0.48±0.05	30±0.03

**All values are expressed as mean ± s.d., n=6 and P<0.01*

Table 4:Content uniformity of different formula (F1 toF9)

Formulation code	Drug content
F1	91.02±0.15
F2	90.23±0.79
F3	93.30±0.26
F4	91.22±0.33
F5	92.56±0.45
F6	95.58±0.98
F7	97.36±0.77
F8	95.12±0.44
F9	98.54±0.32

**All values are expressed as mean ± s.d., n=10; P<0.01*

4.2 Evaluation of press coated tablets

4.2.1 Weight variation[8]

Weight variation for all the tablets (S1F9 to S8F9) is reported in the (Table 5). All the tablets passed weight variation test as the percentage variation was within the Pharmacopoeial limits of ± 5% of the weight. The weights of all the tablets were found to be almost uniform.

4.2.2 Hardness test[8]

Monsanto hardness tester was used to determine hardness of all the tablet formulations. The hardness was maintained to be within 5.12-5.36 kg/cm^2, no variation in the hardness was found which clearly indicates that the blending was uniform.

4.2.3 *Thickness*[8]

The measured thickness by using Vernier calipers of tabletsfor all the formulations ranged between 4.65 - 4.85 mm. This ensures good handling characteristics of all batches.

4.2.4 *Friability test*[8]

Friability for all tablets is reported in (Table 5). Friability was determined using Roche friabilator. The friability of the formulations was found to be between 0.26-0.96 percent and was within the official requirement (i.e. less than 1%).

4.2.5 *Content uniformity*[9]

The drug content values are reported in (Table 6). Assay of tablets (S1F9 to S8F9) was done with the help of UV-Visible spectrophotometer and the drug content was estimated. The % drug content of all tablets was found to be between 86.21%- 92.82% which was within acceptable limits.

Table 5: Evaluation of physical parameters of compressed tablets of simvastatin

Formula	Weight variation (mean± SD, mg)	Hardness	Friability (Percentage)	Thickness
S1F9	492.30±0.11	5.12	0.89	4.78
S2F9	497.56±1.20	5.30	0.78	4.85
S3F9	495.66±2.59	5.16	0.65	4.69
S4F9	498.98±0.45	5.20	0.26	4.70
S5F9	497.79±1.03	5.23	0.78	4.75
S6F9	498.80±1.30	5.22	0.96	4.72
S7F9	497.56±2.18	5.36	0.78	4.85
S8F9	498.98±1.26	5.24	0.26	4.70

All values are expressed as mean ± s.d., n=10; P<0.01

Table 6: Content uniformity of different formula (SIF9 to S8F9)

Formulation code	Drug content
S1F9	91.23±0.20
S2F9	90.63±0.42
S3F9	92.82±0.17
S4F9	90.78±0.08
S5F9	91.30±0.99
S6F9	86.21±0.88
S7F9	90.66±0.88
S8F9	90.71±0.28

All values are expressed as mean ± s.d., n=10; P<0.05

4.3 In vitro *drug release studies of press coated tablets*[15,16]

From the *in vitro* drug release studies it was observed that the formulation S1F9 released maximum drug at the end of 10 hours, S2F9 at the end of 9 hours, S3F9 containing altered tamarind gum and guar gum concentrations released maximum drug at the end of 7 hours due to the higher guar gum concentration (Table 7). By comparing the drug release profiles of the formulations S1F9 to S3F9 formulated using natural polymers the drug release was found to be lagged up to 5 hours in the case of S3F9 containing guar gum and tamarind gum in the ratio of 1.25:0.75. Formulations S4F9, S5F9 and S6F9 were formulated using synthetic polymers like HPMC K4M, HPMC K15M[15,16]. The formulation S4F9 containing HPMC K4M and HPMC K15M in 1:1 ratio showed 79.01 % of drug release at the end of 10 hours due to the higher concentration of the polymer because the cellulose polymers forms a very viscous gel layer which will reduce the seepage of dissolution fluid into the core tablets and thereby retards the drug release[17]. The drug release could be modified by adjusting the ratio of these two polymers in combination i.e., 0.75:1.25 for maintaining the lag phase and released 84.64% of drug at the end of 10 hours as shown from Fig 1 to Fig 3. The formulation S6F9 was formulated by varying the concentrations of the polymer to 1.25:0.75 in which the lag phase was maintained for 5hrs but the burst release was not found.[18,19] By comparing all the drug release of formulations S1F9 to S6F9 the formulation S3F9 showed burst release at the end of 5hrs with maximum drug release at the end of 7hrs. So S3F9 was considered as the optimized formulation for which the drug release kinetics were performed.

Table 7: Cumulative percentage drug release coasted different formulation (SIF 9 to S8F9)

Time (hours)	S1F9	S2F9	S3F9	S4F9	S5F9	S6F9
0	0	0	0	0	0	0
1	0.54±0.02	0.51±0.03	0.22±0.03	0.89±	0.41±0.02	0.55±0.25

2	0.63±0.01	0.77±0.02	0.64±0.05	1.36±	0.97±0.01	1.23±0.02
3	2.03±0.02	3.69±0.21	0.84±0.06	4.47±	1.75±0.05	5.60±0.21
4	4.12±0.03	8.79±0.04	1.97±0.05	9.98±	2.98±0.04	10.23±0.25
5	19.65±0.04	26.65±0.05	13.36±0.07	26.6±	13.69±0.05	14.36±0.21
6	32.30±0.05	48.87±0.02	74.46±0.06	37.48±	38.79±0.05	34.45±0.21
7	44.47±0.04	66.30±0.05	99.97±0.04	49.14±	52.65±0.02	66.54±0.03
8	74.12±0.05	87.90±0.02	--	58.19±	68.78±0.02	82.21±0.02
9	84.20±0.21	99.02±0.02	--	65.24±	79.96±0.03	90.84±0.05
10	98.46±0.02	--	--	79.01±	84.64±0.02	99.72±0.05

**All values are expressed as mean ± s.d., n=6; P<0.05*

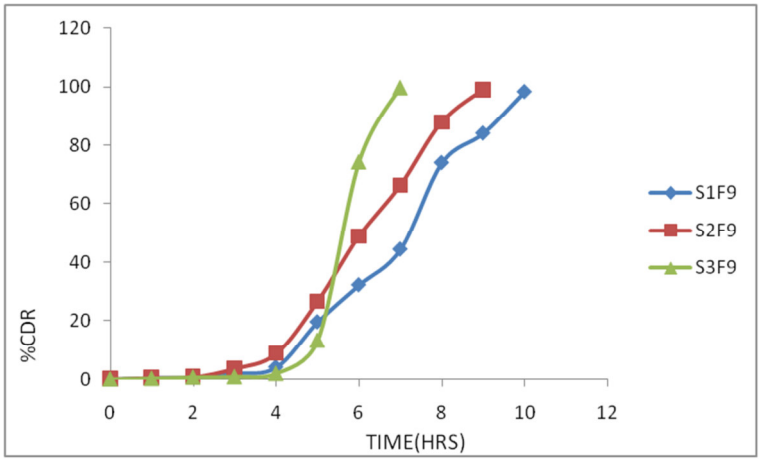

Fig 1: Cumulative percentage drug release of coated formulation S1F9 –S3F9

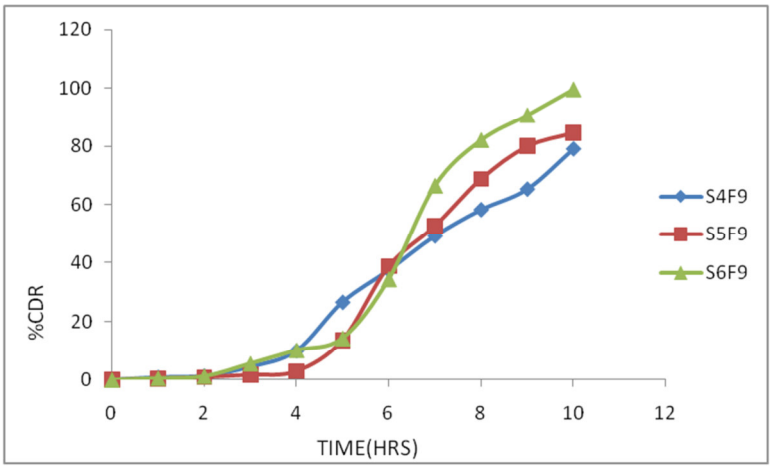

Fig 2: Cumulative percentage drug release coated formulation S4F9-S6F9

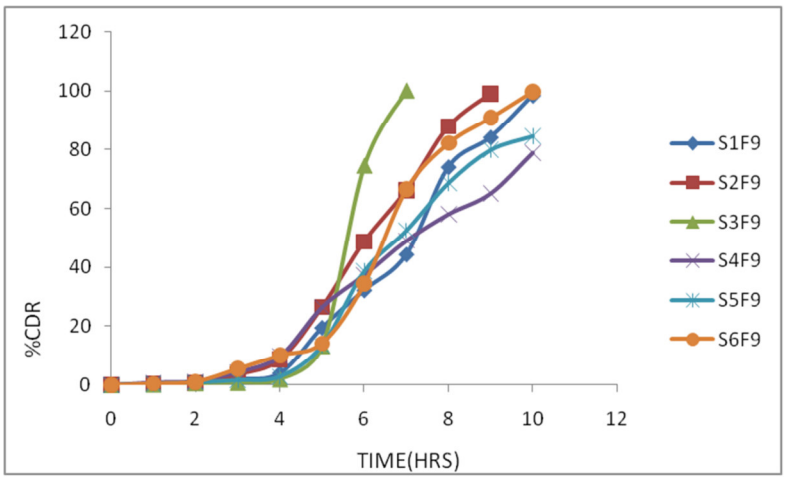

Fig 3: *In vitro* drug release of S1F9 and S6F9

4.5 DISCUSSION

The overall objective of the present study was to formulate and evaluate a press coated pulsatile drug delivery system of simvastatin in order to attain a time controlled release to lower the blood cholesterol level by releasing the drug with a distinct predetermined lag time of five hrs[17,20] .The core formulations were composed of simvastatin and disintegrants like lycoat, SSG, ludiflash in different ratios and was coated with xanthan gum, guar gum, HPMC K4M, HPMC K15M as a release modifier. Core tablets were subjected to evaluation of properties including drug content uniformity, weight variation, tablet hardness, friability and thickness and *in vitro* drug release. All the tablets passed weight variation test as the Percentage weight variation, which was within the Pharmacopoeial limits of ± 5% of the weight. The hardness was maintained to be within 3.12-4.02 kg/cm^2, disintegration time was found to be 30-86 seconds, friability between 0.19-0.77 percent and the % drug content of all tablets was found to be between 90.23%- 98.54%. Press coated tablets were evaluated for weight variation which was within the Pharmacopoeial limits, hardness within 5.12-5.36 kg/cm^2, thickness ranged between 4.65 - 4.85mm,friability between 0.26-0.96 percent and the drug content of all tablets was found to be between 86.21%- 92.82% which was within acceptable limits[18,21]. Drug release profiles of the formulations S1F9 to S3F9 using natural polymers the drug release was found to be lagged up to 5 hours in the case of S3F9 containing guar gum and tamarind gum in the ratio of 1.25:0.75 when compared to S4F9, S5F9 and S6F9 formulations using synthetic polymers like HPMC K4M, HPMC K15M. The formulation S4F9 containing HPMC K4M and HPMC K15M in 1:1 ratio showed 79.01 % of drug release at the end of 10 hours due to the higher concentration of the polymer because the cellulose polymers forms a very viscous gel layer which will reduce the seepage of dissolution fluid into the core tablets and thereby retards the drug release [18, 22]. By comparing all the drug release of formulations S1F9 to S6F9, the formulation S3F9 showed burst release at the end of 5hrs with maximum drug release at the end of 7hrs. So S3F9 was considered as the optimized formulation for which the drug release kinetics was performed[23].

4.6 CONCLUSION

The aim of this study was to explore the feasibility of time dependent pulsatile drug delivery system of simvastatin for reducing the levels of "bad" cholesterol (low-density lipoprotein, or LDL) and triglycerides in the blood. A satisfactory attempt was made to develop a pulsatile system of simvastatin and evaluate it. On the basis of drug content, *in vitro* release studies and its kinetic data F9 of core tablet and S3F9 of coated tablet were selected as optimized formulations for designing pulsatile devices. Therefore the study proved that coated Simvastatin can be successfully used as a time dependent modified chronopharmaceutical formulation. Finally from the above results we can conclude that the pulsatile drug delivery system of Simvastatin can be formulated using natural polymers like tamarind gum and guar gum.

4.7 ACKNOWLEDGEMENTS

The authors are thankful to Dr. Lavu Rathaiah, Chairman, Vignan group of institutions for providing necessary facilities to carry out research work and also to Mr. S.M.Waseem Raja, Spectrum Pharma Research Solutions, Hyderabad who had helped greatly in completion of the project work.

4.8 AUTHORS CONTRIBUTION STATEMENT

Dr.P.V.Kamala Kumari guided in manuscript framing concerning this work. Ms.V.Mounica contributed to collecting the information and did the experimentation of the present work. Dr.Y.Srinivasa Rao analyzed these data and necessary inputs were given towards the designing of the manuscript.

4.9 CONFLICT OF INTEREST

Conflict of interest declared none.

REFERENCES

1. Robert W, Thomas P. Drug therapy for hypercholesterolemia and dyslipidemia. Goodman and Gilmans. The Pharmacol Basis Ther. 2003;10:971-2.
2. Youan BB. Chronopharmaceutics: gimmick or clinically relevant approach to drug delivery. J Control Release. 2004;98(3):337-53. doi: 10.1016/j.jconrel.2004.05.015, PMID 15312991.
3. Bussemer T, Otto I, Bodmeier R. Pulsatile drug-delivery systems. Crit Rev Ther Drug Carrier Syst. 2001;18(5). doi: 10.1615/CritRevTherDrugCarrierSyst.v18.i5.10.
4. Gothaskar AV, Joshi AM, Joshi NH. Pulsatile drug delivery system—a review. Drug Deliv Technol;4.
5. Anal AK. Time-controlled pulsatile delivery systems for bioactive compounds. Recent Pat Drug Deliv Formulation. 2007;1(1):73-9. doi: 10.2174/187221107779814096, PMID 19075876.
6. Suresh S, Chronotherapeutics PS. Emerging role of biorhythms in optimizing drug therapy. Indian J Pharm Sci. 2005;67(2):135.
7. Chhabra VS, Tilloo SK, Walde SR, Ittadwar AM. The essentials of chronopharmacotherapeutics. Int J Pharm Pharm Sci. 2012;4(3):1-8.
8. Mandal AS, Biswas N, Karim KM, Guha A, Chatterjee S, Behera M, Kuotsu K. Drug delivery system based on chronobiology-a review. J Control Release. 2010;147(3):314-25. doi: 10.1016/j.jconrel.2010.07.122, PMID 20691738.
9. Ravilla S. Erythrocytes as Carrier for Drugs, Enzymes and Peptides. J App Pharm Sci. 2012;2(4):166-76.doi: 10.7324/JAPS.2012.2503.
10. Radhika MS, Nidhi MD, KR. Pulsatile drug delivery: a review. International PharmaceuticaSciencia. 2012; 2(2):45-52.
11. Vipul P, Moinuddin S. Pulsatile drug delivery system for treatment of various inflammatory Disorders: a review. Int J Drug Dev Res. 2012;4:67-87.
12. Modasiya MK, Patel VM. Pulsatile drug delivery system for colon–A review. Int J Res Pharm Biomed Sci. 2011;2(3):934-41.
13. Bussemer T, Peppas NA, Bodmeier R. Evaluation of the swelling, hydration and rupturing properties of the

swelling layer of a rupturablepulsatile drug delivery system. Eur J Pharm Biopharm. 2003;56(2):261-70. doi: 10.1016/S0939-6411(03)00070-5,

14. Singh B, Purohit S, Saini G, Bhandari A, Awasthi D. Colon specific chronotherapeutic drug delivery for nocturnal asthma: Eudragit S-100 coated calcium alginate gel beads-entrapped salbutamol sulphate. Int J Pharm Pharm Sci. 2013;5:362-7.ISSN: 0975-1491.
15. Kulkarni PA, Jaiswal M, Jawale SB, Shirolkar SV, Kasture PV. Development and evaluation of press coated tablets for chronopharmaceutical drug delivery using gellable and permeable polymers. Pharm Lett. 2010;2(4):482-97.
16. Dash S, Murthy PN, Nath L, Chowdhury P. Kinetic modeling on drug release from controlled drug delivery systems. Acta Pol Pharm. 2010;67(3):217-23.ISSN: 0001-6837. PMID 20524422.
17. Ramteke KH, Dighe PA, Kharat AR, Patil SV. Mathematical models of drug dissolution: a review. Sch. Acad. J Pharmacol. 2014;3(5):388-96.
18. Bandameedi R, Pandiyan S. Formulation and evaluation of floating osmotic tablets of nizatidine. J Appl Pharm. 2015;08(1):2. doi: 10.4172/1920-4159.1000209.
19. Nawaj SS. Development optimization and evaluation of dual mechanism based gastro floatable and bioadhesive drug delivery system for simvastatin. Asian J Pharm. 2017;11(02).
20. Patil P, Patil V, Paradkar A. Formulation of a self-emulsifying system for oral delivery of simvastatin: in vitro and in vivo evaluation. Acta Pharm. 2007;57(1):111-22. doi: 10.2478/v10007-007-0009-5, PMID 19839411.
21. Lai J, Chen J, Lu Y, Sun J, Hu F, Yin Z, Wu W. Glycerylmonooleate/poloxamer 407 cubic nanoparticles as oral drug delivery systems: I. In vitro evaluation and enhanced oral bioavailability of the poorly water-soluble drug simvastatin. AAPS PharmSciTech. 2009;10(3):960-6. doi: 10.1208/s12249-009-9292-4.
22. Serajuddin ATM, Ranadive SA, Mahoney EM. Relative lipophilicities, solubilities, and structure-pharmacological considerations of 3-hydroxy-3-methylglutaryl-coenzyme a (HMG-COA) reductase inhibitors pravastatin, lovastatin, mevastatin, and simvastatin. J Pharm Sci. 1991;80(9):830-4. doi: 10.1002/jps.2600800905, PMID 1800703.
23. Swain RP, Pendela S, Panda S. Formulation and evaluation of gastro-bilayer floating tablets of simvastatin as immediate release layer and atenolol as sustained release layer. ijps. 2016 Jul 10;78(4):458-68. doi: 10.4172/pharmaceutical-sciences.1000140