International Journal of Pharmacy and Industrial Research (IJPIR)

IJPIR |Vol.13 | Issue 2 | Apr - June -2024

www.ijpir.com

DOI : https://doi.org/10.61096/ijpir.v13.iss2.2024.129-138

ISSN: 2231-3656
Print: 2231-3648

Research

Formulation and in vitro characterization of gastro retentive floating tablets of quetiapine fumarate

M. Sowmiya[*1], A. Vasanthan[2], Senthil Kumar. K.L[3]

[1]Scholar, Department of Pharmaceutics Sri Vijay vidyalaya college of pharmacy, Nallamballi, Dharmapuri, Affiliated to the TN Dr. MGR Medical University, Guindy , Chennai, Tamil Nadu, India.
[2]Head of the Department, Department of Pharmaceutics, Sri Vijay vidyalaya college of pharmacy, Nallamballi, Dharmapuri, Affiliated to the TN Dr. MGR Medical University, Guindy, Chennai, Tamilnadu, India.
[3]Principal, Sri Vijay vidyalaya college of pharmacy, Nallamballi, Dharmapuri, Affiliated, to the TN Dr. MGR Medical University, Guindy, Chennai, Tamil Nadu, India.

*Author for Correspondence: M. Sowmiya, M.Phar
Email: sowmiyamani1306@gmail.com

Published on: 07 May 2024

Published by:
DrSriram Publications

Abstract

This research focuses on the development and evaluation of gastroretentive floating tablets of Quetiapine Fumarate to enhance its bioavailability by prolonging gastric residence time. Quetiapine Fumarate, an antipsychotic used primarily for treating psychiatric disorders, exhibits absorption predominantly in the stomach, making it an ideal candidate for gastroretentive drug delivery systems (GRDDS). The floating tablets were formulated using a direct compression method incorporating hydrophilic polymers HPMC K100M and K4M and sodium bicarbonate as a gas-forming agent to achieve buoyancy. The study systematically analyzed the formulation process through the optimization of polymer concentrations and gas-forming agents to regulate the floating lag time and total floating duration, crucial for sustained drug release. In vitro evaluation of the tablets involved assessing physical parameters such as hardness, friability, drug content, and dissolution profiles. The results showed that the tablets maintained buoyancy over 12 hours and released the drug following zero-order kinetics, indicating a controlled release mechanism. The discussion elaborates on the interaction between the formulation components and their impact on the drug release behavior. Increasing polymer concentrations were found to extend the floating lag time, whereas higher concentrations of sodium bicarbonate reduced it. The optimized formulation achieved a balance between these components, resulting in a consistent and prolonged drug release. This study demonstrates the potential of floating tablets to improve therapeutic outcomes for patients requiring controlled drug delivery in the gastrointestinal tract.

Keywords: Gastroretentive drug delivery systems, Floating drug delivery systems, Quetiapine Fumarate, Controlled release, Gastric residence time.

INTRODUCTION

Gastro Retentive Drug Delivery System

Oral is the most preferred route of administration that delivers drugs in a non-invasive manner. However, it faces several limitations administering drugs[1]. Drugs that have narrow absorption window are absorbed only if these are in close proximity with their absorption window. Crossing through the absorption window drugs face lesser/negligible amount of the absorption and hence show decreased bioavailability as the time of absorption is very less in such conditions. Another major problem associated with some of the drugs is first-pass metabolism. After getting absorbed through the GI tract, drug has to pass through the liver where it gets metabolized and the maximum amount of the dose gets depleted in this step. Some of the other limitations are short gastric residence time, unpredictable gastric emptying time [2], and frequent dosing of the drugs (with short biological half-lives). To overcome these limitations, gastro-retentive drug delivery systems (GRDDS) came into the scenario. GRDDS approach has been used for site-specific drug release and ensuring local or systemic action in the upper GI tract [3] specially for the drugs having absorption window in the stomach region [4]. These systems help increase the drug's gastric residence time, thus increase bioavailability. GRDDS increases the drug release duration by retaining the drugs in stomach for a longer period of time [5]. They also increase the solubility of the drugs which are less soluble at intestinal pH [2]. Thus, these delivery systems are of great importance nowadays and a lot of work is being carried out as evident from various recent reports. Understanding of the physiology and anatomy of the GIT is necessary for the evolution of different types of gastro retentive technologies derived from the respective understandings [5]. Many of them have already entered into the huge pharmaceutical market, whereas others need attention for gaining their access into the global market. Clinical studies are to be envisaged in a more efficient way for overcoming trial failures. Several combination therapies are being studied for their enhanced efficacy, reduced side effects, and extended gastro-retention than the individual therapies. Several reports are getting published daily but the number of technologies which are getting market access is much lower as compared to the investigations published day by day [6].

Therefore, the main aim should be towards equalizing this number, which will result in a huge benefit to the mankind. Thus, we summarized various types of GRDDS technologies in this article to evaluate their clinical pertinence in the recent years.

Floating Drug Delivery System

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal. To measure the floating force kinetics, a novel apparatus for determination of resultant weight (RW) has been reported in the literature. The RW apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to maintain the submerged object. The object floats better if RW is on the higher positive side. This apparatus helps in optimising FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations. RW or F = F buoyancy - F gravity = (Df - Ds) gV, Where, RW = total vertical force, Df = fluid density, Ds = object density, V = volume and g = acceleration due to gravity. The FDDS can be divided into gas-generating and non-effervescent systems.

Floating tablets have emerged as a cornerstone in the advancement of oral drug delivery systems, particularly for enhancing the bioavailability and efficacy of drugs with specific absorption characteristics. These innovative dosage forms are designed to remain buoyant in the stomach's gastric fluids after oral administration, thus significantly prolonging their gastric residence time compared to conventional tablets. This extended residence in the stomach can be critical for drugs that are primarily absorbed in the stomach or the upper parts of the small intestine, where they can exert their effects most efficiently.

The concept of floating tablets is based on the principle of gastro retentive drug delivery systems (GRDDS), which aim to localize a drug in the stomach or upper gastrointestinal tract to optimize and control drug release. By doing so, these systems can enhance the dissolution and absorption of drugs that are either less soluble in a high pH environment or degrade in the lower parts of the intestine. This targeted delivery not only maximizes the drug's therapeutic efficacy but also reduces side effects associated with higher systemic exposure.

The development of floating tablets addresses several challenges faced by traditional oral dosage forms, including the short gastric residence time and the inability to provide sustained release over extended periods. Drugs such as antibiotics for H. pylori infections, antacids, or drugs used in diabetes and hypertension management, where controlled release is beneficial, are prime candidates for this form of delivery.

Floating tablets has also been driven by the need to improve patient compliance. Traditional drug regimens, which often require multiple daily dosages, can be inconvenient and lead to poor adherence. By allowing for once-daily dosing through controlled release mechanisms, floating tablets significantly simplify the dosing schedule and help ensure more consistent drug intake.

Floating tablets exemplify a significant innovation in pharmaceutical technology, providing a strategic solution to the challenges of conventional oral dosage forms. Their ability to remain in the gastric environment for extended periods facilitates a more effective and efficient drug absorption process, marking a significant step forward in the development of patient-friendly and effective therapeutic options. [7-10]

MATERIALS & METHODOLOGY

Table 1:List of Materials

Chemicals	Manufacturers
Drug	Gift samples Dr Reddy, Hyderabad.
HPMC K 100	Research Lab Fine Chem Industries (Mumbai)
Ethyl cellulose	SD Fine Chemicals, Mumbai
Chloroform	SD Fine Chemicals, Mumbai
Methanol	SD Fine Chemicals, Mumbai
Propylene glycol	SD Fine Chemicals, Mumbai.
Glycerol	SD Fine Chemicals, Mumbai.
Ultra pure water	SD Fine Chemicals, Mumbai..

Table 2: List of Equipment

Instrument	Company
Electronic weighing balance	Shimadzu corporation (JAPAN)
UV Visible spectrophotometer	Lab India
Magnetic stirrer	REMI
pH meter	Lab india
FTIR	Brucker
Hot air oven	Lawrence and Mayo Pvt Ltd, Mumbai
Franz Diffusion cell	REMI

METHODOLOGY

Preparation of floating tablets of Quetiapine fumarate by direct compression method

Quetiapine fumarate (15mg) and all other ingredients were weighed separately and passed through sieve no. 25. The active ingredient, HPMC, Avicel (Microcrystalline cellulose), Sodium bicarbonate and citric acid were mixed together. The mixture was then compacted in a slugging machine to form the compacts. The compacts were then milled and passed through sieve no. 18 followed by sieve no. 60. Finally the mixture were added to lubricant i.e. magnesium stearate .The final blend was compressed into tablets using single punch tablet rotary press (Karnavati).

Evaluation of floating tablets of Quetiapine fumarate

Weight Variation Test

To ensure uniformity in the weight of each tablet within a batch, which directly impacts dose accuracy and uniformity. This test is performed by weighing individually a sample of tablets (usually 20 tablets) using an analytical balance. The average weight is calculated and each tablet's weight is compared against the average.

Calculation: Percentage Deviation= (Individual Weight−Average Weight Average Weight)×100 Percentage Deviation = (Average Weight Individual Weight−Average Weight)×100

Regulatory Standard: According to pharmacopeial standards (e.g., USP), no more than two of the individual weights deviate from the average weight by more than the permitted percentage (usually 5%), and none should deviate by more than twice that percentage. Not more than two of the individual weights deviate from the average weight by more than the percentage limits. As per Indian Pharmacopoeial Specification.

Weight Variation

Average weight of tablets(mg)	Maximum % difference allowed
Less than 80	10

80- 250	7.5
Above 250	5

$$\% \text{ Deviation} = \frac{\text{Tablet weight-Average weight}}{\text{Tablet weight}} \times 100$$

Friability test

For each formulation, the friability of 10 tablets was determined using Roche's Friabilator. In friability test tablets were subjected to the combined effect of abrasion and shock by using a plastic chamber that resolves at 25rpm droppings. The tablets fall from a distance of 6 inches with each revolution. Previously weighed 10 tablets were placed in friabilator which is then set for 100 revolutions. Then the tablets were dusted and weighed.

Friability=weight loss/initial weight x 100.

Acceptance Criterion: Tablets are generally considered acceptable if the friability is less than 1%.

Hardness Test

To determine the mechanical strength of a tablet which must be sufficient to withstand handling yet should not be too high to impede dissolution. The hardness test is performed using a hardness tester, such as the Monsanto or Pfizer tester. Each tablet is placed between two anvils, and force is applied until the tablet fractures. The force applied at the point of fracture is recorded as the tablet hardness.

Calculation: Hardness (kg/cm2) = Force at fracture

Tablet hardness typically ranges from 4 to 10 kg/cm² for most floating tablets.
The hardness of tablet was carried out by using Monsanto type hardness tester. The hardness of the tablet kg / cm² was measured.

Thickness Test

Control of physical dimension of the tablets such as sizes and thickness is essential for consumer acceptance and to maintain tablet to tablet uniformity. The dimensional specifications were measured using verniar calipers. Six tablets from each batch were tested and average values were calculated. The thickness of the tablet is mostly related to the tablet hardness can be uses as initial control parameter.

Drug Content (Assay)

To verify the actual amount of drug in a tablet, ensuring each contains the correct dosage. Tablets are finely powdered, a specified amount of the powder is dissolved in an appropriate solvent, and the solution is analyzed using analytical techniques such as HPLC or UV spectrophotometry. Ensures dose accuracy and uniformity critical for therapeutic efficacy and safety. This comprehensive description of each quality control test, including detailed methodologies and calculations, provides a robust framework for evaluating the quality of gastro retentive floating tablets. This information is pivotal in ensuring that the developed formulations meet all the required specifications for clinical effectiveness and regulatory compliance.

Floating Lag Time and Total Floating Time

To determine the time required for the tablet to rise to the surface of a dissolution medium and the duration it remains afloat. A tablet is placed in a dissolution medium, and the time taken to rise to the surface (floating lag time) and the time it remains floating (total floating time) are recorded. Critical for gastroretentive drug delivery systems, ensuring prolonged gastric residence time and potentially enhancing drug bioavailability.

Dissolution Test

To determine the rate and extent of drug release from the tablet under simulated physiological conditions. Conducted using a dissolution test apparatus (USP Apparatus II – paddle method is common). The medium (e.g., 0.1 N HCl at 37°C) is used, and samples are withdrawn at specified time points and analyzed for drug content, typically by UV spectrophotometry.

Calculation:

Cumulative percentage of drug released=(Amount of drug released at time *t*Total drug content)×100Cumulative percentage of drug released=(Total drug contentAmount of drug released at time *t*)×100
The dissolution profile provides essential information on the release kinetics and mechanism of the drug from the tablet.

In vitro dissolution studies

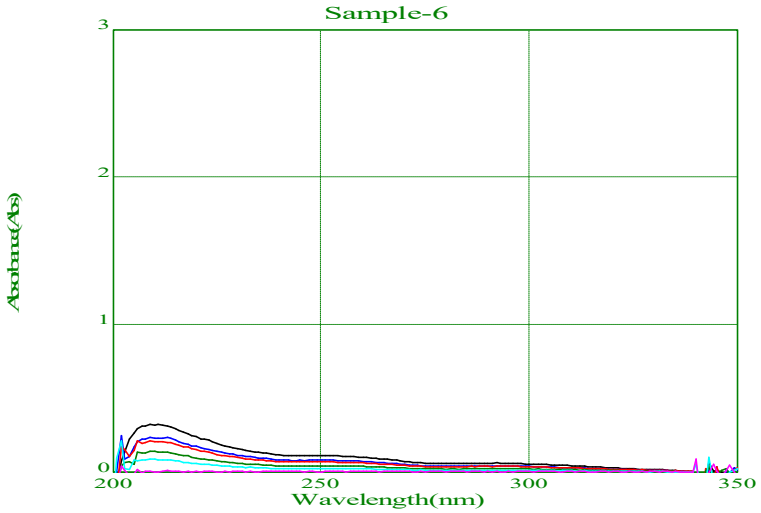
The release of propranolol HCl from floating tablets was determined by using Dissolution Tester USP XXIII (LABINDIA, Disso 200). The dissolution test was performed using 900 mL 0.1 N HCl solution at 37 ± 0.5 °C and the paddles were rotated at 50 rpm. At appropriate time interval, 5 mL of aliquot was withdrawn from the dissolution medium and it was replaced with fresh medium to maintain the volume constant. The samples were filtered and diluted to suitable concentrations with 0.1 N HCl. The absorbance of the solutions were measured at 289 nm for propranolol HCl with a UV-Visible double beam spectrophotometer (Elico SL210, India). Cumulative percentage drug release was calculated using an equation obtained from standard curve. The dissolution experiments were done in triplicate.

RESULTS AND DISCUSSIONS

Table 3: Description of Quetiapine fumarate

Description	Quetiapine fumarate
colour	Yellow
Odour	Breath odor
Melting point	172-176 °C
Molecular formula	$C_{46}H_{54}N_6O_8S_2$
Molecular weight	883.09

Spectra of Quetiapine fumarate in UV



It shows a Lamda max 207 nm.

Fig 1: Spectra of Quetiapine fumarate

Standard Curve of Quetiapine fumarate in various buffer

UV-Spectro-photometric method was used for the estimation of Quetiapine fumarate. A solution of Quetiapine fumarate (10µg/mL) was scanned in the wavelength range of 200-400 nm and found to have maximum absorption (λmax) at 207 nm. The standard plots of Quetiapine fumarate wereprepared in 0.1 N HCl (pH 1.2), Phosphate buffer pH 6.8 and in Phosphate buffer pH 7.4. The standard graphs showed good linearity with R^2 = 0.999 values ranging from 0-10 µg.

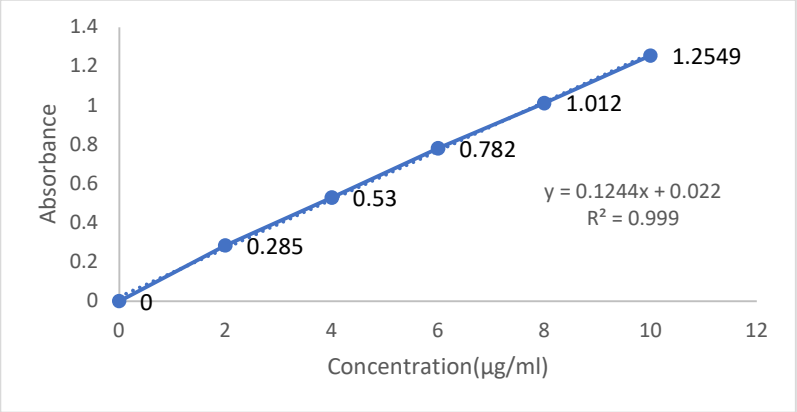


Fig 2: Standard curve of Quetiapine fumarate in 0.1N HCI at 207nm

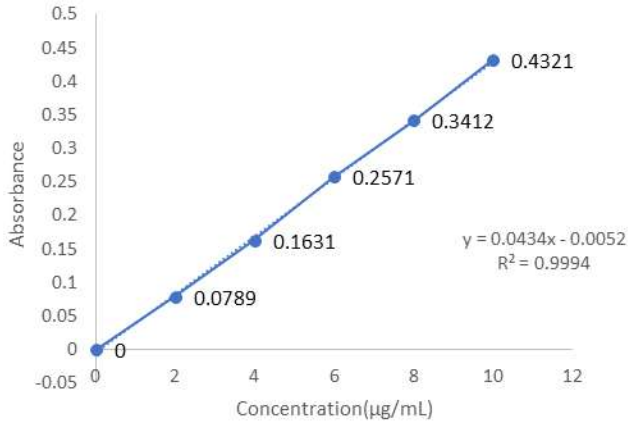


Fig 3: Standard graph of Quetiapine fumarate in 6.8 pH buffer at 207nm

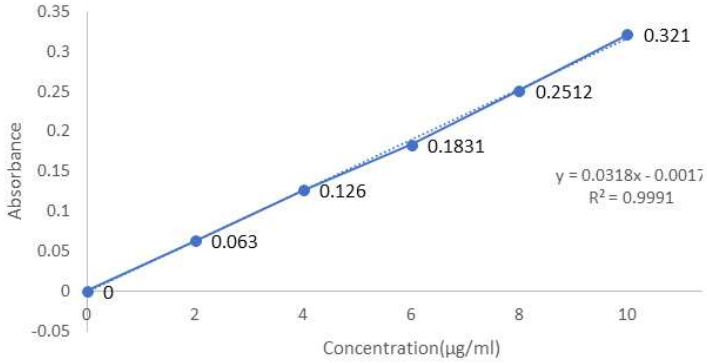


Fig 4: Standard graph of Quetiapine fumarate in 7.4 pH buffer at 207nm

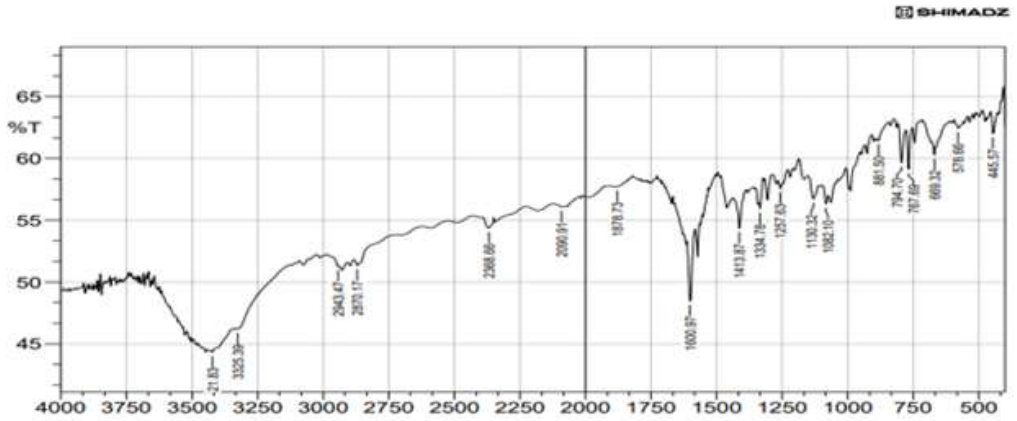


Fig 5: FTIR of pure Quetiapine fumarate

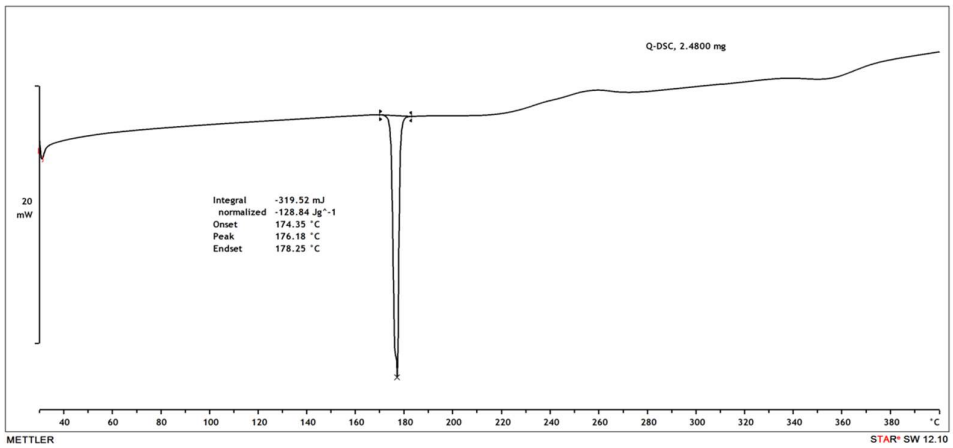


Fig 6: DSC Study of Quetiapine fumarate

Table 4: Composition of Unit Quetiapine Fumarate Floating tablets

Ingredients (mg)	QFB1	QFB2	QFB3	QFB4	QFB5	QFB6	QFB7	QFB8	QFB9
Quetiapine Fumarate	200	200	200	200	200	200	200	200	200
Cellulose Microcrystalline	130	95	60	130	95	60	130	95	60
Povidone K-30	15	15	15	15	15	15	15	15	15
(HPMC K 4 M)	55	70	85	55	70	85	55	70	85
(HPMC K 100M)	80	90	100	80	90	100	80	90	100
Sodium bicarbonate	10	20	30	10	20	30	10	20	30
Citric Acid	5	5	5	5	5	5	5	5	5
Magnesium Stearate	5	5	5	5	5	5	5	5	5
Total weight	**500**	**500**	**500**	**500**	**500**	**500**	**500**	**500**	**500**

Table 5: In vitro evaluation of Quetiapine fumarate Floating Tablets

Batch Code	Weight Variation	Friability %	Hardness(kg/cm^2)	Drug Content%
QFB1	501	0	5.5	99.23
QFB2	498	0.19	5.2	99.83
QFB3	502	0.26	5.4	98.65

QFB4	500	0.15	4.8	99.85
QFB5	495	0.24	5.0	99.12
QFB6	506	0.29	4.9	99.64
QFB7	492	0.41	5.1	99.72
QFB8	489	0.23	4.8	98.45
QFB9	504	0.29	5.1	99.73

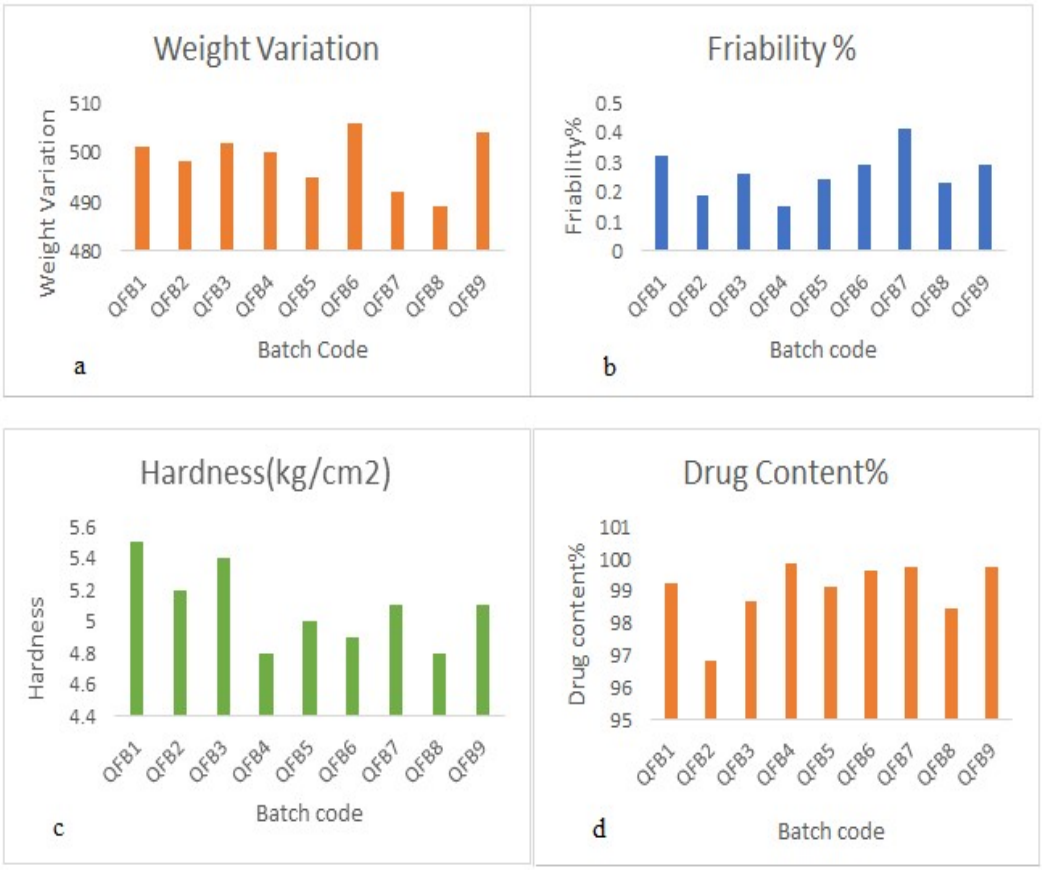


Table 6: In-vitro buoyancy study of Quetiapine fumarate Floating Tablets

Formulation code	Floating Lag time (seconds)	Total floating time (hours)
QFB1	18	>12
QFB2	16	>12
QFB3	17	>12
QFB4	15	>12
QFB5	16	>12
QFB6	19	>12
QFB7	16	>12
QFB8	15	>12
QFB9	18	>12

In – Vitro Drug Release Data and Profile

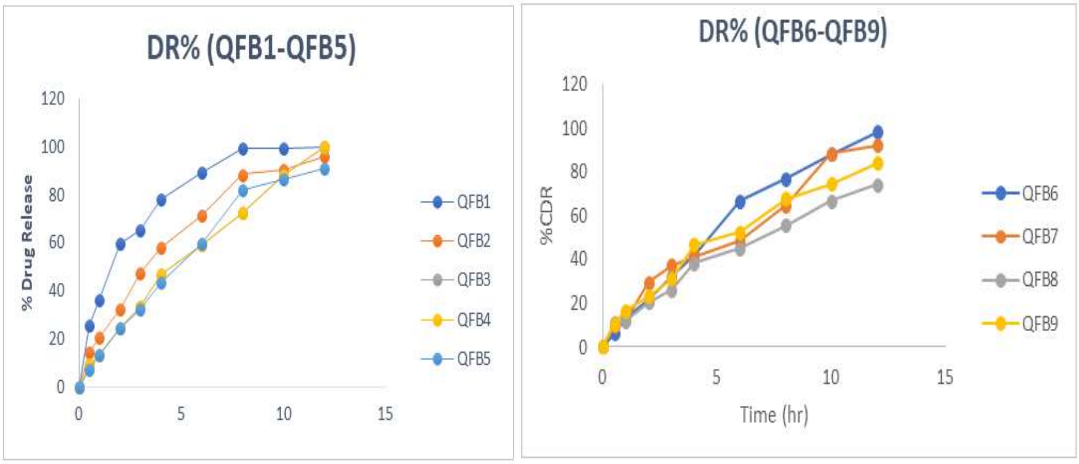


Table 7: Regression coefficient (R^2) values of single unit floating tablets for different kinetic models

Formulation code	r^2				Peppas (n)
	Zero	First	Higuchi	Korsmeyer& Peppas	
QFB1	0.71	0.99	0.65	0.73	0.36
QFB2	0.92	0.97	0.76	0.72	0.51
QFB3	0.94	0.96	0.75	0.99	0.78
QFB4	0.93	0.98	0.85	0.99	0.71
QFB5	0.81	0.99	0.86	0.99	0.80
QFB6	0.94	0.87	0.85	0.99	0.83
QFB7	0.82	0.94	0.65	0.99	0.81
QFB8	0.91	0.99	0.96	0.99	0.86
QFB9	0.99	0.93	0.92	0.90	0.73

The correlation coefficient (r^2) values of all the formulations from FQB1 to FQB15 showed zero order release kinetics.

SUMMERY & CONCLUSION

Quetiapine Fumarate is a dibenzo thiazepine derivative used primarily as an antipsychotic agent in the treatment of schizophrenia, bipolar disorder, and depressive disorders. Its pharmacological activity involves targeting several receptors, including the serotonin 5-HT2, histamine H1, adrenergic alpha1 and alpha2, and dopamine D1 and D2 receptors.

For the purpose of enhancing drug delivery, a floating tablet formulation of Quetiapine Fumarate was developed using the wet granulation method. This formulation involved various trials using rate-modifying polymers such as HPMC K100M, HPMC K4M, and Eudragit RSPO. Among these, HPMC K4M was selected due to its superior performance in reducing floating lag time and enhancing total floating duration, key parameters for ensuring prolonged gastric retention.

Additionally, HPMC K100M was chosen as the hydrophilic polymer rate-modifying agent based on insights gleaned from previous studies. The formulation process was rigorously designed and optimized using a Box Behnken design approach, facilitated by Design Expert software V.12. The formulation variables adjusted were concentrations of HPMC K100M (X1), HPMC K4M (X2), and sodium bicarbonate (X3). These variables influenced critical quality attributes such as floating lag time (Y1), swelling index percentage (Y2), and cumulative drug release percentage at 12 hours (Y3).

A comprehensive analysis was conducted on fifteen trial batches (FQB1 to FQB15), evaluating key physicochemical parameters including weight variation, hardness, friability, thickness, and drug content. All batches met the Pharmacopeial standards, underscoring the robustness of the manufacturing process. The investigation into the floating characteristics of the tablets revealed optimal floating lag time and total floating duration. The in-vitro drug release profile was assessed in 0.1N HCl, identifying the formulation with the

maximum drug release, which was then selected for further optimization. The drug release kinetics for most formulations aligned with zero-order kinetics, indicating a consistent release rate.

The study also elucidated the interactions between the formulation components, particularly noting that increasing concentrations of HPMC K100M and HPMC K4M generally extended the floating lag time of the tablets. In contrast, an increase in sodium bicarbonate concentration decreased the floating lag time. Notably, a higher polymer concentration resulted in decreased drug release rates, demonstrating an antagonistic effect between polymer concentration and both swelling index and drug release percentage at 12 hours.

Overall, the development of the optimized floating tablet of Quetiapine Fumarate represents a significant advancement in the pharmacological management of psychiatric disorders, offering a promising approach to improve therapeutic outcomes through enhanced gastric retention and controlled drug release.

REFERENCES

1. Adepu S, Ramakrishna S. Controlled drug delivery systems: current status and future directions. Molecules. 2021 Sep 29;26(19):5905. https://www.mdpi.com/1420-3049/26/19/5905
2. Liu X, Yang Y, Yu DG, Zhu MJ, Zhao M, Williams GR. Tunable zero-order drug delivery systems created by modified triaxial electrospinning. Chemical Engineering Journal. 2019 Jan 15;356:886-94. https://www.sciencedirect.com/science/article/pii/S138589471831814X
3. Murugesan S, Gowramma B, Lakshmanan K, Reddy Karri VV, Radhakrishnan A. Oral modified drug release solid dosage form with special reference to design; an overview. Current Drug Research Reviews Formerly: Current Drug Abuse Reviews. 2020 Jun 1;12(1):16-25. https://www.ingentaconnect.com/content/ben/cdrr/2020/00000012/00000001/art00005
4. Bastiancich C, Malfanti A, Préat V, Rahman R. Rationally designed drug delivery systems for the local treatment of resected glioblastoma. Advanced drug delivery reviews. 2021 Oct 1;177:113951. https://www.sciencedirect.com/science/article/pii/S0169409X21003446
5. Alhalmi A, Altowairi M, Saeed O, Alzubaidi N, Almoiliqy M, Abdulmalik W. Sustained release matrix system: an overview. World J Pharm Pharm Sci. 2018 Apr 17;7(6):1470-86. https://www.academia.edu/download/64234471/1527920851.pdf
6. Jurak M, Wiącek AE, Ładniak A, Przykaza K, Szafran K. What affects the biocompatibility of polymers?. Advances in Colloid and Interface Science. 2021 Aug 1;294:102451. https://www.sciencedirect.com/science/article/pii/S0001868621000920
7. Chen Y, Li W, Zhang C, Wu Z, Liu J. Recent developments of biomaterials for additive manufacturing of bone scaffolds. Advanced Healthcare Materials. 2020 Dec;9(23):2000724. https://onlinelibrary.wiley.com/doi/abs/10.1002/adhm.202000724
8. Rezaie HR, Esnaashary M, Abolfazl Aref arjmand, Öchsner A. A Review of Biomaterials and Their Applications in Drug Delivery. Singapore:: Springer; 2018 Jul 12. https://link.springer.com/content/pdf/10.1007/978-981-10-0503-9.pdf
9. Shukla SS, Pandey RK, Kalyani G. Controlled Drug Delivery Systems: Contemporary Significance and Advances–Overview and Advances for Controlled Drug Delivery Systems. Advancements in Controlled Drug Delivery Systems. 2022:184-204. https://www.igi-global.com/chapter/controlled-drug-delivery-systems/300406
10. Shukla SS, Pandey RK, Kalyani G. Controlled Drug Delivery Systems: Contemporary Significance and Advances–Overview and Advances for Controlled Drug Delivery Systems. Advancements in Controlled Drug Delivery Systems. 2022:184-204. https://www.igi-global.com/chapter/controlled-drug-delivery-systems/300406