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DEVELOPMENT AND EVALUATION OF GASTRORETENTIVE FLOATINGTABLETS OF ATORVASTATIN CALCIUM

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ABSTRACT

Background: Atorvastatin calcium could be a 3-hydroxy-3-methyl glutyryl coenzyme A (HMG CoA) reductase inhibitor is a statin with well-known lipid lowering effects. The oral bioavailability of atorvastatin calcium is 14% due to incomplete intestinal absorption or gut wall extraction. Floating drug delivery systems are the gastro retentive forms that precisely control the discharge rate. This can be achieved by use of assorted polymeric substances including natural polymers. These polymers are inexpensive, safe and available in an exceedingly form of structures with versatile characteristics. **Objective:** The aim of the study was to enhance oral bioavailability of atorvastatin calcium ingastro retentive floating dosage form by using natural and artificial gums. **Methods:** Gastro retentive floating tablets of atorvastatin calcium were formulated by wet granulation method using altered concentrations of HPMC K15, Tamarind gum and Sterculia gum as polymers. The prepared tablets of atorvastatin calcium were evaluated for precompression and post compressions parameters. **Results:** The varying concentration of polymers were found to effect on *in-vitro* drug release rate. Atorvastatin calcium gastroretentive floating tablets were shown that the formulation F9 was found to be the best formulation as it releases 87.66 % atorvastatin calcium in a very controlled manner for an extended period of your time (up to 8 h). The discharge data was fitted to numerous-mathematical models like higuchi, Korsmeyer-Peppas, first order and zeroorder to gauge the kinetics and mechanism of the drug release. **Conclusion**: From the study it had been concluded that Gastroretentive effervescent floating tablet formulation F9 (1: 7 ratio) of Atorvastatin calcium using Sterculia gum as natural polymer by wet granulation technique.

KEYWORDS: Atorvastatin calcium, Gastro retentive, Floating tablet, Total floating time.

INTRODUCTION

Oral drug delivery systems have more advantages than other delivery systems for human administration because of its advantages including easy administration, storage and transportation, flexibility, cost-effectiveness, and high patient compliance. This systems face challenges like low bioavailability, pH, and gastric retention time of the dosage form, expanse and enzymatic activity. Conventional drug delivery systems have more issues within the canal (GIT) like incomplete drug release, decrease in dose effectiveness, and frequent dose requirement. Because of this issues causes in the GIT may result in the event of GRDDS. These systems provide prolonged gastric continuance of dosage forms within the stomach, increased therapeutic efficacy by improving drug absorption, and targeted delivery within the stomach. GRDDS enhance the delivery of medicine by continuously releasing the drug for an extended period at desired rate and absorption site until the drug is totally released from the dosage form.

Different approaches are proposed to retain the dosage form within the stomach. Those approaches include preparation of high density dosage form, concomitant administration of medication or excipients, preparation of bio-adhesive or mucoadhesive dosage form. But the only and possibly the foremost elegant way to improve drug absorption is to carry a drug delivery system on and above the absorption window. Because most absorption windows are located within the proximal gut (duodenum), the foremost effective strategy are to carry the formulation within the stomach.

When a drug is formulated with gel forming hydrocolloid such as hydroxyl propyl methylcellulose (HPMC) and carbon dioxide generating agents like citric acid and sodium hydrogen carbonate it swells within the gastric fluid because it gets contact with the aqueous medium. Formation of carbon dioxide (CO_2) and entrapment of that gas into the polymeric gel causes swelling of the dosage resulting a bulk density less than 1. It then remains buoyant and floats in the gastric fluid that is accountable for prolonged gastric duration. This floating dosage form is well known as a Hydro dynamically Balanced System (HBS). It's has been suggested that an energetic material should be formulated within the form of an HBS to reinforce bioavailability of those drugs having a dissolution or stability problem within the small intestinal fluid, drugs which are being locally effective in the stomach and medicine with a narrow therapeutic window.

Atorvastatin calcium may be a synthetic lipid lowering agent agent and it inhibits hepatic hydroxymethyl-glutaryl coenzyme A (HMG- CoA) reductase, the enzyme whichcatalyzes the conversion of HMG- CoA to mevalonate, a key step in cholesterol synthesis. The oral bioavailability of Atorvastatin calcium is 14% due to incomplete intestinal absorption or extensive gut wall extraction. It also undergoes high first pass metabolism. It is absorbed more within the upper part of the GIT. So oral absorption of atorvastatin will be increased by increasing gastric retention time of the drug.

The aim of the work is to develop gastro retentive floating tablets of Atorvastatin calcium using effervescent technique to enhance absorption and bioavailability by using natural and artificial gums. Tamarind and Sterculia gum as a natural gums and HPMC K15 as synthetic polymers. Sodium bicarbonate and citric acid were incorporated within the formulation as gas generating agent. Effect of the polymer loading upon the floating lag time of the tablets, swelling index release rate, and release mechanism were evaluated with the assistance of varied mathematical models.

MATERIALS AND METHODS

Materials

Atorvastatin Calcium were obtained from Reine life science as gift samples. HPMC K15, sodium bicarbonate, citric acid were collected from Fourt's India private laboratories. All other ingredients were of analytical grade and procured form local market.

Methods

Preparation of calibration curve

The stock solutions were prepared by dissolving 100 mg of Atorvastatin calcium in 100 ml volumetric flask and so made up to the answer up to the mark using methanol for obtaining the solutions of strength 1000 µg/ml (stock I). 1ml of this solution was diluted to 10 ml with methanol to obtain a solution of strength 100 µg/ml (stock II).1ml of this solution was diluted with 10 ml methanol to obtain a solution of strength 10 µg/ml. From this stock solutions required concentrations 0,2,4,6,8,10 µg/ml were prepared. The solution was scan at a wavelength of 200-400 nm on UV spectrophotometer. The very best absorbance peak was obtained at a peak of 245 nm in which was the λ_{max} of the drug.

Drug excipient interaction study by Fourier Transform Infrared (FTIR) Spectroscopy

Drug excipient interaction studies are significant for the successful formulation of each dosage

form. Fourier Transform Infrared (FTIR) Spectroscopy studies were used for the assessment of physicochemical compatibility and interactions, which helps within the prediction of interaction between drug and other excipients. The sample were studied using FTIR JASCO 4100 within the wavenumber range from 400 to 4000 cm^{-1}.

Evaluations of Powder Blend for Tableting

Pre - Compressional Evaluation of powder blend

Flow properties and compressibility properties of powder mixture were evaluated by measurement of angle of repose, bulk density, tapped density, Carr's index and hausner's ratio.

Angle of repose (θ)

The angle of repose was firm by using fixed funnel method. The formulated powder blend was meant to measurement of the funnel was fixed at a specified height (2.5 cm) on a stand and the powder sample was well- versed through the funnel until it formed a pile. Further addition of powder was stopped as soon as because the pile touches the tip of the funnel. A circle was drawn across it without disturbing the pile and also the radius and height of the pile were noted.

The angle of repose was calculated by following equation

$$\theta = \tan\text{-}1(h/r)$$

Where, h and r are the peak and radius of the powder cone respectively

Bulk Density

BD was determined by pouring the weighed amount of powder into a measuring cylinder. The initial volume was noted which represented because the bulk volume. Using this value, the bulk density was calculated according to the formula mentioned below. It had been expressed in g/mL.

Bulk Density= Bulk Mass/Bulk Volume

Tapped Density

The volume was measured by tapping the bulk powder for 100 times. It had been expressed in g/mL.

Tapped density= Powder weight /tapped volume of the powderCompressibility index

The flow ability of the powdered material was evaluated by comparing the bulk density and tapped density of powder and therefore the rate at which the powder gets compressed is known as compressibility index. Compressibility index was calculated using the subsequent

formula,

$$\text{Carr's index (\%)} = [(\text{TBD} - \text{LBD})/\text{TBD}] \times 100$$

Hausner's Ratio

H.R defines because the measurement of frictional resistance of the drug. The ideal range for H.R should be within 1.2-1.5, and was determined by dividing tapped density and bulk density

$$\text{Hausner's ratio} = \text{Tapped density}/\text{Bulk density}$$

Formulation of Floating tablets of Atorvastatin calcium

Atorvastatin calcium were prepared by wet granulation method. Accurately weighed quantities of polymer were taken in a mortar and mixed geometrically to this required quantity of Atorvastatin Calcium was added and mixed with pestle. Accurately weighed quantity of sodium bicarbonate and citric acid was then mixed with the drug blend. Iso propyl alcohol was used as granulating agent. Granules were prepared by passing the wet coherent mass through #60 sieve. The granules were dried in hot air oven at a temperature of 45˚C. Dried granules were sieved through #20 sieve then lubricated with magnesium stearate and talc before compression and mixed for about 3 minutes. Finally this lubricated granules were compressed into tablets by using 10 station rotary machine 13mm flat round tablet machine.

Table 1: Composition of Atorvastatin calcium floating tablets.

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Atorvastatin calcium	20	20	20	20	20	20	20	20	20
HPMC K15	60	100	140	-	-	-	-	-	-
Tamarind gum	-	-	-	60	100	140	-	-	-
Karaya gum	-	-	-	-	-	-	60	100	140
Sodium bicarbonate	15	15	15	15	15	15	15	15	15
Citric acid	10	10	10	10	10	10	10	10	10
PVP K30	10	10	10	10	10	10	10	10	10
Lactose	50	50	50	50	50	50	50	50	50
Magnesium stearate	3	3	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3	3	3
Mcc	129	89	49	129	89	49	129	89	49
Total weight (mg)	300	300	300	300	300	300	300	300	300

Evaluation of floating tablets of Atorvastatin calcium

Post compressional estimation of Atorvastatin calcium floating tablet

Formulated tablets which were subjected to assessment tests these also shows hardness, diameter, Uniformity of Weight, Drug Content, *In Vitro* Buoyancy Studies, *In vitro* dissolution studies and Swelling index studies.

Hardness

For each formulation, the hardness of five tablets were determined using the Monsanto hardness tester.

Friability

The friability of a sample of 10 tablets were measured using a Friability tester (Electro Lab).Ten tablets were weighed, rotated at 25 rpm for 4 minutes. Tablets were reweighed after removal of fines (dedusted) and the percentage of weight loss was calculated.

$$F= (1- W/ WO) \times 100$$

Where, Wo is that the initial weight of tablet, W is that the final weight of tablet.

Uniformity of Weight

Twenty tablets were randomly selected from each batch individually weighed, the average weight and variance of 20 tablets were calculated.

Drug Content

Twenty tablets were taken and amount of drug present in each tablet was determined. The tablets were crushed in a mortar and the powder equivalent to 100 mg of drug was transferred to 100 ml standard flask. The powder was dissolved in methanol and made up to volume with methanol and filtered. The filtered solution was diluted suitably and analysed for drug content by UV spectrophotometer at a λ_{max} of 245 nm using methanol as blank.

***In Vitro* Buoyancy Studies**

The *in vitro* buoyancy was determined by floating lag time. Here, the tablet was placed in a 100 ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time and total duration of time by which dosage form remain buoyant is called Total Floating Time (TFT).

***In vitro* dissolution studies**

Dissolution studies were carried out using USP II dissolution apparatus. The stirring speed was 50 rpm and 0.1N hydrochloric acid was used as dissolution medium (900 ml). It was maintained at 37± 1˚C. Samples of 5 ml were withdrawn at predetermined time intervals, filtered and replaced within 5ml of fresh dissolution medium. The collected samples were suitably diluted with dissolution fluid wherever necessary and were analysed 245 nm by using a double beam UV spectrophotometer.

Swelling index studies

The swelling index of tablets was determined by using 0.1 N HCl (pH 1.2) at room temperature. The swollen weight of the tablets was determined at predefined time intervals. The swelling index was calculated by the following equation:

$$\text{Swelling index (SI)} = W_t - W_o / W_o \times 100$$

Where, W_t. = Weight of tablet at that time t, W_O = Initial weight of that tablet

***In Vitro* drug release kinetics studies**

To analyse the *in vitro* release data and to determine the release mechanism various kinetic models were used.

Zero Order Kinetics

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly (assuming that area does not change and no equilibrium conditions are obtained) can be represented by the following equation

$$W_O - W_t = K_o t$$

Where, W_o is the initial amount of drug in the pharmaceutical dosage form, W_t is the amount of drug in the pharmaceutical dosage form at time t and kept k is proportionality constant. A graphical relationship between drug dissolved versus time to get the zero-order constant from the slope.

First Order Kinetics

The relation expressing this model

$$\text{Log } Q_t = \text{Log } Q_o + K_t t / 2.303$$

Where Q_t is that the amount of drug released in time t, Q_o is initial amount of drug in the solution and K_t is the primary order release rate constant.

In this way a graphical relationship between log percent drug remaining versus time to urge the first order constant from the slope.

Korsmeyer - Peppas model

Korsmeyer et al., (1983) developed an easy simple semi empirical model, relating exponentially the drug release to the amount of your time (t).

$$Qt / Qa = Kkt^n$$

Where, K_k can be a constant incorporating structural and geometric characteristic of the drug dosage form and n is the discharge exponent, indicative of the drug release mechanism. For tablets, an n value of < 0.5 indicates diffusion – controlled mechanism while an n value of <1.0 indicates erosion. If the value of n is 0.5, it indicates Fickian transport, a value of 0.5 and 1.0 non – Fickian transport, and the values close to 1.0 indicates that system is releasing drug in a zero-order manner irrespective of the actual mechanism of release.

Higuchi Model

$$Qt = KHt^{1/2}$$

Where, Q_t = the amount of drug released at time t, K_H= the Higuchi release rate

This can be often the foremost widely used model to clarify drug release from pharmaceutical matrices. A linear relationship between the basis slow versus the concentration indicates that the drug release follows strict Fickian diffusion. For purpose of data treatment, the above equation is usually reduced to:

$$Q = Kt^{1/2}$$

Therefore a plot of amount of drug released versus the basis of sometime should be linear if drug release from the matrix is diffusion controlled.

RESULTS AND DISCUSSION

Gastro retentive tablets of Atorvastatin calcium were formulated with natural polymers and artificial polymer. The λ_{max} of atorvastatin calcium in methanol was found to be at 245 nm by using UV spectrophotometer in linearity range 2-10 µg/ml were represented in Fig.1. Identification of interaction was done by FTIR spectroscopy with relevancy marker compound. It absolutely was identified from the result of IR spectrum as per specification. Table 2. Shows that the angle of repose values indicates that the powder blend has good flow properties. The bulk density and tapped density of all the formulations was found to be in the range of 0.341-0.426 g/ml (gm/ml) and 0.418- 0.521(gm/ml) showing the powder has good flow properties.

The compressibility index and hausner's ratio of all the formulations was found to be ranging between 15.38 -20.93% and 1.19 which shows that the powder has good flow properties. Atorvastatin calcium tablet control tests such as weight variation, hardness and friability, thickness, drug content and drug release studies in numerous media were performed on the compression tablet. All the parameters such as weight variation, hardness, friability, thickness and drug content were found to be within limits Table 3.

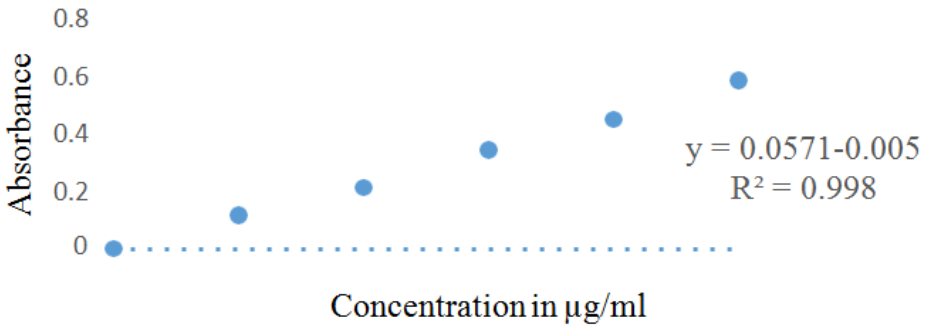

Fig 1: Calibration curve of Atorvastatin calcium in methanol at 245nm.

Table 2: Results of Pre compression Parameters of Atorvastatin calcium GRF Tablet.

Formulation code	Angle of repose	Bulk density (gm/cm³)	Tappeddensity (gm/cm³)	Carr's index (%)	Hausner's ratio
F1	27°35′	0.42	0.52	19.23	1.16
F2	28°19′	0.38	0.48	20.68	1.15
F3	26°59′	0.39	0.46	15.38	1.18
F4	24°18′	0.37	0.47	20.93	1.17
F5	27°39′	0.39	0.50	19.42	1.19
F6	28°′50	0.39	0.49	20.68	1.15
F7	25°72′	0.34	0.41	16.66	1.16
F8	28°73′	0.42	0.50	19.23	1.18
F9	26°45′	0.36	0.43	16.66	1.19

Table 3: Results of Pre Compression Parameters of Atorvastatin calcium GRF Tablets.

Formulation code	Hardness (Kg/cm³)	Friability (%)	Weight variation (mg)	Drug content (%)
F1	6.8	0.63	2.19	85.63
F2	6.5	0.25	2.56	86.88
F3	6.0	0.43	2.13	87.25
F4	5.9	0.44	3.21	89.25
F5	5.6	0.53	2.03	90.18
F6	4.8	0.66	2.88	90.22
F7	5.7	0.75	1.63	91.57
F8	5.5	0.56	2.27	93.26
F9	5.6	0.61	2.46	96.45

In the present study 9 formulations with variable concentration of polymers (HPMC K15, Tamarind gum and Karaya gum) were prepared by wet granulation method and evaluated for physicochemical properties. The results of buoyancy lag time, total floating time and *in vitro* drug release was given in Table 4, 5. The results indicated that optimizes formulation F9 on immersion in 0.1N HCl at 37±0.5°C tablets immediately and remain buoyant upto 12hr without disintegration. These 2 factors are essential for tablets to acquire density< 1, so as that it remains buoyant on the gastric fluids. The *in vitro* drug release data of the optimized formulation was subjected to goodness of fit test by regression analysis towards the mean analysis per zero order, first order kinetic equation, higuchi's and korsmeyer's models so on see the mechanism of drug release. When the statistical values of were compared, it absolutely was observed that 'r' values of zero order was maximum i.e. 0.995 hence indicating drug release from formulations was found to follow zero order release kinetics, Table 6, 7 & fig. 2-6.

Table 4: Results of *In vitro* Buoyancy study of Atorvastatin calcium GRF Tablets.

Formulation	Floating lag time(seconds)	Total floating duration(h)
F1	60	>12
F2	55	>12
F3	60	>12
F4	54	>12
F5	45	>12
F6	38	>12
F7	29	>12
F8	25	>12
F9	20	>12

Table 5: Results of Swelling study of Atorvastatin calcium GRF Tablets.

Time (h)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	30.56	28.62	30.32	25.38	28.33	30.55	32.21	24.24	26.85
2	36.60	34.44	36.88	32.56	35.65	39.23	37.95	36.36	38.23
3	42.35	40.51	45.31	44.69	49.66	51.64	45.51	48.48	47.22
4	56.51	49.55	32.66	59.42	63.26	47.12	53.24	56.26	60.59
5	**61.68**	**58.13**	**59.64**	**65.16**	**55.03**	**67.23**	**63.30**	**66.66**	**76.47**
6	52.66	51.32	65.32	52.30	42.39	56.78	42.12	51.12	55.88

Table 6: In Vitro drug release study Atorvastatin calcium GRF Tablets.

	%Cumulative drug release								
Time (h)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0.25	0.85	0.91	0.96	0.83	0.89	0.94	0.85	0.93	0.12
0.5	1.75	2.28	2.72	2.79	3.75	3.86	3.80	4.81	6.80
1	3.58	4.86	5.63	6.58	8.38	9.81	8.43	10.83	12.43
2	6.15	7.92	9.23	12.26	13.91	17.86	15.63	18.09	21.63
3	9.50	11.38	13.65	18.47	20.51	23.98	27.23	26.98	29.38
4	14.43	16.56	21.14	25.57	28.29	32.87	35.48	36.55	39.95
5	20.63	22.98	29.47	33.37	36.66	41.48	46.22	47.17	50.32
6	27.04	30.77	36.47	41.58	46.02	49.32	58.06	59.22	61.05
7	33.52	38.74	43.68	50.79	55.59	59.79	69.32	71.95	73.10
8	**41.13**	**47.16**	**52.42**	60.36	65.43	71.08	**81.63**	**84.85**	**87.66**

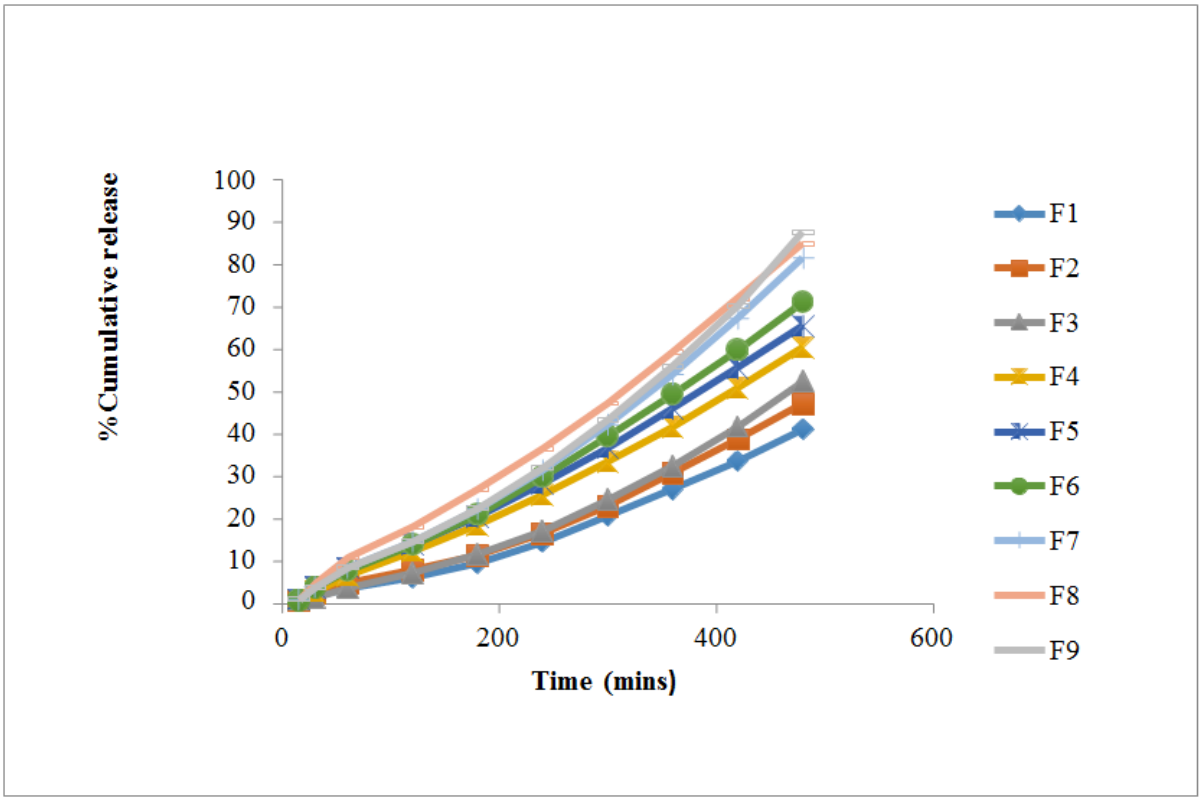

Fig 2: *In -vitro* dissolution drug release study of Atorvastatin calcium GRF Tablets.

Table 7: *In-vitro* drug release data for optimized formulation F9.

Formulation code	Zero order	First order	Higuchi	Korsmeyer-peppas
	R^2	R^2	R^2	R^2
F9	0.995	0.944	0.905	0.853

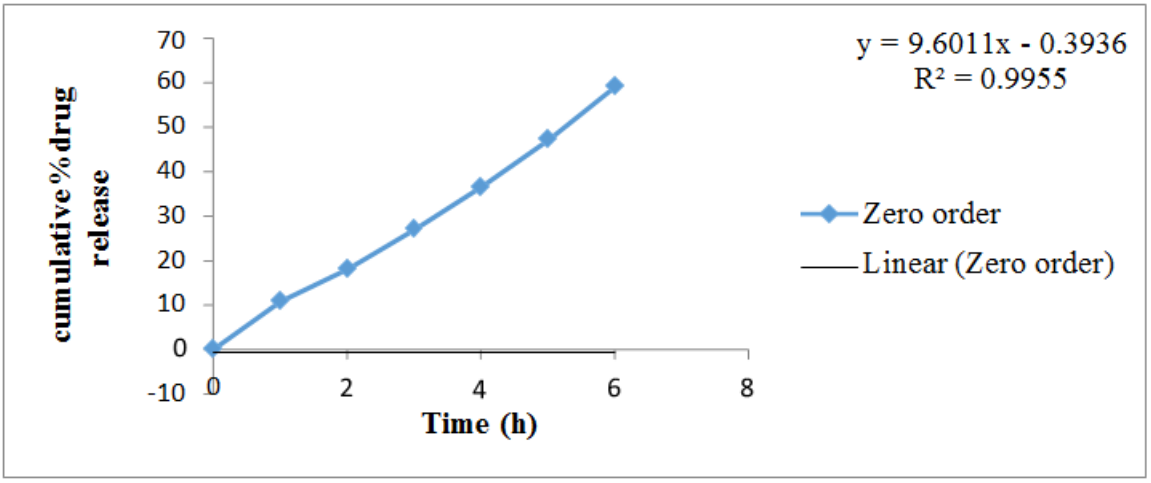

Fig. 3: Zero order release Kinetics.

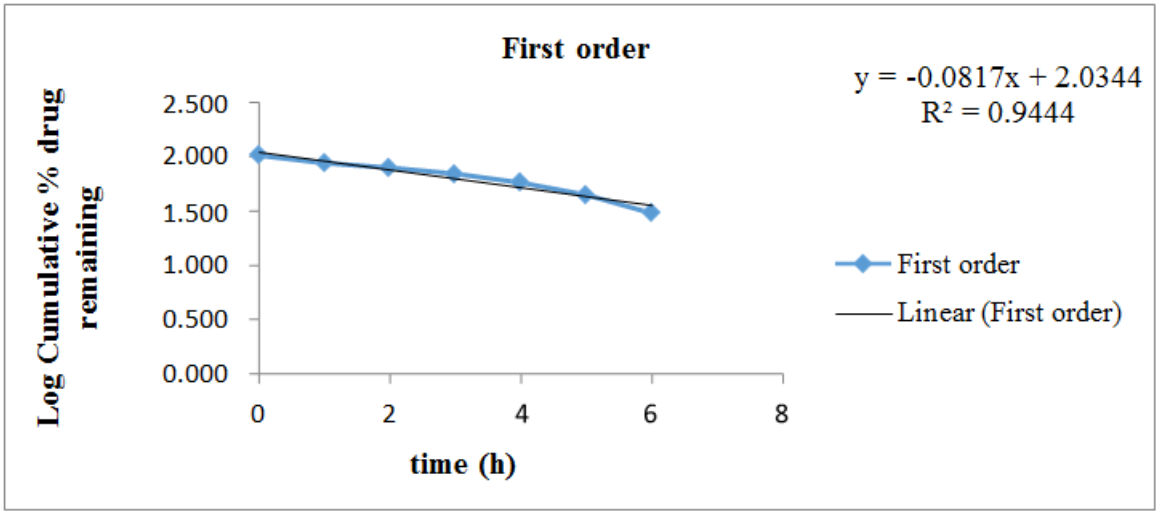

Fig. 4: First order release kinetics.

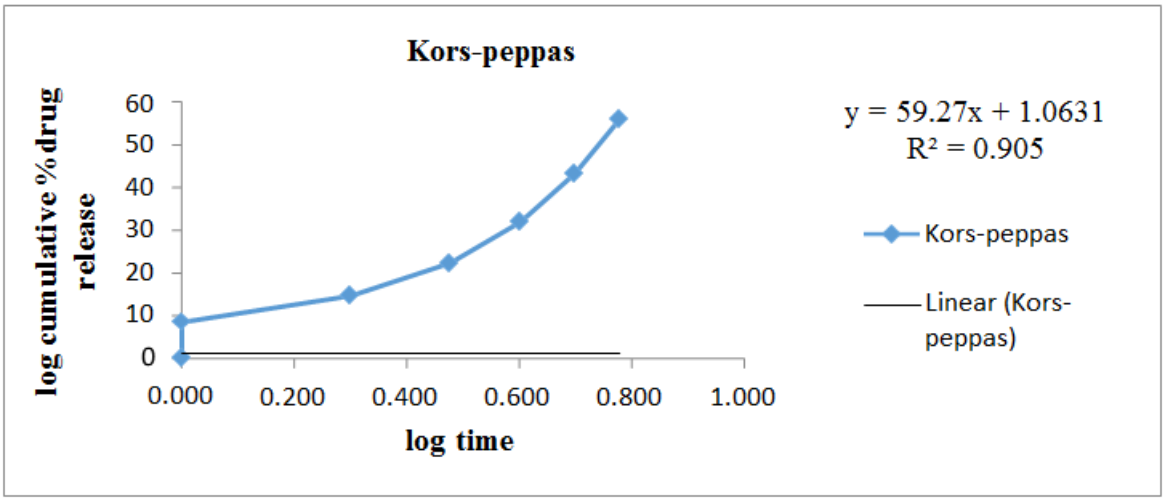

Fig. 5: Korsmeyer peppas plot.

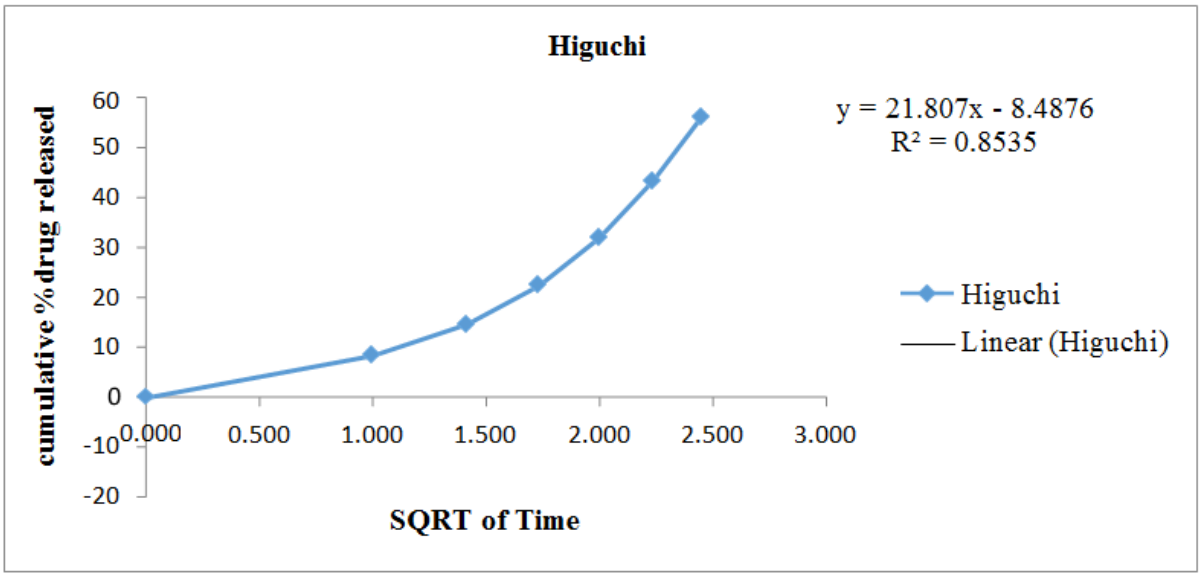

Fig. 6: Higuchi plots.

CONCLUSION

Atorvastatin calcium floating tablets were prepared successfully by effervescent technique. The concept of formulating floating tablet containing Atorvastatin Calcium offers an appropriate, practical approach to achieve a prolonged therapeutic effect by continuously releasing the medication over extended period of time. The addition of gas generating agent was essential to achieve *in vitro* buoyancy. The results of the *in vitro* drug release and *in vitro* buoyancy study showed that the optimized formulation (F9) using Karaya gum with 1: 7 ratio showed (87.66 %) up to 8h and remained buoyant for >12 h.

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