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Development and Evaluation of Gastro-Retentive Effervescent Tablet of Atorvastatin and Aspirin for Enhanced Bioavailability and Gastric Drug Delivery

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Abstract

This investigation aimed to develop and assess gastro-retentive effervescent tablets containing Atorvastatin and Aspirin, utilizing the effervescent floating mechanism to enhance drug delivery within the stomach. The study encompassed pre-formulation investigations, tablet formulation, and comprehensive tablet evaluations. The drug evaluation phase confirmed the physical characteristics of Atorvastatin and Aspirin, establishing their suitability for pharmaceutical formulation. Identification tests through FTIR and UV-Visible spectroscopy provided critical data on these drugs' absorbance wavelengths and melting points. Moreover, solubility tests indicated the drugs' behavior in various solvents and buffer solutions, essential for formulation considerations. Pre-formulation studies focused on powder blend properties, revealing excellent flowability and compressibility. The angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio collectively demonstrated the powder blend's suitability for tablet manufacturing. Physio-chemical evaluations of the tablets demonstrated uniform weight, suitable hardness, and low friability, attesting to their robustness and ease of handling. Additionally, the tablets exhibited significant swelling in an acidic medium, a short floating lag time, and sustained buoyancy for over 8 hours, contributing to controlled drug release. In-vitro dissolution studies revealed sustained drug release profiles, following various kinetic models. The release mechanism involved both zero-order and Higuchi square root of time release rate constants, indicative of effective control over drug release for up to 12 hours. Stability studies on the optimized formulation, F8, showed no significant changes in drug content and percentage drug release over 180 days, confirming its long-term stability. In summary, this research successfully formulated gastro-retentive effervescent tablets of Atorvastatin and Aspirin, which exhibited favorable flow properties, physiochemical attributes, sustained drug release, and long-term stability. These findings hold great promise for improving drug delivery systems, enhancing bioavailability, and enabling targeted drug delivery within the gastric environment.

Keywords: Floating tablet, floating lag time, floating time, in-*vitro* studies, Atorvastatin, Aspirin

Introduction

The quest for optimizing drug delivery systems has long been a driving force in pharmaceutical research and development. The challenge of achieving consistent and prolonged drug release, particularly for drugs with narrow absorption windows and low solubility at higher pH values, has led to the exploration of innovative dosage forms. Among these, gastro-retentive drug delivery systems have emerged as a promising solution.[1] These systems aim to prolong the residence time of drugs within the stomach, thereby enhancing bioavailability and enabling local drug delivery to the gastric region. The need for such gastro-retentive systems is

underscored by the documented poor bioavailability of certain drugs when formulated in conventional controlled-release dosage forms. Factors such as the limited absorption window, reduced solubility in alkaline environments, or susceptibility to enzymatic degradation in the gastrointestinal tract have all contributed to suboptimal drug performance. As a result, the development of oral controlled-release dosage forms has presented a formidable challenge.[2-3]

Gastro-retentive drug delivery systems employ various mechanisms to achieve prolonged gastric retention. These mechanisms include floating systems, high-density systems, bioadhesive systems, and expandable systems. In this study, we focus on the effervescent floating drug delivery system, which has shown promise in addressing the challenges associated with drug absorption.[4-5] Effervescent floating drug delivery systems operate by maintaining buoyancy in the stomach for extended periods. These systems can be further categorized into non-effervescent and effervescent systems. Non-effervescent floating systems swell in gastric fluid and maintain their shape and buoyancy due to their lower density compared to gastric fluid. In contrast, effervescent systems employ components that release carbon dioxide upon contact with gastric fluid. This liberated gas becomes trapped in a gel layer formed by hydrocolloids, creating an upward buoyant force that prolongs the residence time of the dosage form.[5-7]

The aim of this research project is to formulate and evaluate a gastro-retentive effervescent tablet of Atorvastatin and Aspirin. By leveraging the effervescent floating mechanism, this study seeks to extend the gastric residence time of these drugs, improve their bioavailability, and enable targeted drug delivery to the stomach. The specific objectives of this project include pre-formulation studies and analytical evaluation of the Atorvastatin and Aspirin active pharmaceutical ingredients (APIs), formulation of the gastro-retentive effervescent tablet, and comprehensive evaluation of the tablet's physical properties, buoyancy characteristics, drug content, and in-vitro dissolution behavior. Additionally, mathematical modeling of the dissolution data and stability studies of the formulated tablet will be conducted to provide a comprehensive understanding of the developed dosage form.

In conclusion, this research endeavor addresses the critical need for enhanced drug delivery systems, with a particular focus on optimizing the therapeutic potential of Atorvastatin and Aspirin. By developing a gastro-retentive effervescent tablet, we aim to contribute to the advancement of pharmaceutical science, potentially improving patient outcomes through increased drug bioavailability and targeted delivery within the gastric environment.

Method and Materials

Drug and Excipients

Atorvastatin and Aspirin are the active pharmaceutical ingredients (APIs). HPMC K4M functions as a release-controlling agent and swellable polymer. Sodium bicarbonate and citric acid serve as effervescent agents, while Avicel (MCC) acts as a diluent. Talc and magnesium stearate play roles as a glidant and lubricant, respectively, in the formulation of gastro-retentive effervescent tablets.

Equipment and Instruments

These included an electronic weighing balance, pH meter, Ultra-Sonicator, UV-Visible spectrophotometer, hardness tester, Fourier Transfer Infrared Spectroscopy (FTIR), dissolution apparatus, Tablet Press Machine, and Bulk Density Apparatus. These tools facilitated accurate measurements, chemical analysis, and tablet formulation, ensuring the research's reliability and precision.

Drug Evaluation

Drug evaluation involved visual inspection, FTIR and UV-Visible spectroscopy for Atorvastatin and Aspirin identification. Melting points were determined through capillary melting, and solubility tests were conducted in various solvents and buffer solutions. These evaluations ensured a comprehensive understanding of the drugs' physical characteristics and analytical parameters, facilitating their incorporation into the formulation of gastro-retentive effervescent tablets.

Preformulation Studies

The preformulation studies encompassed crucial evaluations of drug-excipient compatibility, flow properties, and density characteristics to ensure the formulation's quality and performance. The angle of repose was measured to determine the flow properties of granules, while bulk and tapped densities were calculated to assess granule packing and compressibility. Additionally, the Hausner's ratio provided insights into granular material flowability. These assessments contribute to the formulation's manufacturability and therapeutic product quality, ensuring it meets the desired standards for flow characteristics and compressibility.

Table 1. Formulation Batches

Sr. No.	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1.	Atorvastatin	10	10	10	10	10	10	10	10	10	10
2.	Aspirin	75	75	75	75	75	75	75	75	75	75
3.	HPMC K4M	--	--	--	--	--	100	120	130	80	60
4.	HPMC K100M	60	75	80	90	100	--	--	--	--	--
5.	Sodium bicarbonate	45	50	--	--	40	25	--	--	35	45
6.	Citric acid	--	--	15	20	--	--	25	20	--	--
7.	Avicel (MCC)	56	36	66	51	21	36	16	11	46	56
8.	Talc	2	2	2	2	2	2	2	2	2	2
9.	Magnesium stearate	2	2	2	2	2	2	2	2	2	2
Total weight (mg)		**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**

Evaluation of formulated tablet

The evaluation of the floating tablets involved several crucial tests to assess their quality and performance.

Physiochemical Test of Tablet

First, the uniformity of weight was determined by weighing twenty tablets individually, calculating the average weight, and checking the percentage deviation as per the Indian Pharmacopoeia (IP) standards. Hardness, representing the force required to break a tablet, was measured in kg/cm² using a Monsanto tablet hardness tester. The tablets' strength, or friability, was assessed using a friabilator, which rotated the tablets at 25 rpm for four minutes, measuring the percentage loss in tablet weight. The swelling index was determined by placing tablets in an HCl solution (pH 1.2) at 37°C for 8 hours, calculating the difference in weight before and after immersion.

In-vitro studies

The tablets' in-vitro floating characteristics were examined, including the Buoyancy Lag Time (BLT) and Total Floating Time (TFT), which measured the time taken for the tablets to emerge on the medium's surface and how long they remained buoyant.

In-vitro dissolution studies were conducted using a USP type II apparatus with 0.1N HCl (pH 1.2) as the dissolution medium. Samples were analyzed for drug content using a UV-Visible spectrophotometer, and drug release data were analyzed to understand the mechanism of drug release, with calculations involving zero-order release rate constants, Higuchi square root of time release rate constants, and the diffusion exponent (n) indicating the release mechanism.

Results and Discussion

Drug Evaluation

Descriptive Test:

In the descriptive test, both Atorvastatin and Aspirin were observed to possess a similar white color, signifying their physical appearance. Additionally, both substances were characterized by their crystalline powder form, reflecting their fine and granular texture. These visual attributes provide valuable information regarding the physical characteristics of these drugs, serving as initial indicators of their suitability for pharmaceutical formulation and compatibility with excipients.

Identification Test:

a. FTIR Spectroscopy

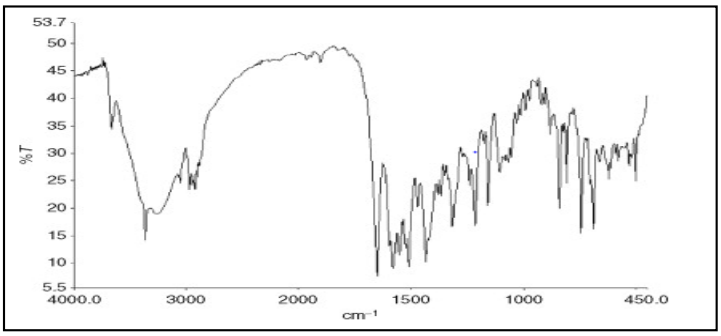

Figure 1. FTIR of Atorvastatin

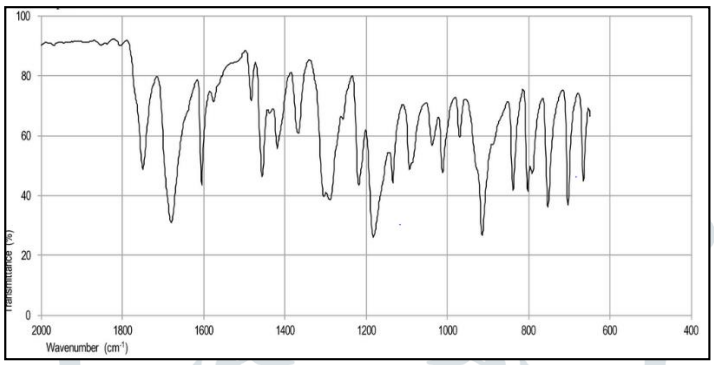

Figure 2. FTIR Spectra of Aspirin

a. UV-Visible Spectroscopy

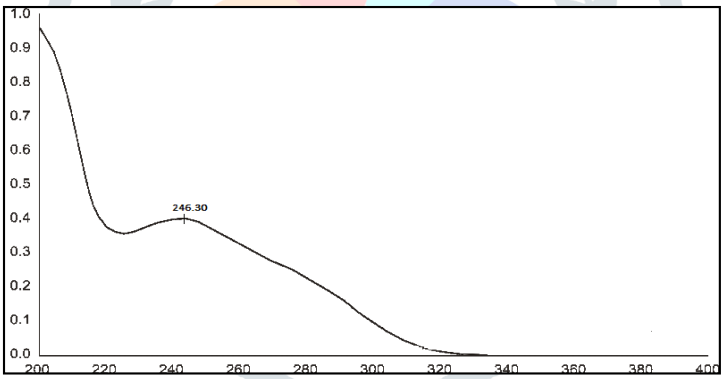

Figure 3. UV Spectrum of Atorvastatin

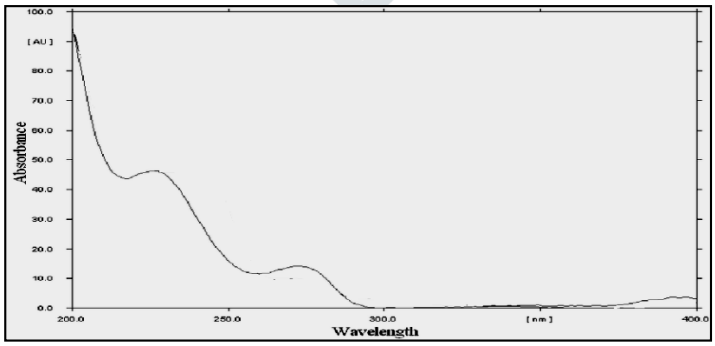

Figure 4. UV Spectrum of Aspirin

The respective λ_{max} values for Atorvastatin and Aspirin were determined, indicating the wavelengths at which these drugs exhibit maximum absorbance. Atorvastatin demonstrated a λ_{max} of 246 nm, while Aspirin exhibited a λ_{max} of 230 nm, crucial information for subsequent UV-Visible spectrophotometric analysis. The melting points of these drugs were determined using the capillary method, Atorvastatin exhibited a melting point of 164.2°C, while Aspirin displayed a melting point of 136.7°C, providing essential data regarding their physical characteristics. Atorvastatin was found to be very slightly soluble in water, slightly soluble in methanol,

soluble in a buffer solution with a pH of 1.2, and slightly soluble in a buffer solution with a pH of 6.8. In contrast, Aspirin demonstrated slightly soluble solubility in water, being freely soluble in methanol, and soluble in both pH 1.2 and 6.8 buffer solutions.

Micrometric Evaluation

Table 2. Preformulation parameters for powder blend

Batch	Bulk Density (gm/cm)	Tap Density (gm/mL)	Carr's Index	Hausner's Ratio	Angle of Repose
F1	0.48±0.046	0.744±0.056	13.357±0.73	1.247±0.03	24.7±0.64
F2	0.49±0.059	0.726±0.045	13.935±0.71	1.227±0.06	24.1±0.49
F3	0.35±0.076	0.719±0.067	13.236±0.64	1.285±0.05	24.4±0.38
F4	0.42±0.025	0.753±0.049	13.945±0.36	1.246±0.07	25.1±0.35
F5	0.33±0.048	0.733±0.041	13.457±0.32	1.264±0.07	24.4±0.58
F6	0.45±0.076	0.731±0.036	13.276±0.25	1.226±0.07	24.9±0.53
F7	0.46±0.071	0.739±0.036	12.276±0.25	1.226±0.07	24.9±0.53
F8	0.39±0.005	0.716±0.067	14.236±0.64	1.285±0.05	24.4±0.38
F9	0..46±0.043	0.767±0.056	12.357±0.73	1.247±0.03	24.7±0.64
F10	0.43±0.044	0.723±0.045	11.935±0.71	1.227±0.06	24.1±0.49

The powder mixtures prepared for compression of floating tablets were evaluated for their flow properties. Angle of Repose was in range of 24.1° – 25.1°, Tapped density was found to be in the range 0.716-0.767 gm/mL. Carr's Index was in the range of 11.935-14.236 and Hausner's ratio was in the range of 1.226-1.285 for the powder mixture of different formulation. All the result indicated that the powder blend possesses good flowability and compressibility properties.

Physio-chemical Evaluation of Tablet

Table 3. Physio-chemical evaluation of Tablet

Batch	Hardness (Kg/cm^2)	Friability (%)	Weight Variation	Swelling Index 12 hr	Floating Lag Time (min)	Floating Time	Drug Content (%)
F1	4.6±0.03	0.27±0.04	253±1.42	96.89±0.754	4.7±0.35	>10 hr	96.79±0.26
F2	4.3±0.07	0.28±0.06	256±1.24	92.12±0.346	4.9±0.14	>8 hr	98.67±0.12
F3	4.2±0.04	0.23±0.03	251±1.64	91.35±0.156	4.8±0.24	>10 hr	98.86±0.19
F4	4.7±0.05	0.27±0.05	251±1.43	94.42±0.535	4.7±0.13	>8 hr	99.15±0.26
F5	4.4±0.03	0.29±0.06	254±1.13	96.65±0.764	4.6±0.15	>10 hr	99.57±0.25
F6	4.2±0.01	0.25±0.04	253±1.64	94.34±0.963	4.4±0.27	>10 hr	97.35±0.22
F7	4.4±0.03	0.22±0.46	251±5.35	97.24±0.567	4.3±0.13	>9 hr	99.28±0.24
F8	4.6±0.04	0.22±0.04	250±3.35	93.46±0.723	4.9±0.12	>10 hr	98.36±0.23
F9	4.5±0.01	0.23±0.07	259±3.62	96.53±1.353	5.0±0.24	>10 hr	98.31±0.13
F10	4.4±0.08	0.24±0.01	252±7.95	93.64±1.134	5.1±0.14	>10 hr	99.35±0.34

***In-vitro* drug release drug study of different batches of tablets:**

Table 4. Percent Cumulative drug release of Batches F1 to F10

Batch	Cumulative Drug release at 1 hr	Cumulative Drug release at 2 hr	Cumulative Drug release at 4 hr	Cumulative Drug release at 8 hr	Cumulative Drug release at 10 hr	Cumulative Drug release at 12 hr
F1	24.24±0.233	41.24±0.735	58.24±1.244	76.88±0.567	88.56±1.357	94.48±0.748
F2	26.64±0.236	34.24±0.636	56.36±1.753	73.24±0.245	89.34±1.754	95.53±0.986
F3	27.46±0.535	47.52±0.574	58.56±1.357	78.97±0.543	86.86±1.457	93.35±0.346
F4	22.35±0.235	38.45±0.735	59.34±1.754	72.07±0.753	85.75±1.724	92.55±0.864
F5	24.85±0.457	35.76±0.852	56.86±1.457	71.43±0.357	88.45±1.524	95.88±0.567
F6	29.45±0.544	41.67±0.257	55.75±1.724	79.24±0.932	86.94±0.843	94.45±0.735
F7	20.93±0.567	38.45±0.735	58.45±1.524	78.64±0.556	84.24±0.233	95.76±0.852
F8	30.41±0.969	55.5±0.377	66.01±0.357	75.27±0.924	81.24±0.735	96.01±0.357
F9	30.05±1.539	48.01±0.357	58.40±0.246	73.75±0.934	84.24±0.636	94.41±0.733
F10	20.12±0.831	44.41±0.733	54.31±1.378	79.53±0.986	87.52±0.574	93.31±1.378

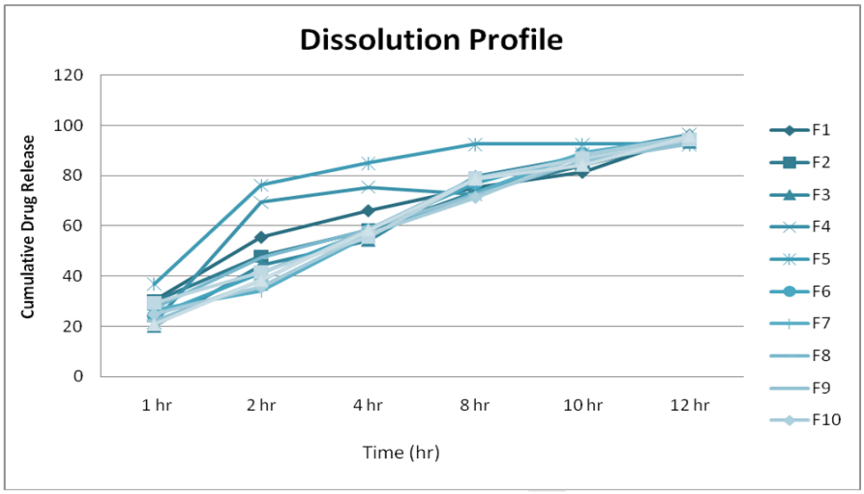

Figure 5. Dissolution Profile

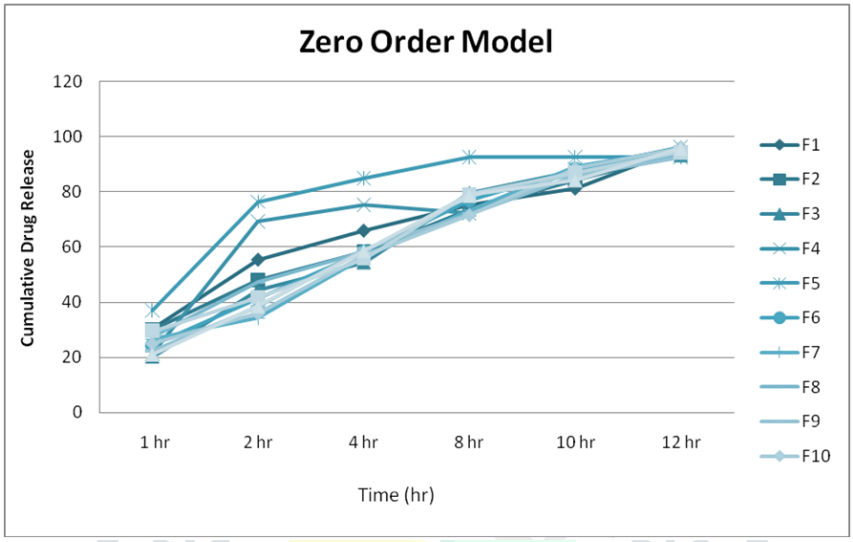

Figure 6. Zero Order Model

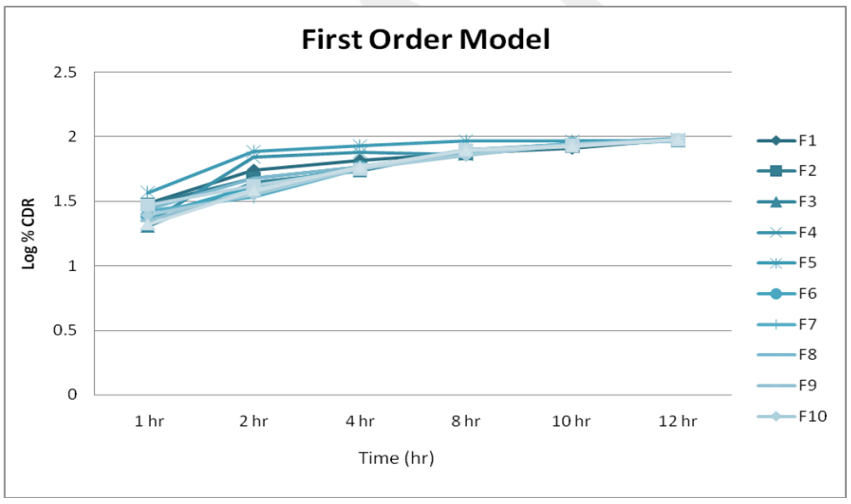

Figure 7. First Order Model

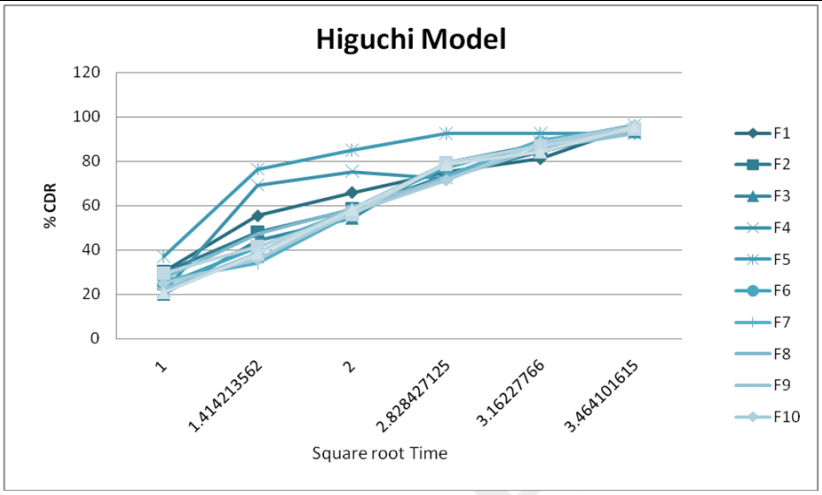

Figure 8. Higuchi Model

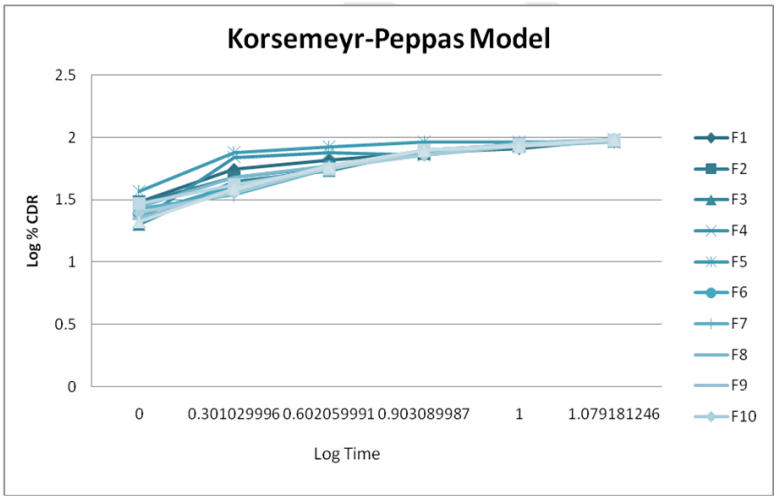

Figure 9. Korsemeyr-Peppas Model

Stability Studies

The stability studies parameters with readings as shown in table 5. It is well observed that the FDT retained more than 95 % of their active ingredients and revealed no significant changes in rate of release of Atorvastatin and Aspirin after 180 days of storage at desired conditions. Despite this, it is very much essential and hence, highly recommended to prevent their prolonged exposure to high temperature and humidity.

Table 5. Stability Studies of Atorvastatin and Aspirin Floating tablet

Batch F8	Weight Variation	Friability (%)	Swelling Index 12 hr	Floating Lag Time (min)	Drug Content (%)
Initial	251±1.43	0.25±0.04	96.65±0.764	4.6±0.15	97.48 %
1 month	252±1.13	0.29±0.06	94.34±0.963	4.4±0.27	95.14 %
3 months	251±1.64	0.27±0.05	91.35±0.156	4.8±0.24	96.22 %

Stability Studies showed that there was no significant change in drug content and percentage drug release for the optimized formulation F8.

Discussion

The preformulation studies and subsequent evaluations of the floating tablet formulations (F1 to F10) have yielded promising results. Flow properties and density characteristics, including angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio,

indicate that the powder blend possesses excellent flowability and compressibility, ensuring uniform tablet properties. Physiochemical evaluations of the tablets confirm uniform weight, appropriate hardness, and low friability, indicating their robustness and suitability for handling and transportation. These tablets also demonstrate desirable characteristics such as significant swelling in an acidic medium, a floating lag time of under 5 minutes, and sustained buoyancy for over 8 hours, facilitating controlled drug release. Moreover, the in-vitro dissolution studies reveal sustained drug release profiles, following various kinetics models, implying effective control of drug release over 12 hours. Stability studies on the optimized formulation, F8, confirm its long-term stability with more than 95% retention of active ingredients and no significant changes in drug release rates over 180 days. Overall, these findings suggest that formulation F8 shows promise as a pharmaceutical product with excellent flow properties, physiochemical attributes, sustained drug release, and long shelf life.

Conclusion

In conclusion, this research project aimed to formulate and evaluate gastro-retentive effervescent tablets of Atorvastatin and Aspirin. The study successfully addressed its objectives, including preformulation studies, tablet formulation, and comprehensive evaluation of tablet properties. The results demonstrate that the formulated tablets exhibit excellent flow properties, desirable physiochemical characteristics, sustained drug release, and stability, particularly in the case of the optimized formulation, F8. These findings hold promise for enhancing drug delivery systems, improving bioavailability, and enabling targeted drug delivery in the gastric environment.

Conflict of Interest

We declare that we have no conflict of interest.

Acknowledgement

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