IJBPAS, July, 2024, 13(7): 3401-3415

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

FORMULATION AND EVALUATION OF ATORVASTATIN CALCIUM ORO DISPERSIBLE TABLETS USING DESIGN EXPERT

HAARIKA B*[1], MADHURI P[2] AND NIKITHA S[3]

Department of Pharmaceutics, Sarojini Naidu Vanita Pharmacy Maha Vidyalaya, 12-5-31/32, Vijayapuri colony, Tarnaka, Secunderabad, 500017, Telangana, India

***Corresponding Author: Dr. Balusu Haarika: E Mail: haarikabalusu09@gmail.com**

Received 15th March 2023; Revised 8th July 2023; Accepted 5th Oct. 2023; Available online 1st July 2024

https://doi.org/10.31032/IJBPAS/2024/13.7.8167

ABSTRACT

Atorvastatin calcium is used to lower the amount of cholesterol in the blood and to prevent stroke, heart attack and angina (chest pain). It is also called as HMG CoA reductase inhibitors which is a competitive inhibitor and inhibits 3 hydroxy-3-methylglutaryl-coenzyme reductase which is the rate determining enzyme located in hepatic tissue which produces mevalonate an early step in cholesterol biosynthesis. resulting in fast disintegration and enhanced drug release. Sublimation method was used to prepare orally disintegrating tablets of formulations F1 to F11. The preliminary trials were done using the super disintegrant Ac Di Sol and sublimating agent menthol. Optimization of atorvastatin calcium orally disintegrating tablets (F1 to F11) were done by optimizing independent variables such as concentration of super disintegrant and sublimating agent (Ac Di Sol as 0.5, 2.75 and 5% and menthol as 2.5, 8.75 and 15%) and dependent variables like disintegration time, percent friability and percent drug release. Optimization was done using Design export 13 software by Central composite design from Response surface methodology. ANOVA elucidates the impact of independent variables on dependent variables. In preliminary studies, it was found that, apart from Ac Di Sol, formulations containing Ac Di Sol and menthol combinations shown fast disintegration and increased percent drug release. The optimized formulation F8 (using Design expert software) having 5% Ac Di Sol and 8.75% menthol showed disintegration time of 14 sec, percent friability of 0.88% and 98.6% drug release. The optimized formulations were characterized using Fourier transform infrared spectroscopy (FTIR), Differential scanning calorimetry (DSC)

and Powder x-ray diffraction (PXRD) studies which showed that there was no interaction between drug and excipients of formulation. Based on disintegration and dissolution studies, the optimized formulations were subjected to stability studies and had indicated good stability.

Keywords: Disintegration, sublimation, optimization, characterization, friability, percent drug release

INTRODUCTION

Oral disintegrating tablets (ODTs) are solid oral dosage forms which quickly disintegrate in few seconds, when placed in the oral cavity. They are used due to their better patient compliance and acceptance, compared to conventional oral dosage forms **[1]**. Atorvastatin belongs to a class of drugs, called HMG CoA reductase inhibitors which is a competitive inhibitor and inhibits 3 hydroxy-3-methylglutaryl-coenzyme reductase which is the rate determining enzyme located in hepatic tissue which produces mevalonate an early step in cholesterol biosynthesis. Recommended dosage is 10 mg to 80 mg once daily. The half-life is 14 hours, while its active metabolites have a half-life of about 20 to 30 hours. However, the longer half-life of atorvastatin compared to other shorter half-life statins like Lovastatin, Fluvastatin provides great flexibility in terms of dosing intervals **[2]**.

Design of Experiments (DOE) is an active means in direction to optimise the formulation with the least possible runs and identify the factors that have the great impact on formulated tablets [5]. The relationship between factors and responses (independent and dependent variables) noticed by DOE and the variability in responses were determined. The goal of the study is to formulate Atorvastatin Orally Disintegrating Tablets to improve its solubility, bioavailability and provide rapid onset of action followed by fast disintegration **[3]**.

MATERIALS AND METHODS

Atorvastatin Calcium was supplied from Suraksha Pharma Pvt. Ltd., Hyderabad, India. SMCC HD 90, Ac Di Sol were obtained from Srivar Pharma Pvt Ltd, Tirupati, Andhra Pradesh, India. menthol, mannitol, talc and magnesium stearate were purchased from SD Chem Fine, Hyderabad, India. All excipients and solvents used were of analytical grade. Double distilled water is used.

Accurate amount of active pharmaceutical ingredient and all other additives were homogenously blended using geometric dilution. After passing through sieve number 22 and talc and magnesium stearate were added for lubrication and triturated well. The blended material was then compressed on 8mm standard concave punch using 16 station rotary tablet

punching machine (Cadmach, Ahmedabad, India). The total weight of the formulation is made up to 150mg were shown in **Table 1 [4]**.

Preliminary trials were conducted on nine possible combinations of thymol, menthol, and ammonium bicarbonate as sublimating agents, each of which was included in three different formulations at concentrations of 5%, 10%, and 15%, in addition to other excipients. Out of all three sublimating agents at different percentages, 10% of menthol in combination with super disintegrant presented good results based on its disintegration time, percent friability and percent drug release. Additional optimization of Atorvastatin calcium oro dispersible tablets was done by assessing independent variables in two levels such as concentration of super disintegrant (0.5, 2.75 and 5%) and sublimating agent (2.5, 8.75 and 15%) and dependent variables like disintegration time, percent friability and percent drug release by using Central composite design from Response surface methodology using Design Expert 13 software. According to Central Composite Design, atorvastatin calcium oro dispersible tablets were developed with eleven (F1 to F11) possible combinations was shown in **Table 2**. This optimization revealed how independent variables affects dependent variables using ANOVA [5]. It was observed that 8.75% of menthol in combination with 5% super disintegrant shown good results based on its disintegration time, percent friability and percent drug release. Therefore, 5% of Ac Di Sol and 8.75% of menthol were considered as fixed qualities. These responses were evaluated using a statistical model that comprises two – factor interactive polynomial term.

Sublimation technique is used to produce highly porous orally disintegrating tablets of atorvastatin calcium. Volatile and sublimating agent, menthol is added, and tablets are punched using direct compression technique. The compressed tablets were placed in hot air oven at 40 to 60°C temperature for one hour. Heating causes menthol to evaporate, which results in the residual bulk becoming highly porous which is an essential feature and helps to achieve fast disintegration in saliva **[6]**.

Pre compression parameters

Prior to compression, the powder mixtures should be assessed for their bulk and tapped density and from these results, Carr's compressibility index and Hausner's ratio must be calculated, while the flow properties of blend should be measured by angle of repose shown in **Table 3 [7]**.

Post compression parameters

Weight variation

Randomly twenty tablets were selected from each formulation and weighed using a

digital balance (BL-220H/ Shimadzu). the mean ±SD were calculated **[8]**.

Thickness

Ten tablets from each preparation were taken randomly and their thickness was calculated using a digital screw gauge micrometre. The mean ±SD were calculated **[9]**.

Hardness

Hardness of the orally disintegrating tablet formulations was determined in Kgs/cm^2 using the Monsanto hardness tester **[10]**.

Content uniformity

20 tablets were randomly chosen from each formulation and pulverised to a fine powder. An amount equivalent to 100mg of atorvastatin calcium was weighed and dissolved in small quantity of methanol, sonicate using ultra sonicator (BIO-TECHNIQUES) for 15 min, and dilute with same to get 100ml. Filter this solution and further dilutions were done to get 5 µg/ml in phosphate buffer pH 6.8. measure the absorbance at 246 nm using UV-Visible spectrophotometer (UV LAB INDIA, India) against phosphate buffer pH 6.8 as blank **[11]**.

Friability

The friability of Oro dispersible tablet formulations was measured using friability test apparatus (ANALAB). Pre weighed ten tablets were placed in friabilator attached to a motor evolving at a speed of 25rpm for 4 min. tablets were then dedusted, reweighed and % weight loss is determined **[12]**.

$$\%\ Friability = \frac{initial\ weight - final\ weight}{initial\ weight} \times 100$$

In vitro disintegration time

This test was performed using disintegration test apparatus (DBK). Six tablets were taken and placed in basket assembly which is immersed in 500ml of phosphate buffer pH 6.8 at 37 ± 0.5°C. the time required for the tablets to disintegrate entirely into smaller particles were recorded **[13]**.

In vitro drug release studies

In vitro drug release studies were performed using USP dissolution test apparatus type II (Paddle method (Electro lab)). The apparatus is rotated at a speed of 75 RPM for 30 min at 37±0.5°C using 900ml of pH 6.8 phosphate buffer as dissolution medium was poured in vessels. At specific time intervals 10ml of aliquots were collected and substituted with equal volume of fresh buffer into the vessels and then filtered through 0.45µm pore size (PVDF filter) and analysed under UV-Visible spectrophotometer ((LAB INDIA/UV 3200, India) at a wavelength of 246nm. The amount of drug release from the tablets at different time intervals was calculated using atorvastatin calcium standard graph **[14]**.

Characterization of Atorvastatin Calcium oral dispersible tablets

Characterization studies of placebo (tablet), atorvastatin calcium Oro dispersible tablet formulation and standard atorvastatin calcium were carried out using FTIR-ATR spectrophotometer (bruker), DSC (DSC 6, Perkin Elmer, USA) and PXRD (XRD x' pert PRO MPD PAN Analytical, USA) **[15]**.

Stability studies

The optimised formulation subjected to stability studies as per ICH guidelines. The samples were packed in aluminium foil and stored the formulation at 40±2°C / 75± 5% RH in stability chamber up to 3 months. For every 30 days interval, analyse the samples for disintegration time, percent friability and percent drug release **[15]**.

RESULTS

Standard graph of Atorvastatin calcium

Weigh accurately about 100mg of atorvastatin calcium working standard and transfer to 100ml standard flask, dissolved, and diluted up to the mark with methanol. From this, take 5ml and diluted to 50ml with phosphate buffer pH 6.8. Further dilutions were done using phosphate buffer pH 6.8 to get 1,2,4,6,8,10 µg/ml concentration of atorvastatin calcium. The absorbances of all the solutions was analysed using UV-Visible spectrophotometer (LAB INDIA/UV 3200, India) at 246nm shown in **Figure 1**.

Preliminary trials

Preliminary trials were conducted on nine possible combinations of thymol, menthol, and ammonium bicarbonate as sublimating agents, each of which was included in three different formulations at concentrations of 5%, 10%, and 15%, in addition to other excipients. Out of all three sublimating agents at different percentages, menthol in combination with super disintegrant showed best result. From the above trials, menthol was found to be best sublimating agent. Further nine tablet formulations were prepared by varying concentration of menthol from 5 – 15% along with other excipients. The optimised formulation of atorvastatin calcium ODTs was shown in **Table 1**.

The factorial formulations were evaluated for micromeritic properties, and all the formulations exhibited good flow properties. The various flow properties were represented in **Table 2**. The results indicating angle of repose ranging from 31.03° to 33.97°, Carr's compressibility index ranging from 10.21% to 13.56% and Hausner's ratio ranging from 1.11 to 1.18.

The results from pre compression parameters revealed that, all the designed formulations were of uniform weight with acceptable weight variation and thickness. The hardness ranging from 0.4 ± 0.28 to 4.17 ± 0.6 Kg/cm^2 percent friability ranging from 0.60 to 0.92% of all formulations which shown good mechanical resistance.

The content uniformity for all nine formulations were in acceptable limits, in the range 98.6±0.23 to 101.7±0.17 %. The disintegration time results are ranging from 4 to 70 seconds was shown in **Table 3**.

The percent drug release for all nine formulations F1 to F9 were ranged from 82.1 to 98.6% in 10 min. the formulation F8 showed DT of 4 sec, friability of 0.88% and showed highest percent drug release of 98.6% at 10 min interval.

OPTIMIZATION BY CENTRAL COMPOSITE DESIGN

To evaluate the response, with two-factor interactive polynomial statistical model terms in the systems was used.

$Y = b_0 + b_1 X_1 + b_2 X_2 + b_3 X_1 X_2 + b_4 X_1^2 + b_5 X_2^2 + b_6 X_1 X_2^2 + b_7 X_1^2 X_2 + b_8 X_1^2 X_2^2$

Where Y is dependent variable, b_0 is intercept, which is the average response for eleven runs shown in **Table 2**. B1 and b2 are evaluated coefficients for factors (X1 and X2). Correlation between all independent and dependent variables before the treatment of regression and was expressed as correlation coefficient shown in **Table 4**.

DISINTEGRATION TIME:

Disintegration time was found to be 14 to 70 seconds for F1 to F11 formulations. The minimum DT (14 sec) was found in F3 formulation which contains 5% Ac Di Sol (super disintegrant) and 8.75% menthol (sublimating agent). The Model F-value of 56.70 implies the model is significant **(Table 5)**.

FRIABILITY:

Friability was found to be between 0.60 to 0.92% from F1 to F11 formulations. The minimum percent friability (0.60%) was found in F3 formulation which contains 5% Ac Di Sol (super disintegrant) and 8.75% menthol (sublimating agent). The model F-value of 76.17 implies the model is significant **(Table 6)**.

PERCENT DRUG RELEASE

Percent drug release was found to be between 82.1 to 98.6% from F1 to F11 formulations. The maximum drug release (98.6%) was found in F3 formulation containing 5% Ac Di Sol (super disintegrant) and 8.75% menthol (sublimating agent). The Model F-value of 75.22 implies the model is significant **(Table 7)**.

CHARACTERIZATION OF ATORVASTATIN CALCIUM ODTs

FTIR (Fourier Transform Infrared Spectroscopy)

FT-IR spectra of placebo (tablet), atorvastatin calcium standard and atorvastatin tablet are shown in **Figure 7**. The pure atorvastatin calcium showed characteristic peaks at 1798 cm^{-1} (C=O stretching), and standard atorvastatin calcium exhibits characteristic peaks at 1693 cm^{-1} indicating ketone bond

stretching, 1424 cm^{-1} shows presence of aromatic compounds.

Differential scanning calorimetry (DSC)

The thermo tropic behaviour and the physical states of the drug in orally disintegrating tablets were obtained from the DSC thermo grams of placebo (tablet), atorvastatin calcium ODT tablet formulation (F4) and standard atorvastatin calcium. It was shown from **Figure 8** that the onset of peak for standard atorvastatin calcium was found at 142.87°C, and a sharp intensive peak at 155.75°C was observed. Whereas in atorvastatin calcium ODT tablet formulation the onset of peak was noticed at 163.60°C and sharp intensive peak at 168.15°C and no peak is observed between 160°C to 169°C for placebo tablet formulation. This shows that there were no polymorphic changes in the atorvastatin calcium ODT formulation.

Powered X ray diffraction (PXRD)

The pure drug showed numerous characteristic high intensity diffraction peaks indicating the crystalline nature of atorvastatin calcium **(Figure 9)**. The peak at about 22.64(2Ɵ) corresponds to main peak in standard atorvastatin calcium at about 22.57(2Ɵ). This shows that the crystallinity of atorvastatin calcium was not changed in standard atorvastatin calcium and atorvastatin calcium ODT formulation.

Evaluation of stability studies

The optimized formulation was subjected to stability studies by storing F3 formulation at 40±2°C/ 75±5% RH in stability chamber for three months at thirty days' time interval where, disintegration time, percent friability and percent drug release were assessed. The optimized formulations are stable and did not show much difference in any of the parameters as shown in **Table 8**.

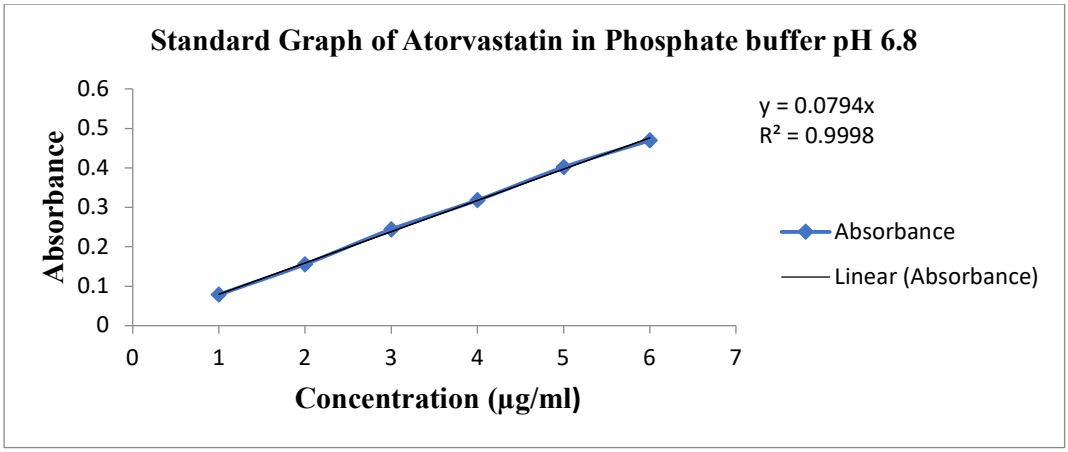

Figure 1: Standard Graph of Atorvastatin in Phosphate buffer pH 6.8

Table 1: Factorial design formulations of atorvastatin calcium oro dispersible tablets.

Formulation code	Atorvastatin (mg)	SMCC HD 90 (mg)	Ac Di Sol (mg)	Menthol (mg)	Mannitol (mg)	Talc (mg)	Magnesium stearate (mg)	Total weight (mg)
F1	20	63.86	0.75	3.75	59	1.9	0.74	150
F2	20	54.49	0.75	13.125	59	1.9	0.74	150
F3	20	45.11	0.75	22.5	59	1.9	0.74	150
F4	20	60.49	4.12	3.75	59	1.9	0.74	150
F5	20	60.49	4.12	3.75	59	1.9	0.74	150
F6	20	60.49	4.12	3.75	59	1.9	0.74	150
F7	20	41.74	4.12	13.125	59	1.9	0.74	150
F8	20	41.74	4.12	22.5	59	1.9	0.74	150
F9	20	57.11	7.5	3.75	59	1.9	0.74	150
F10	20	47.73	7.5	13.125	59	1.9	0.74	150
F11	20	38.36	7.5	22.5	59	1.9	0.74	150

Table 2: Central composite design Powder Flow Properties of Atorvastatin calcium tablet formulation

Formulation code	Angle of repose (θ)	Bulk density(gm/cm^3)	Tapped density(gm/cm^3)	Compressibility index (I)	Hausner's ratio
F1	31.13±0.06	0.23±0.01	0.36±0.01	11.38±0.22	1.12±0.00
F2	31.13±0.06	0.21±0.01	0.28±0.01	11.64±0.22	1.12±0.01
F3	31.03±0.05	0.32±0.01	0.39±0.01	13.56±0.28	1.11±0.02
F4	32.67±0.03	0.34±0.01	0.34±0.01	10.21±0.21	1.14±0.02
F5	33.77±0.03	0.26±0.00	0.37±0.01	10.85±0.24	1.13±0.00
F6	33.97±0.02	0.30±0.01	0.29±0.01	12.06±0.27	1.15±0.01
F7	31.57±0.01	0.26±0.01	0.22±0.01	13.46±0.48	1.18±0.01
F8	32.63±0.00	0.20±0.01	0.36±0.01	10.96±0.20	1.17±0.00
F9	32.41±0.05	0.25±0.01	0.21±0.01	15.36±0.05	1.16±0.01

Data is expressed as Mean ± SD (n=3)

Table 3: Post compression parameters of ODTs by sublimation method

Formula	Weight Variation(mg)*	Thickness (mm) **	Hardness (kg/cm^2) *	Content uniformity (%) **	Disintegration time (sec)*	Friability (%) **
F1	151.3±0.31	3.10±0.03	4.0±0.0	99.6±0.43	70	0.60
F2	150.3±0.32	3.17±0.12	4.17±0.0	99.9±0.58	53	0.76
F3	150.1±0.18	3.02±0.36	4.0±0.5	100.8±0.18	48	0.87
F4	149.8±0.21	3.20±0.51	4.0±0.29	100.5±0.31	60	0.70
F5	150.7±0.70	3.15±0.61	4.17±0.0	98.8±0.04	33	0.82
F6	152.3±1.33	3.11±0.24	4.17±0.5	99.7±0.61	27	0.91
F7	150.6±0.62	3.16±0.33	4.0±0.0	98.6±0.23	30	0.71
F8	150.4±0.41	3.18±0.41	4.17±0.29	101.7±0.17	14	0.88
F9	150.5±0.51	3.17±0.12	4.0±0.0	100.4±0.19	18	0.92

***Data is expressed as Mean ± SD (n=6); **Data is expressed as Mean SD (n=20)**

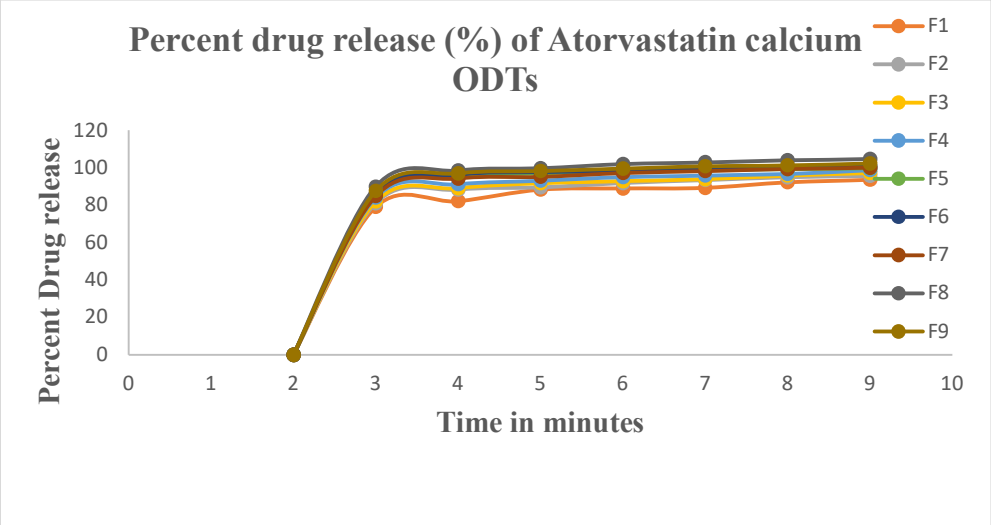

Figure 2: Percent drug release of atorvastatin calcium ODTs

Table 4: Independent variables and dependent variables of atorvastatin calcium orally disintegrating tablets using central composite design

Std	Run	Independent variables		Dependent variables		
		A: Conc of Ac Di Sol (%)	B: Conc of Menthol (%)	DT (Seconds)	Percent Friability (%)	Percent Drug Release (%)
11	1	2.75	8.75	33	0.82	95.4
7	2	2.75	2.5	60	0.7	91.1
6	3	5	8.75	14	0.88	95.5
2	4	5	2.5	30	0.71	94.2
5	5	0.5	8.75	53	0.76	88.3
9	6	2.75	8.75	33	0.82	95.4
3	7	0.5	15	48	0.87	89.1
10	8	2.75	8.75	33	0.82	95.4
8	9	2.75	15	27	0.91	96.2
1	10	0.5	2.5	70	0.6	82.1
4	11	5	15	18	0.92	97

Table 5: Results of ANOVA for predicting disintegration time (Y1)

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	2947.61	3	982.54	56.70	< 0.0001	significant
A-Conc of CCS	1980.17	1	1980.17	114.27	< 0.0001	
B-Conc of Menthol	748.17	1	748.17	43.18	0.0003	
B^2	219.28	1	219.28	12.65	0.0093	
Residual	121.30	7	17.33			
Lack of Fit	121.30	5	24.26			
Pure Error	0.0000	2	0.0000			
Cor Total	3068.91	10				

Table 6: Results of ANOVA for predicting percent friability (Y2).

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	0.0958	3	0.0319	76.17	< 0.0001	significant
A-Conc of CCS	0.0131	1	0.0131	31.18	0.0008	
B-Conc of Menthol	0.0794	1	0.0794	189.36	< 0.0001	
B^2	0.0033	1	0.0033	7.97	0.0256	
Residual	0.0029	7	0.0004			
Lack of Fit	0.0029	5	0.0006			
Pure Error	0.0000	2	0.0000			
Cor Total	0.0987	10				

Table 7: Results of ANOVA for predicting percent drug release (Y3)

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	207.19	5	41.44	75.22	0.0001	significant
A-Conc of CCS	123.31	1	123.31	223.82	< 0.0001	
B-Conc of Menthol	37.00	1	37.00	67.16	0.0004	
AB	4.41	1	4.41	8.00	0.0367	
A^2	26.98	1	26.98	48.97	0.0009	
B^2	5.80	1	5.80	10.53	0.0228	
Residual	2.75	5	0.5509			
Lack of Fit	2.75	3	0.9182			
Pure Error	0.0000	2	0.0000			
Cor Total	209.94	10				

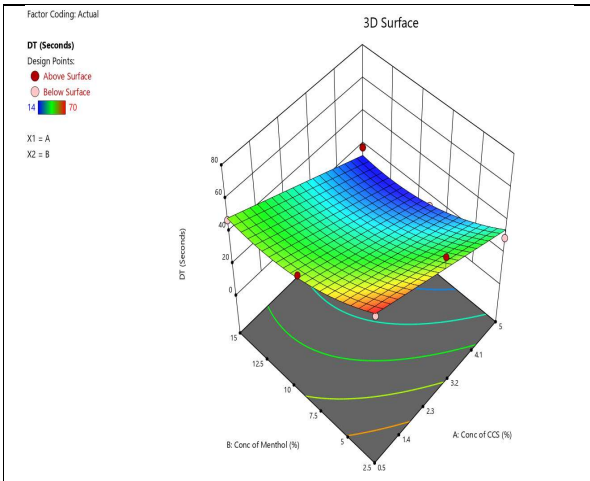

Figure 3

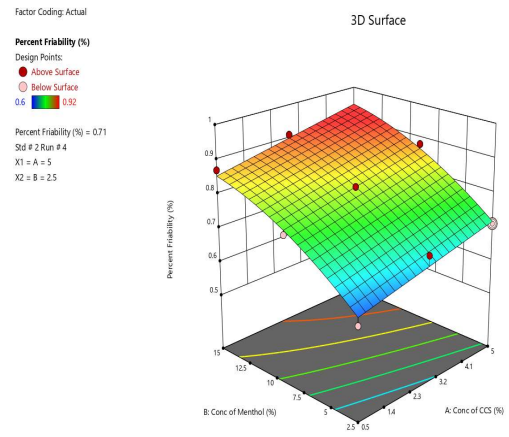

Figure 4

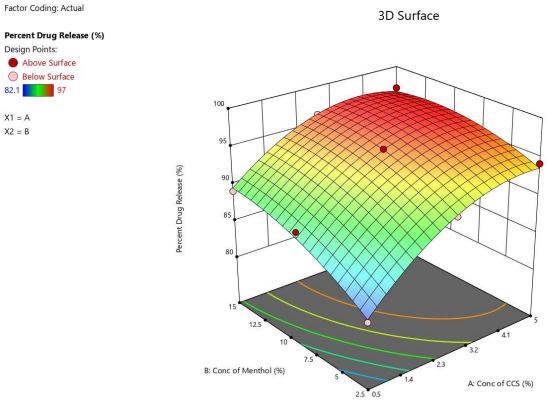

Figure 5

Figure 3: Super disintegrant and sublimating agent in relation to DT in 3D surface response graph.
Figure 4: Super disintegrant and sublimating agent in relation to percent friability in 3D surface response graph.
Figure 5: Super disintegrant and sublimating agent in relation to percent drug release in 3D surface response graph.

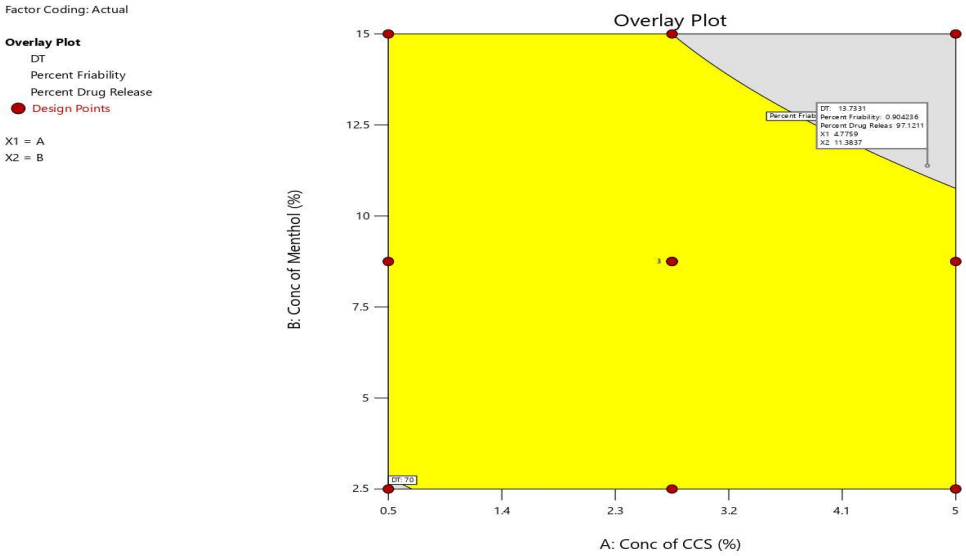

Figure 6: Overlay plot

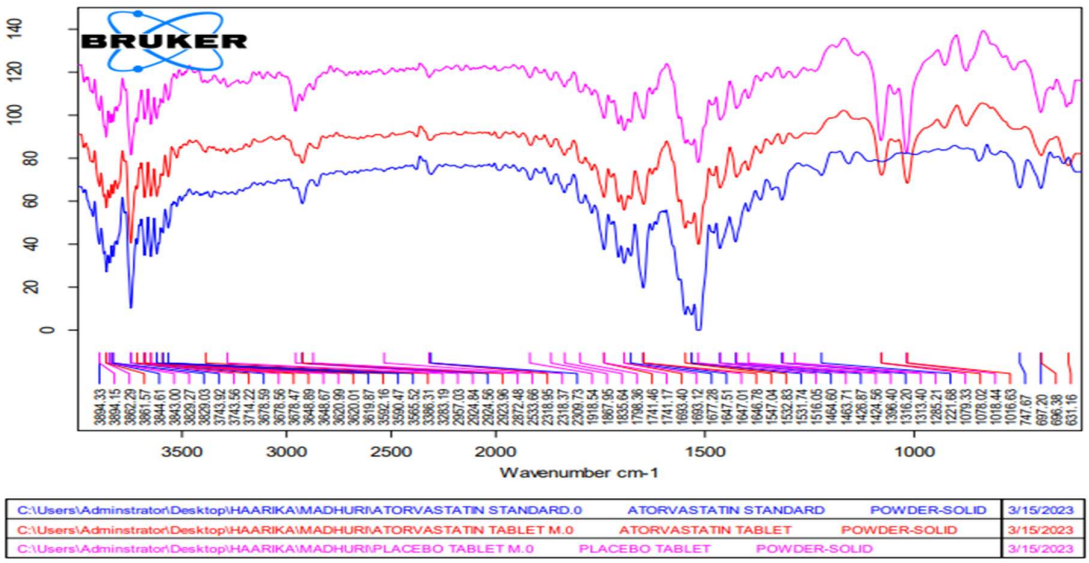

Figure 7: FT-IR spectra of standard atorvastatin calcium, atorvastatin calcium ODT tablet formulation and placebo (tablet)

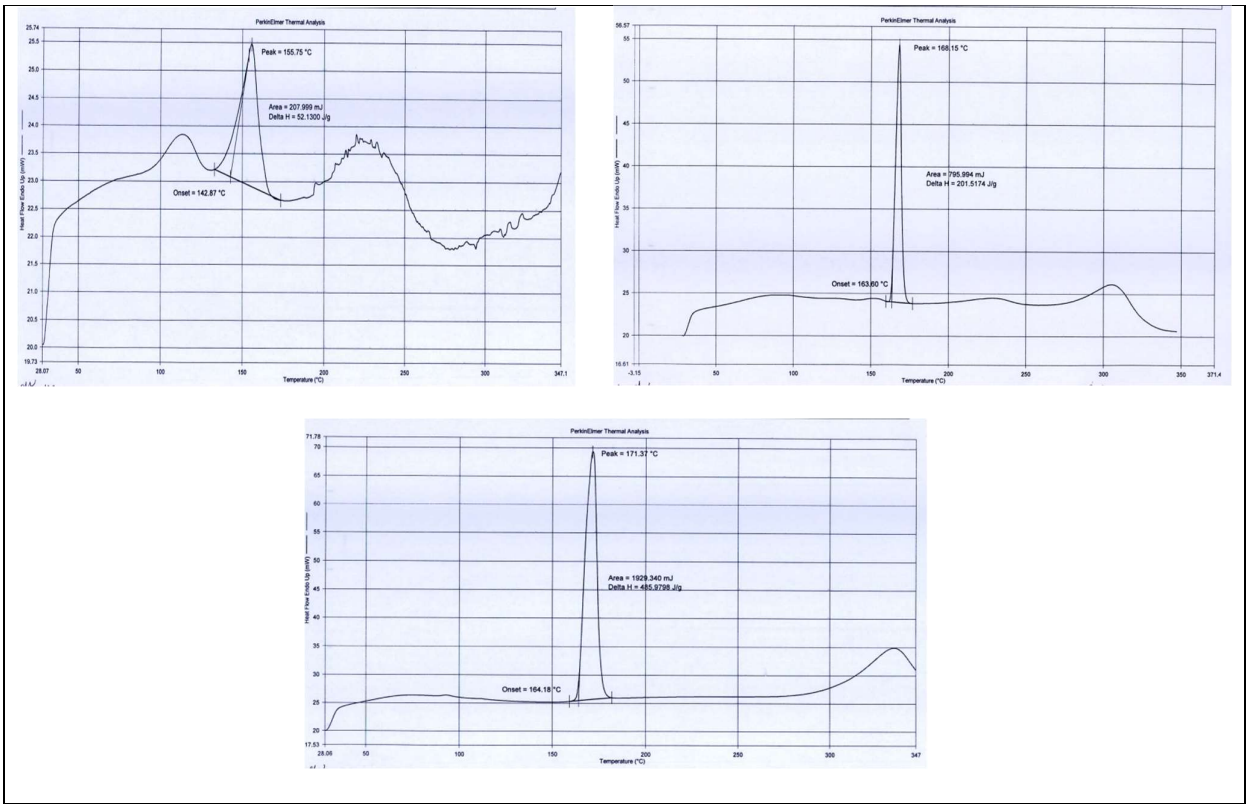

Figure 8: DSC curves of standard atorvastatin calcium, atorvastatin calcium ODT formulation and placebo

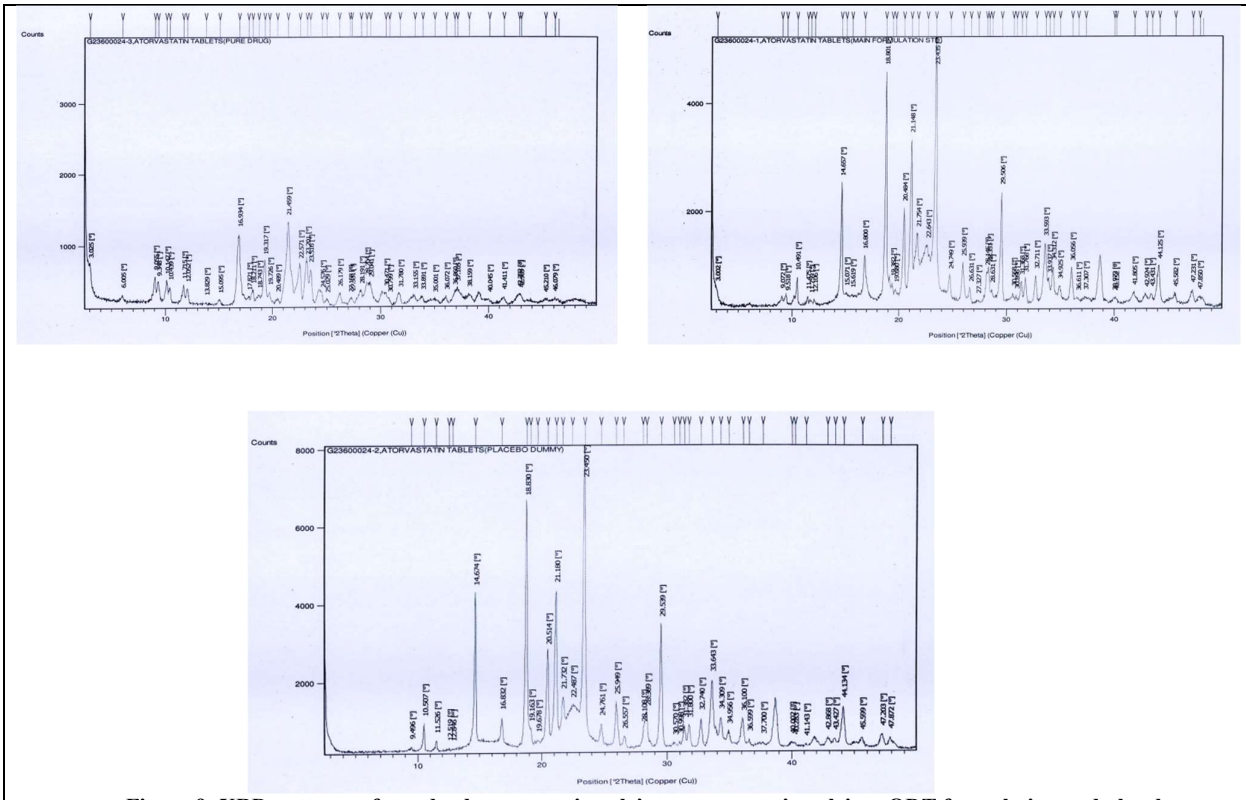

Figure 9: XRD patterns of standard atorvastatin calcium, atorvastatin calcium ODT formulation and placebo

Table 8: Effect of storage of optimized formulation F6 at 40±2°C/ 75±5% RH

Formulation code F3/ day	Disintegration time (sec)	Friability (%)	Percent drug release (%)
1st day	14.60±0.12	0.88±0.14	98.6±0.21
30th day	14.59±0.22	0.89±0.33	98.8±0.32
60th day	14.59±0.15	0.89±0.25	98.6±0.15
90th day	14.60±0.13	0.88±0.21	99.1±0.11

DISCUSSION

Atorvastatin calcium ODTs were prepared by sublimation method using Ac Di Sol as super disintegrant and menthol as sublimating agent. Ac Di Sol shows water wicking and swelling action where liquid is drawn up or wicked into these pathways through capillary action and rupture the inter particulate bonds causing tablet to break apart.in this tablet formulations. SMCC HD 90 consists of MCC and colloidal silicon dioxide was used as a free flowing diluent. Mannitol was used as a diluent because of its sweet taste and imparts a cooling sensation because of its negative heat of solution. Talc and magnesium stearate were used as flow promoters. This factorial design formulation showed good flow properties.

The disintegration time, which is the most important parameter, needs to be optimised in fast dissolving tablets to get the optimised formulation with less disintegration time. As concentration of super disintegration increases DT will decrease. A combination of super disintegrant (Ac Di Sol, 5%) and sublimating agent (menthol, 8.75%) results

in high porosity which leads to decrease in wetting time due to capillary action of super disintegrant, bringing about fast disintegrant. The percent drug release for all nine formulation F1to F9 ranged from 82.1 to 98.6% in 10 min. The formulation F8 showed DT of 14 sec, friability of 0.88% and percent drug release of 98.6% at 10 min interval, hence it was considered as optimised formulation.

the drug with excipients compatibility was confirmed by FTIR, DSC AND PXRD. The FTIR studies reveal that drug with excipient are compatible with each other. The substantial changes in IR absorption bands were not observed in drug in ODT formulation compared with pure drug.

Analysis of variance for disintegration time, percent friability and percent drug release were performed. The coefficients X_1 (Ac Di Sol) and X_2 (menthol) showed significant effect ($P < 0.05$) on selected responses.

The response surface lots for dependent variables disintegration time, percent friability and percent drug release were generated and the effect of independent variables, X1 and X2 was studied.

The effect of formulation variables in disintegration time can be described by model equation, Y1 (dis integration time) = $+33.20-18.17X_1-11.17X_2+8.97X^2$. Negative sign for X1 and X2 indicated that, as concentration of Ac Di Sol and menthol increase, DT decrease (R^2 = 0.9605) indicating good correlation between independent and dependent variables. The term with ($P< 0.01$) was considered significant.

Friability can be described by the model equation, Y2 (friability) = $+0.82+0.0467 X_1+0.1150X_2-0.0350X_1X_2$. Positive sign for X_1 indicates increase in concentration of super disintegrant. Initially as the concentration of menthol increases, friability decreases followed by a slight increase in friability within the acceptable pharmacopeial limits. The effect of independent variables on friability was significant. ($P< 0.01$) was considered significant and indicates good correlation.

The model for percentage drug release was Y3 (% drug release) = $+95.31+4.53X1+2.48X2-1.05X1X2-3.26X_1^2-1.51X_2^2$. Positive sign for X_1 and X_2 indicates as concentration of super disintegrant and menthol increases, percent drug release increases. R^2 value indicated good correlation between independent and dependent variable. ($P< 0.01$) was considered significant

Results from stability studies of F8 formulation at 40±2°C/75±5% RH in stability chamber for 3 month at 30 days' time interval and analysed for disintegration time, percent friability and percent drug release. The optimised F8 formulation was stable and did not show much variation in any of the above parameters.

CONCLUSION

Oro dispersible tablets of atorvastatin calcium were developed to give fast release and better patient compliance. Different formulations of atorvastatin calcium Oro dispersible tablets from F1 to F11 were prepared by sublimation method. In preliminary trials, it was found that, apart from super disintegrant, formulation containing menthol as sublimating agent showed best DT and better drug release. Further optimization of atorvastatin calcium Oro dispersible tablets (F1 to F11) was done by optimizes independent variables such as concentration of independent variables (0.5, 2.75 and 5%) and concentration of sublimating agent (2.5, 8.75 and 15%) as assessing dependent variables disintegration time, percent friability and percent drug release by Central composite design from Response surface methodology. Combination of variables was suggested by software with the desirability function of 1. Optimized formulation (F8) exhibited a DT of 14 sec, percent friability of 0.88% and percent drug release of 98.6%. It was suggested that the generated model would work well for oro dispersible tablets optimization.

ACKNOWLEDGEMENT

We would like to thank the management of Sarojini Naidu Vanita Pharmacy Maha Vidyalaya for providing access to research facilities and QbD Expert Software.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

REFERENCES

[1] Deshpande KB, Ganesh NS. Orodispersible tablets: an overview of formulation and technology. Int J Pharm Bio Sci 2011;2(1):726–34.

[2] Sandhya Mandadi, Vishwanadham Yerragunta, Umema Naaz Tarkash, Formulation and Evaluation of Atorvastatin Calcium Sustained Release Tablets 2016; 6(3): 124-130, ISSN 2249-1848

[3] Kumar S, Ali J, Baboota S. Design Expert (®) supported optimization and predictive analysis of selegiline nanoemulsion via the olfactory region with enhanced behavioural performance in Parkinson's disease. Nanotechnology. 2016;27(43):435101. doi: 10.1088/0957-4484/27/43/435101, PMID 27655136.

[4] Peter CGV, Vijaya RC, Siddharth K, Siva SKM, Hari PR. Formulation, and optimization of coated PLGA–zidovudine nanoparticles using factorial design and in vitro in vivo evaluations to determine brain targeting efficiency. Saudi Pharm J. 2014;22(2):133-40. doi: 10.1016/j.jsps.2013.04.002, PMID 24648825.

[5] Balusu Haarika and Prabhakar Reddy Veerareddy Formulation and Evaluation of Fast Disintegrating Rizatriptan benzoate Sublingual tablets, Malaysian Journal of Pharmaceutical Sciences 2012; . 10, no. 1, 45–60.

[6] Sadi JAl. Designing experiments: 3 level full factorial design and variation of processing parameters methods for polymer colors, advances in science, technology, and engineering systems. 2018;3(5):109-15. doi: 10.25046/aj030515.

[7] S. Darade, P. Patil, and R. Kalkotwar, "Formulation and assessment of orodispersible tablet containing piroxicam by sublimation method," Indian Journal of Pharmacy and Pharmacology, 2017; vol. 4, no. 2, pp. 77–82,.

[8] Patel VN, Gupta MM. Emerging trends in oral dispersible tablet. Journal of Drug Delivery and Therapeutics 2013;3(2):199-206.

[9] Ashok T, Veeravalli SK, Pavan KM, Roshitha B. Effect of effervescence in combination with super disintegrants in the formulation of propranolol HCL oral disintegrating tablets. Asian J Pharm Clin Res 2017; 10:227-34.

[10] Shivangi S, Navneet Verma. Taste masked orodispersible tablets: a highly patient complaint dosage form. Asian J Pharm Clin Res 2016; 9:385-91.

[11] Biswajit Basu *et al*. Formulation and evaluation of fast dissolving tablets of cinnarizine using superdisintegrant blends and subliming material, Journal of Advanced Pharmaceutical Technology & Research 2011 Oct; 2(4):266-73.

[12] Nabeela Shaheen, Shahiq uz Zaman, Development of fast dissolving tablets of flurbiprofen by sublimation method and it's in vitro evaluation. Brazilian Journal of Pharmaceutical Sciences 2018;54(4): e17061.

[13] Kadria AE, Hassan MA, Afifi SA. Formulation and optimization of orodispersible tablets of flutamide. Saudi Pharm J 2014; 22:53-61.

[14] Shinkar DM, Dhake AS, Setty CM. Development of UV spectrophotometric method for estimation of carvedilol in bulk and pharmaceutical formulations. Asian J Res Chem 2013; 6:956-9.

[15] Balusu Haarika and Prabhakar Reddy Veerareddy Formulation and Evaluation of Fast Disintegrating Rizatriptan benzoate Sublingual tablets, Malaysian Journal of Pharmaceutical Sciences 2012; vol. 10, no. 1, 45–60.