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Formulation and Evaluation of Fluvastatin Sodium Modified Pulsincap Delivery System

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ABSTRACT

The study focuses on the formulation and evaluation of a floating pulsatile drug delivery system for Fluvastatin Sodium, aimed at achieving site- and time-specific drug release in alignment with circadian rhythms. Fluvastatin Sodium, a short half-life statin, is used to reduce plasma cholesterol levels and prevent cardiovascular diseases. The innovative system is designed to release the drug after a predetermined lag time, targeting early morning hours when cholesterol synthesis peaks. This chronotherapeutic approach improves bioavailability, therapeutic efficacy, and patient compliance. The methodology involved the preparation of immediate-release core tablets, pulsatile tablets, and floating pulsatile formulations using polymers like HPMC. Evaluation tests included pre-compression parameters, in-vitro dissolution, buoyancy studies, and stability assessments. Results demonstrated successful lag-phase control and subsequent burst drug release, confirming the system's suitability for nocturnal hypercholesterolemia. Stability studies further validated the robustness of the formulation. The developed system ensures improved therapeutic outcomes, offering a promising solution for chronotherapy in hypercholesterolemia management.

Keywords: Fluvastatin Sodium, Pulsatile Drug Delivery System, Chronotherapy, Floating Drug Delivery, Circadian Rhythm, Bioavailability.

INTRODUCTION

Human physiological functions follow circadian rhythms, governed by the sleep-wake cycle and regulated by genetic factors [1]. These rhythms influence disease progression and the pharmacokinetics of drugs, including their absorption, distribution, metabolism, and elimination. To maximize therapeutic efficacy, drug delivery systems have evolved to align with these biological patterns [2]. One such approach is the chronotherapeutic drug delivery system, which synchronizes drug release with the body's circadian rhythms [2]. This method is particularly relevant for diseases such as hypertension, asthma, arthritis, and ulcers, where symptom severity varies throughout the day. For instance, conditions like asthma and cardiovascular diseases exhibit peak activity during early morning hours,

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necessitating tailored drug release profiles for improved treatment outcomes.

Floating pulsatile drug delivery systems combine the advantages of floating and pulsatile release mechanisms, allowing precise drug release after a controlled lag phase. These systems employ specialized coatings, such as pH-sensitive or erodible layers, to achieve delayed drug release [3]. By synchronizing drug availability with the body's natural rhythms, they improve therapeutic efficacy while minimizing side effects. Diseases like hypercholesterolemia benefit significantly from these systems, as cholesterol synthesis peaks during the early morning hours. The use of such systems enhances patient compliance, especially for chronic conditions, by reducing dosing frequency and aligning drug action with the body's needs.

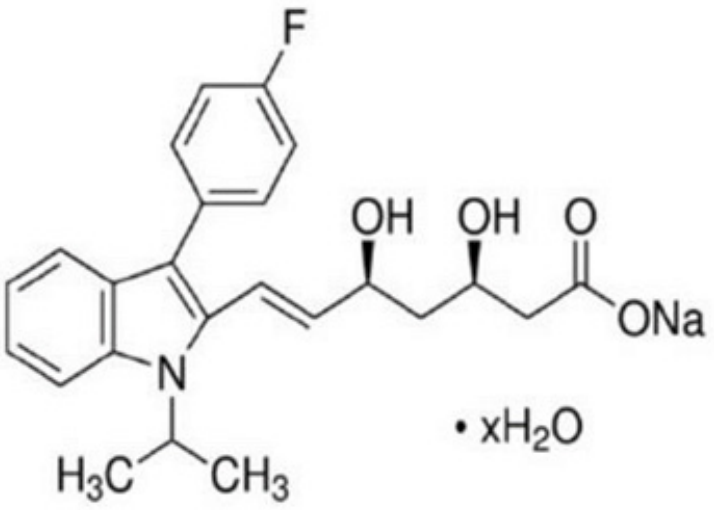

Figure 1. Fluvastatin Sodium.

METHODOLOGY

The methodology for the formulation and evaluation of Fluvastatin Sodium modified Pulsincap delivery system includes the following detailed steps:

Table 1. Materials used in the formulation

S.NO	INGREDIENTS	MANUFACTURER/SUPPLIER	CATEGORY
1.	Fluvastatin Sodium	Dr. Reddy's Laboratories	API
2.	Lactose	DMV-Fontera excipients GMBH	Diluent
3.	Povidone	Jh Nanhang life science	Binder
4.	Sucrose	Eid parry	Binder
5.	Crospovidone XL 10	Star tech products co. ltd	Super disintegrant
6.	Croscarmellose sodium	Mingtai chemicals co	Super disintegrant
7.	Aerosil	Cabot sanmar	Glidant
8.	HPMC E5	Colorcon asia pvt. limited	Rate controlling polymer
9.	HPMC E15	Colorcon asia pvt. limited	Rate controlling polymer
10.	HPMC K4M	Colorcon asia pvt. Limited	Rate controlling polymer
11.	HPMC K100M	Colorcon asia pvt. Limited	Rate controlling polymer
12.	Sodium bicarbonate	Avantor materials India limited	Effervescent
13.	Magnesium stearate	Amishi drugs and limited	Lubricant

Preformulation Studies

Physical Characterization

- The sample of Fluvastatin Sodium was characterized for its physical state, color, and odor (Supplier Name: Dr. Reddy's Laboratories).

Melting Point

- Determined using the capillary tube method [4].

Solubility Study

- Conducted using various solvents to understand solubility characteristics [3].

Compatibility Studies

- FTIR Spectroscopy was used to evaluate physicochemical compatibility and interactions among the drug and excipients [5].

Calibration Curve Preparation

- Fluvastatin Sodium was dissolved in methanol for stock solution preparation, with subsequent dilutions in 0.1N HCl to create a standard solution for UV analysis at 304 nm [6].

Formulation of Rapid Release Core Tablets

Prepared using the wet granulation method:

- Sifting and Blending: Drug and excipients (e.g., lactose, aerosil) were sieved and blended.
- Granulation: Binder solution added, followed by drying and sieving to obtain granules.
- Compression: Final granules mixed with magnesium stearate and compressed into tablets.

Preparation of Pulsatile Release Tablets

Dry Coating Technique:

- Core tablet placed in a die, partially covered with a pulsatile release layer, followed by full encapsulation.
- Coated with polymers like HPMC (K4M, E15, E5) in different concentrations.

Floating Pulsatile Release Tablets (FPRTs)

Optimized using a 3^2 factorial design:

- Independent Variables: HPMC K100M and Sodium Bicarbonate concentrations.
- Tablets formulated to float and release the drug post-lag time using buoyant and pulsatile layers.

EVALUATIONS

Micromeritic Properties

- Properties such as bulk density, tapped density, compressibility index, and Hausner's ratio were measured to determine powder flow characteristics [3].

Post-compression Testing

Tablets were tested for:

- Thickness
- Hardness
- Weight Variation
- Drug Content
- Disintegration Time
- Swelling Index
- Dissolution Studies: Conducted using USP II Paddle Method at 50 rpm [4]

Stability Studies

- Performed under ICH guidelines to ensure long-term formulation stability.

This comprehensive methodology ensured the development of a delivery system optimized for timed drug release aligning with circadian rhythms.

EVALUATION TESTS

The evaluation tests for Fluvastatin Sodium modified Pulsincap delivery system detailed in the document include the following:

Physical Evaluation

1. **Weight Variation**

- Tablets from each batch were individually weighed, and the percentage variation was calculated to ensure uniformity [7].

2. **Thickness**

- Measured using a vernier caliper, ensuring the consistency of dimensions among batches [1].

3. **Hardness**

- Determined using a hardness tester to assess the tablet's mechanical integrity [4].

4. Friability

- Evaluated using a Roche friabilator. Tablets were subjected to 100 rotations at 25 rpm, and the percentage weight loss was calculated using the formula: Friability (%)=(W1−W2)/W1×100, where W1W_1 is the initial weight, and W2W_2 is the final weight [6].

Disintegration Test

- Conducted using the USP apparatus with simulated gastric and intestinal fluids maintained at 37 ± 2°C. The time for the tablet to break into smaller fragments was recorded [3].

Drug Content Uniformity

- Ten tablets were crushed, and the resultant powder was dissolved in methanol. The solution was analyzed spectrophotometrically at 304 nm to calculate the percentage drug content.

Swelling Index

- Tablets were weighed (initial weight W1), placed in distilled water, and reweighed after 30 minutes (W2). The swelling index was calculated using: Swelling Index (\%) = (W2 - W1)/W1*100 [4].

In-Vitro Dissolution Studies

Performed using the USP Type II paddle method:

- Core Tablets: Dissolution in 0.1N HCl at 37 ± 0.5°C. Samples were withdrawn at predetermined intervals, replaced with fresh buffer, and analyzed at 304 nm.
- Pulsatile Release Tablets: Similar procedure with lag time and cumulative release recorded.

Stability Studies

- Conducted according to ICH guidelines. Tablets were stored at 30 ± 2°C, 65 ± 5% RH, and 40 ± 2°C, 75 ± 5% RH for three months. Post-compression parameters such as disintegration time, dissolution, and drug content were analyzed.

These evaluation tests ensured the formulation's efficacy, stability, and suitability for modified release.

RESULTS AND DISCUSSION

The results and discussion section from the document provides insights into the development, characterization, and evaluation of Fluvastatin Sodium Modified Pulsincap delivery system.

Selection of Drug and Excipients

- Fluvastatin Sodium was selected for its compatibility with excipients and suitability for the formulation [8]. It exhibited solubility in methanol, limited solubility in methylene chloride, and was insoluble in water.

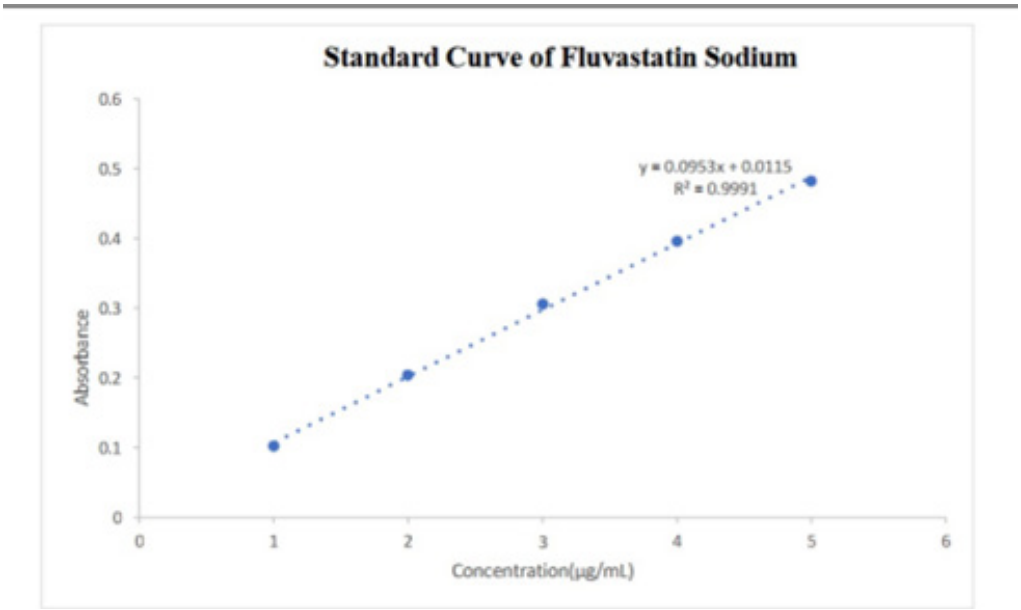

Figure 2. Standard Curve of Fluvastatin sodium.

Calibration Curve

- A UV spectrophotometer at 304 nm was used to analyze the drug.
- The calibration curve showed linearity (R^2 = 0.9991) across concentrations of 1–5 µg/mL, adhering to Beer-Lambert's Law [6].

Precompression Parameters

The granules exhibited favorable flow properties:

- Bulk density ranged from 0.523 to 0.543 g/mL.
- Compressibility indices were between 14.08% and 18.91%.
- Hausner's ratio ranged from 1.164 to 1.733 [7].

Postcompression Evaluations

- Weight Variation: Tablets passed the pharmacopoeial limits.
- **Thickness and Hardness:** Thickness ranged from 2.9 to 3.1 mm, ensuring uniformity, and hardness varied between 3.55 and 3.95 kg/cm^2.
- **Friability:** Less than 1%, indicating mechanical stability.
- **Assay:** Drug content ranged from 97.4% to 99.1%.

In-Vitro Dissolution Studies

- **Rapid Release Core Tablets (RRCTs):** Drug release was rapid, with F6 formulation achieving 99.95% release in 30 minutes.

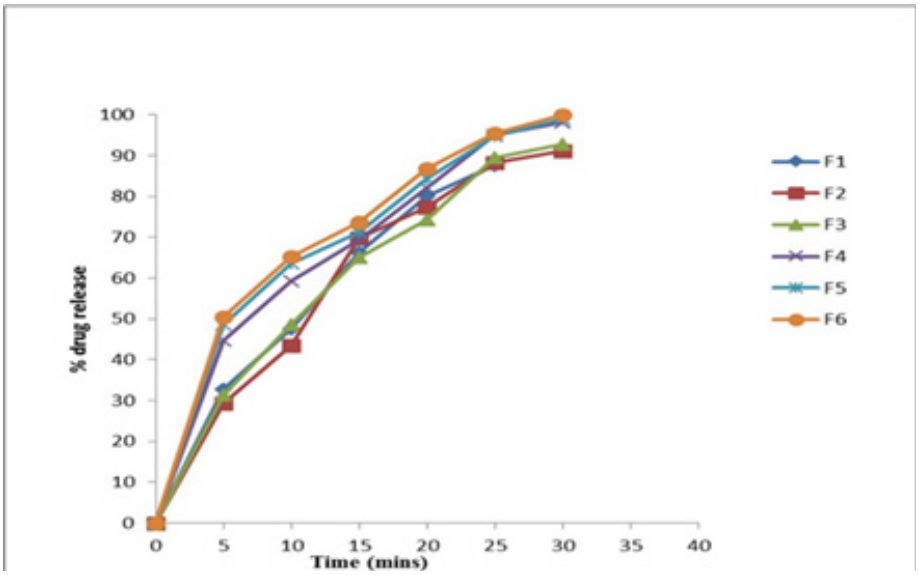

Figure 3. % Drug Release of RRCTs.

- **Floating Pulsatile Release Tablets (FPRTs):** Optimized F6 demonstrated lag times followed by a burst release pattern, achieving 81.21% drug release in 435 minutes.

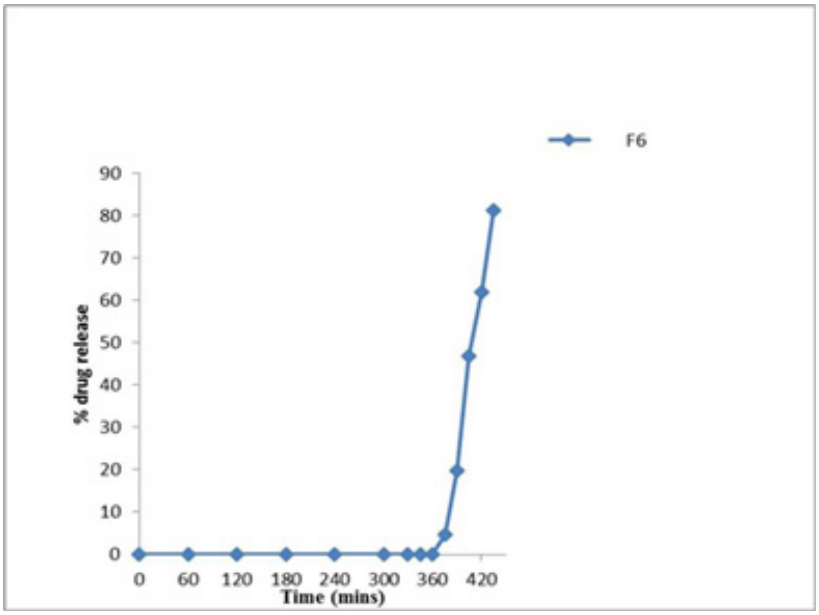

Figure 4. % Drug release of optimized FPRT (F6).

Optimization Using Factorial Design

- The floating lag time and duration were influenced by the concentrations of HPMC K100M and Sodium Bicarbonate.
- Optimized formulation (F6) with desirability 0.918 showed floating lag time of 4.4 minutes and floating time of 14.3 hours.

Stability Studies

- Conducted as per ICH guidelines at 40 ± 2°C and 75 ± 5% RH for 30 days [1].
- Parameters like thickness, drug release, floating lag time, and floating duration remained stable.

CONCLUSION

The study successfully developed a floating pulsatile drug delivery system (FPDDS) for Fluvastatin Sodium, designed to align with the circadian rhythm of cholesterol biosynthesis [1]. By delivering the drug during early morning hours when cholesterol levels peak, the system meets the chronotherapeutic needs of cardiovascular patients [7]. The optimized formulation, F6, utilized HPMC K100M and sodium bicarbonate to achieve a desired lag time of 4.4 minutes and a floating duration of 14.3 hours. The drug release followed a burst mechanism after the lag phase, ensuring precise delivery aligned with therapeutic requirements. Stability studies confirmed the formulation's robustness under ICH conditions, maintaining its physical and functional integrity. Response Surface Methodology (RSM) effectively optimized the formulation variables, achieving a desirability index of 0.918. The release mechanism adhered to controlled kinetics, validated by higher R^2 values in zero-order models. This innovative delivery system enhances bioavailability, reduces dosing frequency, and improves therapeutic outcomes, offering significant potential for treating hypercholesterolemia while ensuring better patient compliane [8].

Future Directions and Clinical Implications:

The future directions and clinical implications outlined in the document emphasize the potential of the floating pulsatile drug delivery system (FPDDS) for treating hypercholesterolemia and other conditions influenced by circadian rhythms. This system is designed to align drug release with the early morning peak of cholesterol biosynthesis, enhancing therapeutic outcomes. The integration of advanced materials, such as HPMC polymers and buoyant layers, ensures precise control over drug release timing. Future research could focus on scaling up production, exploring novel polymers for better control, and evaluating the system's efficacy across a broader spectrum of patients. Clinically, FPDDS offers the potential to improve patient compliance by minimizing dosing frequency and side effects. Its application could extend to other diseases requiring chronotherapy, such as hypertension and asthma, through further optimization and innovation [9,10].

ACKNOWLEDGMENTS

None.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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