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Original Article

DESIGN AND CHARACTERIZATION OF A GASTRO-RETENTIVE FLOATING ATORVASTATIN CALCIUM TABLET

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ABSTRACT

This study focuses on the formulation and evaluation of gastro-retentive floating tablets (GRFT) of atorvastatin calcium, aimed at improving its bioavailability and therapeutic efficacy. Atorvastatin calcium is a lipid-lowering agent with poor bioavailability due to extensive first-pass metabolism and a short half-life. Floating tablets were prepared using hydrophilic polymers, including HPMC K15M and xanthan gum, along with gas-generating agents such as sodium bicarbonate and citric acid, employing a direct compression method. The formulations were evaluated for physical parameters, in vitro buoyancy, swelling behavior, and drug release kinetics. Among the formulations, F5 exhibited the best performance, with a floating lag time of 10.58 seconds and a total floating time of up to 24 hours. Drug release studies revealed a sustained release of 99.70% over 12 hours for F5, attributed to an optimized balance of HPMC K15M and xanthan gum. Swelling studies demonstrated the highest swelling index (89.75% at 360 minutes) for F5, highlighting its enhanced hydration and gel formation properties. The drug release kinetics showed an inverse relationship between polymer concentration and drug release rate, indicating that higher polymer concentrations result in slower release due to a denser gel matrix. All formulations met pharmacopoeial standards for hardness, friability, weight variation, and content uniformity. The optimized formulation F5 successfully enhanced gastric retention and controlled drug release, making it a promising system for improving atorvastatin bioavailability and patient compliance. This approach can also be applied to other drugs with absorption windows in the upper gastrointestinal tract.

KEYWORDS: Atorvastatin calcium, gastro-retentive floating tablets, HPMC K15M, xanthan gum, controlled drug release.

1. Introduction

Atorvastatin calcium, a potent lipid-lowering agent, is widely used for the management of hyperlipidemia and the prevention of cardiovascular diseases. Despite its therapeutic efficacy, atorvastatin is associated with some limitations, including its poor bioavailability due to extensive first-pass metabolism and its short half-life, which often necessitates multiple doses throughout the day [1]. To overcome these challenges, advanced drug delivery systems such as GRFDDS have been proposed as a promising solution to improve the bioavailability and therapeutic efficacy of atorvastatin [2]. The concept of FDDS is based on the buoyancy principle, where the formulation floats on the gastric fluids, extending the residence time in the stomach and allowing for controlled drug release [3].

The design of gastro-retentive floating systems has gained significant attention due to their potential to provide prolonged drug release in the stomach, thereby improving the absorption of drugs that are predominantly absorbed in the upper GI tract [4]. In the case of atorvastatin, its absorption is mainly confined to the jejunum, and its bioavailability is considerably influenced by its dissolution rate [5]. Thus, the development of a floating formulation can significantly enhance the drug's residence time in the stomach, leading to better absorption and improved therapeutic outcomes [6].

The mechanism of floating drug delivery involves the incorporation of materials that either generate gas upon contact with gastric fluids or have low density, ensuring that the dosage form remains buoyant [7]. Various polymers, such as hydrophilic polymers and gas-

generating agents, have been explored to design and optimize floating systems for drugs like atorvastatin [8]. These systems not only prolong the gastric retention time but also provide controlled release, ensuring a steady therapeutic level of the drug in the bloodstream over an extended period [9].

Recent advancements in floating drug delivery technology have focused on overcoming the challenges of controlling the buoyancy and drug release kinetics. The primary objective is to achieve optimal gastric retention by tailoring the system's physical properties, such as particle size, porosity, and swelling capacity [10]. Hydroxypropyl methylcellulose (HPMC), sodium bicarbonate, and ethylcellulose have been widely used as matrix-forming agents in such formulations due to their ability to maintain buoyancy and modulate drug release [11]. The combination of these materials allows for an ideal balance between drug retention, release profile, and patient compliance.

In addition to its buoyancy and release properties, the evaluation of gastro-retentive floating systems also involves the assessment of several important parameters, including the in vitro release profile, buoyancy behavior, floating lag time, and gas generation capacity [12]. These parameters are critical for ensuring the formulation's performance in vivo, where the drug needs to float in the stomach for an adequate duration while releasing the active ingredient at a controlled rate. The use of in vitro testing methods, such as dissolution studies in simulated gastric fluid, allows for the prediction of the in vivo performance of the floating system [13]. The ability to monitor the floating duration and drug release kinetics provides valuable insights into the formulation's efficiency and effectiveness in sustaining drug levels over an extended period [14].

The formulation of gastro-retentive FDDS for atorvastatin calcium also aims to minimize the fluctuations in drug concentration, which are typically observed with conventional dosage forms [15]. This can result in enhanced patient compliance, as the need for frequent dosing is reduced. Furthermore, by enhancing the bioavailability and providing sustained release, the floating system can potentially reduce the risk of side effects associated with atorvastatin, such as muscle pain and liver toxicity, by maintaining a consistent therapeutic level of the drug [16].

The application of gastro-retentive floating drug delivery systems is not limited to atorvastatin but also holds promise for the delivery of other poorly soluble and short-acting drugs. The versatility and effectiveness of this technology make it an attractive option for improving the therapeutic efficacy of various drugs used in chronic diseases, such as hypertension, diabetes, and dyslipidemia [17].

2. Materials and methods

2.1. Materials

Maan Pharmaceuticals Ltd. in Mehsana provided a complimentary sample of atorvastatin. Otto Chemie PVT LTD, located in Mumbai, provided xanthan gum and HPMC K15M. Every other chemical and reagent utilized was of analytical quality.

2.2. Methods

2.2.1. Formulation of floating tablets

Using a direct compression approach and varied polymer concentrations, a floating tablet containing atorvastatin calcium was created. Every powder was precisely weighed. After that, every additional item was mixed evenly in a glass mortar. A rotating single punch tablet machine (Karnavati, Ahmadabad) was used to compress the blend into tablets with an average weight of 120 mg. The composition of the tablets is given in Table 1.

Table 1. The composition of various gastro-retentive atorvastatin calcium tablet formulations (F1–F5), highlighting the differing concentrations of polymers such as HPMC K15M and xanthan gum used to evaluate their impact on the tablet's floating behavior and drug release profile.

	F1	F2	F3	F4	F5
Atorvastin calcium	40	40	40	40	40
HPMC K15M	-	-	15	5	25
Xanthan Gum	20	30	15	25	5
Magnesium Stearate	1	1	1	1	1
Talc	1	1	1	1	1
Sodium Bicarbonate	20	20	20	20	20
Citric acid	10	10	10	10	10
Dicalcium Phosphate	28	18	38	28	18
Total	120	120	120	120	120

2.2.2. Evaluation of Tablets

2.2.2.1. Diameter and Thickness

The diameter and thickness of tablets are commonly measured using a Vernier caliper to ensure uniformity in size. In a typical procedure, tablets from multiple batches are selected, and their individual thickness and diameter are measured. Average values are calculated, and the test is considered passed if no single tablet deviates more than ± 5% from the average values. This ensures consistency in the physical properties of the formulation, which is critical for further quality control and therapeutic efficacy evaluations [18,19].

2.2.2.2. Hardness

Hardness is defined as the force required to crush a tablet and is an essential parameter to evaluate the mechanical strength of tablets during production and handling [20]. The hardness of the tablets is commonly measured using devices such as the Monsanto hardness tester or the Pfizer tester [21]. In this procedure, the tablets are placed diametrically between two plungers; the lower plunger is adjusted to contact the tablet, and the reading is set to zero to ensure accuracy in measurement [22].

2.2.2.3. Weight variation test

In accordance with established practice for pharmaceutical testing, a sample of 20 tablets was chosen at random and precisely weighed using a single pan balance [23]. To evaluate the variation in tablet weights, the standard deviation was computed after the average weight of the tablets was recorded [24]. To guarantee the homogeneity of the product, a batch of tablets is deemed acceptable if no more than two tablets deviate from a certain percentage limit [25]. Additionally, no tablet must differ by more than twice the percentage threshold in order to pass the quality control test [26].

2.2.2.4. Friability

The tablets were subjected to friability testing, which is a standard measure of mechanical strength and resistance to abrasion. The initial weight of the tablets (Wi) was approximately 6.5 g, ensuring uniformity across samples [27]. During the test, the tablets were rotated in a friabilator drum and allowed to fall repeatedly from a height of 6 inches, simulating handling stress during packaging and transportation [28]. After the test, the final weight of the tablets (Wf) was recorded, and the friability was calculated using the formula:

$$\text{Friability (\%)} = Wi - Wf/Wi \times 100$$

This calculation determines the percentage weight loss and ensures that the tablets comply with pharmacopeial limits, typically less than 1% [29]. Testing conditions, such as rotation speed and duration, were maintained as recommended in standard pharmacopeial guidelines to ensure reproducibility [30]. Tablets with a friability of 0.5% to 1% are considered acceptable.

2.2.2.5. Content uniformity

We took five tablets and ground them into powder [31]. 25 mg of the medication was weighed out of that sample and put into a 100 mL volumetric flask [32]. To dissolve the medication, 20 mL of methanol was added, and the mixture was then slowly heated over a water bath [33]. After allowing the liquid to settle to ambient temperature, methanol was added to bring the volume up to par [34]. Filtration was done on the resultant solution [35]. One milliliter (mL) of the filtrate was moved to a fresh container and diluted with 0.1 HCl [36]. Using the designated analytical technique, the final solution's absorbance was determined [37].

2.2.2.6. In-Vitro Buoyancy study

A random selection of tablets from each of the six formulations was put into a 250 mL beaker with 200 mL of 0.1 N hydrochloric acid [38]. The Floating Lag Time (FLT) was defined as the amount of time it took for the tablet to rise to the surface and float [39]. Total Floating Time (TFT) was defined as the amount of time the tablet stayed afloat in the medium [40]. Table 3 summarizes the floating lag time (TFT) and total floating time of the designed formulations (F1 to F5), demonstrating their ability to remain buoyant in the gastric environment, which is critical for ensuring prolonged gastric retention and sustained drug release.

2.2.2.7. Swelling Study

A technique frequently employed to investigate the release characteristics of pharmaceutical tablets is the evaluation of the swelling index of polymers based on their capacity to absorb water and experience swelling [41]. Three tablets of each formulation were put in a petri dish with 0.1 N HCl solution for this evaluation [42]. The pills were taken out of the solution after a specified amount of time, wiped to get rid of any extra liquid, and then weighed again [43]. The swelling index, which quantifies the extent of swelling in relation to the tablet's original weight, was then computed using a standard method [44].

2.2.2.8. In-Vitro Dissolution Study

The in vitro dissolution study was conducted using a USP Dissolution Testing Apparatus at a rotational speed of 50 rpm, which is a standard approach for evaluating the release profile of pharmaceutical formulations [45]. A total of 900 mL of 0.1 N HCl (pH 1.2) was chosen as the dissolution medium, based on the dissolution conditions commonly employed for the analysis of oral dosage forms [46]. The tablet was placed in the dissolution vessel, and the temperature was maintained at 37 ± 0.5°C, reflecting the standard physiological temperature for dissolution testing [47]. Samples of 5 mL were withdrawn from the dissolution apparatus at specified time intervals over 12 hours, following the established protocol for dissolution testing [48]. After each withdrawal, the same volume was replaced with fresh dissolution medium to maintain the volume in the vessel [49]. The withdrawn samples were filtered through a 0.45 µm Whatman filter paper, which is recommended to remove particulates and ensure clarity for spectrophotometric analysis [50]. The filtered samples were then diluted with an appropriate volume of plain dissolution medium to achieve the required concentration for analysis [51]. The collected samples were analyzed using a Lab India 3000 UV-visible double beam spectrophotometer at a wavelength of 246 nm, which is the commonly used wavelength for the active ingredient in this formulation.

The analysis was conducted using 0.1 N HCl as the blank, in accordance with the typical procedure for UV spectrophotometric analysis in dissolution studies [52].

3. Results and Discussion

3.1. Atorvastatin calcium drug's FTIR spectra

Fig. 1 displays the FTIR spectrum of pure atorvastatin calcium, indicating the characteristic functional group peaks used to confirm the structural integrity and purity of the drug.

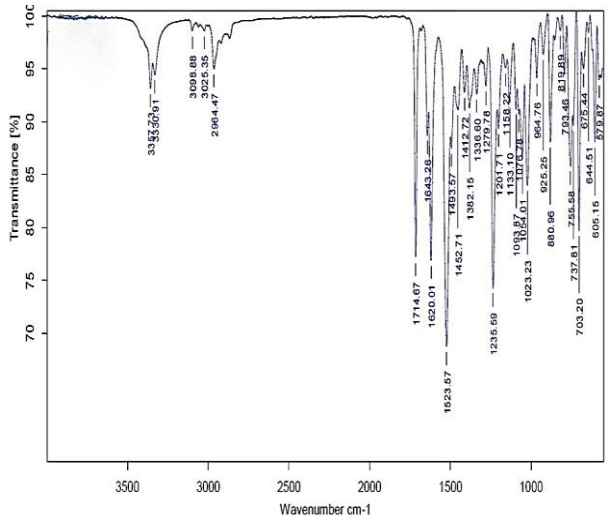

Fig 1. Atorvastatin calcium FTIR spectra [53]

3.2. Characteristics of the intended formulation after compression

Table 2 summarizes the post-compression characteristics of the formulated gastro-retentive atorvastatin calcium tablets, including hardness, weight variation, friability, thickness, and content uniformity, to ensure the tablets meet standard pharmacopeial quality requirements.

3.2.1. Hardness

The hardness of the tablets ranged from 4.0 to 4.6 kg/cm^2, indicating the mechanical strength of the tablets (Table 2). Formulations F4 and F5 showed the highest hardness (4.6 kg/cm^2), which ensures sufficient resistance to physical stress during handling and storage, while F1 had the lowest hardness (4.0 kg/cm^2).

3.2.2. Weight Variation (mg)

The weight variation for the formulations fell within the range of 99.2 mg to 102.7 mg (Table 2), complying with IP pharmacopoeial limits for tablets. F3 had the highest average weight (102.7 mg), while F1 exhibited the lowest (99.2 mg), demonstrating good control over the tablet manufacturing process.

3.2.3. Friability

The friability values were between 0.17% and 0.20% (Table 2), well below the IP pharmacopoeial limit of 1%, indicating excellent tablet resistance to chipping, cracking, or breaking. F3 had the highest friability (0.20%), while F1 and F4 showed the lowest friability (0.17%), ensuring durability during transportation and handling.

3.2.4. Thickness (mm)

The thickness of the tablets ranged from 2.01 mm to 2.21 mm (Table 2), which reflects uniformity in tablet dimensions. F3 was the thickest formulation (2.21 mm), whereas F2 was the thinnest (2.01 mm). Consistency in tablet thickness ensures proper dosage and aesthetic uniformity.

3.2.5. Content Uniformity (%)

The content uniformity results were within the acceptable range of 97.65% to 99.67% (Table 2), ensuring consistent drug distribution within the tablets. F1 exhibited the highest content uniformity (99.67%), while F4 showed the lowest (97.65%), indicating slightly lower drug distribution uniformity for F4.

Table 2. Characteristics of the specified formulations after compression

Formulation code	Hardness	Weight variation (mg)	Friability	Thickness (mm)	Content Uniformity
F1	4.0	99.2	0.17	2.10	99.67
F2	4.2	102.4	0.18	2.01	99.23
F3	4.1	102.7	0.20	2.21	98.72
F4	4.6	100.35	0.17	2.05	97.65
F5	4.6	99.5	0.18	2.10	99.25

3.3. Buoyancy Study

Fig. 2 presents the total floating time (TFT) and floating lag time of the designed formulations, demonstrating their buoyancy performance and the time taken for the tablets to start floating in the dissolution medium. Table 3 summarizes the floating lag time (TFT) and total floating time of the designed formulations (F1 to F5), demonstrating their ability to remain buoyant in the gastric environment, which is critical for ensuring prolonged gastric retention and sustained drug release.

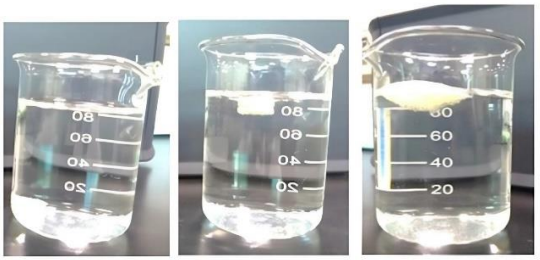

Fig. 2. The TFT and floating lag time of designed formulations

Table 3. The TFT and floating lag time of designed formulations

Formulation code	Floating lag time (Sec)	Total Floating Time (Hrs)
F1	10.52	20
F2	10.78	19
F3	10.66	18
F4	10.35	20
F5	10.58	24

Table 4. Swelling Study

Swelling index (%)					
Time (Min)	F1	F2	F3	F4	F5
30	40.18	41.25	42.95	41.67	38.43
60	47.80	48.61	47.26	46.58	47.91
120	60.29	56.46	55.65	57.18	51.94
180	62.82	61.78	61.68	60.96	57.95
240	68.49	68.24	68.42	65.45	65.27
300	72.34	73.65	72.85	73.12	75.36
360	88.95	87.15	86.14	87.80	89.75

3.4. Swelling Study

Table 4 presents the swelling index percentages of five different formulations (F1 to F5) measured at various time intervals from 30 to 360 minutes, demonstrating the progressive water absorption capacity and swelling behavior of each formulation over time.

Formulation F5 showed the highest swelling index at the final time point (360 minutes) (Table 4), suggesting it may have a faster dissolution rate compared to the others, especially in the later stages. Formulations F1 and F2 provided more consistent and sustained swelling over time, with F1 showing the highest release at 30, 60, 120, and 180 minutes. Formulation F4 had the lowest swelling index at early stages (30 minutes and 60 minutes) but showed consistent performance later, especially at 240 minutes. Formulation F3 provided a moderate performance, falling between F1 and F4 in terms of swelling efficiency at most time intervals.

3.5. Release of drugs in vitro dissolutions

Fig. 3 illustrates the in vitro drug release profiles of various formulations over time, highlighting how different polymer concentrations affect the rate and extent of drug dissolution.

Different concentrations of xanthan gum are present in formulations F1 and F2. The release values for Formulations F1 and F2 were 95.10 and 94.85, respectively (Fig. 3). It was shown that medication release decreased with increasing polymer concentration.

The polymer HPMC K15M and xanthan gum are combined in formulas F3, F4 and F5. After 12 hours, the drug release was 89.65%, 97.02%, and 99.70%, respectively. Therefore, the tablet with the optimal concentration of both polymers demonstrated better control of drug release, with a 99.70% release rate for up to 12 hours. The polymer concentration had a significant impact on the drug's release in each formulation. The concentration of polymers in the matrix had an inverse relationship with the rate of drug release.

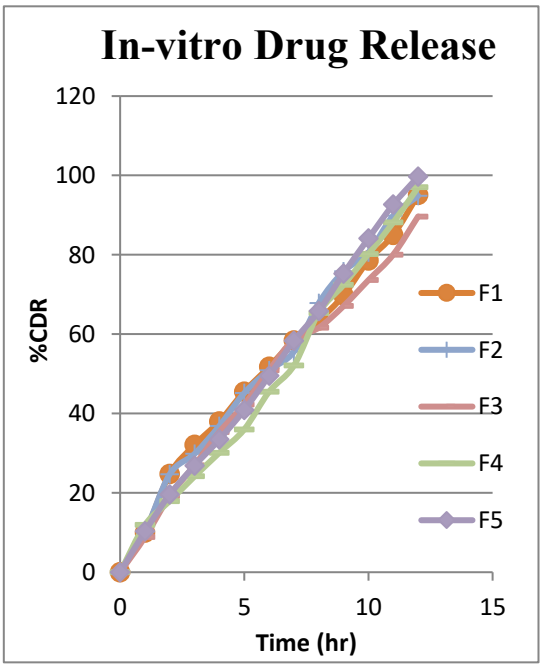

Fig. 3. Release of drugs in vitro dissolutions

4. Conclusion

The study successfully developed and evaluated gastro-retentive floating tablets of atorvastatin calcium using polymers such as HPMC K15M and xanthan gum to achieve prolonged drug release and enhanced bioavailability. The floating mechanism, driven by gas-

generating agents like sodium bicarbonate and citric acid, ensured buoyancy, with floating lag times ranging between 10.35 to 10.78 seconds and total floating times extending up to 24 hours in some formulations. These properties effectively increased gastric retention time, improving the absorption of atorvastatin in the upper gastrointestinal tract, where its absorption is most efficient.

Among the formulations, F5 demonstrated the highest drug release (99.70%) over 12 hours, indicating optimal control of drug release kinetics through a balanced combination of HPMC K15M and xanthan gum. The swelling studies also revealed that F5 exhibited the highest swelling index (89.75% at 360 minutes), suggesting enhanced polymer hydration and swelling capacity, which contributed to sustained drug release. Formulations F1 and F2 showed slower drug release compared to F5, highlighting the impact of polymer concentration on drug release rates. Formulations F3 and F4, which combined the polymers, achieved controlled release, with F4 showing a consistent release profile over time.

The in vitro evaluations, including weight variation, friability, thickness, hardness, and content uniformity, confirmed that all formulations met IP pharmacopoeial standards. The findings demonstrated that variations in polymer concentration significantly influence drug release profiles, with higher concentrations resulting in slower release due to a denser gel matrix that restricted drug diffusion. The incorporation of both hydrophilic and gas-generating components ensured the desired buoyancy and controlled drug release.

In conclusion, the gastro-retentive floating tablet of atorvastatin calcium optimized with HPMC K15M and xanthan gum (formulation F5) provides a promising drug delivery system for improving therapeutic efficacy and patient compliance. This approach not only enhances atorvastatin's bioavailability but also offers potential applicability for other drugs with similar absorption characteristics.

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