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Formulation, Optimization and Evaluation of Gastro-retentive Raft Forming Tablets of Atenolol for the Treatment of Hypertension

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ABSTRACT

The present study aimed to develop and evaluate raft-forming controlled-release tablets of Atenolol using a floating drug delivery system to enhance gastric retention and sustain drug release. Formulations were prepared by the direct compression method using sodium alginate, sodium bicarbonate, and HPMC K15M as key excipients, with microcrystalline cellulose as a binder, talc as a diluent, and magnesium stearate as a lubricant. Precompression studies confirmed that the powder blends possessed good flow properties, while post-compression evaluations demonstrated satisfactory hardness, friability, weight uniformity, thickness, and drug content. In vitro buoyancy studies revealed that the combination of sodium bicarbonate and sodium alginate significantly influenced the floating lag time, ensuring prolonged gastric residence. Dissolution studies showed that the optimized formulation, F3, exhibited a controlled drug release over 12 hours, highlighting the role of HPMC K15M in modulating release kinetics. Raft strength measurements confirmed the mechanical stability of the gel, and preliminary stability studies indicated formulation robustness under accelerated conditions. Overall, these findings suggest that the optimized raft-forming tablets of Atenolol have potential for sustained therapeutic effects, improved patient compliance, and enhanced management of hypertension and related conditions...

Keywords: *Atenolol, Raft-forming tablets, Floating drug delivery system, Controlled-release formulation, Sodium alginate, HPMC K15M, In vitro buoyancy, Sustained drug release*

1. INTRODUCTION

The development of gastro-retentive raft-forming tablets of Atenolol is an innovative approach aimed at improving the drug's pharmacokinetic profile by extending its residence time in the stomach and providing sustained release [1-3]. Atenolol, a β1-selective adrenergic blocker widely used in the management of hypertension and angina pectoris, has a relatively short elimination half-life (approximately 6–7 hours) and limited bioavailability due to incomplete absorption in the lower gastrointestinal tract. These characteristics necessitate multiple daily dosing, which can cause fluctuations in plasma drug concentration, leading to variable therapeutic responses and reduced patient adherence [4-6].

To overcome these limitations, gastro-retentive drug delivery systems (GRDDS) have gained attention, particularly those based on raft-forming mechanisms. In this system, the tablet, upon ingestion, reacts with gastric fluids to form a viscous, gel-like raft that remains buoyant on the stomach contents. This raft acts as a barrier, floating atop the gastric fluids and

retaining the drug in the upper gastrointestinal tract where absorption is more favorable. By remaining in the stomach for an extended duration, the drug is released gradually, ensuring more consistent plasma levels and enhanced therapeutic efficacy [7-10]

The success of this approach hinges on meticulous formulation design, especially the selection and optimization of excipients and polymers that contribute to both raft formation and drug release modulation. Polymers such as sodium alginate play a critical role in gelation when they interact with gastric acid or calcium ions. Additional excipients like calcium carbonate or sodium bicarbonate can generate carbon dioxide, further aiding buoyancy by entrapping gas within the gel matrix [11-14].

The proposed research is centered on the formulation, optimization, and evaluation of gastro-retentive raft-forming tablets of Atenolol, with the ultimate goal of enhancing its therapeutic efficacy and bioavailability in the management of hypertension. The study is envisaged to explore a novel oral drug delivery system that overcomes the limitations associated

with Atenolol's conventional dosage forms, particularly its short biological half-life, poor absorption in the lower gastrointestinal tract, and frequent dosing requirements [15-18].

To address these challenges, the study will involve the development of a raft-forming tablet capable of prolonged gastric retention and controlled drug release. This will be achieved through the incorporation of gel-forming polymers (e.g., sodium alginate) and gas-generating agents (e.g., calcium carbonate or sodium bicarbonate) that facilitate the formation of a buoyant, gel-like raft in the stomach environment. The sustained presence of the tablet in the upper gastrointestinal tract is expected to maximize the absorption window of Atenolol, thereby improving its pharmacokinetic profile and providing consistent antihypertensive action [19-22].

2. MATERIALS AND METHODS

Materials

The materials used in this study included Atenolol (ATN) obtained from IPCA Laboratories Ltd., Ratlam. Sodium alginate, Hydroxypropyl Methylcellulose (HPMC K15M), and Microcrystalline Cellulose were procured from S.D. Fine Chem. Ltd., Mumbai. Sodium bicarbonate and Magnesium Stearate were supplied by Qualigens, while Talc was obtained from LOBA Ltd. All chemicals were of analytical grade and used as received without further purification.

Preformulation Studies

Melting Point

Melting point of the drugs used for the study were determined by taking small quantity of the drug in a capillary tube sealed at one end and was placed in melting point apparatus (Tempo, Mumbai) and temperature range at which drugs melted was noted. The process was performed three times and the melting point range for ATN was determined [23-24].

FTIR of ATN

The FTIR studies were perform by the direct drug analysis in FTIR instrument. The drug sample was prepared in KBr discs (5 mg ATN in 200 mg KBr), and the sampling range was 400–4000 cm^{-1} [25-26].

Preparation of Calibration Curve

Accurately weighed 100 mg of ATN was dissolved in 0.1N HCl and volume was made up to 100 ml, resulting in a stock solution of 1000µg/ml. Then, 10 ml of this stock solution was further diluted to 100ml with 0.1N HCl to get stock solution of 100µg/ml concentration. Stock solution was taken in aliquots of 0.5 ml, 1.0 ml, 1.5 ml upto 3.0 ml in to a series of 10 ml volumetric flasks and volume was made up to the mark with 0.1N HCl. The solutions were filtered through Whatman filter paper no. 1 and filtrate was analyzed at λmax 225nm using UV visible spectrophotometer. 0.1N HCl was used as blank solution. The standard curve was plotted between absorbance and concentration [27-30].

Solubility Studies

The solubility studies were performed in distilled water, 0.1N HCl, ethanol and DMSO, by adding excess amount of drug in each case and keeping the flasks containing excess amount of drug on a rotary shaker for 24 h. After 24 h, solutions were analyzed spectrophotometrically at 225 nm [31].

Drug- excipients compatibility study

The design and formulation of a dosage form must take into account the physical, chemical, and biological properties of all drug compounds and excipients employed in the product's manufacture. Compatibility of ATN with the excipients proposed to be used in the development of tablets was assessed. FTIR analysis was conducted to determine the compatibility of the drug with polymers [32-33].

Precompression Characterization

The powder blend was evaluated for its precompression properties to ensure suitability for direct compression. Bulk density and tapped density were measured using standard apparatus, and these values were used to calculate Carr's index and Hausner ratio, which indicate powder flowability and compressibility. Flow properties were assessed via the fixed funnel method to determine the angle of repose. All parameters were measured before and after incorporating lubricants or glidants, with results compared to standard pharmacopoeial values to confirm acceptable flow and compressibility of the powdered blend [34-36].

Formulation of Raft-Forming Tablets

Floating raft-forming tablets of Atenolol (ATN) were prepared using the direct compression method. The tablet formulation process involved sequential steps of sieving, mixing, lubrication, and compression. Microcrystalline cellulose (MCC) was used as a binder, HPMC K15M as a synthetic hydrophilic polymer, sodium alginate as a viscous gel-forming agent, and sodium bicarbonate as a gas-generating agent. Talc served as a diluent, while magnesium stearate was used as a lubricant

[39-40].

All ingredients were individually powdered in a dry, clean porcelain mortar and accurately weighed according to the formulation design. Each component was passed through a 60# sieve to ensure uniform particle size distribution and proper mixing. Preliminary batches of raft-forming tablets were prepared by blending the drug with the selected polymers, sodium alginate, and MCC for 20 minutes. Subsequently, talc and magnesium stearate were incorporated, and the mixture was further blended for 10 minutes to achieve uniformity. Nine formulations were developed using varying polymer ratios to optimize tablet characteristics. The final powder blends were compressed into tablets containing 50 mg of ATN using an 8 mm flat round punch on a Rimek multi-rotary 16-station tablet compression machine (Table 1) [41-44].

Table 1: Composition of Floating Raft forming approach tablets

Ingredients	Quantity (mg)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Atenolol	50	50	50	50	50	50	50	50	50
Hydroxypropyl methylcellulose	-	-	-	50	100	150	25	50	75
Sodium alginate	50	100	150	-	-	-	25	50	75
Microcrystalline cellulose	160	110	60	160	110	60	160	110	60
Sodium Bicarbonate	20	20	20	20	20	20	20	20	20
Citric acid	10	10	10	10	10	10	10	10	10
Magnesium stearate	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Talc	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Tablet weight	300	300	300	300	300	300	300	300	300

Post-Compression Evaluation of Tablets

The prepared raft-forming tablets of Atenolol (ATN) were evaluated for various post-compression parameters to ensure quality, uniformity, and stability. Hardness was measured using a Monsanto hardness tester on five randomly selected tablets, and the average hardness, expressed in kg/cm², indicated the resistance of tablets to breakage during handling and transportation. Friability was determined using a Roche friabilator, where ten tablets were subjected to 25 rpm for four minutes, and the percentage weight loss was calculated to assess tablet mechanical strength. Weight variation was evaluated by weighing twenty tablets from each formulation using an electronic balance, and individual tablet weights were compared with the average to ensure uniformity of drug content. Thickness was measured using a calibrated vernier caliper on five randomly selected tablets to verify dimensional consistency. Drug content was determined by accurately weighing and powdering tablets equivalent to 25 mg of ATN, dissolving in 60 mL of 0.1 N HCl, sonicating for 15 minutes, and making up the volume to 100 mL. The solution was analyzed using a UV-Visible spectrophotometer, and the drug concentration was calculated to confirm the uniform distribution of ATN in the tablets [45-46].

***In-Vitro* Buoyancy Studies**

The *in vitro* buoyancy of the raft-forming tablets was evaluated by determining the floating lag time and total floating duration. The floating lag time is defined as the time taken for the tablet to rise and float on the surface of the dissolution medium. Tablets were placed in a 100 mL beaker containing 0.1 N HCl, and the time required for the dosage form to emerge and float on the medium was recorded. The duration for which the tablet remained buoyant was also monitored, providing an indication of its floating efficiency in simulated gastric conditions [47].

***In Vitro* Dissolution Studies of RFTs**

The dissolution profile of the raft-forming tablets was assessed using a USP Type II (paddle) dissolution apparatus. Each tablet was attached to the paddle by hydration, and 900 mL of 0.1 N HCl was used as the dissolution medium at 37±0.5°C. The paddle speed was set at 50 rpm. At predetermined time intervals, 5 mL of the sample was withdrawn and replaced with an equal volume of fresh medium. The withdrawn samples were diluted to 10 mL with 0.1 N HCl, filtered, and analyzed using a UV spectrophotometer at 225nm. The percentage cumulative drug release was calculated from a previously constructed calibration curve [48].

Raft Strength Measurement

Raft strength was evaluated to determine the mechanical integrity of the gel formed by the tablet in gastric conditions. Tablet powder equivalent to one unit dose was transferred to 150 mL of 0.1 N HCl in a 250 mL beaker maintained at 37°C. Each raft was allowed to form around an L-shaped wire probe (1.2 mm diameter) held upright throughout the 30-minute gelation period. The raft strength was measured using a modified balance method, wherein water was added dropwise to the pan, and the weight required to disrupt the raft was recorded [49].

Stability Studies

Accelerated and long-term stability studies were conducted on the optimized formulation according to ICH guidelines. Accelerated conditions were maintained at 40 ± 2°C with 75 ± 5% relative humidity for 3 months, while long-term stability was assessed at 25 ± 2°C and 60 ± 5% relative humidity. Tablets were sampled at 1, 2, and 3 months, and changes in appearance, physical integrity, and drug content were monitored using a stability chamber (Thermo Lab, Mumbai) to ensure the formulation retained its quality and efficacy over time [50].

3. RESULTS AND DISCUSSION

Melting point of drug

The melting point of Atenolol (ATN) was determined using the capillary melting point method. The observed melting point was 146°C. This confirms the purity and identity of the received drug sample, as the presence of impurities typically leads to deviations in melting point.

FTIR spectroscopy of drug

FTIR spectra of ATN was obtained and compared with reference FTIR spectra for identification and confirmation of various functional groups. Interpretation of FTIR spectra of ATN suggests that the observed peak list meets with that of the reference peak list. The observation confirms that the drug obtained is pure. FTIR spectrum of physical mixture of drug with HPMC K15M and MCC was also done to find any drug interaction. Results show no interaction between drug and excipients (Figure 1).

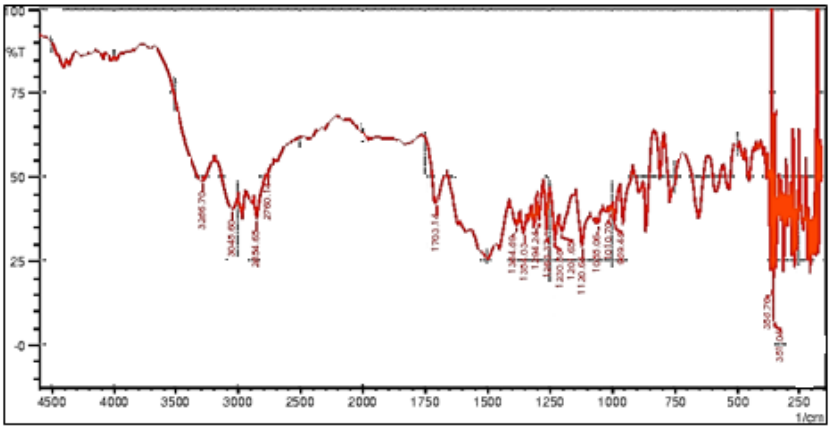

Figure 1: FTIR spectra of physical mixture of ATN, HPMC K15 M and MCC

Calibration Curve of drug

Calibration curve was prepared in 0.1N HCl at 225nm and linearly regressed. The correlation coefficient for standard curves was found to be very near to one which indicates good co-linear correlation between concentration 5-30 µg/ml (Table 2 and Figure 2).

Table 2: Calibration curve of ATN in 0.1N HCl at 225nm

S. No.	Concentration (µg/ml)	Absorbance
1.	0	0.00
2.	5	0.1163
3.	10	0.2364
4.	15	0.3578
5.	20	0.4766
6.	25	0.6024
7.	30	0.7248

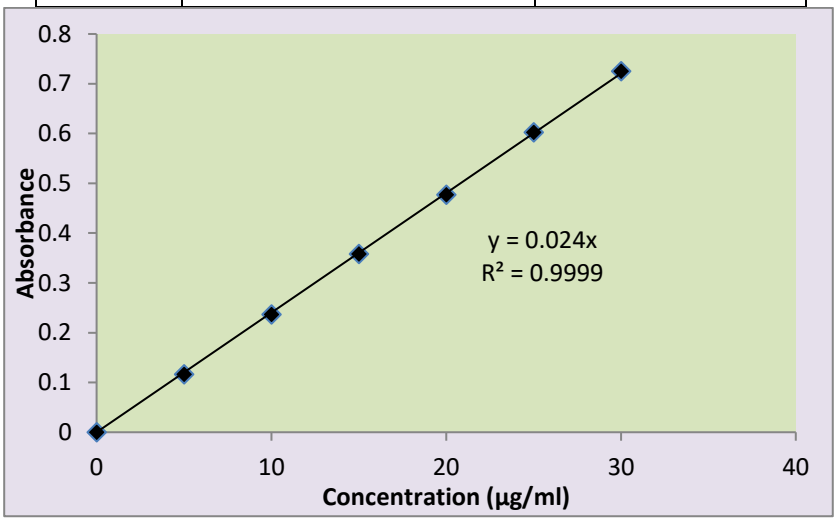

Figure 2: Calibration curve of ATN in 0.1N HCl at 225nm

Solubility studies

ATN was found to be freely soluble in water, 0.1 N HCl, and methanol while it was found to be insoluble in ether (Table 3).

Table 3: Solubility of ATN in different solvents

Solvents	Solubility
Distilled Water	Freely soluble
0.1 N HCl	Freely soluble
Methanol	Freely soluble
Ether	Insoluble

Formulation Development

In the present study attempts were made to get good physical and analytical parameters of the RFTs. As described in the methodology chapter the total nine formulations of RFTs were prepared by direct compression method using various polymers in different ratios. During preparation, the amount of drug and lubricants was kept constant to avoid any possible influence of these factors.

Precompression Characterization of Formulation Blend

Precompression studies were conducted to assess the flow properties of the powder blends, which are critical for achieving uniform and high-quality tablets. The bulk density (0.36–0.45 g/cm³) and tapped density (0.45–0.56 g/cm³) indicated good

free-flowing characteristics. The angle of repose ranged from 25.5° to 29.6°, confirming minimal interparticle friction and smooth flow. Compressibility index values (8.69–30.35%) suggested acceptable compressibility, while the Hausner's ratio (1.09–1.43) further supported good flowability for most formulations, with slight exceptions noted for F1, F2, and F7. Overall, the precompression evaluations demonstrated that the powder blends possessed satisfactory flow properties suitable for direct compression (Table 4).

Table 4: Pre-compression characterization of drug excipients blend

Formula Code	PARAMETERS				
	Angle of Repose (θ)	BD (g/ml)	TD (g/ml)	CI (%)	HR
F1	28.2	0.36	0.49	26.53	1.36
F2	25.5	0.39	0.56	30.35	1.43
F3	28.1	0.39	0.48	18.75	1.23
F4	29.6	0.42	0.46	8.69	1.09
F5	25.7	0.40	0.46	13.04	1.15
F6	27.2	0.38	0.45	15.55	1.18
F7	27.1	0.41	0.53	22.64	1.29
F8	27.8	0.45	0.54	16.66	1.20
F9	27.4	0.39	0.46	15.21	1.17

Post-Compression Evaluation

The compressed raft-forming tablets were evaluated for quality and compliance with standard specifications. Hardness values were below 5 kg/cm², indicating adequate resistance to breakage during handling and storage. Friability for all formulations was below 1%, confirming good mechanical strength. Weight variation remained within ±5%, demonstrating uniformity in tablet weight and consistent content distribution. Tablet thickness ranged from 3.0 to 3.8 mm, ensuring uniform die filling and proper appearance. Drug content analysis revealed values between 98–99%, confirming accurate dosing and uniform drug distribution across all formulations (Table 5).

Table 5: Post Compression Parameters of ATN loaded RFTs

Formula code	Hardness (kg/cm²)	Thickness (mm)	Weight variation (mg)	Friability (%)	(%) Drug content
F1	3.9±0.4	3.0±0.4	2.95±0.05	0.20±0.17	98.23
F2	4.3±0.2	3.1±0.1	3.30±0.08	0.12±0.15	99.52
F3	4.1±0.4	3.8±0.2	3.25±0.04	0.35±0.14	98.48
F4	4.4±0.5	3.4±0.3	3.25±0.02	0.29±0.12	99.01
F5	3.9±0.3	3.7±0.2	3.21±0.03	0.30±0.16	98.26
F6	4.0±0.4	3.5±0.1	3.47±0.06	0.35±0.14	99.11
F7	4.2±0.3	3.8±0.3	3.52±0.04	0.42±0.13	99.10

F8	4.4±0.4	3.9±0.3	3.49±0.05	0.45±0.18	98.65
F9	3.9±0.4	3.3±0.2	4.46±0.08	0.43±0.16	98.47

***In-vitro* Buoyancy Studies**

The all formulation showed good floating lag time and total floating time. The floating lag time and total floating time of the tablets mainly depend on the type of polymer and their concentrate, as shown in table 6.

Table 6: Floating lag time of the Raft forming tablets

Formulation Code	Floating lag time (sec)	Total floating time (hr)
F1	23	12
F2	36	12
F3	28	12
F4	42	12
F5	10	10
F6	16	10
F7	26	12
F8	18	12
F9	31	12

Raft strength

The raft strength of powdered tablets was influenced by the content of sodium alginate and HPMC K15M. Raft strength increased significantly from 1 to 12 g with increasing sodium alginate content (F7, F8, F9) indicating formation of a progressively stronger hydrogel network. However, the addition of 150 mg of HPMC K 100 M to the formulation (F7) reduced the raft strength by approximately 25%, indicating disruption of the alginate gel network (Table 7).

Table 7: Raft strength of the prepared raft forming tablets

Formulation Code	Raft strength (g)
F1	6.0 ± 0.0
F2	5.07 ± 0.2
F3	9.0 ± 0.4
F4	6.8 ± 1.3
F5	10.5 ± 1.0
F6	12.4 ± 0.5
F7	6.9 ± 0.9
F8	9.2 ± 0.3
F9	9.1 ± 0.7

***In vitro* drug release of RFTs**

The *In-vitro* dissolution study of ATN raft forming tablets was performed in 0.1N HCl as dissolution medium. The *In-vitro* drug release study of ATN tablets from each batch (F1 to F9) was carried out by using 0.1N HCl for 12 hrs. The samples were withdrawn at specified time intervals and analyzed by UV-visible spectrophotometer. Percentage drug release was calculated on the basis of mean amount gastro retentive of ATN present in respective formulation. The cumulative percentage of drug release of floating RFTs of ATN on y-axis was plotted against time on x-axis (Figure 3-5).

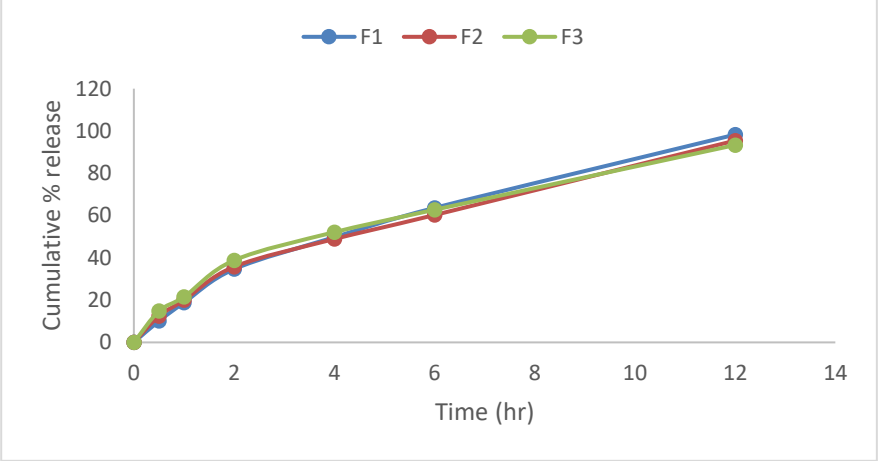

Figure 3: Comparative drug release from formulations F1-F3

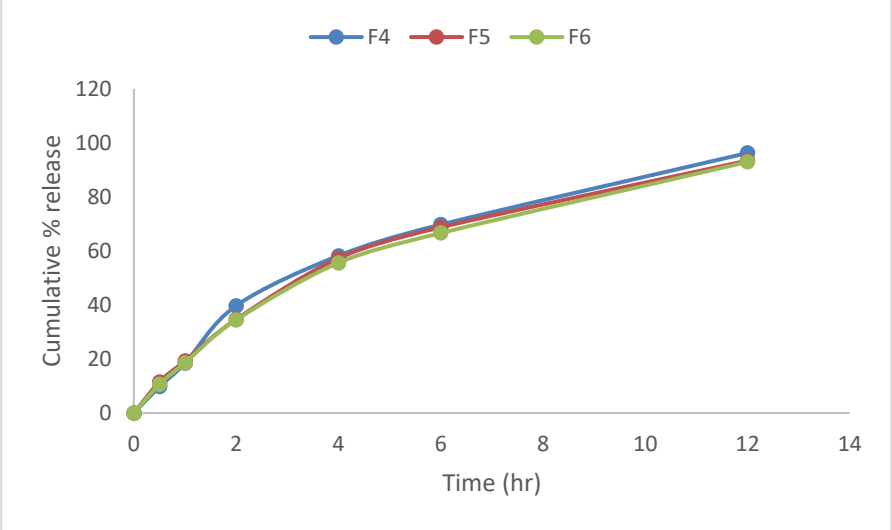

Figure 4: Comparative drug release from formulations F4-F6

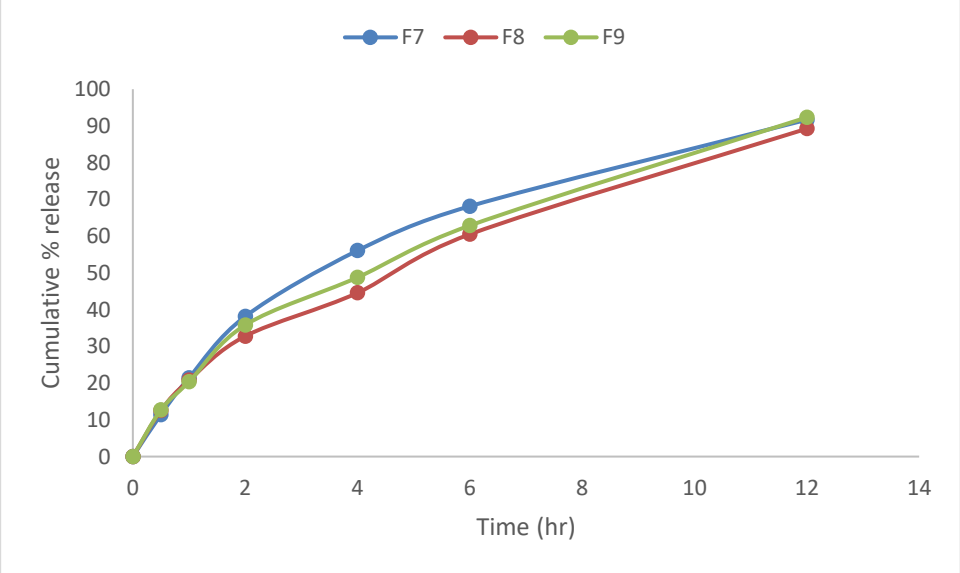

Figure 5: Comparative drug release from formulations F7-F9

Stability Study

Optimized formulation F8 was subjected to stability studies for 1 to 3 months and the tablets were tested for drug content. Formulation F8 was exposed to different storage conditions to determine any changes in final formulation. The results obtained were as in the following table 8.

Table 8: Stability studies at different conditions (F8)

Storage Conditions	Formulation (F8)	Observations on storage for Drug content (%)			
		Initial	1 month	2 months	3 months
25±2^{0}C and 60±5% RH	% Drug Content	100%	100%	99.73±1.6	99.54±1.3%
40±2^{o}C and 75±5% RH	% Drug Content	100%	99.65±2.7	99.38±3.1	99.14±1.6%

Values are mean± SD (n=3)

4. CONCLUSION

The experimental results demonstrate that the combination of sodium bicarbonate and sodium alginate plays a critical role in modulating the buoyancy lag time of floating raft-forming tablets, a key factor in the effectiveness of controlled-release formulations. Enhanced buoyancy ensures that the tablets remain in the gastrointestinal tract for prolonged periods, supporting sustained drug release and improving therapeutic outcomes and patient compliance, particularly for drugs like Atenolol. Additionally, the incorporation of HPMC K15M alongside sodium alginate was found to significantly influence the drug release profile. Among the formulations studied, F3 exhibited a controlled release of Atenolol over 12 hours, indicating its potential to maintain therapeutic plasma levels for extended durations. This controlled release mechanism not only optimizes drug delivery but also reduces dosing frequency, further enhancing patient adherence.

While the results are promising, further in vivo pharmacokinetic and pharmacodynamic studies are necessary to fully establish the efficacy of these raft-forming controlled-release tablets. Evaluating the stability of the formulations under varying storage conditions and physiological environments will provide deeper insights into their clinical applicability. In summary, this study provides a strong foundation for the development of effective Atenolol raft-forming controlled-release tablets, highlighting the critical role of formulation components in achieving desired buoyancy and drug release characteristics. With continued research, these formulations have the potential to improve therapeutic strategies, offering better disease management, enhanced patient compliance, and overall improved quality of life.

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