Research Article

Formulation and Evaluation of Atorvastatin Calcium Floating tablets'

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ABSTRACT:

This investigation describes the preparation and in-vitro evaluation of floating tablets of Atorvastatin Calcium. Some drugs are absorbed in particular portion of the GIT only or absorbed to difficult event in various segments of the GIT. Such drugs are said to have an absorption window which identifies the drug's primary region of absorption in the GIT. This formulation of Atorvastatin Calcium tablets is prepared using Polymers like Xanthan gum, Guar gum, Sodium alginate. Where Sodium bicarbonate and Citric acid are used as effervescent agents to float the tablet in various concentration. The tablets prepared by direct compression technique were evaluated by various quality parameters including weight variation, hardness, and buoyancy studies. Formulation was optimized on basis of floating time and in-vitro release. The seven formulations were developed and evaluated for Pre-compression parameters of Angle of repose, Bulk density, Tapped density, Hausner's ratio,Compressibility index and uniformity of index & uniformity of weight variation. For the Post-compression parameters of hardness, thickness, friability, floating lag time, in-vitro dissolution investigation and FTIR along with DSC were given satisfactory results.In terms of extended release over a 14-hour period, the F1 & F5 formulation performed better than any other. The formulation showed a release of 98.82% CDR and 98.87% CDR respectively.

Key Words: Atorvastatin Calcium, Buoyancy, in-vitro, absorption window

INTRODUCTION:

The gastric emptying process, gastrointestinal transit time, drug release from the dosage form, and site of absorption all play a role in the oral route's potential and efficacy as a drug delivery route.

The efficacy of oral dose forms is limited by physiological factors such as unpredictable gastrointestinal transit, partial drug release, and a shorter period spent in the stomach. A large range of inter- and intra-subject variability in gastric emptying can result from medications with an absorption window in the upper section of the small intestine that may not be fully absorbed. Given that many medications are effectively absorbed in the upper gastrointestinal tract, this variability can lead to non-uniform absorption and unexpected bioavailability. Hence a beneficial delivery system would be one which possesses the ability to control and prolong the gastric emptying time and can deliver drugs in higher concentrations to the absorption site (i.e. upper part of the small intestine). Hollow microspheres are a key component in FDDS, enhancing the performance of hydro dynamically balanced systems (HBS), gas generating systems, and raft forming systems, each with its own advantages and limitations. FDDS is a formulation of a drug with gel forming hydrocolloids meant to remain buoyant in the stomach contents. Drug dissolution and release from the dosage form retained in the stomach fluids occur at the pH of the stomach under fairly controlled conditions. The retentive characteristics of the dosage form are not significant for the drugs that are insoluble in intestinal fluids, act locally and exhibit site-specific absorption. Gastric retention is significantly influenced by the stomach's solubility, which makes it possible to efficiently administer medications like furosemide, cyclosporine, ciprofloxacin, and metformin. However, medications like chlordiazepoxide and cinnarizine that have a reduced solubility in the small intestine are more likely to degrade. The drugs for local action in the stomach (e.g. misoprostol) can be delivered in the form of dosage forms with gastric retention. Antibiotics, catecholamine's,

sedative, analgesics, anticonvulsants, muscle relaxants, antihypertensive and vitamins can be administered in HBS dosage form. Since FDDS, a first proposed in 1962, has a lower bulk density than gastric fluids, it can float freely in the stomach without slowing down the rate at which the stomach empties. This buoyancy enables the medication to be delivered gradually, increasing GRT and improving control of changes in plasma drug concentration in the stomach.[4]

MATERIAL AND METHOD

Preparation of Standard stock solution for Atorvastatin calcium*:* 10mg of Atorvastatin calcium drug and 100ml of methanol is added up to the mark in 100ml volumetric flask that yields 1milligrams per millilitre (i.e 1st stock solution)**.** From stock solution A, pipette out 10 ml (10 mg/10 ml) into a 100 ml volumetric flask. Dilute with 100 ml of methanol to the point where (100 µg/1 ml) is obtained. Pipette out 2ml, 4ml, 6ml, 8ml, and 10ml respectively from stock B solution, this solution is scanned at 246 nm in UV spectroscopy and data's were recorded. Concentration on the X-axis and absorbance on the Y-axis are used to plot the graph.

Calibration curve of Atorvastatin calcium using 1.2 pH phosphate buffers: 10mg of Atorvastatin calcium drug dissolved in 100ml of pH 1.2 buffer in a volumetric flask that is 100 ml in size. It produces 1 mg/ml. Pipette 10 ml of stock solution A, into a 100 ml volumetric flask, then dilute to the proper concentration using pH 1.2 buffer**.** Pipette out 2ml, 4ml, 6ml, 8ml, and 10ml respectively from stock B solution, this solution is scanned at 246 nm in ultra-violet spectroscopy and data's were recorded. Concentration on the X-axis and absorbance on the Y-axis are used to plot the graph. The same procedure is followed for pH 7.4

PREPARATION OF ATORVASTATIN CALCIUM FLOATING TABLETS

The Atorvastatin calcium floating tablet was produced utilizing the direct compression technique, and all of the components were triturated in a mortar and pestle to produce a uniform powder. The many different polymers are utilized in varying ratios, along with effervescent agents to help the tablet float in various concentrations, before glident and additives are added.then the tablet is punched using a rotary tablet compression machine once pre formulation parameters have been examined. And then the hardness of the tablet is evaluated using a pflizer tester. Examining and evaluating the floating tablet.

SL.NO	INGREDIENTS	F1	F2	F3	F4	F5	F6	F7
1	Atorvastatin calcium	10	10	10	10	10	10	10
2	Guar gum	35	25	15	-	50	30	20
3	Xanthan gum	30	35	25	45	-	50	15
4	Sodium alginate	15	20	40	35	30	-	45
5	Sodium bicarbonate	90	90	90	90	90	90	90
6	Citric acid	30	30	30	30	30	30	30
7	Polyvinyl pyrrolidone	25	25	25	25	25	25	25
8	Magnesium stearate	1.0	1.0	1.0	1.0	1.0	1.0	1.0
9	Talc	1.0	1.0	1.0	1.0	1.0	1.0	1.0
10	Lactose	13	13	13	13	13	13	13
	Total weight	250	250	250	250	250	250	250

Table No -1: Formulation of Atorvastatin calcium floating tablets

Pre-compression parameters of Atorvastatin calcium floating tablets

1. **BULK DENSITY[34] :**

It refers to how granules are packaged. The bulk density of the produced granules was evaluated using bulk density measurement equipment. The dosage is supplied by and is shown in gm/ml.And it is stated by,

$$\text{Bulk density} = \frac{\text{Mass of the powder}}{\text{Volume of the bulk powder}}$$

2. **TAPPED DENSITY[34] :**

The weighed tablet mixture had been poured into a graduated cylinder. It was noted the quantity of drug was present. The cylinder was then subjected to 100, 200, and 300 taps in a tap density device. USP states that it was stated by.

$$\text{Tapped density} = \frac{\text{Mass of the powder}}{\text{Tapped volume of the powder}}$$

3. HAUSNER'S RATIO[34]:

It is a measurement of the frictional resistance of the tablet composition. The ideal range should be between 1.2 and 1.5. The ratio of tap density to bulk density was used to estimate it.

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

4. CARR'S INDEX[34]:

The Hausner ratio and compressibility index were utilized to determine how much powder could be compacted. To examine the tablet's packing capabilities, the change in volume that arises from packing rearrangement during tapping was used. And it was determined by using the formula below.

$$\text{Carr's index (\%)} = \frac{\text{Tapped density - Bulk density}}{\text{Tapped density}} \times 100$$

Sr.No	Carr's index	Type of flow
1	5 – 15	Excellent
2	15 – 18	Good
3	18 – 23	Fair to passable
4	23 – 35	Poor
5	35 – 38	Very poor
6	≥40	Extremely poor

5. ANGLE OF REPOSE[35]:

The angle of repose of the powder was determined by the funnel method. The properly measured granules have been poured into the funnel. The funnel was raised to a height where the tip just touched the top of the powder pile (2.0 cm above the hard surface). The granules were allowed to freely pour onto the surface through the funnel.

Sr.No	Angle of repose	Type of flow
1	≤ 25	Excellent
2	25 – 30	Good
3	30 – 40	Passable
4	≥ 40	Very poor

The diameter of the powdered cone was measured, and the following equation was used to calculate the angle of repose:

$$\tan \Theta = \frac{h}{r}$$

Where, Θ = Angle of repose

h = Height of powder heap

r = Radius of the powder cone

POST COMPRESSION PARAMETERS OF ATORVASTATIN CALCIUM FLOATING TABLETS

1. **HARDNESS[36]:**

   The product's hardness has been determined using a Pfizer hardness tester. Five manufactured floating tablets were used for the investigations into hardness uniformity. The hardness data was used to calculate the mean, standard deviation, and percentage of friability. Kg/cm2 was used to measure it. Three tablets were selected at random, and their hardness was determined.

2. **THICKNESS[36]:**

   From the prepared formulation, ten tablets were randomly selected for thickness uniformity testing and were measured in millimeters with a vernier calliper. Using the collected data, mean and standard deviation were calculated.

3. **FRIABILATOR[36]:**

   Using the Roche Friabilator, the friability of the tablets was measured. Before the friability test was carried out, the weight of 20 tablets was first calculated in percentage (%) form and put into the apparatus. After 4 minutes of use with a 25 rpm friabilator, the tablets were weighed once more. The percentage of friability F was then calculated using the formula below:

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} X\ 100$$

Where,

F = Friability of tablets

$W_{initial}$ = Initial weight of the tablets

W_{final} = Final weight of the tablets

4. **WEIGHT VARIATION[36]:**

To evaluate a weight variation twenty tablets of each formulation were individually weighted (WI) and recorded using an electrical balance. The calculation was based on their average weight (WA). The formula below was used to calculate the percent weight variation.

$$\% \text{ Weight variation} = \frac{W_A - W_I}{W_A} x100$$

5. DRUG CONTENT UNIFORMITY[37]:

Ten tablets were measured and each one was crushed separately to ensure a consistent drug content. Powder that equals 50 mg of Atorvastatin calcium was dispensed into a volumetric flask with a capacity of 100 ml, along with 0.1 N HCl. A cellulose acetate membrane with a thickness of 0.45 m was used to pass the fluid. The above-mentioned solution was further prepared by mixing 1 ml of it with 0.1 N HCl. This created 100 ml of the solution. The drug concentration in the resulting solution was analyzed at 205 nm using a UV spectrophotometer.

6. FLOATING/BUOYANCY LAG TIME[37]:

The amount of time required for a dosage form to float on a medium is known as the floating lag time (FLT) or buoyancy lag time (BLT). In a beaker with 100 ml of 0.1 N HCl kept at 37 °C as the experimental medium, the floating time lag was tested. The floating lag time was the time it took for the tablet to float and rise to the surface.

7. FLOATING TIME[37]:

The floating time is the length of time that tablets float above medium. A tablet was added to 900 ml of 0.1N HCl in a vessel of a USP dissolving type II apparatus in order to replicate the gastric environment. The equipment was then used to calculate the floating time at 100 rpm and 37 degrees C. Time was recorded using a stopwatch. The test involved six tablets (n = 14–6). The mean and standard deviation were calculated

8. SWELLING INDEX[38]:

The weight (W1) of the tablet was determined, and the tablet was dissolved in 900 ml of 0.1N HCl using the USP dissolution apparatus II. The weight of the tablets was then determined at different time intervals, including 1hr, 2hr, 3hr, 4hr, 5hr, 6hr, 7hr, and 8hr (W2). Blotting paper was then used to absorb any excess liquid.

9. IN-VITRO DISSOLUTION STUDIES[39] :

Atorvastatin calcium release from floating tablets was measured using the dissolution testing apparatus 2 (USP) (paddle method; Veego Scientific, Mumbai, India). At 3705°C and 75 rpm, the dissolution test was carried out using 900 ml of 0.1 N hydrochloric acid. Every hour, 5 ml of the solution was taken out of the dissolving apparatus, and the samples were then switched out for new dissolution medium. The samples were diluted to the proper concentration with 0.1N hydrochloric acid after being run through a 0.45 membrane filter. An Ultra Violet Double Beam Spectrophotometer (UV 1700, Shimadzu, Japan) was used to measure the absorbance of these solutions at 254 nm. Utilizing an equation derived from a standard curve is necessary to estimate the cumulative percentage of drug release.

10. KINETIC MODELLING OF DRUG RELEASE[40]:

To determine the kinetic modeling of drug release, the dissolution profiles of all the batches were fitted to zero order, first order, matrix, Hixon-Crowell, Korsemeyer, and Peppas models.

11. FOURIER TRANSFORM INFRARED (FTIR) TEST[41]:

FTIR analysis can be used to investigate drug polymer interactions. By mounting the sample on a diamond ATR, the FT-IR spectra of pure drugs, polymers, and optimized Formulations were analyzed around 4000 to 400 cm-1 Hz.

12. DIFFERENTIAL SCANNING CALORIMETRY (DSC)[41]:

The thermal behavior of the polymers, combinations, and pure medicine was investigated using DSC. In sealed aluminum pans with nitrogen flow, the needed number of samples was heated at a temperature between 40 and 250 °C with a 5 °C per minute scanning rate.

13. STABILITY STUDY[42]:

Drug development and drug product stability testing are continuous processes that last until the final chemical or finished product is destroyed. In order to assess the stability of the drug and formulation, stability studies were carried out on the single most effective formulation in accordance with ICH recommendations Q1C. The formulations were kept in a humidity chamber for three months (90 days), with the humidity set at 35 2 °C and 60 5% relative humidity (RH) and 40 °C and 75% RH, respectively. The product's stability and efficacy were then evaluated in light of a number of variables.

RESULT:

Formulation	Hardness (Kg\cm^2)	Thickness (mm)	Friability (%)	Weight variation (mg)	Drug content (%)	Floating time (Hrs)	Floating lag time (sec)
F1	5.0.±0.22	4.2±0.16	0.70±0.07	249±2.1	99.58±1.12	12	55±2.7
F2	3.9±0.124	4.4±0.20	0.72±0.07	248±1.9	96.56±0.95	10	53±2.0
F3	4.8±0.207	4.2±0.16	0.64±0.117	248±2.12	98.46±1.78	11	62±3.0
F4	4.3±0.083	4.3±0.25	0.62±0.119	247±2.2	95.35±1.87	13	68±2.1
F5	4.0±0.13	4.4±0.23	0.74±0.14	246±1.71	98.75±1.71	10	61±2.2
F6	3.8±0.19	4.3±0.21	0.68±0.10	249±1.3	94.88±1.91	14	51±2.8
F7	4.3±0.22	4.1±0.22	0.71±0.08	248±1.7	97.21±1.42	12.5	56±2.9

Table-2 Physico-Chemical Evaluation Parameters of Atorvastatin Calcium Tablets

Sr.No	Time (hrs)	F1	F2	F3	F4	F5	F6	F7
1	0	0	0	0	0	0	0	0
2	1	11.84	12.13	11.68.	12.51	11.32	12.99	13.02
3	2	26.90	24.24	25.24	27.23	24.24	32.23	32.13
4	3	42.23	41.32	40.23	44.54	41.32	38.84	42.84
5	4	78.84	62.11	69.23	72.19	62.11	77.48	75.54
6	5	85.05	75.13	79.13	81.28	75.13	85.28	83.82
7	6	77.06	72.24	77.48	80.04	72.24	80.05	78.06
8	7	83.23	97.13	89.05	88.05	97.13	89.08	85.05
9	8	92.05	95.32	90.01	92.05	95.32	91.05	92.99
10	9	92.54	92.23	91.25	90.08	92.23	92.09	93.00
11	10	94.23	97.32	86.05	89.17	97.32	93.82	89.17
12	11	97.08	97.10	93.04	94.08	97.10	94.84	93.04
13	12	94.98	98.13	94.05	94.26	98.13	94.98	94.05
14	13	97.21	98.02	94.60	95.08	98.02	96.88	96.26
15	14	98.82	98.54	95.76	96.52	98.87	97.56	97.68

Table no- 3 Cumulative percent drug released vs time plots of formulation F1, F2, F3, F4, F5, F6 and F7

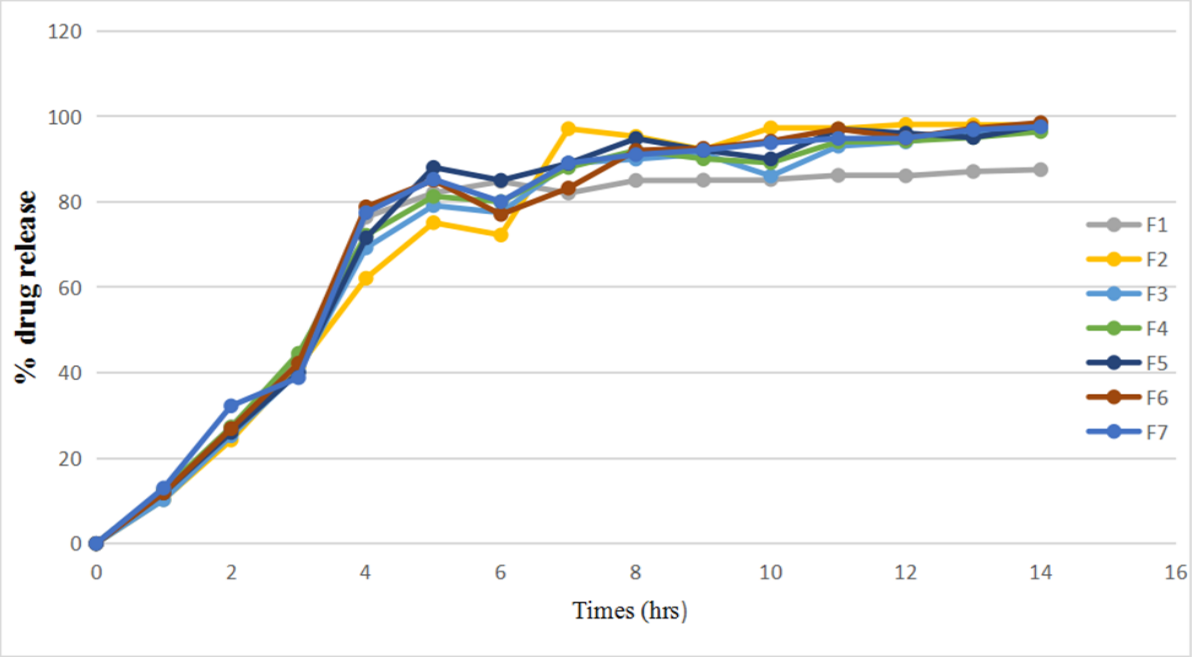

Fig No -1 Cumulative % drug release

Formulations	Zero order	First order	Higuchi	Korsmeyer-peppas	n
	R^2	R^2	R^2	R^2	
F1	0.937	0.946	0.839	0.928	0.600
F2	0.954	0.957	0.810	0.908	0.719
F3	0.972	0.977	0.871	0.964	0.639
F4	0.965	0.969	0.900	0.968	0.673
F5	0.958	0.961	0.861	0.933	0.646
F6	0.969	0.985	0.804	0.979	0.741
F7	0.961	0.965	0.894	0.962	0.478

Table No-4 Drug Release Kinetics

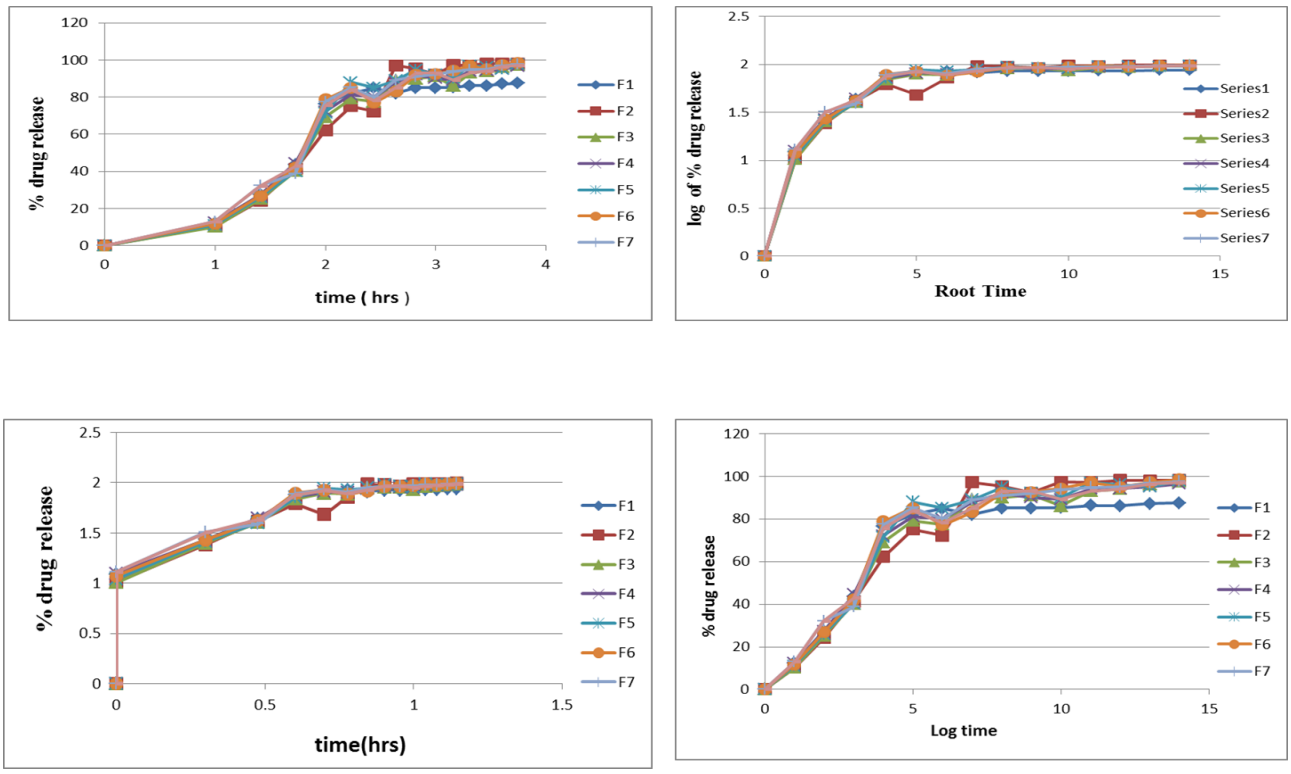

Fig No -2 Drug Release Kinetics

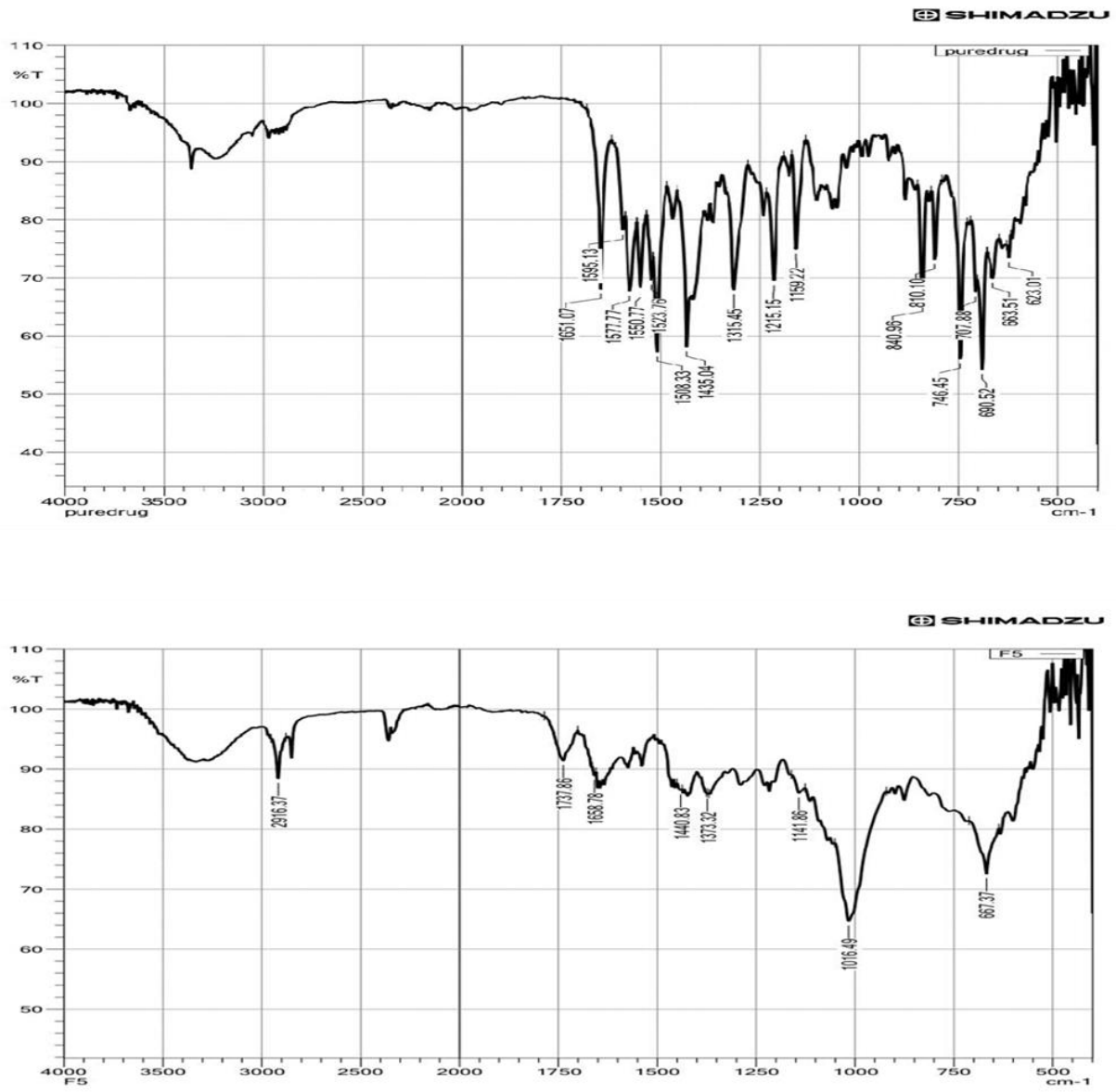

Fig no- 3 FTIR spectra of pure drug atorvastatin calcium and FTIR spectra of formulation 5 (F5)

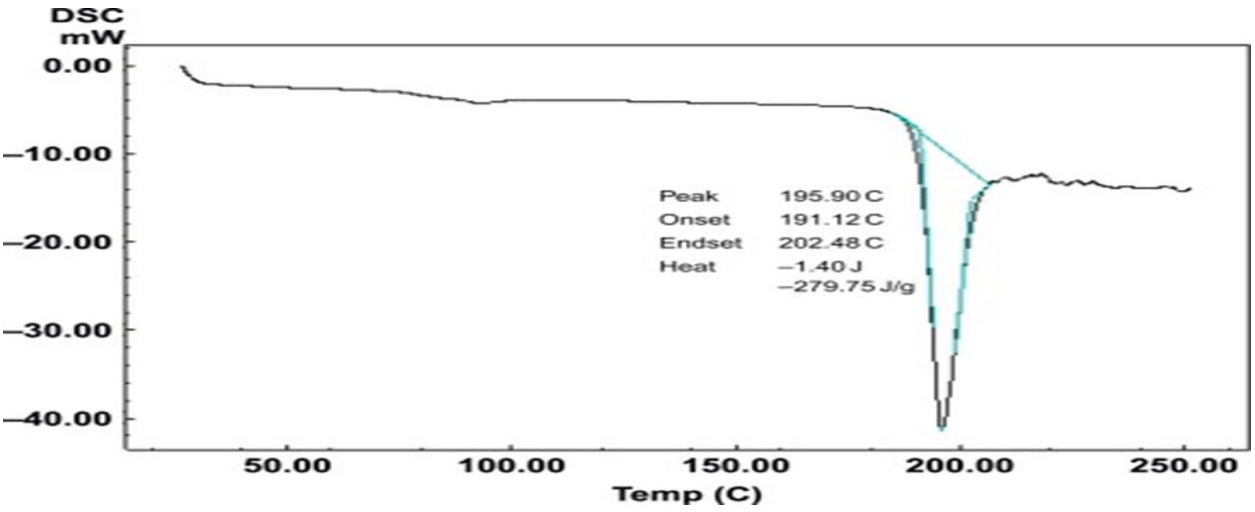

Fig No-4 DSC Curve Of Atorvastatin Calcium + Polymer Mixture and DSC Curve of Atorvastatin Calcium + Polymer Mixture

DISCUSSION

The study aimed to create new floating tablets of Atorvastatin calcium to enhance its oral bioavailability by extending its gastric residence time and allowing it to float in the stomach.In the current work, Atorvastatin calcium floating tablets are manufactured by direct compression method using grades of polymer, including Guar gum, Xanthan gum, Sodium alginate and others.Pre-formulation parameter evaluation of the developed powder showed that all formulations had excellent flow qualities as measured by the angle of repose (24 to 29) and good packing ability as measured by the powder's Carr's index. (Table).Sodium alginate, Guar gum, and Xanthan gum were all used in the manufacture of the Atorvastatin calcium floating tablet (f1, f2, f3, & f7). However F4 was made without Guar gum, F5 was made without Xanthan gum and F6 was made without Sodium alginate. The analysis of the pre compression studies, which evaluated the bulk density, tapped density, angle of repose, and compressibility index, showed that they were within the predetermined limits (Table). It was discovered that the weight, thickness, and amount of drug in each tablet were all uniform. Friability was between 0.62 and 0.74%, the drug content was between 94 and 99%, and the hardness ranged from 3.8 to 5.0 kg/cm2. (Table).A fourier transform infrared analysis was performed on the prepared Atorvastatin calcium floating tablet. Atorvastatin calcium's FT-IR peak values were at 1159.22, 1215.15, 1315.45, 1435.04, 1577.77 and 1651.07 nm for the pure drug, and FTIR peak values of Formulation 1 (F1), 898.83, 1016.49, 1205.51, 1392.61 and 1651.07nm while the Formulation 5 (F5) peaks at 1016.49, 1141.86, 1373.32, 1440.83, 1658.78 nm shown in (Figure 29,30 & 31) DSC was used to perform differential scanning colorimetric on both polymers and pure drug. The pure drug has peaks at 195.90°C, 191.12°C, and 202.48°C, as shown in (Fig. 31), and the interaction between the drug and polymers like Guar gum, Xanthan gum, and Sodium alginate has peaks at 110.22°C, 113.92.10°C, 130.01°C, and 135.10°C, as shown in (Fig. 32).The in-vitro drug release investigation in 0.1N HCL at pH 1.2 and pH 7.4 used a dissolution rate test apparatus. The profiles of dissolution are shown in figure (Fig. no. 20). Comprise the details shown in the tables. The dissolution data clearly show that formulations have shown drug release in the 11% to 98% range in 14 hours. Using the zero order, first order, higuchi, and korsmeyer-peppas equations, and the drug release pattern was extrapolated in order to distinguish between the drug release mechanisms. Figure no. 21, 22, 23 & 24 are clearly describing these. Short-term stability testing was conducted on all formulations while the drug content was observed for 90 days. There was no physical change in the formulations' appearance or color. And F5 and F7 both have good properties.

CONCLUSION:

The main objective of the current work is to keep the dosage form in the stomach for an extended period of time, and this can be accomplished by developing a floating drug delivery system.This floating tablet's main goal is to reduce the floating lag time. Additionally, it improves local action and oral absorption. These polymer varieties, including sodium alginate, guar gum, and xanthan gum, were used to produce this tablet. In addition to Citric acid, Sodium bicarbonate, lactose and polyvinyl pyrrolidine being utilized as additional excipients, lubricants included talc and magnesium stearate. It was found that there were no interactions between the drug, polymer, or excipient using Fourier transform infrared spectroscopy and DSC. The tested characteristics of the manufactured floating tablets included hardness, weight variation, thickness, and friability, uniformity of the drug content, buoyancy lag time, total floating time, swelling index, and in vitro dissolution. The F1, F2, F3, F4, F5, F6 and F7 formulations were the seven that showed effective flotation. It was found that the F1 and F5 formulations were both stable after each formulation's stability was investigated. It was noted that the maximal drug release rates for the F1, F2, and F5 formulations were 98.82%, 98.54%, and 98.87% within 14 hours, respectively.

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