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Research Paper

Development and In Vitro Evaluation of Gastro Retentive Floating Tablets of Atorvastatin Calcium

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ARTICLE DETAILS

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ABSTRACT

The present study aimed to develop and evaluate a gastroretentive floating drug delivery system (GFDDS) for Atorvastatin calcium to enhance its bioavailability and therapeutic efficacy. Preformulation studies, including FTIR spectroscopy, melting point determination, solubility analysis, and standard calibration curves in different pH media, confirmed the drug's identity and physicochemical properties. The drug exhibited characteristic peaks in FTIR, with a melting point of 141–144°C, and demonstrated pH-dependent solubility. Various polymers (HPMC K4M, HPMC K100, Xanthan gum, Carbopol 71G, Sodium alginate) were evaluated for their precompression and post-compression parameters. Drug-excipient compatibility studies (FTIR and DSC) confirmed no significant interactions. Nine formulations (X1–X9) were prepared, and their flow properties, swelling behavior, buoyancy lag time, and drug release kinetics were assessed. Optimized formulation X9 (HPMC K4M with HPMC K100 LV) exhibited excellent floating characteristics (buoyancy lag time: 35 sec, total floating time: 12 h), sustained drug release (99.80% in 12 h), and followed non-Fickian diffusion (n = 0.458). Stability studies (40°C/75% RH for 3 months) confirmed no significant changes in physicochemical properties or drug release profile. The developed gastroretentive system offers a promising approach for enhancing the oral bioavailability of Atorvastatin calcium through prolonged gastric retention and controlled drug release.

1. Introduction

Oral drug delivery remains the most widely used route of administration due to its convenience, cost-effectiveness, and high patient compliance. However, conventional oral dosage forms often suffer from limitations such as short gastric residence time, incomplete drug absorption, and frequent dosing requirements, particularly for drugs with narrow absorption windows or pH-dependent solubility. These challenges can significantly impact therapeutic efficacy, especially for drugs that require sustained plasma concentrations. To address these limitations, gastroretentive drug delivery systems (GRDDS) have been developed, with floating drug delivery systems (FDDS) emerging as a promising approach due to their ability to prolong gastric retention and enhance drug bioavailability[1-6].

Among the various GRDDS strategies, floating tablets have gained considerable attention for their ability to remain buoyant in gastric fluid, thereby extending drug release in the upper gastrointestinal tract (GIT). This system is particularly advantageous for drugs that are primarily absorbed in the stomach or upper intestine, exhibit poor solubility at higher pH levels, or require sustained release to maintain therapeutic plasma concentrations. Drugs such as antacids, antidiabetics, non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics, antihypertensives, and antidepressants have been successfully formulated as floating tablets to improve their pharmacokinetic profiles. Atorvastatin calcium, a widely prescribed HMG-CoA reductase inhibitor used in the management of hyperlipidemia, presents a compelling case for gastroretentive floating drug delivery. The drug exhibits low bioavailability, approximately 12%, primarily due to its pH-dependent solubility and significant first-pass metabolism. A gastroretentive floating formulation of atorvastatin calcium

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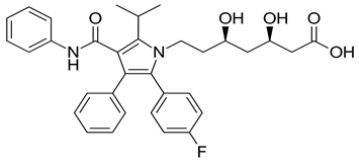
could enhance absorption by prolonging its retention in the stomach, where the acidic environment improves solubility, while also providing sustained release to reduce dosing frequency and improve patient adherence.[7-10]

The development of an effective gastroretentive floating tablet requires careful selection of polymers to achieve optimal buoyancy, controlled swelling, and predictable drug release kinetics. Hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC), xanthan gum, sodium alginate, and Carbopol are commonly used due to their ability to form a gel layer upon contact with gastric fluid, ensuring prolonged floating and controlled drug release. Additionally, mucoadhesive polymers can further enhance gastric retention by adhering to the stomach lining, thereby preventing premature expulsion of the dosage form. This study focuses on the development and in vitro evaluation of gastroretentive floating tablets of atorvastatin calcium. The research encompasses preformulation studies to characterize the drug, including Fourier-transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), solubility analysis, and melting point determination. Various polymer combinations are investigated to optimize formulation parameters such as buoyancy lag time, total floating duration, swelling behavior, and drug release kinetics. In vitro dissolution studies are conducted to assess the sustained release profile, while kinetic modeling is employed to determine the underlying drug release mechanisms. Stability studies under accelerated conditions ensure the robustness of the optimized formulation.[11,12.] By developing a gastroretentive floating tablet of atorvastatin calcium, this study aims to enhance the drug's bioavailability, reduce dosing frequency, and improve therapeutic outcomes. The findings could provide a foundation for further clinical studies and offer a superior alternative to conventional dosage forms, ultimately benefiting patients requiring long-term statin therapy.

Atorvastatin Calcium[12,13,14]



Structure. Atorvastatin calcium

2. Material and Methods

2.1 Materials

Chemicals and Reagents

Atorvastatin calcium was procured from Emcure Pharmaceuticals Ltd. (Pune, India). The polymers used in the study included hydroxypropyl methylcellulose (HPMC K4M, K15M, K100LV) (Colorcon Asia Pvt. Ltd., Goa, India), sodium alginate, carbopol 71G, karaya gum (Loba Chem, India), and xanthan gum (Torrent Laboratory, Ahmedabad, India). Microcrystalline cellulose (MCC KG 100), sodium bicarbonate, anhydrous citric acid, magnesium stearate, and talc were obtained from S.D. Fine Chemicals (Mumbai, India). High-performance liquid chromatography (HPLC) grade solvents such as acetonitrile, methanol, and water were supplied by Merck Specialties Pvt. Ltd. (Mumbai, India). Analytical-grade reagents, including hydrochloric acid, sodium hydroxide, hydrogen peroxide, orthophosphoric acid, and potassium dihydrogen orthophosphate, were procured from Qualigens Fine Chemicals and Research Lab (Mumbai, India).

Instrumentation

The following analytical instruments were used:Fourier-transform infrared (FTIR) spectrophotometer (IR Affinity-1, Shimadzu, Kyoto, Japan) for drug-excipient compatibility studies, Differential scanning calorimeter (DSC) (METTLER DSC 30 S, Mettler Toledo, India) for thermal analysis, UV-Visible spectrophotometer (Shimadzu 1800, Japan) for drug quantification, Dissolution test apparatus (USP Type II, Electrolab TDT 08 L Plus, Mumbai, India) for in vitro drug release studies, Digital hardness tester (Monsanto, India) and friabilator (USP-compliant) for tablet mechanical strength evaluation, Stability chamber (Remi Lab, Mumbai, India) for accelerated stability testing, Tablet compression machine (Jaguar) for formulation development.

2.2 Methods

Preformulation Studies

Drug Identification and Characterization

The identity of atorvastatin calcium was confirmed using FTIR spectroscopy and DSC. The FTIR spectrum was recorded using the potassium bromide (KBr) disk method, and characteristic peaks were analysed. The melting point was determined using a melting point apparatus.

Solubility Studies

The solubility of atorvastatin calcium was assessed in various solvents, including water, pH 1.2 HCl, and pH 3.0 glycine buffer. Excess drug was added to 10 mL of each solvent and shaken at 37 ± 0.5 °C for 24 h. The samples were filtered (0.45 µm), diluted appropriately, and analyzed using UV spectrophotometry at 276 nm.

Standard Calibration Curve

A stock solution (100 µg/mL) of atorvastatin calcium was prepared in pH 1.2 HCl and pH 3.0 glycine buffer. Serial dilutions were madeform 10 to 60 µg/ml and absorbance was measured at 235 nm. A linear regression plot was constructed to determine the correlation coefficient (R^2).

Formulation Development
Experimental Design
A **3^2 full factorial design** was employed to optimize the gastroretentive floating tablets. The independent variables were:
- **X_1:** Concentration of sodium alginate/karaya gum (5.0–8.0%)
- **X_2:** Concentration of HPMC K100LV (8–12%)

The dependent variables included drug release at 4, 8, and 12 h. Nine formulations (X1–X9) were prepared by **direct compression**.

Tablet Preparation
All ingredients were passed through a #40 sieve, blended uniformly, and compressed into tablets (200 mg each) using a rotary tablet press. Magnesium stearate (1.25%) was added as a lubricant.

Evaluation of Tablets
Physicochemical Properties
- **Weight variation:** Twenty tablets were weighed individually, and the percentage deviation was calculated.
- **Thickness:** Measured using a digital Vernier caliper.
- **Hardness:** Determined using a Monsanto hardness tester (kg/cm^2).
- **Friability:** Tablets were rotated at 25 rpm for 4 min, and weight loss was recorded.

In Vitro Buoyancy and Swelling Studies
- **Buoyancy:** Tablets were placed in 0.1 N HCl (900 mL, 37 ± 0.5 °C), and floating lag time was recorded.
- **Swelling index:** Tablets were weighed before (W_1) and after (W_2) immersion in 0.1 N HCl. The swelling index was calculated as:

Swelling Index (%)=(W2−W1)W1×100, Swelling Index (%)=W1(W2−W1)×100

Drug Release Studies
Dissolution was performed using USP Type II apparatus (100 rpm, 37 ± 0.5 °C, pH 3.0 buffer). Samples (10 mL) were withdrawn at predetermined intervals, filtered, and analyzed at 263 nm.

Release Kinetics
Drug release data were fitted into various kinetic models (zero-order, first-order, Higuchi, Korsmeyer-Peppas) using KinetDS 3.0.

Stability Studies
Optimized formulations (X7, X9) were stored at 40 °C/75% RH for 3 months (ICH guidelines). Samples were analyzed monthly for drug content, dissolution, and physical stability.

3. Results and Discussion[15-21]

Preformulation Studies
Drug Identification and Characterization
The identity of atorvastatin calcium was confirmed using Fourier-transform infrared (FTIR) spectroscopy and differential scanning calorimetry (DSC). The FTIR spectrum exhibited characteristic peaks at:3364.21 cm^{-1} (N–H stretching, primary amide), 1649.81 cm^{-1} (C=O stretching, ketone), 1464 cm^{-1} (C–H bending, alkane) and 1506 cm^{-1} (N=O, nitro compound)
These findings align with reported spectra, confirming drug authenticity.

DSC analysis revealed a sharp endothermic peak at 170.92°C, corresponding to the melting point of atorvastatin calcium (141–144°C), further verifying drug purity fig. No. 1.

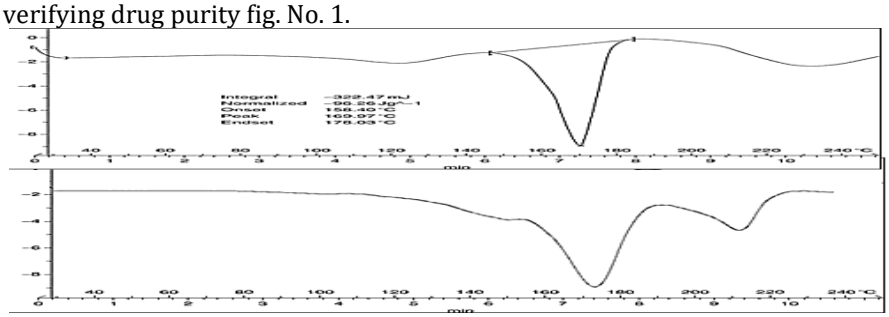


Fig. 1. DSC study of Atorvastatin calcium physical mixture

Solubility Studies
Atorvastatin calcium exhibited pH-dependent solubilityPoor solubility in water (0.60 mg/mL in pH 1.2 HCl), Enhanced solubility in pH 6.8 buffer (1.23 mg/mL)This behaviour supports the need for a gastroretentive delivery system to improve bioavailability.

Calibration Curves

Linear correlations (R^2 > 0.95) were established inpH 3.0 glycine buffer 10–60 µg/mL and pH 1.2 HCl (10–60 µg µg/mL) ant selected wavelengthFig. No. 2. and Fig. No. 3.

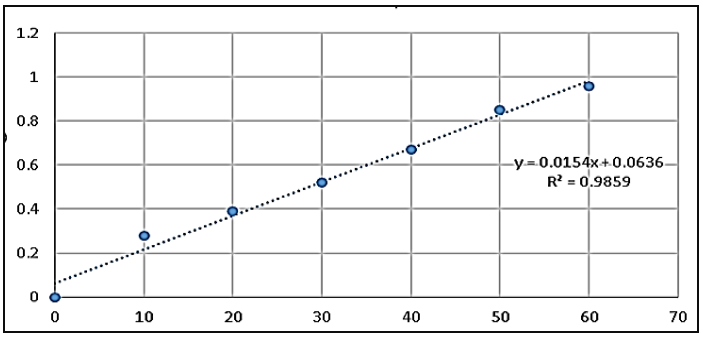


Fig. 2. Standard calibration curve of Atorvastatin calcium in pH 1.2

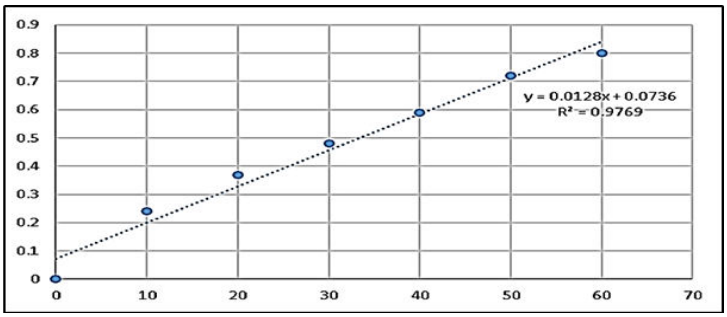


Fig. 3. Standard calibration curve data of Atorvastatin calcium in buffer (pH 3)

Powder Flow Properties

Precompression parameters results indicated: Poor flow for pure drug (Carr's index = 40%, Hausner's ratio = 1.67), Improved flow with excipients (e.g., HPMC K100: Carr's index = 15.38%, Hausner's ratio = 1.18): The precompression studies revealed significant differences in powder flow properties between the pure drug and formulated blends. Atorvastatin calcium in its pure form exhibited poor flow characteristics, as evidenced by a high Carr's compressibility index of 40% and Hausner's ratio of 1.67, indicating very poor flowability according to standard pharmaceutical classifications. This poor flow behaviour was substantially improved upon formulation with pharmaceutical excipients. Notably, the incorporation of HPMC K100 demonstrated marked enhancement in powder flow, showing a Carr's index of 15.38% (indicating fair flow) and Hausner's ratio of 1.18 (classified as good flow). Similar improvements were observed with other excipients, with HPMC K15M showing a Carr's index of 17.46% and Hausner's ratio of 1.21, while sodium alginate exhibited values of 25.80% and 1.34 respectively. These results confirm that the careful selection and combination of excipients successfully addressed the initial flow challenges of the pure drug, enabling direct compression as a viable manufacturing method for the gastroretentive tablet formulation. The angle of repose measurements further supported these findings, with pure drug showing a value of 39.0±1.52° (very poor flow) compared to improved values in the range of 28-35° for most excipient blends, indicating acceptable to good flow properties suitable for tablet production.

Formulation Development and Evaluation

Factorial Design Optimization

A 3^2 full factorial design optimized floating tablets using independent variables sodium alginate/karaya gum (X_1: 5–8%) and HPMC K100LV (X_2: 8–12%) and dependent variables: Drug release at 4, 8, and 12 h. The 3^2 full factorial design systematically optimized floating gastroretentive tablets by evaluating two critical formulation factors: polymer composition (sodium alginate/karaya gum, 5-8%) and matrix-forming polymer concentration (HPMC K100LV, 8-12%). These independent variables were strategically selected based on their distinct physicochemical properties - sodium alginate's ionic gelation capacity and karaya gum's swelling behavior synergized with HPMC K100LV's viscosity-modulating effects to control hydration kinetics and gel layer formation. The design revealed concentration-dependent relationships, where higher HPMC K100LV content (12%) produced more robust gel matrices with sustained drug release profiles, while sodium alginate/karaya gum variations significantly influenced buoyancy duration through gas-entrapment efficiency. The resulting formulations demonstrated pH-responsive swelling characteristics (120-150% index) and controlled erosion patterns that directly correlated with the observed drug release kinetics (88-99% over 12 hours), highlighting how polymer physicochemical interactions govern both floating behavior and drug release mechanisms in this delivery system.

Post-Compression Parameters

All formulations (X1–X9) exhibited good physical properties, demonstrating consistent weight variation (≤5% deviation), optimal mechanical strength (4–5 kg/cm^2 hardness), and minimal friability (<1%), indicating robust tablet integrity. The narrow drug content range (98.64–100.34%) confirmed uniform distribution and processing suitability, while the

physicochemical stability of the polymer matrix (HPMC-sodium alginate/karaya gum) ensured consistent drug release performance. These results validate the formulations' compliance with compendial standards and their potential for reproducible gastroretentive delivery.

Swelling and Buoyancy

The optimized formulations demonstrated excellent swelling (X9: 150±10% at 10h) due to HPMC K4M's hydration capacity, while maintaining rapid buoyancy (20-35s lag time) and prolonged floating (>12h). These properties resulted from synergistic polymer interactions - HPMC K4M enabled rapid gel formation while HPMC K100LV provided structural integrity, creating an effective gastroretentive system with controlled drug release. The combination of swelling polymers and gas-generating agents achieved optimal matrix stability and buoyancy for extended gastric retention.

In Vitro Drug Release[22-31]

Four hydrophilic polymers HPMC K4M, Xanthan gum, Carbopol and Sodium alginate were combined with HPMC K100 to develop floating gastroretentive tablets of Atorvastatin calcium. Formulations (X1–X9) containing Xanthan gum and HPMC K100 LV exhibited controlled drug release (88.37–99.80% over 12 h). Xanthan gum formed a firm gel, enhancing buoyancy and delaying drug release, while HPMC K4M-based tablets showed faster release due to rapid hydration and disintegration. The optimized formulation (X9: HPMC K4M + HPMC K100 LV) demonstrated near-ideal release kinetics, balancing immediate and sustained drug delivery. These results highlight the critical role of polymer selection in modulating drug release from gastroretentive systems.

Release Kinetics

Kinetic modelling of drug release for Floating Gastroretentive tablets. The data obtained from the in vitro drug released studies of formulation X1-X9, were fitted to zero-order, first-order, Higuchi Korsmeyer Peppas equations, and the data were analyzed. The r2 value of the optimized formulation X9 was found 0.999. The n values of the optimized formulation (X9) was found to be 0.510, which fall in the range 0.35<n<0.50 and k value was 17.61 with good floating properties. The value of the diffusion exponent indicates that the drug release follows non-Fickian release mechanism as shown in pareto graph figure No. 4.

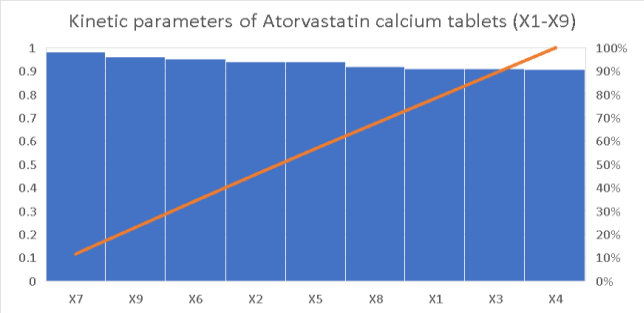


Fig. 4. Kinetic modelling of drug release for floating gastroretentive tablets

Stability Studies

On the basis of the in vitro drug dissolution studies, it may be concluded that formulation X9 is most stable. It showed controlled drug release up to 12 h and stable at 40°C/75 % relative humidity for a period of 3 months may possibly be a better delivery system for drug like drug. There were no significant changes in the physicochemical parameters and drug contents

4. Conclusion

he optimized floating tablet formulation (X9) demonstrated excellent performance characteristics as a gastroretentive drug delivery system. It exhibited controlled drug release kinetics over a 12-hour period, maintaining therapeutic concentrations within the desired range. The formulation showed superior buoyancy properties with a short lag time of 20-35 seconds and sustained floating duration exceeding 12 hours, ensuring prolonged gastric retention. Additionally, the tablets displayed remarkable swelling behavior, achieving a swelling index of 150±10% at 10 hours, which contributed to the sustained release profile. Stability studies confirmed the formulation's robustness under ICH-recommended accelerated conditions (40°C/75% RH), indicating satisfactory shelf-life potential. These findings collectively demonstrate that HPMC-based matrix systems represent a promising approach for enhancing the oral bioavailability and therapeutic efficacy of atorvastatin calcium through improved gastroretention, while addressing the drug's solubility and absorption limitations. The developed formulation shows significant potential for clinical translation and commercial application.

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