



FORMULATION STRATEGIES FOR GASTRORETENTIVE DELIVERY OF ATAZANAVIR: *IN VITRO* EVALUATION AND OPTIMIZATION

Meesa Rajendar*, B. Anuja, M. Dileep, P. Poojitha, and R. Vigneshwari

*Department of Pharmaceutics, SVS Group of Institutions Autonomous bheemaram Hanamkonda Warangal
Telangana-506001, India

*Corresponding Author Email: rajendarmeesapharmacy@gmail.com

ABSTRACT

The present study aims to develop and evaluate gastroretentive floating tablets of Atazanavir sulfate to prolong gastric residence time and enhance oral bioavailability. Atazanavir, a BCS class II drug, exhibits pH-dependent solubility and limited absorption in the upper gastrointestinal tract. Floating drug delivery systems can offer sustained release and enhanced bioavailability by remaining buoyant in the gastric environment. Tablets were formulated using polymers such as Ethyl cellulose, and Sodium alginate in various concentrations. Sodium bicarbonate was incorporated as a gas-generating agent. The tablets were evaluated for pre-compression and post-compression parameters, including hardness, friability, floating lag time, total floating time, drug content, and *in vitro* drug release. The optimized formulation F3 showed a floating lag time of 47 seconds and total floating time exceeding 12 hours, with sustained drug release of over 93.35% at the end of 8 hours. The results support the use of floating matrix tablets as a potential gastroretentive strategy for improving Atazanavir sulfate therapy.

Key words:

Atazanavir sulfate, gastroretentive tablets, floating drug delivery system, HPMC, Carbopol, sustained release, bioavailability.

1. INTRODUCTION

Oral administration remains the most widely accepted route of drug delivery due to its non-invasive nature, ease of administration, and high patient compliance (Singh et al., 2000). However, many drugs exhibit absorption window limitations or pH-dependent solubility, making conventional formulations suboptimal. Atazanavir sulfate, an antiretroviral agent used in HIV therapy, is primarily absorbed in the upper gastrointestinal tract and has poor bioavailability due to limited solubility in alkaline pH (Streubel et al., 2006).

Gastroretentive drug delivery systems (GRDDS) are designed to retain the dosage form in the stomach for an extended duration, thereby enhancing drug absorption in the upper GI tract (Garg & Gupta, 2008). Floating systems are among the most promising GRDDS, particularly for drugs with a narrow absorption window or poor solubility in intestinal pH. These systems rely on low-density

matrices that remain buoyant over gastric fluids and allow sustained drug release.

Uttam Kumar mandal *et al.*, (2019) Gastro-retentive drug delivery system (GRDDS) has gained immense popularity in the field of oral drug delivery recently. It is a widely employed approach to retain the dosage form in the stomach for an extended period of time and release the drug slowly that can address many challenges associated with conventional oral delivery, including poor bioavailability. Different innovative approaches like magnetic field assisted gastro-retention, plug type swelling system, muco-adhesion technique, floating system with or without effervescence are being applied to fabricate GRDDS. Apart from *in vitro* characterization, successful GRDDS development demands well designed *in vivo* study to establish enhanced gastro-retention and prolonged drug release. Gama scintigraphy and MRI are popular techniques to evaluate *in vivo* gastric residence time. However, checking of their overall *in vivo* efficacy still

remains a major challenge for this kind of dosage form, especially in small animals like mice or rat. Reported *in vivo* studies with beagle dogs, rabbits, and human subjects are only a handful in spite of a large number of encouraging *in vitro* results. In spite of the many advantages, high subject variations in gastrointestinal physiological condition, effect of food, and variable rate of gastric emptying time are the challenges that limit the number of available GRDDS in the market. This review article highlights the *in vivo* works of GRDDS carried out in the recent past, including their limitations and challenges that need to be overcome in the near future.

Shwetha *et al.*, (2019) The purpose of writing this review on floating drug delivery systems (FDDS) was to compile the recent literature with special focus on the principal mechanism of floatation to achieve gastric retention. The recent developments of FDDS including the physiological and formulation variables affecting gastric retention, approaches to design single-unit and multiple-unit floating systems, and their classification and formulation aspects are covered in detail. This review also summarizes the *in vitro* techniques, *in vivo* studies to evaluate the performance and application of floating systems, and applications of these systems. These systems are useful to several problems encountered during the development of a pharmaceutical dosage form.

Table 1: Comparison of Effervescent and Non-Effervescent FDDS

Parameter	Effervescent FDDS	Non-Effervescent FDDS
Buoyancy Mechanism	CO ₂ generation via acid-base reaction	Matrix swelling and air entrapment
Onset of Floating	Rapid (upon reaction with gastric acid)	May take time depending on swelling rate
Polymers Used	Methylcellulose, Chitosan, HPMC	HPMC, Polyacrylates, Polycarbonates
Additional Components	Requires gas-generating agents	No need for gas-generating agents
Design Complexity	Slightly more complex	Relatively simple formulation

Mechanism of Action of Atazanavir in the Treatment of HIV Infection

Atazanavir is a protease inhibitor (PI) used as part of combination antiretroviral therapy for the treatment of human immunodeficiency virus (HIV-1) infection. Its mechanism of action involves the selective inhibition of the HIV-1 protease enzyme, an essential viral enzyme required for the cleavage of the gag and gag-pol polyprotein precursors into functional structural proteins and enzymes necessary for viral maturation.

By blocking the activity of HIV protease, Atazanavir prevents the formation of mature, infectious virions,

resulting in the production of immature and non-infectious viral particles. This ultimately leads to a reduction in viral load, slowing the progression of the disease and improving immune function, particularly when combined with other antiretroviral agents such as nucleoside reverse transcriptase inhibitors (NRTIs).

Additionally, Atazanavir exhibits a favorable resistance profile and is often selected for its once-daily dosing and lower risk of metabolic complications compared to other protease inhibitors.

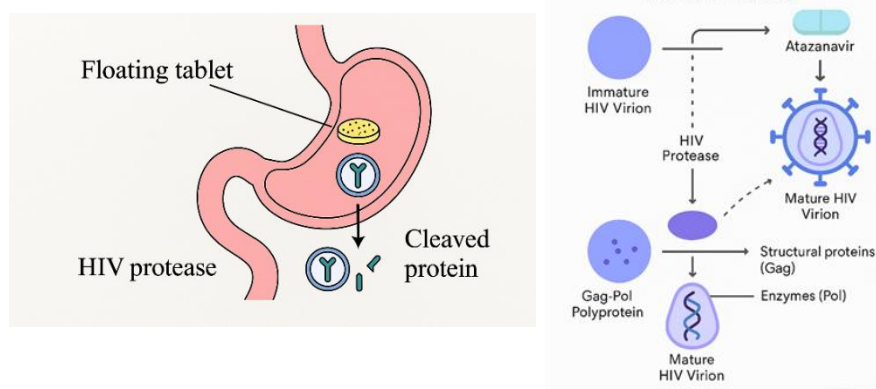


Figure 1: Mechanism of Action of Atazanavir via Floating Drug Delivery in the Stomach.

This study focuses on the formulation and evaluation of floating matrix tablets of Atazanavir sulfate using hydrophilic polymers such as Ethyl Cellulose and Sodium alginate. The goal is to enhance gastric retention, provide sustained release, and improve therapeutic efficacy (Pawar et al., 2014).

2. MATERIALS AND METHODS

Materials

Atazanavir sulfate was obtained as a gift sample from Mylan Laboratories. Ethyl Cellulose and So, sodium bicarbonate, lactose, magnesium stearate, and talc were procured from commercial suppliers and used as received.

Methods

Preformulation Studies

a) Organoleptic Evaluation

The organoleptic properties of the pure drug Atazanavir were examined to record its physical appearance. The

color, odor, and taste of the drug were assessed using descriptive terminology under standard laboratory conditions.

b) Melting Point Determination

The melting point of the drug was determined by the capillary method using a calibrated melting point apparatus. A small amount of powdered drug was packed into a capillary tube, and the temperature at which the drug melted was recorded to evaluate its purity.

c) Solubility Determination

To determine the solubility of Atazanavir, an excess amount of the drug was added to various solvents, and the mixtures were stirred until equilibrium was reached. The solutions were then filtered, and the supernatant was analysed using a Lab India double-beam UV-Visible spectrophotometer. The solubility percentage was calculated using the following formula:

$$\% \text{ solubility} = \text{sample absorbance} / \text{standard absorbance} \times \text{dilution factor} \times 100$$

UV-Visible Spectroscopy

Construction of Calibration Curve of Atazanavir

Preparation of Stock Solution:

10 mg of Atazanavir was accurately weighed and transferred to a 100 mL volumetric flask. About 1 mL of methanol was added to dissolve the drug, and the volume was made up with 0.1 N HCl to obtain a stock solution.

Serial Dilutions: From the stock solution, 1 mL was diluted to 10 mL with 0.1 N HCl to obtain a 100 µg/mL intermediate solution. From this intermediate solution, 1 mL was further diluted to 10 mL with 0.1 N HCl to get a 10 µg/mL working standard solution.

The 10 µg/mL solution was scanned in the range of 200-400 nm using a UV-visible spectrophotometer to determine the λ_{max} , which was observed at 250 nm. This wavelength was used for further quantitative analysis and construction of the standard calibration curve.

FT-IR Spectroscopy

Drug-Excipient Compatibility Study:

FT-IR spectral analysis was performed to evaluate potential chemical interactions between Atazanavir and the selected excipients. The pure drug, physical mixture of the drug with polymers, and the final formulation were subjected to FT-IR analysis. Any significant changes in characteristic peaks were examined to detect possible interactions or structural changes. The analysis was carried out using an FT-IR spectrometer in the wavelength range of 4000–400 cm^{-1} .

Formulation of Floating Tablets

Tablets were prepared using the direct compression method. Atazanavir sulfate was blended with Ethyl Cellulose and Sodium alginate in various ratios along with sodium bicarbonate (gas-generating agent) and excipients. The blends were compressed into tablets using an 8-mm round flat-faced punch.

Table 2: Composition of Atazanavir floating tablets

Ingredients (mg)	F1	F2	F3	F4
Atazanavir	300	300	300	300
Ethyl cellulose	50	100	-	-
Sodium alginate	-	-	50	100
MCC	130	80	130	80
Citric acid	5	5	5	5
Sodium bi carbonate	10	10	10	10
Magnesium stearate	3	3	3	3
Talc	2	2	2	2
Total Wt	500	500	500	500

Evaluation Parameters

Pre-compression studies included bulk density, tapped density, Carr's index, Hausner's ratio, and angle of repose. Post-compression evaluations included tablet thickness, weight variation, hardness, friability, drug content uniformity, floating lag time, total floating duration, and *in vitro* dissolution using USP Type II apparatus in 0.1N HCl for 12 hours. Kinetic modeling was applied to evaluate the drug release mechanism.

3. RESULTS AND DISCUSSION

Preformulation Studies

Preformulation studies were conducted to establish the fundamental physicochemical properties of Atazanavir, which are essential for designing a stable and effective dosage form. These studies included organoleptic evaluation, melting point determination, and solubility testing.

a) Organoleptic Evaluation

Organoleptic properties of the pure drug were assessed visually and sensorially to understand its basic physical characteristics. The results are summarized in **Table 4**.

Table 3: Organoleptic Properties of Atazanavir

Properties	Results
Description	Powder
Taste	tasteless
Odour	odourless
Colour	white crystalline powder

b) Determination of Melting Point

The melting point of Atazanavir was found to be in the range of 195–208°C, which is in accordance with reported literature values. This narrow and consistent melting range indicates the purity and crystalline nature of the drug sample, making it suitable for formulation processes that require thermal stability.

c) Solubility Profile

Atazanavir was found to be sparingly soluble in water but freely soluble in organic solvents such as ethanol and dimethyl sulfoxide (DMSO). This solubility profile suggests that solubility enhancement techniques or suitable excipients may be necessary for effective drug delivery in aqueous environments, such as the gastrointestinal tract.

Standard Graph of Atazanavir

Standard Calibration Curve of Atazanavir in 0.1 N HCl

A standard calibration curve was constructed to determine the linearity and absorbance characteristics of Atazanavir in 0.1 N HCl. The UV absorbance spectrum revealed that Atazanavir exhibits maximum absorbance (λ_{max}) at 250 nm, which was selected as the detection wavelength for all further analyses. A series of standard solutions with concentrations ranging from 10 µg/mL to 18 µg/mL were prepared using 0.1 N HCl. The absorbance of each solution was measured using a UV-visible spectrophotometer at 250 nm. The data obtained are presented in **Table 4**, and the calibration curve is shown in **Figure 2**.

Table 4: Calibration Curve Data of Atazanavir in 0.1 N HCl

S. No	Concentration (µg/ml)	Absorbance
1	0	0
2	10	0.49
3	12	0.56
4	14	0.68
5	16	0.73
6	18	0.85

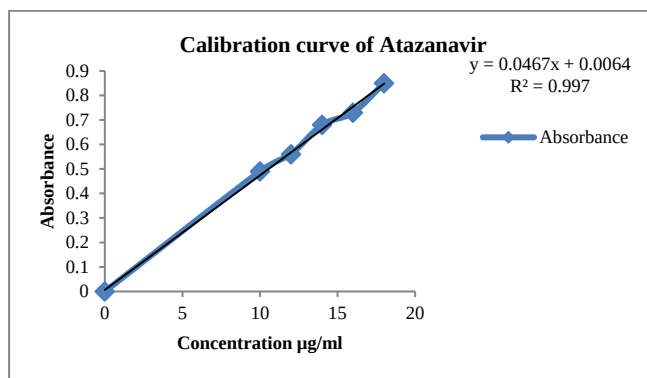


Figure 2: Calibration curve of Atazanavir

FTIR Spectral Analysis of Pure Drug and Formulation

FTIR spectral studies were performed to confirm the structural integrity and compatibility of Atazanavir with excipients used in formulation F3. The spectra of pure

Atazanavir and the optimized formulation (F3) were recorded and analysed to detect any potential chemical interactions.

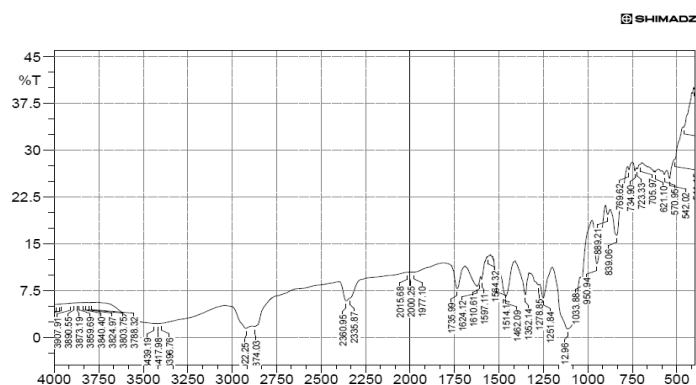


Figure 3: FT-IR Sample for Atazanavir

The FTIR spectrum of Atazanavir revealed distinct and sharp peaks corresponding to functional groups like O–H, C–H, and C–N, which are characteristic of the drug's chemical structure.

When compared with the FTIR spectrum of formulation F3 and the drug-excipient physical mixture, it was

observed that all major peaks of Atazanavir were retained with no significant shifting, disappearance, or appearance of new peaks. This indicates that no chemical interaction occurred between Atazanavir and the polymers or other excipients used in the formulation.

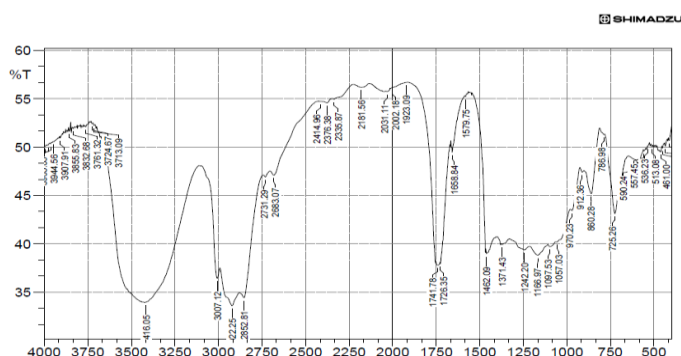


Figure 4: FT-IR Sample for physical mixture of drug and excipients

The IR spectrum of the physical mixture showed all major characteristic peaks corresponding to the functional groups of Atazanavir without any significant shift or

disappearance. Notably, the O–H stretching (3907.91 cm⁻¹), O–H bending (3416.05 cm⁻¹), C–N stretching

(2376.38 cm^{-1}), and C–H stretching (1242.20 cm^{-1}) peaks were clearly observed in the mixture spectrum.

Thus, the FTIR study confirms the stability and integrity of the drug within the formulation, validating the selection of excipients for the development of stable Atazanavir floating tablets.

Evaluation of Pre-Compression Parameters

All formulations showed acceptable pre-compression characteristics with good flowability. Post-compression results showed uniformity in weight, hardness (5–6 kg/cm^2), friability (<1%), and acceptable drug content (98.1–99.6%).

Table 5: Evaluation Parameters of Atazanavir Powder Blends

S. No	Bulk density g/cc	Tapped density g/cc	Compressibility index (%)	Hausner ratio	Angle of repose (θ)
F1	0.485	0.575	15.65	1.18	31 ⁰
F2	0.479	0.580	17.47	1.21	27 ⁰
F3	0.484	0.582	16.83	1.20	30 ⁰
F4	0.489	0.583	16.12	1.19	28 ⁰

Evaluation of Post-Compression Parameters

Table 6: Evaluation parameters of Atazanavir floating tablets

Parameters	F1	F2	F3	F4
Weight variation	500	500	499	500
Thickness (mm)	3.3	3.4	3.3	3.5
Hardness (kg/cm^2)	4.2	4.3	4.6	4.4
Friability	0.45	0.44	0.44	0.47
Content uniformity	79.68	81.02	83.65	82.25
Floating lag time (Sec)	48	52	47	51

Floating Lag Time

Floating behavior was satisfactory in all batches. F3 exhibited the lowest floating lag time of 47 seconds and total floating time of over 12 hours.

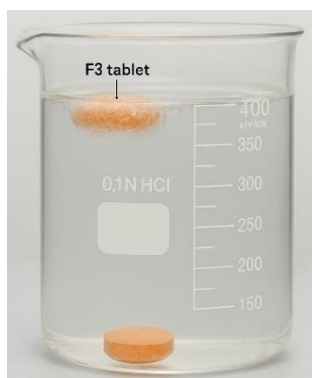


Figure 5: Floating Lag Time of Atazanavir Tablets in 0.1 N HCl Solution

In vitro drug release demonstrated that F3 achieved 93.35% release over 12 hours, showing sustained release behavior. Drug release kinetics suggested that F3 followed Higuchi and Korsmeyer–Peppas models, indicating anomalous (non-Fickian) diffusion.

Among the formulations, **F3 showed the highest cumulative drug release of 93.35% at the end of 8 hours**, followed closely by F4 (92.52%), F2 (91.25%), and F1 (90.35%). The drug release in the first hour was relatively low for all batches (Approximately 13–14%), which is desirable for floating systems as it ensures prolonged gastric retention and sustained release.

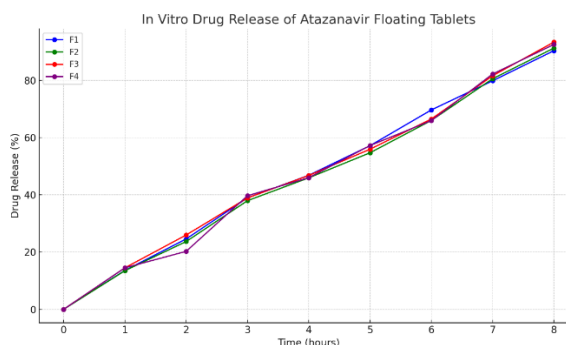


Figure 61: In vitro drug release for all the formulations (F1-F4)

Formulation F3 demonstrated a more controlled and sustained release pattern throughout the study period, which can be attributed to an optimal polymer-to-drug ratio and matrix-forming components that allowed for efficient drug diffusion and swelling behavior. This makes F3 the most promising formulation among those tested, based on its consistent and extended-release profile.

Stability Studies

The stability of the optimized formulation F-3 was evaluated under accelerated conditions as per ICH guidelines over a period of 90 days. The evaluation focused on both physical and chemical parameters, particularly the cumulative percentage drug release at specified intervals (30, 60, and 90 days).

Table 1: Stability study for optimized formulation

Formulation Code	Time (Days)	1st Month (%)	2nd Month (%)	3rd Month (%)	Limits as per Specifications
F-3	0	0.00	0.00	0.00	Not less than
	30	93.35	92.56	91.25	Not less than
	60	93.35	92.41	91.56	Not less than
	90	93.35	92.05	91.25	Not less than

CONCLUSION

The study successfully developed a gastroretentive floating tablet of Atazanavir sulfate using Ethyl Cellulose and Sodium alginate. Among all formulations, F3 demonstrated excellent floating properties, prolonged gastric retention, and sustained drug release up to 12 hours. This approach has potential to enhance bioavailability and therapeutic efficacy of Atazanavir by targeting drug release to its absorption window in the stomach and upper small intestine.

REFERENCES

- Garg, R., & Gupta, G. D. (2008). Progress in controlled gastroretentive delivery systems. *Tropical Journal of Pharmaceutical Research*, 7(3), 1055–1066.
- Streubel, A., Siepmann, J., & Bodmeier, R. (2006). Gastroretentive drug delivery systems. *Expert Opinion on Drug Delivery*, 3(2), 217–233.
- Singh, B. N., & Kim, K. H. (2000). Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. *Journal of Controlled Release*, 63(3), 235–259.
- Pawar, V. K., Kansal, S., Asthana, S., & Chourasia, M. K. (2014). Industrial perspective of gastroretentive drug delivery systems: physicochemical, biopharmaceutical, and technological considerations. *Expert Opinion on Drug Delivery*, 11(4), 601–621.
- Shwetha, R., et al. (2019). Floating drug delivery systems: A comprehensive review. *Asian Journal of Pharmaceutics*, 13(4), 259–270. <https://doi.org/10.22377/ajp.v13i4.2043>
- Mandal, U. K., Chatterjee, B., & Senjoti, F. G. (2016). *Gastro-retentive drug delivery systems and their in vivo success: A recent update*. *Asian Journal of Pharmaceutical Sciences*, 11(5), 575–584.