INTERNATIONAL JOURNAL OF CURRENT ADVANCED RESEARCH
ISSN: O: 2319-6475, ISSN: P: 2319-6505, Impact Factor: 6.614
Available Online at www.journalijcar.org
Volume 12; Issue 07(B); July 2023; Page No. 2344-2351
DOI: http://dx.doi.org/10.24327/ijcar.2023.2351.1508

Research Article

FORMULATION AND EVALUATION OF ATORVASTATIN CALCIUM EFFERVESCENT FLOATING TABLETS

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A R T I C L E I N F O

Article History:
Received 13th April, 2023
Received in revised form 11th May, 2023
Accepted 8th June, 2023
Published online 28th July, 2023

Key words:

Atorvastatin calcium, Effervescent floating tablets, HPMC, Xanthan gum, *In-vitro* evaluation.

A B S T R A C T

The aim of present research work is to develop an ideal floating drug delivery system using Atorvastatin calcium to increase the gastric residence time in stomach and also to assess the *in-vitro* quality control tests for prepared tablet formulation. Materials and Methods: In this study Atorvastatin calcium tablets were prepared using xanthan gum, PVPK30 and HPMCK4M as polymers, sodium bicarbonate as gas releasing agents, citric acid and tartaric acid as acidifying agents, talc and magnesium stearate as flow promoters and avicel pH 101 as a diluent. Direct compression method was used by using a rotary compression machine. Before compression, granular material was evaluated for precompression parameters such as angle of repose, bulk density, tapped density, carr's index and hausner's ratio. After punching, tablets were evaluated for weight variation, friability, hardness, drug content, floating lag time, buoyancy and cumulative percent drug release. The formulations were optimised for different concentrations of HPMCK4M and xanthan gum and their formulations. Optimized formulations were subjected to stability studies and characterization by FTIR. Results and Discussion: All prepared tablets showed good *in-vitro* buoyancy for >9 to>24hours. Optimized formulation showed cumulative percent drug release of 92.8±0.12%, buoyancy lag time 41±0.09sec and duration of buoyancy >24±0.3. Release kinetics of optimized formulation showed zero order with non-fickian diffusion. Conclusion: Out of all nine formulations, F6 has 80mg of xanthan gum was considered as best formulation based on buoyancy, swelling studies and drug release mechanism corresponds to zero order and non-fickian diffusion.

INTRODUCTION

The oral route best and most popular way to distribute medications to the systemic circulation is orally [(1)]. Drugs having a well-controlled release profile and a longer period of action are the subjects of ongoing research. Increasing the dosage in the gastrointestinal tract by lengthening stomach residence time poses the greatest obstacle, even though it is less intrusive. The main routes for medication absorption are the stomach and upper small intestine [(2)]. By increasing the residence duration, which increases drug bioavailability, repeated administration of These are the dose forms that are utilised the most frequently. They offer good physicochemical stability and simple methods of administering active pharmacological ingredients (API) [(3,4)]. medicine is released slowly at the desired pace because the device floats over the gastric contents, prolonging gastric retention duration and reducing dose frequency [(5)]. Local drug administration to specific areas, such as the stomach and proximal small intestine, is made possible via floating drug delivery systems. It exhibits high absorption, improved therapeutic action, and significant patient advantages [(6)]. Effervescent tablets are tablets which are developed to dissolve in water, and release carbon dioxide. To use them, they are dropped into water to make a solution [(6)]. These tablets along with the active medicament, also contain ingredients like sodium bicarbonate, citric acid, and tartaric acid. when tablets are dropped in the presence of water, liberating carbon dioxide, and producing effervescence leading to the dissolution of the tablet, thus fastening solution formation and increasing the palatability.

Atorvastatin is a benzimidazole derivative and is a It is a type of HMG-CoA reductase inhibitor and a type of statin and called as Lipitor. Atorvastatin Calcium is absorbed orally about 15 percent [(4)]. It shows the first pass effect in liver and gastro-intestinal metabolism. It helps to stop feeling or being sick, nausea or vomiting.

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Mechanism of Floating Systems

Various attempts have been made to retain the dosage form in the stomach as a way of increasing the retention time. These attempts include: 1. Introducing floating dosage forms (gas generating systems or swelling or expanding systems), 2. Mucoadhesive systems, 3. Drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of the drug, the residual system is eliminated from the stomach [(7)]. This results in an increased gastric retentive time (GRT) and control of the fluctuations in the plasma drug concentrations. To measure the floating force kinetics, a novel apparatus for determination of resultant weight has been reported in the literature. The apparatus operates by measuring continuously the force equivalent to F as a function of time that is required to maintain the submerged objects [(15)]. The apparatus helps in optimising FDDS with respect to stability and durability of floating forces produced to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations.

$F= F_{buoyancy}-F_{gravity}= (Df – Ds)\ gV$

Where F=total vertical force, Df =fluid density, Ds =object density, V=volume, g=acceleration due to gravity.

MATERIALS AND METHODS

Formulation and Evaluation of Atorvastatin Calcium Effervescent Tablets

Atorvastatin was kindly supplied as a gift sample from Sri Krishna pharmaceuticals limited, Hyderabad, India. Xanthan gum & PVP K30 were supplied by Research lab fine industries, Mumbai, India and HPMC K4M was supplied by SD fine chem Ltd, Hyderabad, India. Sodium bicarbonate, Citric acid & Tartaric acid were supplied by Merck specialities Pvt Ltd, Mumbai, India. Talc, Magnesium stearate and Avicel PH 101 supplied by SD fine chem Ltd, Hyderabad, India. All chemicals were of analytical grade and distilled water was used throughout the experimental studies.

Table 1 Formulation of effervescent floating tablets of atorvastatin calcium

Formulation Code	Drug (mg)	HPMC K4M (mg)	Xanthan gum (mg)	PVP K30	Sodium bicarbonate (mg)	Citric acid (mg)	Tartaric acid (mg)	Avicel PH101 (mg)	Talc (mg)	Magnesiumstearate (mg)	Total weight (mg)
F1	30	40	-	-	50	40	10	68	6	6	250
F2	30	60	-	-	50	40	10	48	6	6	250
F3	30	80	-	-	50	40	10	28	6	6	250
F4	30	-	40	-	50	40	10	68	6	6	250
F5	30	-	60	-	50	40	10	48	6	6	250
F6	30	-	80	-	50	40	10	28	6	6	250
F7	30	-	-	40	50	40	10	68	6	6	250
F8	30	-	-	60	50	40	10	48	6	6	250
F9	30	-	-	80	50	40	10	28	6	6	250

Preparation of Standard Graph of Atorvastatin Calcium in 0.1n Hydrochloric Acid

8.3 ml of concentrated hydrochloric acid was taken and dissolved in distilled water up to 1000 ml to get 0.1N HCl.

Preparation of Atorvastatin Calcium Stock Solution

50 mg of drug was taken and dissolved in 50 ml of 0.1N HCl to make final concentration of 1000 µg/ml. From this stock solution, take 5 ml and diluted to 50 ml with 0.1N HCl to get 100 µg/ml, further dilution was done taking 1ml, 2ml, 3ml, 4ml, 5 ml and 6 ml making up to 100 ml to get a working standard solution of 1, 2, 3, 4, 5 and 6 µg/ml. These solutions were scanned in double beam UV spectrophotometer (Lab India UV 3200) between 200-400 nm and the **λ**max was found to be 246 nm [(9)].

Preparation of Floating Effervescent Tablets Of Atorvastatin

In the present study Atorvastatin Calcium floating effervescent tablets were prepared using Direct Compression technique. The excipients used were Avicel pH 101 as diluent and PVPK30 was used as binder. HPMC K4M and Xanthan Gum were used as swelling and rate controlling polymers. Sodium Bicarbonate was used as gas releasing agent, Citric Acid as acidifying agents and Magnesium Stearate was used as lubricant. Based on preparations availability in the market the tablet weight was fixed. All the ingredients and Atorvastatin Calcium were weighed accurately and mixed in the ascending order of their weights, passed through sieve no 22 to get uniform mixing, then Talc and Magnesium Stearate were then added and punched by using a 16-station rotary tablet compression machine with flat 8mm punches. The total weight of the tablet was made up to 250 mg. The tablets were then weighed and compared with their initial weights and percentage friability was calculated. The powdered blend was prepared as shown in table 1.

Evaluation of Atorvastatin Calcium Effervescent Tablets

Evaluation of Blends

The flow properties of the powder were very important in handling and processing operations. Hence the following micromeritic properties were studied on the Atorvastatin Calcium powder formulations.

Angle of repose (θ)

It is described as the maximum possible angle among the surface piles of powder to the horizontal plane [(14)].

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

Where θ-is repose angle, h is height in cm and r is radius in cm

The angle of repose was analysed by means of conventional fixed funnel processes. 100 gm of the drug powder had flown through the funnel which was fixed to the stand at a fixed height (h). Then the height and radius of the powder bed was noted.

Bulk density (Db)

This is defined as the ratio of mass of the powder formulation to the volume of powder bulk. It was determined by placing 100 gm of powder material into the measuring cylinder and

noted the initial volume of the powder. This is called a bulk volume. Through this bulk volume, bulk density was calculated by using the following formula [9,13].

Db= M/Vb

Where M is powder formulation mass. Vb is powder formulation bulk volume. Db is the bulk density of powder.

Tapped density (Dt)

It is defined as the ratio of mass of total powder to the tapped volume of powder. This was determined by tapping the 100 gm of powder for 75 times and noted the volume using tap density tester USP (Bulk density apparatus, Secor, India). The tapping is further continued till the difference between two successive volumes is <2% and is expressed in gm/ml, given by [7,13].

Dt=M/Vt

Where M is powder formulation mass, Vt is powder formulation tapped volume.

Carr's Index (Compressibility percentage)

It can be calculated from bulk and tapped density which shows powder flow properties and is expressed as

I = Dt-Db / Dt X100 Where Dt is tapped density of the powder and Db is the bulk density of the powder [18,22].

Hausner's Ratio

It is an indirect index of ease of powder flow and is calculated from the bulk and tapped density of Atorvastatin Calcium powder formulation, expressed as [16,20].

Hausner's ratio = Dt /Db

Where Dt is powder formulation tapped density and Db is powder formulation bulk density

Determination of Physical Properties of Tablets

The tablets from each formulation were subjected to the following tests.

Appearance

The general appearance of the tablet, and overall elegance and visual identity is very much needed for consumer acceptance [11,22].

Tablet thickness and diameter

Thickness and diameter of the tablet is a very important characteristic in reproducing appearance. Some filling equipment utilises the counting mechanism to get uniform thickness. Randomly 10 tablets were taken from each formulation and the thickness and diameter was determined with a vernier calliper (Mitutoyo, Japan). The size of the tablet should be dimensionally described, monitored, and controlled [8,10,14].

Weight variation

A group of 20 tablets were taken from each formulation randomly selected and weighed using an electronic balance (Mettler-Toledo, Switzerland) Then individual weight of each tablet was determined using digital electronic balance and was compared with average weight [9,10].

Hardness of tablets

Strength of the tablet is defined as tensile strength (N: Newton). The crushing load on a tablet is defined as the force necessary to fracture a tablet into 2 halves by applying compression. The hardness of the tablet was measured by tablet hardness tester (Monsanto hardness tester, India) [12,18].

Friability

It is a measurement of the mechanical strength of a tablet. The friability is determined to evaluate the effects of rubbing and shocks which may frequently cause tablet to damage, cap or rupture. For this purpose, Friabilator (Roche friabilator Analab, India). A pre-weighed group of 20 tablets was charged in the fabrilator and subjected to 100 revolutions (USP). The dusted tablets were then reweighed. Compressed tablets must not drop more than 1% of their weight [19]. The friability (F) is expressed by F= W initial-W final / W initial x100

Drug content

20 tablets were randomly selected and weighed. The average weight was noted. Tablets were crushed in a mortar pestle, powder equivalent to 10mg of Atorvastatin Calcium was taken, shaken, and diluted with 0.1N HCl in 100 ml volumetric flask. Filter the solution and to the necessary dilutions using 0.1NHCl to get 5 µg/ml of Atorvastatin Calcium. Measure the absorbance of the resulting solution at 246 nm against a blank solution containing all the components except the drug and analysed using a double beam UV spectrophotometer (Lab India UV 3200) [11,17].

Swelling index

The swelling behaviour of the tablets was determined in triplicate, tablets were weighed individually and placed in a glass beaker, containing 200 ml of 0.1 N HCl, placed in a water bath at 37 ºC ± 0.5 ºC. At fixed time intervals, the tablets were removed, and the excess surface liquid was carefully removed using tissue paper. The swollen tablets were then re-weighed. The percentage swelling Index (SI) was calculated using the formula [21].

$(SI\%) = W_{final} - W_{Initial} / W_{final} \times 100$

Buoyancy lag time

The floating lag time (FLT) is determined by taking three tablets randomly and placing them im in a beaker containing 200 mL of 0.1 N HCl with a temperature maintained at 37±0.5 ºC using a water bath. The time required for the tablet to rise from the bottom of the beaker to the surface and float was determined [13].

Duration of buoyancy

The total floating duration, that is, the time during which the tablet remains buoyant, was recorded to be the Floating Lag Time (FLT) and the duration of time in which the tablet constantly floated is called Total floating time [13,18].

Cumulative percentage in vitro drug release

In vitro dissolution study of Atorvastatin Calcium tablets was carried out in USP Dissolution apparatus type II in 900 ml of 0.1 N HCl and the temperature was maintained at 37± 0.5ºC with a rotating speed of 75 rpm. Samples of 10 ml were withdrawn from the isolation apparatus at pre-determined intervals i.e., 0.5 hr, 1 hr, 2 hr, 3hr, 4hr, 5hr, 6hr, 7hr, 8hr, 9hr, 10hr, 11hr, 12 hr and 24 hr analysed using double beam UV spectrophotometer (Lab India UV 3200) between 200-400 nm.

Application of Release Rate Kinetics to Dissolution Data

The in vitro dissolution data of optimised formulation F6 was subjected to examine kinetics of drug release rate by plotting the release rates of drug at different time intervals in Zero order, First order, Higuchi and Korsemeyer Peppa's plot.

Characterization of Atorvastatin Calcium Effervescent Floating Tablets

Fourier Transform Infrared Spectroscopy (FT-IR) Studies

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 400 to 4000 cm-1 and 1 cm-1 resolution using (Bruker alpha FT-IR/ATR, Lab India) FT-IR with ATR facility. The sample was placed and scanned. In the spectra, that was appeared on the screen, the baseline was corrected. The similar spectrum was also taken for placebo tablets as well as for optimised Atorvastatin Calcium effervescent floating tablets. Compare this spectrum of Atorvastatin Calcium effervescent floating formulation and placebo tablets with standard atorvastatin [14,17].

RESULTS AND DISCUSSIONS

Standard graph of Atorvastatin Calcium in 0.1N HCl

Atorvastatin calcium has maximum absorbance at 246 nm. The standard graph of in Atorvastatin Calcium 0.1NHCl was plotted by taking the concentration range from 1µg/ml to 6µg/ml. The calibration curve for Atorvastatin Calcium in 0.1N hydrochloric acid was linear from 1µg/ml to 6µg/ml with R^2>0.999.

Table 2 Standard graph of Atorvastatin Calcium 0.1NHCl

Standard graph of Atorvastatin Calcium 0.1NHCl	
Concentration(µg/ml)	Absorbance
1	0.109
2	0.222
3	0.329
4	0.432
5	0.541
6	0.65

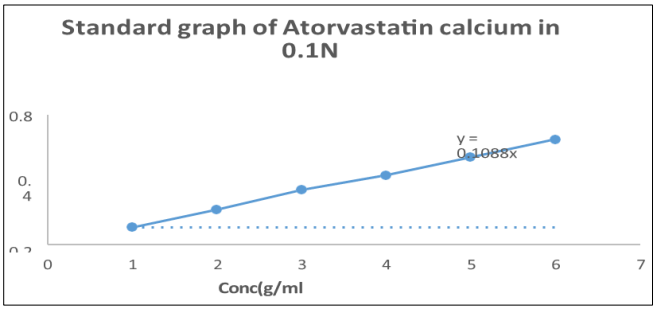

Figure 1 Standard graph of Atorvastatin calcium 0.1N HCl

Evaluation of Atarvastatin Effervescent Tablets

Evaluation of blend

The micromeritic properties of Atorvastatin Calcium powder formulation is essential in handling operations because the uniformity of the dose and ease of filling the powder into the container is determined by its flow properties. The powder formulation flow properties can be accessed from Carr's index, Hausner's ratio and angle of repose. Results for powder formulation formulations were represented in Table 3. Results indicate angle of repose ≤31.7±0.14° assuring that the flow properties were good for all the formulations. Apart from this, Carr's index and Hausner's ratio were ≤15.3±0.15 % and ≤ 1.18±0.15 respectively for all the nine formulations and showed good mixing, flowability and compressibility.

Table 3 Pre compression parameters of powder (F1 to F9) (n=3, mean ±SD)

Formulation Code	Angle of repose (°)	Bulk density (g/cc)	Tapped density (g/cc)	Compressibility index (%)	Hausner's ratio
F1	30.2±0.15	0.22±0.12	0.25±0.31	13.6±0.03	1.12±0.03
F2	31.3±0.13	0.26±0.07	0.29±0.33	11.5±0.21	1.11±0.24
F3	30.3±0.13	0.22±0.15	0.25±0.29	12.6±0.13	1.18±0.15
F4	31.6±0.11	0.23±0.16	0.34±0.11	14.3±0.02	1.13±0.05
F5	30.7±0.10	0.26±0.12	0.30±0.13	15.3±0.15	1.15±0.12
F6	30.3±0.13	0.25±0.01	0.29±0.12	12±0.06	1.15±0.15
F7	30.6±0.15	0.25±0.13	0.28±0.17	12±0.04	1.13±0.06
F8	31.7±0.14	0.29±0.22	0.34±0.11	13.3±0.16	1.12±0.17
F9	30.5±0.16	0.25±0.11	0.28±0.13	10.7±0.12	1.12±0.21

Evaluation of Prepared Atorvastatin Calcium Effervescent Tablets

The prepared tablets from each formulation are white, circular, odorless which were analyzed for thickness, diameter, weight variation, hardness, friability, buoyancy lag time, duration of buoyancy, swelling index, *in vitro* dissolution and drug content showed in tables-4.3 and table-4.4**.** The diameter and thickness of all the tablet formulations were almost uniform. The average weight of the tablet in all formulations ranged from 249±0.07 mg to 251 ±0.12 mg. All the tablets formulated in this studymet the USP needs for weight variation (USP 31)**.** The hardness of the tablets ranged from 3.9±0.08to 4.1±0.07kg/cm^2 which indicated good mechanical strength during compression. The percentage friability for all nine formulations ranged from to 0.15±0.01 to 0.38±0.11 demonstrating the friability was within the acceptable limits (USP 31), indicating that the tablets are not brittle and can handle without difficulty.

All the formulations were checked for drug content uniformity. The uniformity of drug results was good among various batches of tablets and the percentage of drug content for all formulations was found to be greater than 98.08±0.21. The results also indicated acceptable and uniform dispersionof drugs in all tablet formulations shown in Table 4.

Table 4 Post Compression evaluation parameters (n=3, mean ±SD)

Formulation code	Weight variation (mg)	Hardness (Kg/cm^2)	Friability(%)	Drug content(%)
F1	251±0.12	4.0±0.11	0.15±0.01	98.08±0.21
F2	250±0.02	3.9±0.08	0.19±0.10	99.41±0.21
F3	249±0.07	4.0±0.11	0.37±0.12	99.13±0.09
F4	251±0.02	4.1±0.07	0.34±0.01	99.14±0.07
F5	250±0.12	3.9±0.03	0.32±0.08	99.56±0.08
F6	250±0.03	4.1±0.08	0.27±0.01	99.94±0.15
F7	251±0.04	3.9±0.01	0.38±0.11	99.23±0.13
F8	250±0.11	3.8±0.02	0.37±0.08	99.24±0.13
F9	251±0.02	3.9±0.07	0.35±0.07	99.37±0.17

In-vitro buoyancy studies were performed to evaluate the duration of buoyancy and buoyancy lag time in the presence of various rate-controlling polymers. The duration of

buoyancy varied from >9±0.23hr to >24±0.04hr and buoyancy lag time varied from 60±0.04sec to >120±0.03 sec for all the nine formulations. F6 formulation exhibited a short buoyancy lag time of 43±0.09 sec as well as a high swelling index of 29.2±0.05. Xanthan gum is a natural, swellable, sustainable polymer havingzero order drug release. When this natural xanthan gum is present along with sodium bicarbonate and citric acid, upon influx into the stomach, carbon dioxide is released, causing the formulation to float in the stomach, thereby improving the bioavailability of the drug with substantial benefits, furtherdrug wastage was reduced.

Swelling index

The hydration ability of the formulation may have a significant result on tablet buoyancy and release kinetics. The swelling behavior of a tablet depends on the swellable polymers present in the formula. The formulations F1, F2, and F3 have 40mg, 60mg and 80mg of HPMC K4M. An increase in the concentration of HPMC K4M showed an increase in the viscosity of the gel layer and an increase in the time for water to reach the inner core of the tablet. F1 to F3 formulations showed swelling indices of 2.1±0.03, 2.06±0.12, and 1.98±0.12 respectively. Formulations F4, F5 and F6 showed swelling indices of 19.1±0.13, 22.6±0.14 and 29.2±0.05 respectively. Formulations F7, F8, and F9 showed swelling indices of 16.2±0.12, 18.3±0.11 and 19.4±0.06, respectively. The formulation F6 showed the highest swelling index (29.2±0.05) among all nine formulations and contained 80mg of xanthan gum per tablet. It is observed that as the percentage of xanthan gum in formulation increases the swelling rate of formulations increased as shown in Table 5.

Table 5 *In vitro* buoyancy studies and swelling index of Atorvastatin Calcium Effervescentfloating tablets (n=3, mean ± SD)

Formulation code	Buoyancy lag time(sec)	Duration of buoyancy (hr)	Swelling Index (%)
F1	70±0.13	>9±0.23	2.1±0.03
F2	73±0.03	>10±.21	2.06±0.12
F3	79±0.08	>12±0.20	1.98±0.12
F4	66±0.21	15±0.03	25.1±0.13
F5	60±0.04	18±0.12	28.6±0.14
F6	41±0.09	>24±0.03	30.3±0.05
F7	60±0.13	>24±0.04	16.2±0.12
F8	90±0.08	>24±0.03	18..3±0.11
F9	120±0.03	>24±0.02	19.4±0.06

In vitro Dissolution Studies

In vitro dissolution studies of all the floating effervescent tablet formulations of Atorvastatin Calciumwere carried out in 0.1NHCl in 900ml for up to 24 hr. At different time intervals, cumulative percent drug release was calculated.[40] The *in vitro* drug release data of all formulations from F1 to F9 was tabulated in Table 6. The percent cumulative drug release verse time in hours was plotted and was shown in Fig. 2.

Formulations F1, F2 and F3 had HPMC K4M at 40mg, 60mg and 80mg, while formulations F4, F5and F6 were prepared by using xanthan gum 40mg, 60mg and 80mg and formulations F7, F8 andF9 were prepared by using PVPK30 as 40mg, 60mg and 80mg each in each formulation respectively. Cumulative percent release for 24 h for F1 to F9 ranges from 79.7±0.02 to 92.8±0.12 Among all nine formulations, F6 showed the maximum percentage of drug release 92.8 ±0.12 % within 24 hours. As the concentration of xanthan gum increases in formulations showed greater release for prolonged periods at higher rates. Hence F6 formulation containing xanthan gum as 80mg was optimised formulation.

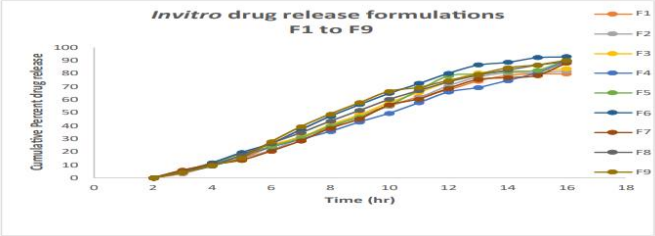

Figure 2 In vitro drug release formulations (F1 to F9)

Application of Release Rate Kinetics to Dissolution Data

From the *in vitro* dissolution studies, the optimised formulation F6 was further tested for the mechanism of drug release kinetics. The data were fitted into Zero order, first order, Higuchi and Korsmeyer Peppas mathematical models to study the drug release mechanism. The drug release mechanism was inferred to be zero order and non-Fickian diffusion in the sense that drug release was independent of the concentration of drug, and the mechanism of drug release in F6 is swellingor relaxation of the polymer chain.

Table 6 Cumulative percent drug release of formulations F1 to F9 (n=3, mean ± SD)

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
0.5	3.2±0.12	3.56±0.10	4.22±0.08	5.22±0.04	5.24±0.06	4.23±0.08	5.86±0.12	4.32±0.11	4.08±0.110
1	9.58±0.08	9.13±0.06	10.19±0.02	10.45±0.08	11.52±0.04	11.41±0.01	10.21±0.12	9.05±0.08	9.56±0.02
2	14.87±0.02	14.84±0.01	18.95±0.10	16.87±0.08	18.52±0.01	19.42±0.09	13.55±0.14	17.32±0.04.	15.24±0.12
3	23.95±0.06	21.07±0.01	25.68±0.08	23.61±0.13	24.09±0.02	26.44±0.06	20.53±0.09	26.47±0.03	27.62±0.12
4	31.45±0.04	30.42±0.10	31.09±0.09	29.52±0.02	30.47±0.08	36.93±0.03	28.41±0.04	34.51±0.08	39.07±0.13
5	38.13±0.07	39.57±0.09	40.66±0.13	35.57±0.11	39.63±0.13.	47.22±0.06	37.93±0.10	43.42±0.15	48.86±0.08
6	48.42±0.10	47.12±0.11	48.31±0.09	42.84±0.04	46.52±0.06	56.23±0.02	45.22±0.06	51.73±0.04	57.54±0.06
7	55.06±0.13	55.07±0.03	57.76±0.05	49.53±0.08	55.67±0.10	64.84±0.06	55.92±0.13	60.14±0.09	66.32±0.02
8	62.13±0.014	61.46±0.02	65.53±0.02	57.52±0.16	67.09±0.07	72.33±0.02	60.43±0.01	66.95±0.6	69.21±0.01
9	67.45±0.16	70.45±0.11	73.67±0.02	65.74±0.07	78.08±0.13	80.21±0.12	68.52±0.01	73.52±0.08	74.53±0.10
10	74.21±0.11	77.11±0.16	80.42±0.08	69.15±0.15	79.56±0.07	86.53±0.08	75.32±0.10	78.63±0.13	79.22±0.02
11	78.42±0.08	80.43±0.07	81.57±0.10	74.53±0.13	81.54±0.15	88.62±0.10	76.78±0.02	82.64±0.04	84.21±0.02
12	79.67±0.03	80.52±0.05	82.08±0.08	80.51±0.07	82.43±0.11	92.21±0.11	78.42±0.08	86.31±0.01	86.45±0.02
24	79.7±0.02	81.8±0.11	83.6±0.14	89.4±0.06	90.1±0.05	92.8±0.12	88.1±0.03	89.15±0.07	89.97±0.13

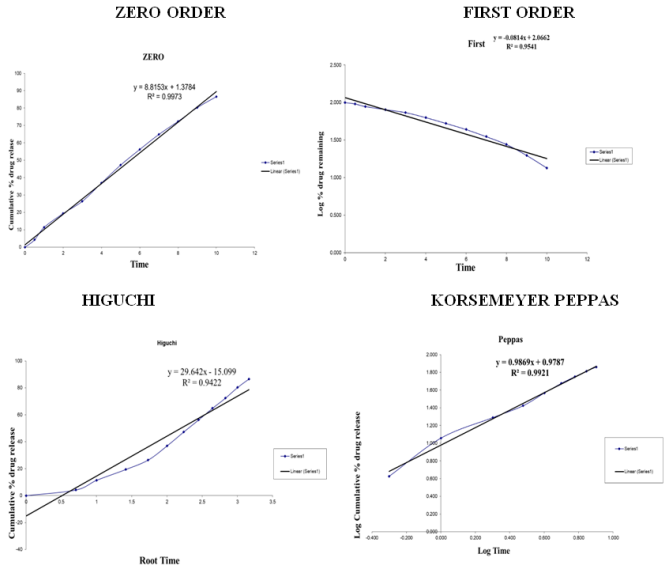

Figure 3 Release kinetic mathematical models of optimised formulation F6

Table 7 Kinetic Mathematical Model Applied To In Vitro Release Data of F6

Formulation Code	Zero order	First order	Higuchi kinetics	Korsmeyer peppas	
F6	R^2 0.9973	R^2 0.9541	R^2 0.9422	N 0.98	R^2 0.9891

Characterization of Atorvastatin Calcium Effervescent FloatingTablets

Fourier Transform Infrared Spectroscopy (FT-IR) Studies

FTIR spectra of Atorvastatin Calcium effervescent floating tablets and Atorvastatin Calcium standard were shown in Figure 4. The significant all peaks of Atorvastatin Calcium were present in the entire spectrum obtained between drug and excipients. The FTIR spectra revealed that there is no interaction between drug and formulation excipients.

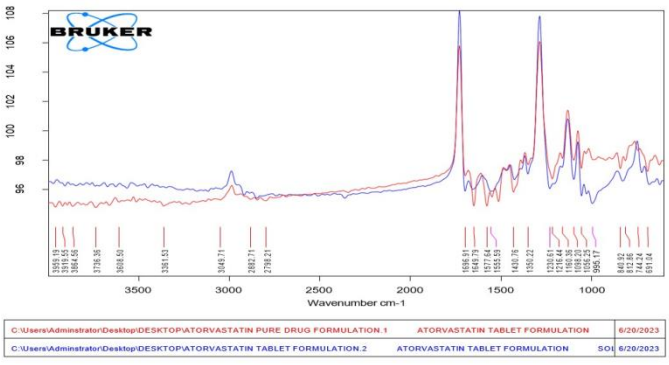

Figure 4 FTIR spectra's of a) Atorvastatin Calcium effervescent floating tablet formulation b) Atorvastatin Calcium standard

DISCUSSION

In the current study floating Atorvastatin Calcium effervescent tablets were prepared using PVPK30, HPMC K4M, xanthan gum as swelling and rate-controlling polymers, sodium bicarbonate as gas releasing agent, citric and tartaric acid as acidifying agent, talc, and magnesium stearate aslubricants.

Direct compression technique was employed, and tablet weight was fixed as 250mg.

All the ingredients and Atorvastatin Calcium were weighed accurately and mixed in the ascending order of their weights, passed through sieve no 22 to get uniform sized powder formulations. Then these powders formulations were passed through sieve no 22 . Then talc and magnesium stearate were added to the powder formulation and punched by using a 16-station rotary tablet punching machine with flat 10mm punches. The micromeritic properties of Atorvastatin Calcium powder formulation can be accessed from Carr's index, Hausner's ratio and angle of repose. Results indicate angle of repose ≤31.7±0.14° assuring that the flow properties were good for all the formulations. Apart from this, Carr's index and Hausner's ratio were ≤15.3±0.15 % and ≤ 1.18±0.15 respectively for all the nine formulations and showed good mixing, flowability and compressibility.

The prepared tablets from each formulation are white, circular, odorless which were analyzed for thickness, diameter, weight variation, hardness, friability, buoyancy lag time, duration of buoyancy, swelling index, *in vitro* dissolution, and drug content. The diameter and thickness of all the tablet formulations were almost uniform. The average weight of the tablet in all formulations ranged from 249±0.07 mg to 251 ±0.12 mg. All the tablets formulated in this study met the USP needs for weight variation (USP 31). The hardness of the tablets ranged from 3.9±0.08 to 4.1±0.07kg/cm^2 which indicated good mechanical strength during compression. The percentage friability for all nine formulations ranged from to 0.15±0.01 to 0.38±0.11 demonstrating the friability was within the acceptable limits (USP 31), indicating that the tablets are not brittle and can handle without difficulty.

All the formulations were checked for drug content uniformity. The uniformity of drug results was good among various batches of tablets and the percentage of drug content for all formulations was found to be greater than 98.08±0.21. The results also indicated acceptable and uniform dispersionof drugs in all tablet formulations. In *In vitro* buoyancy studies were performed. The duration of buoyancy varied from >9±0.23hr to >24±0.04hr and buoyancy lag time varied from 60±0.04sec to >120±0.03 sec for all the nine formulations. F6 formulation exhibited a short buoyancy lag time of 41±0.09 sec as well as a high swelling index of 30.3±0.05. Xanthan gum is a natural, swellable, sustainable polymer having zero order drug release. When this natural xanthan gum is present alongwith sodium bicarbonate and citric acid, upon influx into the stomach, carbon dioxide is released, causing the formulation to float in the stomach, thereby improving the bioavailability of the drug with substantial benefits, further drug wastage was reduced.

The swelling behavior of a tablet depends on the swellable polymers present in the formula. The formulations F1, F2, and F3 have 40mg, 60mg and 80mg of HPMC K4M. An increase in the concentration of HPMC K4M showed an increase in the viscosity of the gel layer and an increase in the time for water to reach the inner core of the tablet. F1 to F3 formulations showed swelling indices of 2.1±0.03, 2.06±0.12, and 1.98±0.12 separately. F4, F5 and F6 showed swelling indices of 19.1±0.13, 22.6±0.14 and 29.2±0.05 respectively. F7, F8, and F9 showed swelling indices of 16.2±0.12, 18.3±0.11 and 19.4±0.06, respectively. F6 showed the highest swelling index 29.2±0.05and contained 80mg of xanthan gum per tablet. It is observed that as the percentage of xanthan gum in formulation increases the swelling rate of formulations increased.

In vitro dissolution studies of Atorvastatin Calcium tablets were carried out in 0.1NHCl in 900ml for up to 24 hr. At fixed time intervals, cumulative percent drug release was calculated. The percent cumulative drug release verse time in hours was plotted. F1, F2 and F3 had HPMC K4M at 40mg, 60mg and 80mg, while F4, F5 and F6 were prepared by using xanthan gum 40mg, 60mg and 80mgand F7, F8 and F9 were prepared by using in combinations both xanthan gum and HPMC K4M as 20mg, 30mg and 40mg each in each formulation respectively. Cumulative percent release for 24 hfor F1 to F9 ranges from 79.7±0.02 to 92.8±0.12 Among all nine formulations, F6 showed the maximum percentage of drug release 92.8±0.12% within 24 hours. As the concentration of xanthan gum increases in formulations showed greater release for prolonged periods at higher rates. Hence F6 formulation containing xanthan gum as 80 mg was optimized formulation.
From the *in vitro* dissolution studies, the optimized formulation F6 dissolution data was used for themechanism of drug release kinetics. The data were fitted into Zero order, first order, Higuchi and Kors Meyer, Peppas models to study the drug release mechanisms. The drug release mechanism was found to be zero order and non-Fickian diffusion in the sense that drug release was independentof the concentration of drug, and the mechanism of drug release in F6 is swelling or relaxation of the polymer chain.

The FTIR spectra showed that there are no significant changes in chemical integrity of drug formulation.

CONCLUSION

Atorvastatin effervescent floating tablets were prepared using HPMC K4M and xanthan gum as polymers in various proportions. Direct compression technique was proceeded. The results of present research exhibited that the tablet containing atorvastatin calcium alone cannot effectively maintain its release rates for 24hrs. In the present study this problem can be minimized by using xanthan gum in various proportions, which helps in increasing the viscosity of the dissolution fluid, thereby prolonging the release of the drug at higher release rates for 24 hours. Among all nine formulations, the F6 formulation containing 80 mg of xanthan gum was considered the best formulation based on buoyancy and swelling studies. From the present study, it was concluded that the formulation F6 has shown high swelling or relaxation of polymers. The drug release mechanisms of F6 formulation correspond to zero order and Non-fickian diffusion behavior.

Acknowledgment

We would like to thank the management of Sarojini Naidu Vanita Pharmacy Maha Vidyalaya for providing access to research facility.

Conflict of Interest

The authors declare that there is no conflict of interest.

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How to cite this article:

Balusu Haarika *et al* (2023) 'Formulation and Evaluation of Atorvastatin Calcium Effervescent Floating Tablets', *International Journal of Current Advanced Research*, 12(07), pp. 2344-2351.
DOI: http://dx.doi.org/10.24327/ijcar.2023.2351.1508

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