

Research Article

Formulation and Characterization of Gastroretentive Floating Tablets of Atorvastatin Calcium using Central Composite Design

Beena Kumari, Parijat Pandey, Harish Dureja*

Department of Pharmaceutical Sciences, Maharshi Dayanand University, Rohtak, India – 124001



DOI:10.18579/jprkc/2017/16/3/118782

Received on: 06/07/2017

Revised on: 12/09/2017

Accepted on: 21/09/2017

Corresponding author:

Prof. Harish Dureja

Department of Pharmaceutical Sciences
Maharshi Dayanand University
Rohtak, 124001, India
harishdureja@gmail.com

ABSTRACT

The aim of the study was to develop a gastroretentive floating drug delivery system of atorvastatin calcium by effervescence technique.

Design/methodology/approach: The objective behind the study was to investigate the effect of concentration of HPMC K4M (X_1), concentration of guar gum (X_2), concentration of sodium bicarbonate (X_3) on the release of atorvastatin calcium using central composite design. The floating tablets were formulated using atorvastatin calcium (20% w/w), HPMC K4M (5-15% w/w), guar gum (5-15% w/w), sodium bicarbonate (4-12% w/w), lactose (q.s.), talc (2% w/w) and magnesium stearate (1% w/w). Atorvastatin calcium floating tablets were evaluated for physical characterization viz. hardness, swelling index, floating capacity, weight variation, friability, *in vitro* drug release and kinetic studies.

Findings: All tablets were floated for more than 12 hrs in 0.1 N HCl at $37 \pm 0.5^\circ\text{C}$ and the *in vitro* drug release was found to be vary from 79% to 93%. The percentage cumulative drug released was maximum at low value of HPMC, low value of guar gum and high value of sodium bicarbonate. A mathematical model was developed to formulate floating tablets of atorvastatin calcium. The data fitting to Korsmeyer-Peppas equation revealed that the release mechanism from the dosage form followed the non-fickian transport.

Value: The gastroretentive floating tablets of atorvastatin calcium will enhance the patient compliance and play a vital role in improving patient's quality of life.

Keywords: Atorvastatin calcium, central composite design, *in vitro* drug release, floating tablets.

INTRODUCTION

Gastro retentive drug delivery system (GRDDS) is novel site-specific drug delivery for promoting retention with in the stomach, duodenum or small intestine can prolong drug released to controlled manner. The oral administration approaches to achieve prolong release of drug is the use of gastro-retentive systems. The idea is to prolong the residence time of the drug delivery in the stomach known as gastric residence time (GRT)¹.

In floating drug delivery system (FDDS), the bulk density of these systems is more than the gastric fluids and therefore, without affecting gastric emptying rate they remain buoyant in the stomach for a long-time period. When the system is floating on the gastric fluid; the drug releases slowly. The residual system is emptied from the stomach when drug is released. This results in an increased gastric residence time and a good control of the rise and fall in plasma drug concentration².

Effervescent floating drug delivery systems are the matrix type systems formulated with the help of swellable polymers such as polysaccharides or

hydroxyl propyl methyl-cellulose and chitosan with various effervescent components like sodium bicarbonate, tartaric acid, calcium carbonate and citric acid. These dosage forms are formed such that, when they interact with gastric juice in the stomach, carbon dioxide liberated and trapped in the swollen hydrocolloids. This provides buoyancy to the dosage form. These buoyant delivery systems are prepared with swellable polymers^{3,4}.

Atorvastatin calcium lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and by increasing the number of hepatic LDL receptors on the cell-surface to enhance uptake and catabolism of LDL; atorvastatin also reduces LDL production and the number of LDL particles. HPMC K4M which is a stable material and soluble in cold water, forming a viscous colloidal solution; practically insoluble in chloroform, ethanol (95%) and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloro-methane, and mixtures of water and alcohol. In the present case of floating tablets HPMC K4M helps to control the drug release from the tablet⁴.

The aim of the work is to develop a gastroretentive floating drug delivery system of atorvastatin calcium by effervescence technique. The objective behind the study was to analyze the effect of -concentration of HPMC K4 (X_1), concentration of guar gum (X_2), concentration of sodium bicarbonate (X_3) on the release of atorvastatin calcium using central composite design.

MATERIALS AND METHODS

Materials

Atorvastatin calcium was obtained as a gift sample from Synmedic Laboratories, India. HPMC K4M was supplied by Brown laboratories Ltd., Faridabad as a gift sample. Guar gum, sodium bicarbonate, potassium dihydrogen phosphate and disodium hydrogen phosphate were purchased from Loba Chemie, Mumbai, India. All other ingredients used for HPLC method were of HPLC grade and used as received.

Methods

Preparation of granules of atorvastatin calcium floating tablets

In this method, atorvastatin calcium (20%), HPMC K4M (5-15%) and sodium bicarbonate (4-12%), and lactose were mixed by using binder solution of guar gum (5-15%) in slightly warm water and mixed with above powder mixture to form wet mass screens. Coarse screening of wet mass was done by using a suitable sieve # 12. Granules were dried at 45°C for 1 h and passed through sieve # 20 and then pre-compression studies were carried out. The average total weight of each tablet was 200mg.

Optimization of floating atorvastatin calcium tablets using central composite design

Batches of atorvastatin calcium floating tablets were formulated according to the central composite design to study the effect of independent variables on percentage cumulative drug release. In the present study, three factors (n) were evaluated at the two levels (k) and accordingly, the central composite design consisted of full factorial design (1F-8F), 6(2n) batches on axial points (1S-6S) and 6 replicates at centre points (1C-6C) and the selected independent variables. The factors selected were X_1 = concentration of HPMC K4M (%w/w); X_2 = concentration of guar gum (%w/w); X_3 = concentration of sodium bicarbonate (%w/w). The twenty batches (F1-F20) of atorvastatin calcium floating tablets were prepared as per CCD are enlisted in Table 1.

Preparation of atorvastatin calcium floating tablets

Tablets were prepared by wet granulation technique. The dried granules were passed through a number 60 sieve and then mixed with talc (2%) and magnesium stearate (1%) as per the composition of each tablet having total weight of 200 mg/tablet. Finally, the exact amount of each mixture was weighed (200 mg) and fed manually into the die of a single punch tablet machine with a round concave 8 mm punch and compressed. The formulated tablets were preceded for further evaluation⁵. The composition of atorvastatin calcium floating tablet is enlisted in Table2.

Table 1: Formulation of FDDS using central composite design

Batch No.	X ₁ (HPMC K4M) (%w/w)	X ₂ (Guar gum) (%w/w)	X ₃ (Sodium bicarbonate) (%w/w)
F1	-1 (5)	-1 (5)	-1 (4)
F2	-1 (5)	-1 (5)	+1 (12)
F3	-1 (5)	+1 (15)	-1 (4)
F4	-1 (5)	+1 (15)	+1 (12)
F5	+1 (15)	-1 (5)	-1 (4)
F6	+1 (15)	-1 (5)	+1 (12)
F7	+1 (15)	+1 (15)	-1 (4)
F8	+1 (15)	+1 (15)	+1 (12)
F9	-1.682 (1.59)	0 (10)	0 (8)
F10	+1.682 (18.41)	0 (10)	0 (8)
F11	0 (10)	-1.682 (1.59)	0 (8)
F12	0 (10)	+1.682 (18.41)	0 (8)
F13	0 (10)	0 (10)	-1.682 (1.272)
F14	0 (10)	0 (10)	-1.682 (14.728)
F15	0 (10)	0 (10)	0 (8)
F16	0 (10)	0 (10)	0 (8)
F17	0 (10)	0 (10)	0 (8)
F18	0 (10)	0 (10)	0 (8)
F19	0 (10)	0 (10)	0 (8)
F20	0 (10)	0 (10)	0 (8)

Table 2: Composition of tablet

Ingredients	Amount (%)
Atorvastatin calcium	20
HPMC K4M	5-15
Guar gum	5-15
Sodium bicarbonate	4-12
Lactose	q.s.
Talc	2
Magnesium stearate	1

Characterization of atorvastatin calcium floating tablets

Pre-compression studies⁵

The pre-compression studies were carried out to

check the flow properties of granules includes angle of repose, bulk density and tapped density, compressibility index and Hausner's ratio.

Angle of repose

This is the angle between the horizontal plane and surface of a pile of granules. It was determined by using the funnel method. The perfectly weighed granule blend is being taken in the funnel. The altitude of the funnel adjusted to the maximum cone height (h) and granules blend was poured through the funnel freely on to the surface. Then the radius of the heap (r) was measured and angle of repose was calculated. The diameter of the granule cone will be measured and then the angle of repose.

$$\tan \theta = \frac{h}{r} \text{ eq}^n(1)$$

Bulk density (BD) and Tapped density (TD)

2 g of granules blend was introduced to a measuring cylinder of 100 ml. The cylinder was tapped 100 times and the tapped volume of packing was recorded. BD and TB are calculated using the following formulae:

$$BD = \frac{\text{weight of the granule blend}}{\text{Untapped volume of the granules}} \text{ eq}^n(2)$$

$$TD = \frac{\text{weight of the granule blend}}{\text{Tapped volume of the granules}} \text{ eq}^n(2)$$

Compressibility index

It was calculated by using the Carr's compressibility index as given in equation 4.

$$\text{Carr's Index} = \frac{(TD - BD) \times 100}{TD} \text{ eq}^n(4)$$

Where, TD is tapped density and BD is bulk density.

Hausner's ratio

It is an index of ease of powder flow; calculated using the following formula:

$$\text{Hausner's Ratio} = \frac{TD}{BD} \text{ eq}^n(5)$$

Where, TD is tapped density and BD is bulk density.

Differential scanning calorimetry (DSC)

DSC measurements were carried out on DSC Q10 (Waters Corporation, USA). The instrument was calibrated using indium as standard. Samples were placed in sealed aluminium pans and heated from 30°C to 300°C at a rate of 10°C/min under nitrogen atmosphere (60ml/min), with empty pan as reference.

Fourier transform infrared (FTIR) spectroscopy

It was used to predict any incompatibility or any interaction between the different ingredients in a formulation. FTIR spectra were recorded using Alpha-Bruker, FTIR Spectrophotometer, Bruker, Germany. Firstly, the background was scanned and then crystal window was closed. Samples were finely ground with infra-red grade KBr then pressed into pellet and IR spectra were taken in transmission over the range of 4000-500 cm^{-1} at ambient temperature. The sample was pressed and scanned. In the spectra, that was appeared on the screen, the baseline was corrected. The drug was identified by infrared spectroscopy and characteristic peak obtained compared with standard spectra of pure drug reported in official monograph.

Weight variation

Twenty tablets from each batch were selected randomly and their average weight was calculated. Then individual weight of each tablet was determined using digital electronic balance and was compared with average weight.

Friability

Using a Roche friabilator, friability of the tablets was determined. Ten pre-weighed tablets were placed in the friabilator and run the friabilator at 25 rpm for 4min. The tablets were taken out, de-dusted and reweighed. It was measured using the following formula:

$$\% \text{Friability} = \frac{(\text{Initial weight} - \text{Final weight}) \times 100}{\text{Initial weight}} \text{ eq}^n (6)$$

Hardness

Using a Monsanto type tester, crushing strength of tablets was measured. Twenty tablets were selected randomly and average force which is used for crushing them was recorded.

Floating Lag Time

It is determined in order to assess the time taken by the dosage form to float on the top of the dissolution medium, after it is placed in the medium⁶.

Total Floating Time

The time for which the dosage form continuously floats on the dissolution media is termed as floating time. All the formulations constantly floated on dissolution medium for more than 12 h, while the floating lag time varied from 5 to 30 seconds⁶.

Swelling index

The swelling properties of tablets were determined. The weighed tablets (w_1) were placed at $37 \pm 0.5^\circ\text{C}$ in the basket of dissolution apparatus in 900 ml of 0.1 N HCl. Periodically tablets were removed and the swollen weight (w_2) was measured after removing free water⁷. Swelling Index (S.I.) was determined using the following formula:

$$\text{S.I.} = \frac{(W_2 - W_1) \times 100}{W_1} \text{ eq}^n (7)$$

Where, w_1 = weight of tablet before swelling, w_2 = final weight of tablet after swelling.

In-vitro release of drug and kinetics of drug release

In vitro dissolution study of atorvastatin calcium tablets was carried out in USP Dissolution apparatus type II in 900 ml 0.1 N HCl (pH 1.2), temperature maintained at $37 \pm 0.5^\circ\text{C}$ with a speed of 75 rpm. Samples of 10 ml were withdrawn from the dissolution apparatus at pre-determined intervals i.e. 10 min, 20 min, 40 min, 1 hr, 2 hr, 4 hr, 6 hr and 12 hr and analyzed using HPLC instrument at 246 nm⁵. For the release data analysis, cumulative percent drug release versus time (zero order kinetics), the log cumulative percent drug remaining versus time (first order kinetics), cumulative percent drug release versus

thesquare root of time (Higuchi kinetics), and log cumulative percent drug release versus log time (Korsmeyer-Peppas kinetics) was plotted.

Statistical analysis of the data and validation of the model

Response surface modellingand evaluation of the quality of fit of the model for the current study were performed employing Design Expert® software (Version 8.0.7.1, StatEase Inc., Minneapolis, MN). The models were generated for all the response variables using multiple linear regression analysis. 3D response plots were constructed using Design Expert software⁸.

RESULTS & DISCUSSION

Physical characterization of powder blend

The powder blend was evaluated for flow properties. Bulk density of powder blend was found between 0.515 to 0.580 g/cm³, and tapped density ranged between 0.517 to 0.651 g/cm³. Carr's index was found to be in the range of 5.21 to 14.73, indicating good flow. Hausner's ratio values for all the formulations were found to be about 1.1, indicating low interparticle friction. Angle of repose was found to be in the range of 20.07 to 26.80. The values of angle of repose were less than 30, indicating good flowability. These values indicate the prepared blend exhibited good flow properties.

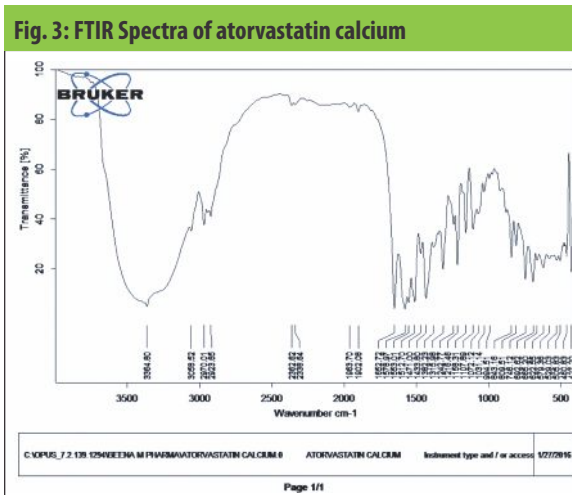
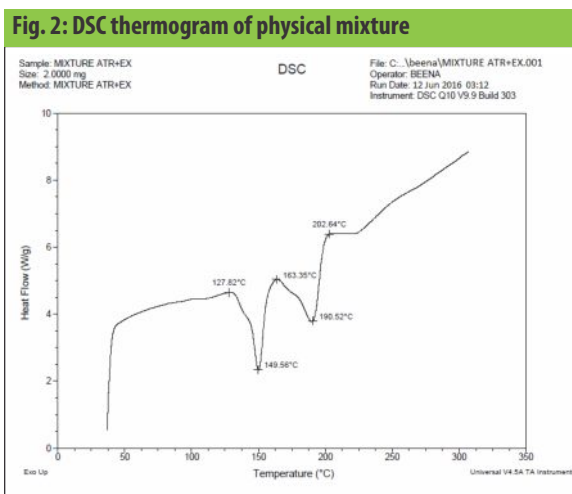
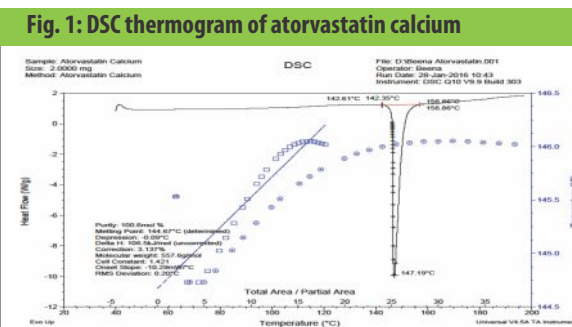
Differential scanning calorimetry (DSC)

The drug was confirmed by DSC analysis and there was a sharp peak at 144.67°C corresponding to its melting point as shown in Figure 1. The absence of interaction between physical mixtures was further confirmed by DSC analysis and there were two sharp peaks at 147.56°C and 175.52°C, which are corresponding to melting of drug and polymer, represented that there was no interaction between the excipients as shown in Figure 2.

Fourier transform infrared (FTIR) spectroscopy

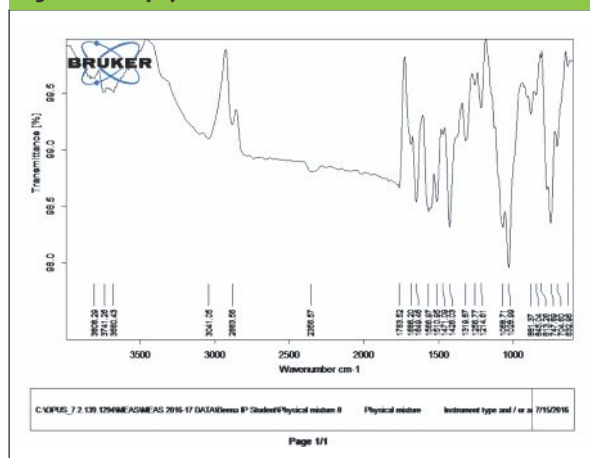
The IR spectra of atorvastatin calcium showed characteristics peaks at 1652 cm⁻¹ due to C=O stretching, at 3364.90 cm⁻¹ due to O-H stretching, 1316.56 due to C-O stretching, 3058.43 due to N-H

stretching, 1217.08 due to C-N stretching, 1435.82 due to C-F stretching and at 692.62 due to aromatic out-of-plane bend. The FTIR spectrum of drug is shown in Figure 3.



The existence of interaction between components was investigated by FTIR studies. FTIR spectra of pure atorvastatin calcium and physical mixture containing HPMC K4M, guar gum, sodium bicarbonate, lactose, talc and magnesium stearate are shown in Figure 4.

Fig. 4: FTIR of physical mixture



The FTIR spectrum of physical mixture shows characteristic absorption bands at 1028, 1068, 1619, 1689, 1763 and 3011 cm^{-1} . In the FTIR spectra of physical mixture of drug with polymers, there is no shift(s) in the peaks, indicating there is no significant interaction between drug and polymers occur.

Evaluation of floating tablets

Weight variation, friability and hardness

Weight variation was found in the range 192.97–206.66 mg which lies within the limits as per IP. Hardness of the prepared tablets ranged between 2.9 to 4.4 kg/cm^2 . Friability was found to be less than 0.51 – 0.69% which is less than 1% or is in the acceptable limit. The results of weight variation, friability and hardness are shown in Table 3.

Floating behavior

All the formulations consistently floated for more than 12 h, while the floating lag time varied from 20 to 145 seconds. Tablet batches with high polymer content have large lag time (> 100 secs) compared with the

batches having medium polymer content (30 to 50 secs). The results of floating behaviour are tabulated in Table 3.

Swelling Index

Tablets composed of polymeric matrices build a gel layer around the tablet core upon coming in contact with water. This gel layer governs and affects the drug release. To obtain floating, the balance between swelling and water acceptance must be restored^{9, 10}. Combination of HPMC K4M and guar gum resulted in a higher swelling index varying from 96% to 99% (Table 3).

In vitro drug release

The percentage cumulative drug release of all batches of floating tablets (F1–F20) was determined for 12 h (using *Dissolution Data Solver* software) and were found to vary from $79.02 \pm 2.32\%$ to $92.54 \pm 1.21\%$. Batch F3 shows lowest %CDR ($79.02 \pm 2.32\%$), whereas batch F7 shows highest %CDR ($92.54 \pm 1.21\%$). The data of *in vitro* release profiles of all the batches (F1–F20) are shown in Table 3 and *in vitro* release profile of all batches (F1 – F20) are shown in Figure 5.

ANOVA on percentage cumulative drug release from various formulations

HPMC K4M decreases the drug release in formulation with increase in concentration while sodium bicarbonate increases drug release in formulation with increase in concentration. % CDR increases with the increase in concentration of sodium bicarbonate (X_3) while it increases with a decrease in amount of polymer HPMC K4M. The drug release is lowest when the binder (guar gum) concentration is maximum, while it is highest when the concentration of guar gum and HPMC K4M is lower and sodium bicarbonate is high due to their synergistic effect. The effect plot of coefficient of % cumulative drug release is shown in Figure 6.

The percent release was maximum at a low value of HPMC, low level of guar gum and high level of sodium bicarbonate. The %CDR increases with increase in amount of sodium bicarbonate to ensure complete effervescence of the tablets. On the basis of percent

Figure 5: *In vitro* release profile of floating tablets (F1-F20)

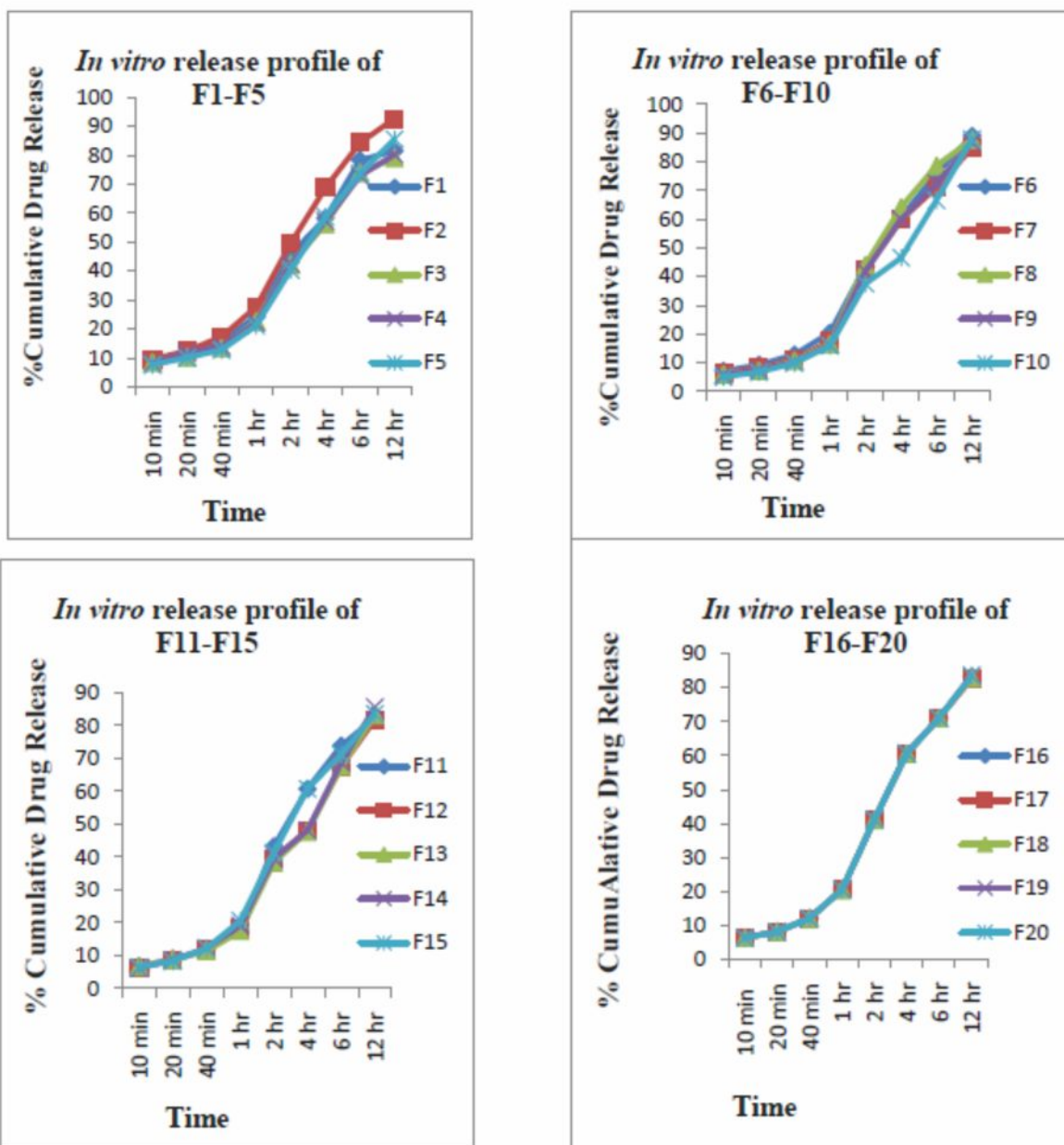
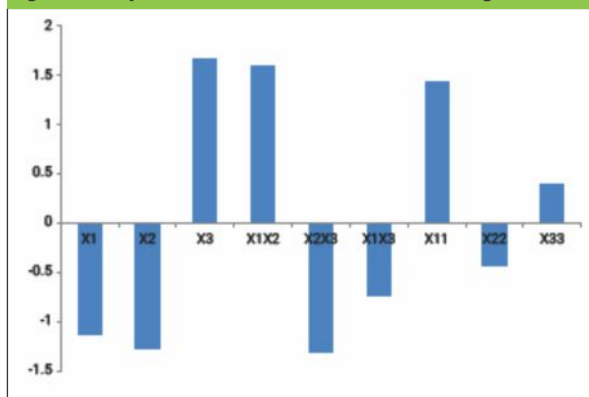


Fig. 6: Effect plot of coefficient of % cumulative drug release


cumulative drug release (%CDR) and all the evaluation parameters, batch F2 was selected as the optimized batch due to $92.54 \pm 1.21\%$ cumulative drug release. ANOVA was applied on %CDR to study the fitting and significance of model. The model developed from

Table 4: ANOVA of the Regression (%CDR)

	Degree of freedom	Sum of squares	Mean square	F	F-significance
Regression	9	152.80	16.98	4.39	0.0151*
Residual	10	38.66	3.87	-	-
Total	19	191.46		-	-

multiple linear regression to estimate effect (Y) can be presented mathematically as:

$$Y = 83.44 - 1.14 X_1 - 1.28 X_2 + 1.66 X_3 + 1.60 X_1 X_2 - 0.73 X_1 X_3 - 1.31 X_2 X_3 + 1.44 X_1^2 - 0.44 X_2^2 - 0.40 X_3^2$$

Where, Y is % CDR, X_1 is concentration of HPMC K4M, X_2 is concentration of guar gum and X_3 is concentration of sodium bicarbonate.

ANOVA was applied using on the % cumulative drug

Table 3: Physical characterization, floating behaviour, swelling index and cumulative percent release of batches (F1 – F20)

Batch No.	Weight Variation (mg)	Friability (%)	Hardness (kg/cm ²)	Floating Lag Time (secs)	Total Floating Time (hr)	Swelling Index (%)	% Cumulative drug release
F1	197.773.75	0.530.06	4.40.02	300.5	> 12	98.460.46	81.422.13
F2	201.42	0.580.08	3.60.08	100.3	> 12	98.410.41	92.541.21
F3	192.97	0.620.04	3.60.04	150.6	> 13	98.270.27	79.022.32
F4	206.66	0.580.06	4.20.06	050.9	> 12	98.190.19	80.212.11
F5	199.78	0.540.07	3.50.07	120.3	> 12	96.710.71	85.411.57
F6	203.37	0.560.05	4.30.06	150.4	> 12	96.450.45	88.922.61
F7	196.927.37	0.510.04	4.20.05	180.3	> 13	97.810.81	84.721.32
F8	207.35	0.530.02	4.00.09	160.3	> 12	97.040.54	87.671.23
F9	200.56	0.540.06	3.70.07	100.8	> 12	97.620.62	86.671.87
F10	203.12	0.690.07	2.90.04	200.4	> 12	97.350.35	87.922.31
F11	202.64	0.620.04	3.50.05	230.5	> 12	98.230.43	82.232.88
F12	199.19	0.560.08	3.00.02	240.7	> 14	97.480.51	81.711.76
F13	197.45	0.610.05	3.90.03	100.6	> 13	96.690.72	83.212.08
F14	198.80	0.540.04	3.70.04	210.3	> 12	96.200.68	85.521.98
F15	200.54	0.580.06	3.90.04	250.4	> 12	96.990.53	83.452.31
F16	201.44	0.590.03	3.80.06	260.4	> 14	98.410.33	83.252.12
F17	200.14	0.560.03	3.60.02	250.7	> 13	97.670.45	82.592.33
F18	199.54	0.570.07	3.90.07	260.4	>12	97.650.41	82.952.42
F19	203.54	0.550.04	3.40.06	250.5	>12	97.660.39	83.582.45
F20	201.54	0.570.05	3.50.05	260.4	>12	97.670.29	83.442.61

Fig. 7: Three-dimensional surface of % cumulative drug release as a function of formulation variables.

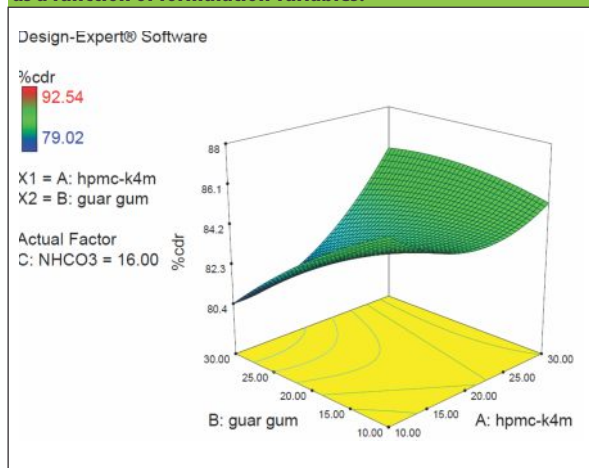
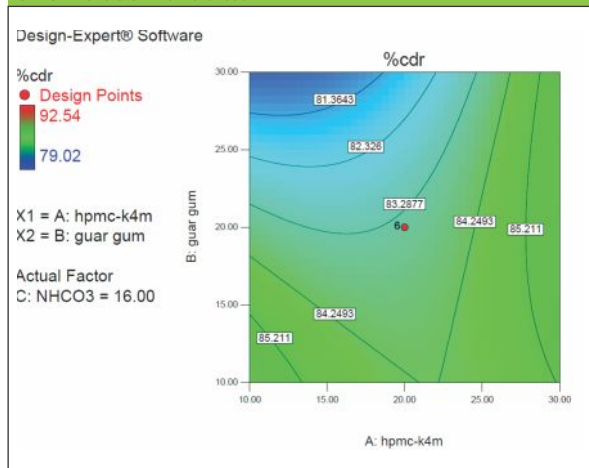


Fig. 8: Contour plot of % cumulative drug release as a function of formulation variables.



release to study the fitting and significations of model in Table 4. F-test was carried out to compare the regression mean square with the residual mean square. The ratio $F = 4.39$ shows regression to be significant. The estimated model, therefore, may be used as response surface for the %CDR as shown by three-dimensional surface model graph and contour plots employing *Design Expert* software (Version 8.0.7.1, Stat-Ease Inc., Minneapolis, MN). The developed model can further be utilized to determine the desired %CDR. Figures 7 and Figure 8 display the 3D surface and contour plot of cumulative percent of

drug release as a function of formulation variables. The result showed that the *in vitro* drug release was found to be varying from 79% to 93%. The percent release was maximum at low value of HPMC K4M, low value of guar gum and high value of sodium bicarbonate.

Drug release kinetic studies

The release profile of the optimized batch F2, fitted best to the Korsmeyer Peppas model (0.9695). Thus, it may be concluded that drug release from gastroretentive atorvastatin calcium tablets is best explained by the Korsmeyer Peppas model. In Korsmeyer Peppas model if the value of n (slope) = 0.5 indicates a Fickian diffusion mechanism, for $0.5 < n < 1.0$, indicates anomalous (non-Fickian) and $n=1$ implies class 2 transport. In the present study, as per the Korsmeyer Peppas model the value of n (slope) was calculated 0.596, which is a characteristic of non-Fickian drug diffusion mechanism.

CONCLUSION

Atorvastatin calcium floating tablets were successfully prepared using central composite design. The combination of sodium bicarbonate (12%) and guar gum (5%) with HPMC K4M(5%) was found to achieve optimum *in vitro* release. *In vitro* release data were fitted to various kinetic models and drug release predominantly follows non-Fickian diffusion mechanism. Hence it is concluded that an effervescent floating based system of Atorvastatin calcium could be promising gastroretentive drug delivery system with sustained release characteristics.

REFERENCES

1. Chuch H, Zia H, Rhodes C. Development of oral drug delivery system using floating microspheres. *Drug Development and Industrial Pharmacy*. 1995; 2(1): 1725-35.
2. Bansal AK, Chawla G, Gupta P, Koradia V. Gastroretention: A means to address regional variability in intestinal absorption. *Pharmaceutical Technology*. 2003;2(1):50-68.
3. Sharma N, Agarwal D, Gupta MK, Khinchi M. A comprehensive review on floating drug delivery system. *International Journal of Research and Pharmaceutical Biomedical Sciences*. 2011;2(2):428-41.
4. Kumar M, Pandey P, Dureja H. Box-Behnken designed gastroretentive floating tablets of famotidine. *Drug Development and Delivery*. 2015;15(3):62-7.

5. Elmowafy EM, Awad GA, Mansour S, El-Shamy AE. Release mechanisms behind polysaccharides-based famotidine controlled release matrix tablets. *AAPS PharmSciTech*. 2008;9(4): 1230-9.
6. Baumgartner S, Kristle J, Vrečer F, Vodopivec P, Zorko B. Optimization of floating matrix tablets and evaluation of their gastric residence time. *International Journal of Pharmaceutics*. 2000; 195:125-35.
7. Srivastava AK, Wadhwa S, Ridhurkar D, Mishra B. Oral sustained delivery of atenolol from floating matrix tablets - formulation and in vitro evaluation. *Drug Development and Industrial Pharmacy*. 2005; 31: 367-74.
8. Shahiwala A. Statistical optimization of Ranitidine HCl floating pulsatile delivery system for chromotherapy of nocturnal acid breakthrough. *European Journal of Pharmaceutical Sciences*. 2009; 37: 363-9.
9. Timmermans J, Moes AJ. How well do floating dosage forms float? *International Journal of Pharmaceutics*. 1990; 62: 207-11.
10. Chordiya M, Gangurde H, Borkar V. Technologies, optimization and analytical parameters in gastroretentive drug delivery systems. *Current Sciences*. 2017; 112(5): 946-53.