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Development of Carbomer Based Controlled Release Matrix Tablet of Atorvastatin and Evaluation of their Buoyancy and Release Pattern

Md. Abdullah Al masum[1], Florida Sharmin[2], Md. Mofazzal Hossain[2], Tasnim Sharmin[2], Rezaur Bin Islam[2]

1.Research and Development Formulation Department, Incepta Pharmaceuticals Ltd, Savar, Dhaka, Bangladesh.

2. Department of Pharmacy, University of Asia Pacific, Dhammondi-1209, Dhaka, Bangladesh

ABSTRACT

Atorvastatin Tablet is one of the best selling drugs in the world, but still it suffers inadequate bioavailability problem from oral dosage. An attempt was taken to evaluate the floating drug delivery system for Atorvastatin by incorporating it in different grades of Carbomer matrix. Direct compression technique was selected and different once daily formulations were designed. The tablets were successfully floated over prolonged time and released the drug at a controlled fashion depending on the grade and quantity of Carbomer used. The tablets were evaluated for different physical tests including weight variation, friability, hardness, diameter and thickness. The compatibility between drug and polymers were confirmed by FT-IR spectra. Buoyancy characteristics of the tablets were determined by observing lag time, swelling index and total buoyancy period. The mechanism of drug release from the matrixes was assumed by fitting the release profile with different mathematical equations. Formulation F-5 and F-10 were found to release the drug at most sustaining manner and also had the longest total floating time.

Keywords: Gastro-retentive, buoyancy, compatibility, swelling index and kinetics.

*Corresponding Author Email: almasum@inceptapharma.com

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INTRODUCTION

Atorvastatin belongs to statin group which similarly to others competitively inhibit HMG CoA reductase enzyme involved in hepatic cholesterol synthesis. This inhibition of biosynthesis causes increase in LDL uptake by the hepatocytes and a resulting decrease in plasma cholesterol level. Atorvastatin is also responsible for reduction in blood triglyceride level. It is the drug of choice in moderate to severe familial or non-familial hypercholesterolemia[1]. It is also prescribed as secondary preventive drug in people with coronary heart disease and multiple risk factors for myocardial infarction, stroke and unstable angina[2]. It has got maximum rate of absorption in the upper GI tract[1], still the absolute bioavailability of Atorvastatin is 12% after a 40 mg oral dose[3]. These limitations left opportunities to improve its oral absorption and oral bioavailability.

The best way to improve the absorption of a drug from oral route is to release the active moiety into its favorable absorption area. For highest absorption rate of Atorvastatin in upper GIT, its extent of absorption will be improved if it can be confined into gastric region. Among various ways to achieve prolong gastric residence time, floating drug delivery has been proven its efficacy over time. Researchers from around the globe are conducting experiments to find out suitability, application and advantages of floating dosage forms for newly developed drugs. Statins are suitable candidate for gastroretentive drug delivery systems for their efficacy and advanced pharmacological aspects. Hussain *et al*., 2012[4] reported formulation of floating tablet of Simvastatin, Kulkarni and Bhatia, 2009[5] stated benefits of gastric regioselective drug delivery of lovastatin and Arunkumar *et al*., 2008[6] described formulation of Atorvastatin gastroretentive tablets.

Previously Atorvastatin was studied by incorporating into microcapsules[1], self-emulsifying drug delivery system (SEDDS)[7], in combination of other cardiovascular drug[8] and floating tablet dosage forms to improve its release profiles with two hydrophilic cellulose derivatives[9]. This study was planned to formulate a gastro-confined once daily Atorvastatin sustained release tablet with effervescent system containing Carbomer polymers. These Carbomer polymers are linked monomers of acrylic acid cross-linked with polyalkenyl ethers or divinyl glycol. Carbomers have been used as bioadhesive carriers, binder, emulsifying agents and release retarding agents depending on their grades and degree of cross linking between monomers. In this experiment, Carbomer 971P and Carbomer 940 were used as rate retarding agent. Citric acid and sodium bicarbonate were incorporated as gas generating agents for effervescent system. The gastro retentive tablets were undertaken to several buoyancy determining tests, compatibility

investigation and *in vitro* release study.

MATERIALS AND METHODS

Materials

Atorvastain Calcium Trihydrate manufactured by Ind-swift Laboratories Ltd, India was purchased. Carbomer 971P and Carbomer 940 were manufactured by Lubrizol Advanced Materials, Inc and collected as generous gift sample from Incepta Pharmaceuticals Ltd, Bangladesh. All other ingredients were of analytical grade and collected from local market.

Preparation of floating tablets of Atorvastatin

Effective ratio of gas generating agents for floating tablet of Atorvastatin was determined by several trials. Direct compression technique was selected for the tablets using several trials incorporating varying ratio of rate retarding polymers (Table 1). Each of the ingredients was weighed carefully by Shimadzu AY-200 electronic balance and uniformly mixed in a mortar and pestle set. Ingredients for a single tablet was weighed individually and compressed by using a single punch tablet compression machine. Die and punch surface were lubricated before and after compression each time. Tablets of each batch were stored in airtight glass contained in a desiccator. 86.7 mg of Atorvastatin Calcium Trihydrate was considered equivalent to 80 mg of Atorvastatin.

Table 1: Composition of different formulations for floating tablets of Atorvastatin (in mg).

Ingredients	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9	F-10
Atorvastatin Calcium	86.7	86.7	86.7	86.7	86.7	86.7	86.7	86.7	86.7	86.7
Carbomer 940	20	40	60	80	100	–	–	–	–	–
Carbomer 971P	–	–	–	–	–	20	40	60	80	100
Povidone K-30	40	40	40	40	40	40	40	40	40	40
Ludipress	243.3	223.3	203.3	183.3	163.3	243.3	223.3	203.3	183.3	163.3
$NaHCO_3$	60	60	60	60	60	60	60	60	60	60
Citric acid	40	40	40	40	40	40	40	40	40	40
Mg. Stearate	5	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5	5
Total weight	500	500	500	500	500	500	500	500	500	500

Evaluation of tablets

Tablets of each batch were evaluated for thickness, diameter, weight variation, hardness, and friability. 10 tablets of each batch were evaluated for thickness, diameter followed by weight variation test individually. Each tablet was separately weighed and the average weight & standard deviation of 10 tablets was calculated. The tablets were then tested by Monsanto Hardness Tester. Another ten tablets were weighed and placed in the Electorlab Friabilator and the apparatus was

operated for 100 rotations. After revolutions the tablets were dedusted and weighed again and percent friability was determined.

***In vitro* buoyancy studies**

Buoyancy of the tablets was determined by buoyancy lag time according to the method of Hussain *et al*., 2012[4]. Randomly selected 3 tablets from each formulation were placed in a 250 ml beaker containing 0.1N HCl, pH 1.2. The beaker was placed in a water bath at a temperature of 37 ± 0.5°C for 24 hour. The time required to appear on the surface of the media after introduction of the dosage form is termed as buoyancy lag time and total extent of time by which the dosage form remain buoyant over the media is total floating time. The test was repeated thrice for each batch.

Study of swelling index (SI)

Swelling Index (SI) is a key determinant of bulk density of the floated tablet. To determine the SI, tablets were placed separately in a glass beaker containing 200 ml of 0.1 N HCl and incubated at 37°C±1°C for 5 hour. At each 1 hr interval, the tablets were taken out of the beaker and the excess surface liquid was removed carefully using the tissue paper. The swollen floated tablets were then re-weighed and swelling index (SI) was calculated using the below formula.[4]

$SI = \{(W_t - W_0)/W_0\} \times 100$

Where, W_t is the weight of tablet at time *t* and

W_0 is the initial weight of the tablet.

Compatibility study

FT-IR spectra of the drug Atorvastatin and two representative batches were taken in IR-Prestige 21, Shimadzu, Japan by scanning the sample in potassium bromide (KBr) discs over a frequency range of 400 to 4000 cm^{-1} on FT-IR. To examine any degradation or interaction between drug and used excipients, Infrared spectra of Atorvastatin and granules of the batches were compared.

***In vitro* drug release studies**

Dissolution studies of floating tablets were carried out by Dissolution Tester USP XXII in paddle stirrer. The dissolution test was performed using 900 ml of 0.1N HCl solution with 1% Sodium Lauryl Sulphate maintained at 37°C ± 0.5°C temperature and operated at 75 rpm. Initially at 30 minutes and then in every 1 hour interval, aliquots of 10 ml were withdrawn from the dissolution medium and fresh medium was replaced immediately to keep the volume constant. The samples were filtered, diluted and assayed by using a Shimadzu UV-1201 UV/Visible double beam spectrophotometer (Shimadzu, Japan) at 245 nm for Atorvastatin Calcium. Cumulative percentage drug release was calculated using standard curve equation.

Kinetic studies

The dissolution profile of all the batches were fitted to zero order, first order, Higuchi, Korsemeyer-peppas and Hixon Crowel model to assume the mechanism of drug release from the matrix tablets. For further characterization, the drug release rate in different experimental conditions, $T_{25\%}$,$T_{50\%}$ (mean dissolution time) and $T_{80\%}$ were calculated from dissolution data according to the following equations[4]:

$T_{25\%} = (0.25/k)^{1/n}$

$T_{50\%} = (0.5/k)^{1/n}$

$T_{80\%} = (0.8/k)^{1/n}$

Mean dissolution time (MDT) value is an indicator of drug release retarding ability of a certain matrix. Higher the value of MDT, lower the drug releasing ability of the rate modifying polymer or the matrix system. Mean Dissolution Time can be calculated by the following equation.

$MDT = (n/n+1).\ K^{-1/n}$

Where *k* is the antilog of intercept & *n* is a release exponent of Korsmeyer's plot.

RESULTS AND DISCUSSION

Floating tablets of Atorvastatin were prepared by direct compression technique. The tablets were evaluated for various physical tests including weight variation, friability, hardness, diameter and thickness for all the formulations (F-1 to F-10). No significant difference was observed in the weight of individual tablets from the average weight. The hardness of tablets of all formulations was in acceptable limits (23-30 kg/cm^2). All the formulation showed % friability less than 1.0%, which indicates ability of tablets to withstand shocks. No significant difference was observed in the thickness of individual tablet from the average.

Table 2: Physical characterization of prepared tablets.

Formulation	Diameter (mm)	Thickness (mm)	Hardness (Kg/cm^2)	Average weight (mg)	Friability (%)
F-1	13.12±0.012	2.58±0.020	26±0.114	500±0.64%	0.17
F-2	13.12±0.016	2.60±0.025	27±0.104	500±0.74%	0.14
F-3	13.12±0.014	2.58±0.020	29±0.221	500±0.04%	0.11
F-4	13.16±0.018	2.69±0.025	29±0.114	500±0.87%	0.17
F-5	13.10±0.017	2.59±0.027	30±0.107	500±0.96%	0.09
F-6	13.13±0.014	2.56±0.025	23±0.232	500±0.88%	0.13
F-7	13.10±0.013	2.56±0.025	26±0.224	500±1.01%	024
F-8	13.12±0.013	2.62±0.025	25±0.117	500±0.98%	0.14
F-9	13.13±0.017	2.67±0.026	24±0.174	500±0.71%	0.15
F-10	13.13±0.015	2.59±0.025	28±0.156	500±0.94%	0.14

FT-IR Spectra of Atorvastatin Calcium showed its characteristic peaks at 3363 cm-1 (C=O stretching), 2955 cm^{-1} (C-H stretching), , 1657 cm^{-1} (C=C bending), 1565 cm^{-1} (C=O stretching

amidic group), 1313 cm^{-1} (C-N stretching). Narasaiah *et al.*, 2011[10] also reports the similar findings in his research article of Atorvastatin solid dispersions. Formulations of both grades of Carbomer were found to retain the major peaks of Atorvastatin as they showed peaks at 2955 cm^{-1} and at 1313 cm^{-1}. The presence of characteristic peak positions and similar intensities indicate towards compatibility of incorporated excipients and the active drug component.

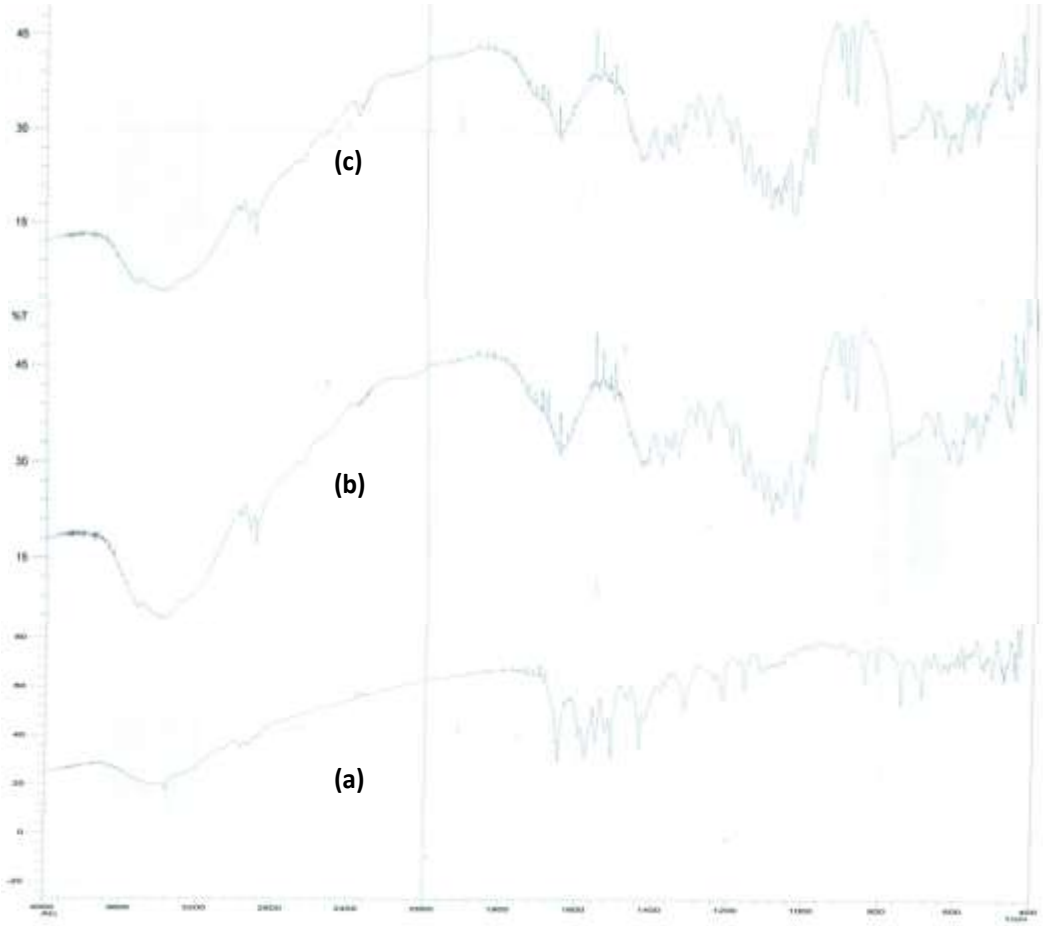

Figure 1: FT-IR Spectra of a) Atorvastatin, b) spectra of formulation F-3 and c) spectra of formulation F-8.

Floating capacity of prepared floating tablets was evaluated by two buoyancy indicating parameters eg. lag time and total buoyancy period. All the formulations comprising of Carbomer 940 were found to have comparatively higher lag time than those containing Carbomer 971P. At higher concentrations, lag time was found notably lower for both of the polymer grades that signifies to the impact of polymers on tablet floating. Similarly total floating time was found dependent on the concentration of polymer used in the formulation. Higher the amount of Carbomer in the formulation, greater was the total floating time. Formulation F-4 and F-7 showed faster floating.

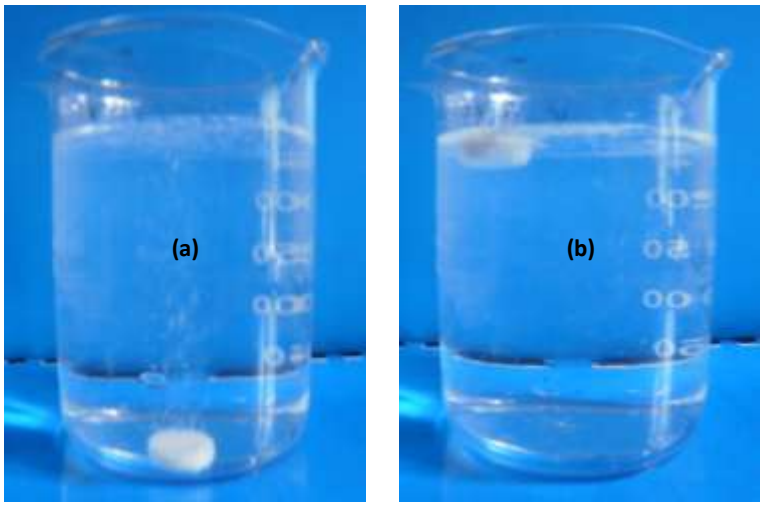

Figure 2: Buoyancy of Atorvastatin floating tablet (formulation F-5) at a) initial time and b) after 30 seconds.

Table 3: *In vitro* characterization of floating capacity.

Formulation	Buoyancy Lag Time (Sec)	Total Floating Time (Hour)
F-1	280	>8hrs
F-2	260	>10hrs
F-3	230	>16hrs
F-4	10	>20hrs
F-5	28	>24hrs
F-6	65	>10hrs
F-7	8	>12hrs
F-8	12	>18hrs
F-9	12	>20hrs
F-10	11	>24hrs

The swelling indexes for all formulation F-1 to F-10 are shown in Table 4. Tablet buoyancy is directly related to swelling capacity of the matrix. Swelling indexes for formulations containing lower content of polymer (F-1, F-2, F-6 and F-7) showed decreasing order of swelling index as the matrix was eroding and getting dissolved with time. Consequently these formulations had higher floating lag time and burst release within hours in the *in vitro* dissolution study. On the contrary, rest of the formulations showed a growing order of swelling index mainly due to the rapid water intake of Carbomer. This swelling of the matrix lessened the bulk density below 1 and kept the matrix afloat over a longer period of time. These formulations also had a longer total floating time. John *et al*., 2010[11] also reported the higher swelling and hydration on greater quantity of Carbomer in the formulation.

Table 4: Swelling index studies.

Formulation	Swelling Index (%)				
	1 hr	2 hr	3 hr	4 hr	5 hr
F-1	78.40	38.40	34.84	29.00	10.06
F-2	79.40	51.24	41.20	36.06	31.00
F-3	80.76	104.30	107.26	117.92	119.40
F-4	84.84	105.12	111.20	119.52	304.60
F-5	86.40	134.00	138.10	141.36	144.76
F-6	73.20	69.20	56.90	40.96	31.04
F-7	79.44	74.80	61.40	53.06	42.80
F-8	80.46	91.20	96.40	105.40	111.36
F-9	89.20	100.80	114.92	117.90	124.08
F-10	81.20	97.40	101.72	117.20	123.26

The cumulative percent drug release data obtained for formulations F-1 to F-10 are plotted in Fig 3. Tablets were found to release the active component depending on the ratio and content of Carbomer in the formulation. Formulations containing lower amount of Carbomer (F-1, F-2, F-6 and F-7) showed burst release from the second hour for both grades. An indication of rate controlling was found on using the polymers at 12% and above concentration. Among formulations employing Carbomer 940, F-3, F-4 and F-5 were found to release 46.84%, 25.92% and 14.71% of incorporated drug after eight hours of dissolution respectively. On the other hand, tablets containing Carbomer 971P at ratio of 12%, 16% and 20% released 41.82%, 26.69% and 9.92% of incorporated drug upon dissolution after 8 hours. Though the polymers had different viscosity grades, rate retardation of Atorvastatin tablet was found similar when used at same ratio in matrix tablets.

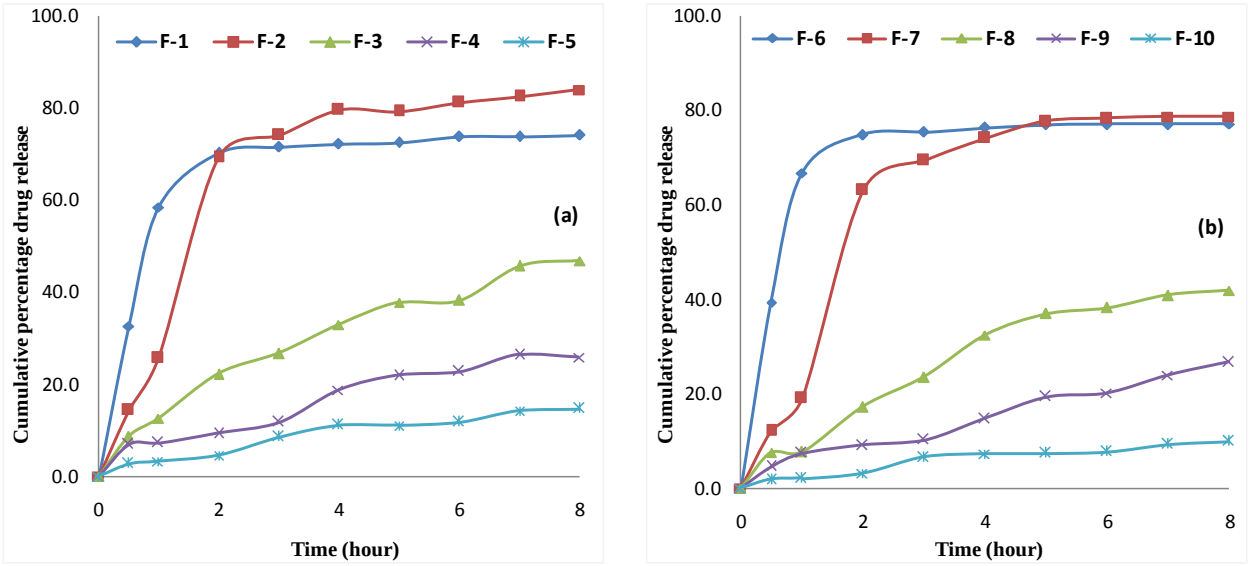

Figure 3: *In vitro* release profile of Atorvastatin floating tablet.

The differences in the release behavior by different ratio of polymers became more explicable by MDT and fractional dissolution time points (Table 5). Formulations containing lesser amount of polymer showed MDT value much lower for both grades. But on increasing the polymer content in the matrix reduced the release rate and extent as indicated by greater MDT value. F-5 and F-10 were found to have larger MDT value 53.60 and 97.29 hours respectively. Other fractional dissolution time values ($T_{25\%}$, $T_{50\%}$ and $T_{80\%}$) also indicate the same and concluded the highest ratio (20%) of polymer slowed down the rate of release significantly.

Table 5: Mean dissolution time and fractional dissolution time values of formulations of Atorvastatin (in hour).

Formulation	MDT	$T_{25\%}$	$T_{50\%}$	$T_{80\%}$
F-1	3.51	0.06	1.03	7.17
F-2	2.81	0.80	2.42	5.10
F-3	9.72	2.72	8.31	17.71
F-4	33.79	7.68	27.03	63.44
F-5	53.60	16.95	47.54	95.67
F-6	3.12	0.01	0.53	6.07
F-7	3.13	1.06	2.83	5.52
F-8	9.68	3.36	8.82	16.98
F-9	30.59	8.52	26.11	55.78
F-10	97.29	30.76	86.29	173.67

For further classification of release behavior and mechanism, the dissolution data obtained at each time point was fitted with different mathematical equations (Table 6). Formulations containing 12% or more polymers in the formulation showed good linearity with zero order kinetics for both polymers. Similar happenings were found in case of First order, Korsmeyer-Peppas and Higuchi models. This indicates to the diffusion based release profile of the matrixes. However, the release data did not show good fitting to the Hixon Crowel mathematical model that revealed that surface area and diameter of the granules in the tablet did not have significant influence over the drug dissolution. The diffusion exponent *n* of Korsmeyer equation is another marker of mechanism of drug release. The release exponent was found to have values within ($0.45 < n < 0.89$) except formulation F-1 and F-6 which pointed towards the non-Fickian anomalous release behavior[3]. Drug diffusion and erosion of the matrix based on dissolving of the hydrophilic polymer may lead to anomalous diffusion in these formulations.

Table 6: *In vitro* release kinetics of formulations of Atorvastatin.

Formulation	Zero order		First order		Higuchi		Korsmeyer		Hixon-Crowell	
	k_0	R^2	k_1	R^2	k_h	R^2	n	R^2	k_{hc}	R^2
F-1	6.272	0.510	-0.056	0.610	23.45	0.759	0.242	0.723	0.273	0.342
F-2	9.729	0.715	-0.099	0.825	33.01	0.875	0.629	0.859	0.367	0.533
F-3	5.554	0.945	-0.033	0.974	17.42	0.989	0.621	0.992	0.309	0.639
F-4	3.188	0.946	-0.016	0.956	9.810	0.953	0.551	0.912	0.254	0.646
F-5	1.803	0.946	-0.008	0.952	5.576	0.961	0.672	0.956	0.218	0.679
F-6	6.080	0.453	-0.058	0.551	23.31	0.709	0.193	0.685	0.265	0.312
F-7	9.618	0.731	-0.089	0.820	32.29	0.877	0.705	0.865	0.376	0.563
F-8	5.379	0.934	-0.031	0.956	16.76	0.966	0.718	0.957	0.318	0.682
F-9	3.086	0.978	-0.015	0.982	9.321	0.949	0.619	0.958	0.257	0.687
F-10	1.185	0.928	-0.005	0.932	3.688	0.955	0.672	0.945	0.189	0.668

Carbomer 971P and Carbomer 940 have viscosity ranges of 4000-11000 mPas and 40,000-60,000 mPas[12, 13]. But owing to having different viscosity grades, the matrix tablets showed similar release profiles and rate retardation. Shivhare *et al*., 2009[14] also reported to similar happenings when they employed two discrete viscosity grades of Carbomer in sustained release formulation of Aceclofenac. They explained the fact by describing the mechanism of drug diffusion through gelatinous layer of hydrated Carbomer. They figured out some influential factors that control the dissolution rate like molecular structure of polymer, rate of hydration, swelling, pH of the environment, extent of dispersion of drug particles. For Atorvastatin tablets these two polymer grades acted in a similar fashion and retard the rate significantly. Variation between the two release profiles would be visible over further dissolution study for longer hours.

CONCLUSION

Atorvastatin Calcium floating tablets were prepared using two different viscosity grade of Carbomer. The tablets were successfully floated on gastric juice over a prolonged period. The tablets were efficiently sustain the rate of drug release and therefore, further investigation could be conducted to observe the *in vivo* performance of the prepared formulations.

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