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Formulation and Evaluation of Floating Drug Delivery System of Diltiazem Hydrochloride

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ABSTRACT:

This study aimed to formulate a floating drug delivery system of Diltiazem hydrochloride and to evaluate the physicochemical characteristics, dissolution kinetics, and in vitro release profiles of floating tablets. The tablets were prepared using wet granulation method, and their physicochemical properties, including hardness, friability, and drug content, were determined. Dissolution kinetics were analysed using various mathematical models, and plasma drug concentration-time profiles were measured in a rat model. The floating tablets exhibited sustained release profiles with prolonged gastric retention times, while the immediate-release tablets showed faster release kinetics and shorter gastric retention times. Pharmacokinetic parameters such as Cmax, Tmax, and AUC were calculated to compare the drug exposure between the formulations. The results demonstrated that while the immediate-release tablets achieved higher peak plasma concentrations and total drug exposure, the floating tablets provided a more controlled and sustained release of the drug, potentially offering benefits for drugs requiring prolonged action and reduced dosing frequency.

Keywords: Floating drug delivery, Diltiazem, Calcium channel blocker, Gastric retention

1. Introduction

Controlled drug delivery systems (CDDS) represent a pivotal advancement in pharmaceutical technology, offering convenient means of drug delivery aimed at reducing the frequency of drug administration while ensuring rapid absorption and elimination. These systems have been developed to address the need for maintaining therapeutic drug concentrations in systemic circulation for an extended period, thereby enhancing efficacy and reducing side effects associated with fluctuating plasma drug levels (Adepu & Ramakrishna, 2021). Among the various approaches to increase gastric retention, the Intragastric Floating Drug Delivery System (IGFDDS) stands out as a promising strategy. This approach involves formulating dosage forms that are designed to float and remain buoyant in the gastric fluid, thus prolonging their residence time in the stomach. By leveraging principles such as buoyancy and gastric motility, IGFDDS ensures sustained release of the drug, allowing for continuous absorption and maintenance of therapeutic drug levels (Adepu & Ramakrishna, 2021; Park, 2014). Other approaches to enhance gastric retention include swelling and expanding systems, altered density dosage forms, inflatable gastrointestinal delivery systems, intragastric osmotically controlled drug delivery systems, non-effervescent and effervescent floating drug delivery systems, bioadhesive systems, and modified-shaped systems. These approaches employ a

variety of mechanisms to prolong gastric residence time, including physical expansion, manipulation of buoyancy, osmotic pressure, and adhesive interactions with the gastric mucosa (Park, 2014). By extending the duration of drug release and maintaining optimal drug concentrations in the systemic circulation, these innovative drug delivery systems offer significant advantages over conventional dosage forms. They not only improve patient compliance by reducing dosing frequency but also enhance therapeutic outcomes by minimizing fluctuations in plasma drug levels and reducing the risk of adverse effects. In summary, controlled drug delivery systems, particularly those designed to increase gastric retention such as IGFDDS, represent a paradigm shift in drug delivery technology. By harnessing innovative approaches to prolong gastric residence time, these systems offer the potential to optimize drug therapy, improve patient outcomes, and enhance the overall quality of healthcare delivery. Continued research and development in this field hold promise for the development of advanced drug delivery systems with even greater efficacy, safety, and patient acceptability (Bruck, 1983; Park, 2014).

Floating drug delivery systems (FDDS) represent a specialized form of controlled-release drug delivery designed to prolong gastric retention and enhance drug bioavailability. This innovative approach offers several advantages over conventional drug delivery systems, making it an attractive option for various therapeutic applications. One of the primary advantages of floating drug delivery systems is their ability to prolong gastric residence time. By remaining buoyant in the stomach and floating on the gastric fluid surface, these systems can evade the rapid emptying of the stomach and extend the duration of drug release (Mohammed, Alqahtani, & Ahmed, 2024; Munusamy & Shanmugasundharam, 2024b; Rajora & Nagpal, 2022; Saady et al., 2024). This prolonged residence time allows for sustained drug release and absorption, leading to enhanced therapeutic efficacy and reduced dosing frequency. Moreover, by maintaining the drug within the stomach for an extended period, FDDS can target specific regions of the gastrointestinal tract, such as the upper small intestine, where optimal drug absorption occurs. Another key advantage of floating drug delivery systems is their potential to improve drug solubility and bioavailability, particularly for poorly water-soluble drugs. By keeping the drug in close proximity to the absorption sites in the gastrointestinal tract, FDDS can facilitate drug dissolution and enhance drug absorption. Additionally, the controlled release of the drug from floating systems can minimize fluctuations in plasma drug concentrations, thereby reducing the risk of adverse effects and improving patient compliance (Dsouza, Dinesh, & Sharma, 2024; Kállai-Szabó et al., 2024; Mohammed et al., 2024; Munusamy & Shanmugasundharam, 2024b; Rajora & Nagpal, 2022; Saady et al., 2024; Zheng et al., 2023).

Floating drug delivery systems also offer versatility in formulation design, allowing for customization of drug release profiles to suit specific therapeutic needs. Formulation variables such as polymer type, drug loading, and excipient composition can be optimized to achieve desired release kinetics, ranging from immediate release to sustained release or pulsatile release. This flexibility enables tailoring of FDDS to meet the requirements of different drugs and patient populations, enhancing therapeutic outcomes and patient satisfaction. Furthermore, floating drug delivery systems can improve drug stability and reduce drug degradation in the acidic environment of the stomach. By minimizing drug exposure to gastric acid and enzymatic degradation, FDDS can enhance drug stability and prolong shelf-life, thereby ensuring the efficacy and safety of the pharmaceutical product. In addition to these advantages, floating drug delivery systems offer several practical benefits for pharmaceutical formulation and manufacturing (Ullah et al., 2023; Yehualaw, Tafere, Yilma, & Abrha, 2023; Yuan, Zhang, & Hu, 2023). These systems are relatively simple to develop and scale up for commercial production, making them cost-effective and commercially viable. Moreover, floating formulations can be administered orally in the form of conventional tablets, capsules, or multiparticulate systems, facilitating ease of administration and patient acceptance (Albetawi,

Abdalhafez, & Abu-Zaid, 2021; Kumari, Khansili, Phougat, & Kumar, 2019; Rajora & Nagpal, 2022; Rathor, Aamir, Bhatt, Kumar, & Kumar, 2021; Sheraz, Ahsan, Khan, Ahmed, & Ahmad, 2016). In a nutshell, floating drug delivery systems represent a promising approach to enhance drug delivery and optimize therapeutic outcomes. With their ability to prolong gastric retention, improve drug solubility and bioavailability, offer formulation versatility, and enhance drug stability, FDDS hold great potential for the development of advanced pharmaceutical products with enhanced efficacy, safety, and patient compliance (Agyeman et al., 2023; Alqahtani, Mohammed, Fatima, & Ahmed, 2023; de Dios Andres & Städler, 2023; Deng, Xie, Kong, Tang, & Zhou, 2023; Dsouza et al., 2024; Fu et al., 2023; Zheng et al., 2023).

Diltiazem hydrochloride (HCl) is a calcium channel blocker that is commonly used in the treatment of various cardiovascular conditions, including hypertension, angina pectoris, and certain arrhythmias. It exerts its therapeutic effects by inhibiting the influx of calcium ions into cardiac and smooth muscle cells, leading to vasodilation, and reduced myocardial contractility, which in turn lowers blood pressure and improves myocardial oxygen supply. One of the primary rationales for selecting diltiazem hydrochloride as a drug candidate for floating drug delivery is its pharmacokinetic profile and dosing regimen. Diltiazem hydrochloride is known to have a short biological half-life (approximately 3.5 to 4 hours) and undergoes extensive first-pass metabolism in the liver, resulting in low oral bioavailability (around 30% to 40%) (Kállai-Szabó et al., 2024; Munusamy & Shanmugasundharam, 2024b; Ullah et al., 2023; Yuan et al., 2023). Additionally, the drug exhibits pH-dependent solubility, with optimal dissolution occurring at higher pH levels, such as those found in the proximal small intestine. By formulating diltiazem hydrochloride into floating tablets or capsules, it is possible to prolong gastric residence time and enhance drug absorption. The prolonged gastric retention allows for sustained release of the drug in the stomach, which can facilitate dissolution and improve bioavailability by maintaining the drug in the absorption window for an extended period. This can be particularly advantageous for drugs with pH-dependent solubility, as it ensures optimal drug dissolution and absorption in the desired region of the gastrointestinal tract.

Furthermore, the controlled-release characteristics of floating drug delivery systems can help minimize fluctuations in plasma drug concentrations and provide a more consistent and predictable pharmacokinetic profile. This can be especially beneficial for diltiazem hydrochloride, which requires careful titration of dosage to achieve therapeutic efficacy while minimizing the risk of adverse effects such as hypotension or bradycardia. In addition to its pharmacokinetic properties, diltiazem hydrochloride is a suitable candidate for floating drug delivery due to its clinical indications and therapeutic requirements. Patients with cardiovascular conditions often require long-term treatment with diltiazem hydrochloride to manage their symptoms and prevent disease progression. By formulating the drug into a floating dosage form, it is possible to improve patient compliance by reducing dosing frequency and simplifying the dosing regimen, which can ultimately lead to better treatment outcomes and quality of life for patients ("Calcium Channel Blockers," 2012; "Diltiazem," 2012; Mayow et al., 2024; Sajid, Whitehouse, Sains, & Baig, 2013).

Moreover, the versatility of floating drug delivery systems allows for customization of drug release profiles to meet the specific therapeutic needs of diltiazem hydrochloride. By adjusting formulation variables such as polymer type, drug loading, and release kinetics, it is possible to optimize drug release and achieve desired therapeutic effects, such as sustained antihypertensive or antianginal activity (Budriesi et al., 2007; Elliott & Ram, 2011; Essali, Deirawan, Soares-Weiser, & Adams, 2011; Triggle, 2006). Overall, diltiazem hydrochloride presents a compelling rationale for selection as a drug candidate for floating drug delivery, given its pharmacokinetic properties, clinical indications, and therapeutic requirements. By harnessing the benefits of floating drug delivery systems, it is possible to enhance the pharmacological properties of diltiazem hydrochloride and improve patient outcomes in the

management of cardiovascular conditions. Considering all the above facts and details, this present study aimed to fabricate and evaluate a floating drug delivery system of Diltiazem hydrochloride for gastric retention.

2. Material and Methods

Chemicals and Drugs

Various chemicals and drugs were used in the preparation and evaluation of floating tablets in this study. Diltiazem HCl was employed as the active pharmaceutical ingredient and received as a gift sample from Resenta Pharma, Baddi, India. Excipients included Hydroxypropyl methylcellulose (HPMC) K100M, Carbopol 934P, citric acid, sodium bicarbonate, Polyvinylpyrrolidone (PVP) k-30, magnesium stearate, and talc were procured from Sigma Aldrich, Mumbai, India. These chemicals and drugs were selected based on their compatibility with the formulation requirements and their established use in pharmaceutical preparations. Distilled water was used for preparing solutions and media, while 0.1 N HCl at pH 1.2 was utilized as a dissolution medium for in vitro studies. Additionally, analytical grade chemicals and reagents were used for analytical procedures, such as UV spectroscopy, to determine drug content and release rates.

Preparation of Floating tablets

By using the wet granulation process, tablets were made. Wet granulation was used to create the Diltiazem HCl floating tablets (Munusamy & Shanmugasundharam, 2024a; Putta et al., 2024). The composition of the formulation included sodium bicarbonate, citric acid, magnesium stearate, talc, Hydroxypropyl methylcellulose (HPMC) K100M, Carbopol 934P, and Diltiazem HCl as the active component. For every tablet, the ingredients were weighed in accordance with the prescribed formulation. After that, a mixer was used to completely combine them to ensure even distribution. To create a moist mass, a tiny amount of purified water was gradually added. This was then run through a granulator to create granules of the appropriate size. To get a consistent particle size, the granules were dried and then put through sieves. In the end, a tablet press was used to compress the granules into tablets, and a drying chamber was used to dry them. The tablets were then carefully packaged under controlled circumstances using appropriate materials for further evaluations.

Table 1. Composition of floating tablets of Diltiazem HCL. (Ingredients are presented as mg/tablet)

Formulation	Drug	HPMCK 100M	Carbopol 934P	Citric acid	Sodium bicarbonate	PVP k-30	Magnesium Stearate	Talc
FTF1	180	90	-	12	45	70	4	4
FTF2	180	140	-	12	45	70	4	4
FTF3	180	-	90	12	45	70	4	4
FTF4	180	-	140	12	45	70	4	4
FTF5	180	70	70	12	45	70	4	4

Tablet Evaluation

Weight Variation

The average weight of twenty tablets that were chosen at random was determined. Next, each tablet was weighed separately, and the results were compared to the average weight (Shaikh, Payghan, & Desouza, 2011).

Hardness and Friability

A Monsanto hardness tester was used to determine how hard three tablets were. A Roche friabilator was used to determine the friability of ten pre-weighed tablets. It was rotated 100 times. Following the friabilator procedure, the pills were reweighed and dusted. For accuracy, this procedure was carried out three times (Shaikh et al., 2011).

Estimation of Drug Content

For every formulation, twenty tablets were weighed and ground into a powder. A 100 ml volumetric flask containing 100 mg of the drug's powder was filled with it and mixed with 70 ml of distilled water (Shaikh et al., 2011). Using water, the volume was adjusted to 100 ml. Using an Elico UV spectrophotometer, the solution was filtered, appropriate dilutions were prepared, and absorbance was measured at 233 nm. Three iterations of this experiment were conducted.

Swelling Index

Each tablet was precisely weighed and stored in 50 millilitres of water. After 60 minutes, the tablets were carefully removed, the water on the top was wiped using filter paper, and they were precisely weighed. Using the formula, the percentage swelling (swelling index) was determined (Saxena, Gaur, Singh, Singh, & Dashora, 2014; Younis, Tareq, & Kamal):

Swelling index (%) = Wet Weight – Dry Weight / Dry Weigh X 100

Floating or Buoyancy Test

In 900 millilitres of simulated stomach fluid at pH 1.2, the floating behaviour of the tablets was assessed in a USP type II dissolving device at 37±0.5°C. The floating lag time (FLT) or buoyancy lag time (BLT) was the amount of time it took for the tablet to appear on the medium's surface, and the total floating time (TFT) was the amount of time the dosage form was floating on the surface (Younis et al.).

***In Vitro* Drug Release Study**

A paddle dissolving test device approved by the USP was used for the in vitro release investigations. The dissolution medium, 900 millilitres of 0.1 N HCl (pH 1.2), was stirred at 100 revolutions per minute while being kept at 37±0.5°C. Over the course of 12 hours, samples were taken out at prearranged intervals, and the same volume of new medium was added. The samples were examined with an Shimadzu UV spectrophotometer at 233 nm. The dissolution data were plotted as follows: log cumulative percentage drug retention versus time for first-order release kinetics, cumulative percentage drug release versus square root of time for Higuchi equation, log of fraction of drug released versus log time for Korsmeyer-Peppas equation, and cumulative percentage drug release versus time for zero-order kinetics.

***In vivo* Pharmacokinetic study**

The objective of this in vivo pharmacokinetic study was to assess the pharmacokinetic parameters and gastric retention of Diltiazem HCl from floating tablets in a rat model. The study design entailed a randomized, crossover study in male Wistar rats weighing 200-250g. The study duration consisted of multiple dosing and sampling periods over a period of 12 hours. The procedure involved fasting the rats overnight with free access to water before the study, followed by the administration of a single oral dose of either the floating tablets or immediate-release tablets of Diltiazem HCl. Blood samples were collected via tail vein puncture method at predetermined time points (e.g., 0.5, 1, 2, 4, 6, 8, and 12 hours) after dosing for the analysis of plasma concentrations of the drug using a validated analytical method. Gastric retention of the tablets were assessed by visual observation of the stomach contents after sacrifice. Pharmacokinetic parameters such as Cmax, Tmax, and AUC were calculated and compared between the best and immediate release formulations. Statistical analysis were conducted to compare pharmacokinetic parameters using appropriate tests such as t-test or ANOVA (Bębenek et al., 2024; Souza et al., 2024; Vaidya et al., 2024; Xiao et al., 2024).

Statistical analysis

In this study, statistical analysis was conducted using GraphPad Prism software to rigorously evaluate the data obtained from experimental procedures. A One-Way Analysis of Variance (ANOVA) was employed to assess the variability and significance among multiple groups, followed by Turkey's tests as *post hoc* for multiple comparisons between specific groups of interest. The data were meticulously processed and represented as mean values ± standard deviation (SD) to provide a clear and concise summary of the experimental outcomes. By averaging each variable three times, the precision and accuracy of the results were enhanced, minimizing the influence of potential outliers or random fluctuations. The significance level was set at p value less than 0.05.

3. Results and Discussions

Physicochemical Characteristics

The table 2 presented the physicochemical characteristics of the floating tablets, with values expressed as mean ± standard deviation (S.D.). Hardness (Kg/cm²) parameter indicated the tablet's resistance to crushing forces. The values range from 5.1 to 6.2 Kg/cm², suggesting that the tablets have adequate mechanical strength. Friability (%) is a measure of the tablet's tendency to break or crumble. The values range from 0.53% to 0.79%, which is within the acceptable limit of less than 1%, indicating that the tablets have good mechanical stability. Drug Content (%) uniformity is crucial for ensuring that each tablet delivers the intended dose. The drug content values range from 95.4% to 97.8%, indicating good uniformity across batches. Buoyancy Lag Time is the time taken for the tablet to start floating on the dissolution medium. The values range from 2 minutes 41 seconds to 4 minutes 9 seconds, indicating that the tablets exhibit a relatively fast onset of buoyancy. Total Floating Time (hrs) is the duration for which the tablet remains floating on the dissolution medium. The values range from >7 to >12 hours, indicating that the tablets exhibit prolonged floating behaviour, which is desirable for sustained drug release in the stomach. Overall, the physicochemical characteristics of the floating tablets, as presented in the table, suggest that they have suitable hardness, low friability, good drug content uniformity, and desirable buoyancy properties for achieving prolonged gastric retention and sustained drug release

Table 2. Physicochemical Characteristics of Tablets (All values are expressed as mean ± S.D.; n=3)

Batch	Hardness (Kg/cm²)	Friability (%)	Drug Content (%)	Buoyancy Lag Time	Total Floating Time (hrs)
FTF1	5.1±0.4	0.53±0.05	97.5±0.61	2 min 41sec	>7
FTF2	5.1±0.2	0.65±0.03	95.4±0.71	3 min 56sec	>8
FTF3	6.1±0.2	0.58±0.04	95.7±0.44	4 min 09sec	>11
FTF4	5.1±0.3	0.79±0.05	96.3±0.58	3 min 34sec	>12
FTF5	6.2±0.5	0.76±0.04	97.8±0.68	3 min 17sec	>11

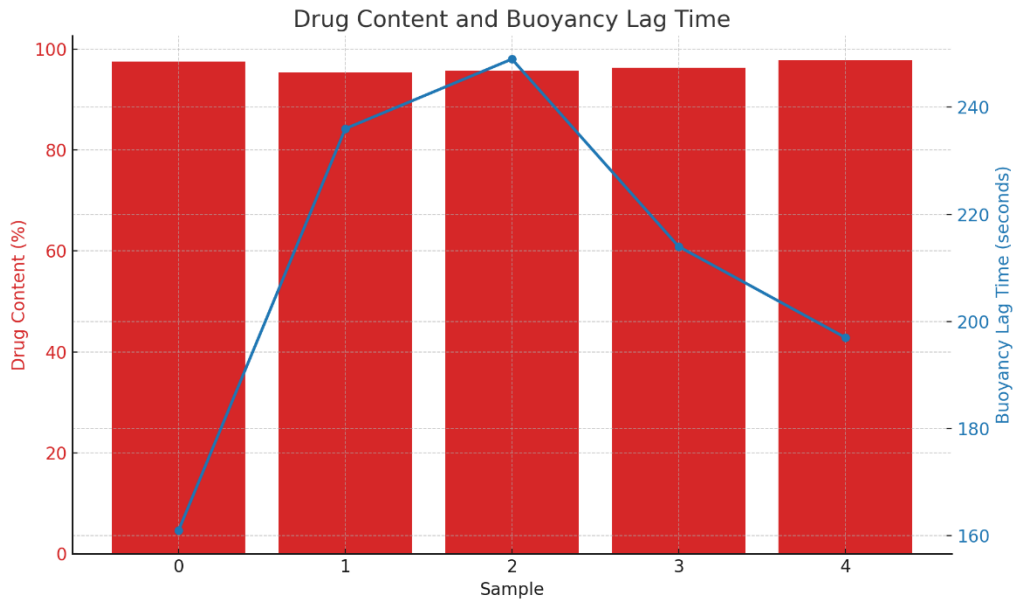

Figure 1. Combination graph depicting visually the drug content and buoyancy lag time.

Cumulative percentage drug release

The table 3 presented the cumulative percentage drug release profiles (mean± S.D.; n=3) from various formulations of floating tablets over a 12-hour period. FTF1 showed a gradual release of the drug, reaching almost complete release (100%) by the end of 10 hours. FTF2, similar to FTF1, FTF2 also showed a sustained release profile, with nearly complete release by 10 hours. FTF3 exhibited a faster release compared to FTF1 and FTF2, with approximately 92% release by 12 hours. FTF4 showed a moderate release profile, with around 96% release by 12 hours. FTF5 showed a slower release profile, with approximately 80% release by 12 hours. The marketed formulation showed a release profile similar to FTF3, with around 95% release by 12 hours. In inference, the data suggested that the different formulations of floating tablets exhibited varying drug release profiles, with some formulations showing sustained release characteristics and others exhibiting faster release kinetics. The choice of formulation would depend on the desired release profile for the specific therapeutic application.

Table 3. Cumulative % drug release (mean± S.D.; n=3) from various formulations Time (hr)

Formulation	**1**	**2**	**4**	**6**	**8**	**10**	**12**
FTF1	27.34±0.61	50.88±0.91	69.5±0.48	83.2±0.45	99.06±0.55	100±0.98	-
FTF2	23.56±0.38	42.99±0.74	64.5±0.62	78.8±0.66	97.94±0.72	99.96±0.92	-
FTF3	24.33±0.68	31.69±0.25	45.2±0.64	56.7±0.87	74.91±0.68	83.87±0.85	91.86±0.88
FTF4	21.71±0.77	25.36±0.67	50.9±0.75	66.4±0.98	78.48±0.65	84.43±0.799	95.77±0.89
FTF5	19.55±0.65	31.66±0.64	36.5±0.88	44.5±0.88	67.77±0.74	71.32±0.65	79.66±0.59
Marketed Formulation	26.46±0.77	36.56±0.55	61.4±0.78	76.7±0.91	83.78±0.498	92.46±0.98	94.98±0.98

Pharmacokinetic Mathematical Modelling

The results in table 4 provided dissolution kinetics and parameters for Diltiazem HCl floating tablets using different mathematical models. The first-order dissolution kinetics described the drug release rate as proportional to the remaining drug concentration. The 'r' values ranged from 0.983 to 0.9959, indicating a good fit of the data to the first-order model. The 'k' values ranged from 0.1497 to 0.1847, representing the rate constant of drug release. The zero-order dissolution kinetics described drug release as a constant rate regardless of the remaining drug concentration. The 'r' values ranged from 0.9784 to 0.9909, indicating a good fit of the data to the zero-order model. The 'k' values ranged from 5.3427 to 6.9277, representing the zero-order release rate constant. The Higuchi model described drug release as a square root of time-dependent process, typically indicating diffusion-controlled release. The 'r' values ranged from 0.9831 to 0.9939, indicating a good fit of the data to the Higuchi model. The 'k' values ranged from 0.996 to 0.9998, representing the Higuchi release rate constant. The Peppas model was used to characterize drug release from polymeric systems. The 'n' values ranged from 0.562 to 0.6727, indicating that the release mechanism may be non-Fickian or anomalous diffusion, where both diffusion and polymer relaxation contributed to drug release. In inference, the dissolution kinetics and parameters suggested that the floating tablets exhibited controlled and sustained drug release characteristics, with the release mechanism likely governed by both diffusion and polymer relaxation processes.

Table 4. Dissolution kinetics and dissolution parameters of Diltiazem HCL floating tablets

Formulation	**First order eqn. (r)**	**First order eqn. (k)**	**Zero order eqn. (r)**	**Zero order eqn. (k)**	**Higuchi eqn. (r)**	**Higuchi eqn. (k)**	**Peppas eqn. (n)**
FTF1	0.9942	0.1497	0.9859	5.3427	0.9939	0.9998	0.6617
FTF2	0.9959	0.1587	0.9909	6.7327	0.9893	0.9965	0.6617
FTF3	0.983	0.1667	0.9812	6.157	0.9831	0.9988	0.6587
FTF4	0.9852	0.1777	0.9784	6.0927	0.9915	0.9981	0.6727
FTF5	0.9909	0.1847	0.9899	6.9277	0.9841	0.996	0.562

***In vivo* Pharmacokinetic study**

The results indicated that the immediate-release tablets of Diltiazem HCl achieved a higher maximum plasma concentration (Cmax) compared to the floating tablets, suggesting a more rapid release of the drug into the systemic circulation. Both formulations reached their Cmax at the same time (Tmax), indicating similar absorption rates once the drug is released. However, the floating tablets demonstrated a longer gastric retention time compared to the immediate-release tablets, which was expected due to their design to remain in the stomach for an extended period. This prolonged gastric retention might result in a more controlled and sustained release of the drug over time. The area under the curve (AUC), which represents the total exposure to the drug over time, was lower for the floating tablets compared to the immediate-release tablets. This could be attributed to the slower and more sustained release profile of the floating tablets, which may lead to a lower overall drug exposure but potentially improved drug delivery efficiency over time. In assumption, while the immediate-release tablets showed a higher Cmax and AUC, indicating a more rapid and intense drug release, the floating tablets demonstrated a longer gastric retention time and a more controlled release profile, which could be advantageous for drugs requiring sustained release and reduced dosing frequency.

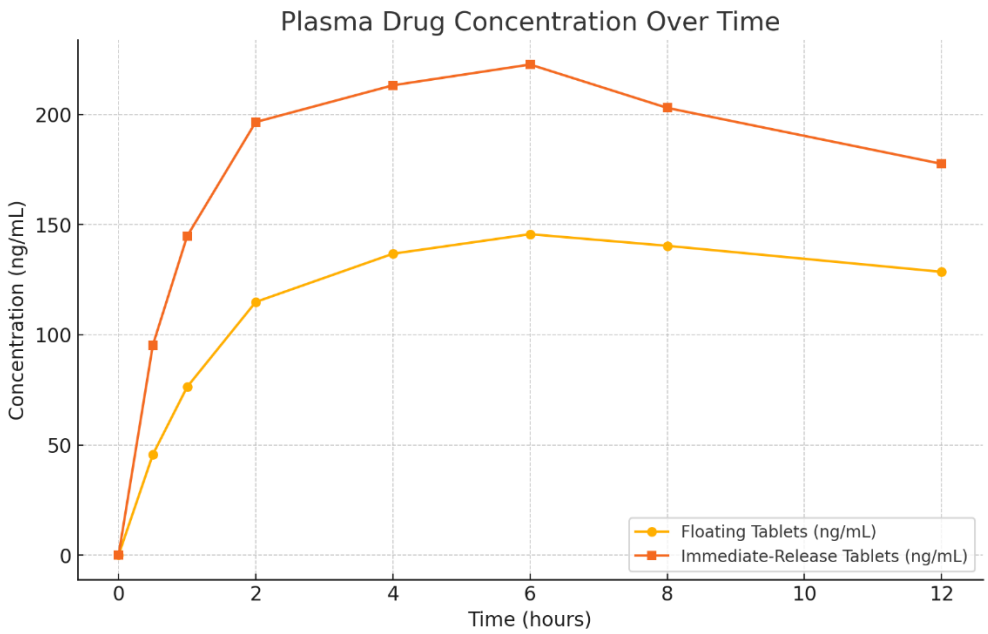

Figure 2. Plasma drug concentration vs time profile graph comparing the drug release profile of the formulated floating tablet and the immediate release tablet.

Table 5. Pharmacokinetic Parameters for the floating tablets (FTF3) and immediate-Release Tablets

Parameter	**Floating Tablets (FTF3)**	**Immediate-Release Tablets**
Cmax (ng/mL)	145.66	222.67
Tmax (hours)	6	6
AUC (ng·h/mL)	933.51	1220.89
Gastric Retention Time	12 hours	<1 hour

4. Conclusions

In conclusion, the study successfully formulated the floating tablets of Diltiazem hydrochloride and highlighted the differences in release kinetics and pharmacokinetic profiles between floating tablets and immediate-release tablets of Diltiazem HCl. The floating tablets exhibited prolonged gastric retention and sustained release characteristics, suggesting their potential for controlled drug delivery compared to immediate-release tablets which showed faster and more intense drug release. Further *in vivo* studies demonstrated superior pharmacokinetic profile of the floating tablets formulation. However further *in vivo* pharmacodynamic studies can be designed to confirm these findings and evaluate the clinical relevance of the observed differences. Overall, this study provided valuable insights into the floating tablet formulation and performance of floating tablets for extended drug delivery.

5. References

1. Adepu, S., & Ramakrishna, S. (2021). Controlled drug delivery systems: current status and future directions. *Molecules, 26*(19), 5905.
2. Agyeman, A. A., López-Causapé, C., Rogers, K. E., Lucas, D. D., Cortés-Lara, S., Gomis-Font, M. A., Landersdorfer, C. B. (2023). Ceftolozane/tazobactam plus tobramycin against free-floating and biofilm bacteria of hypermutable Pseudomonas

aeruginosa epidemic strains: Resistance mechanisms and synergistic activity. *Int J Antimicrob Agents, 62*(3), 106887. doi:10.1016/j.ijantimicag.2023.106887

3. Albetawi, S., Abdalhafez, A., & Abu-Zaid, A. (2021). A Review on Recent Controlled Release Strategies for Oral Drug Delivery of Repaglinide (a BCS Class II Drug). *Pharm Nanotechnol, 9*(5), 326-338. doi:10.2174/2211738510666211221165318
4. Alqahtani, A. A., Mohammed, A. A., Fatima, F., & Ahmed, M. M. (2023). Fused Deposition Modelling 3D-Printed Gastro-Retentive Floating Device for Propranolol Hcl Tablets. *Polymers (Basel), 15*(17). doi:10.3390/polym15173554
5. Bębenek, E., Rzepka, Z., Hermanowicz, J. M., Chrobak, E., Surażyński, A., Beberok, A., & Wrześniok, D. (2024). Synthesis, Pharmacokinetic Profile, Anticancer Activity and Toxicity of the New Amides of Betulonic Acid-In Silico and In Vitro Study. *Int J Mol Sci, 25*(8). doi:10.3390/ijms25084517
6. Bruck, S. D. (1983). *Controlled drug delivery* (Vol. 1): CRC Press Boca Raton, Florida.
7. Budriesi, R., Cosimelli, B., Ioan, P., Carosati, E., Ugenti, M. P., & Spisani, R. (2007). Diltiazem analogues: the last ten years on structure activity relationships. *Curr Med Chem, 14*(3), 279-287. doi:10.2174/092986707779941122
8. . Calcium Channel Blockers. (2012). In *LiverTox: Clinical and Research Information on Drug-Induced Liver Injury*. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases.
9. de Dios Andres, P., & Städler, B. (2023). Micromotor-Assisted Keratinocytes Migration in a Floating Paper Chip. *Small, 19*(13), e2201251. doi:10.1002/smll.202201251
10. Deng, Q., Xie, J., Kong, S., Tang, T., & Zhou, J. (2023). Long-Term Retention Microbubbles with Three-Layer Structure for Floating Intravesical Instillation Delivery. *Small, 19*(14), e2205630. doi:10.1002/smll.202205630
11. . Diltiazem. (2012). In *LiverTox: Clinical and Research Information on Drug-Induced Liver Injury*. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases.
12. Dsouza, F. P., Dinesh, S., & Sharma, S. (2024). Understanding the intricacies of microbial biofilm formation and its endurance in chronic infections: a key to advancing biofilm-targeted therapeutic strategies. *Arch Microbiol, 206*(2), 85. doi:10.1007/s00203-023-03802-7
13. Elliott, W. J., & Ram, C. V. (2011). Calcium channel blockers. *J Clin Hypertens (Greenwich), 13*(9), 687-689. doi:10.1111/j.1751-7176.2011.00513.x
14. Essali, A., Deirawan, H., Soares-Weiser, K., & Adams, C. E. (2011). Calcium channel blockers for neuroleptic-induced tardive dyskinesia. *Cochrane Database Syst Rev*(11), Cd000206. doi:10.1002/14651858.CD000206.pub3
15. Fu, K., Zhou, Y., Hou, J., Shi, T., Ni, J., Li, X., & Zhang, H. (2023). Floating poly(lactic-co-glycolic acid)-based controlled-release drug delivery system for intravesical instillation. *J Int Med Res, 51*(4), 3000605231162065. doi:10.1177/03000605231162065
16. Kállai-Szabó, N., Farkas, D., Lengyel, M., Basa, B., Fleck, C., & Antal, I. (2024). Microparticles and multi-unit systems for advanced drug delivery. *Eur J Pharm Sci, 194*, 106704. doi:10.1016/j.ejps.2024.106704
17. Kumari, B., Khansili, A., Phougat, P., & Kumar, M. (2019). Comprehensive review of the role of acrylic acid derivative polymers in floating drug delivery system. *Polim Med, 49*(2), 71-79. doi:10.17219/pim/122016
18. Mayow, A. H., Sinha, T., Ahmad, M., Myint, Y. K., Balaji, S., Chaudhari, S. S., . . . Khan, A. (2024). Comparison of the Effectiveness and Safety of Metoprolol and Diltiazem in Atrial Fibrillation With Rapid Ventricular Rate Patients: A Systematic Review and Meta-Analysis. *Cureus, 16*(3), e56560. doi:10.7759/cureus.56560

19. Mohammed, A. A., Alqahtani, A. A., & Ahmed, M. M. (2024). Design and fabrication of 3D-printed gastric floating tablets of captopril: effect of geometry and thermal crosslinking of polymer on floating behavior and drug release. *Pharm Dev Technol*, 1-13. doi:10.1080/10837450.2024.2352491
20. Munusamy, R., & Shanmugasundharam, S. (2024a). Enhanced gastric residence time of acyclovir by floating raft formulation using box-behnken design. *Heliyon, 10*(2), e24301. doi:10.1016/j.heliyon.2024.e24301
21. Munusamy, R., & Shanmugasundharam, S. (2024b). Improved gastric residence time of famotidine by raft-forming drug delivery system using DOE. *Int J Immunopathol Pharmacol, 38*, 3946320241249429. doi:10.1177/03946320241249429
22. Park, K. (2014). Controlled drug delivery systems: past forward and future back. *Journal of Controlled Release, 190*, 3-8.
23. Putta, S. K., Kb, K., Nayak, U. Y., Pai, K. S., Pathuri, R., & Hn, A. R. (2024). Design of floating formulations and antiulcer activity of Desmostachya bipinnata. *AAPS PharmSciTech, 25*(3), 44. doi:10.1208/s12249-024-02745-6
24. Rajora, A., & Nagpal, K. (2022). A Critical Review on Floating Tablets as a Tool for Achieving Better Gastric Retention. *Crit Rev Ther Drug Carrier Syst, 39*(1), 65-103. doi:10.1615/CritRevTherDrugCarrierSyst.2021038568
25. Rathor, S., Aamir, S., Bhatt, D. C., Kumar, K., & Kumar, V. (2021). A Comprehensive Review on Microbubble Concept, Development and Its Application in Therapeutic Drug Delivery and Clinical Management of Disease. *Curr Pharm Biotechnol, 22*(11), 1424-1443. doi:10.2174/1389201021999201109221102
26. Saady, M., Shoman, N. A., Teaima, M., Abdelmonem, R., El-Nabarawi, M. A., & Elhabal, S. F. (2024). Fabrication of gastro-floating sustained-release etoricoxib and famotidine tablets: design, optimization, in-vitro, and in-vivo evaluation. *Pharm Dev Technol*, 1-16. doi:10.1080/10837450.2024.2343320
27. Sajid, M. S., Whitehouse, P. A., Sains, P., & Baig, M. K. (2013). Systematic review of the use of topical diltiazem compared with glyceryltrinitrate for the nonoperative management of chronic anal fissure. *Colorectal Dis, 15*(1), 19-26. doi:10.1111/j.1463-1318.2012.03042.x
28. Saxena, A., Gaur, K., Singh, V., Singh, R. K., & Dashora, A. (2014). Floating microspheres as drug delivery system. *American Journal of Pharmacy and Pharmaceutical Sciences, 1*(2), 27-36.
29. Shaikh, K. N., Payghan, S. A., & Desouza, J. I. (2011). Formulation of gastroretentive drug delivery system (floating tablets) of nifedipine. *International Journal of Pharmaceutical Sciences and Research, 2*(11), 2929.
30. Sheraz, M. A., Ahsan, S. F., Khan, M. F., Ahmed, S., & Ahmad, I. (2016). Formulations of Amlodipine: A Review. *J Pharm (Cairo), 2016*, 8961621. doi:10.1155/2016/8961621
31. Souza, L., Oliveira, J., Fernandes, A. D. S., Macedo, A. F., Araujo-Lima, C. F., & Felzenszwalb, I. (2024). UHPLC-MS metabolomic profile and in silico pharmacokinetic approach of Kalanchoe daigremontiana Raym.-Hamet & H. Perrier aqueous extracts. *J Pharm Biomed Anal, 238*, 115827. doi:10.1016/j.jpba.2023.115827
32. Triggle, D. J. (2006). L-type calcium channels. *Curr Pharm Des, 12*(4), 443-457. doi:10.2174/138161206775474503
33. Ullah, G., Nawaz, A., Latif, M. S., Shah, K. U., Ahmad, S., Javed, F., . . . Lim, V. (2023). Clarithromycin and Pantoprazole Gastro-Retentive Floating Bilayer Tablet for the Treatment of Helicobacter Pylori: Formulation and Characterization. *Gels, 9*(1). doi:10.3390/gels9010043
34. Vaidya, V. G., Naik, N. N., Ganu, G., Parmar, V., Jagtap, S., Saste, G., . . . Hingorani, L. (2024). Clinical pharmacokinetic evaluation of Withania somnifera (L.) Dunal root

extract in healthy human volunteers: A non-randomized, single dose study utilizing UHPLC-MS/MS analysis. *J Ethnopharmacol, 322*, 117603. doi:10.1016/j.jep.2023.117603

35. Xiao, T., Wu, A., Wang, X., Guo, Z., Huang, F., Cheng, X., . . . Tao, L. (2024). Anti-hypertensive and composition as well as pharmacokinetics and tissues distribution of active ingredients from Alpinia zerumbet. *Fitoterapia, 172*, 105753. doi:10.1016/j.fitote.2023.105753
36. Yehualaw, A., Tafere, C., Yilma, Z., & Abrha, S. (2023). Formulation and In Vitro Evaluation of Furosemide Floating Matrix Tablets Using Boswellia papyrifera Resin as Matrix Forming Polymer. *Biomed Res Int, 2023*, 4322375. doi:10.1155/2023/4322375
37. Younis, M. K., Tareq, A. Z., & Kamal, I. M. (2018). *Optimization of swelling, drug loading and release from natural polymer hydrogels*.
38. Yuan, H., Zhang, Z., & Hu, L. (2023). Development and characterization of gastro-floating sustained-release capsule with improved bioavailability of levodopa. *Drug Deliv Transl Res, 13*(1), 9-17. doi:10.1007/s13346-022-01188-5
39. Zheng, K., Zhao, J., Wang, Q., Zhao, Y., Yang, H., Yang, X., & He, L. (2023). Design and Evaluation of Ginkgolides Gastric Floating Controlled Release Tablets Based on Solid Supersaturated Self-nanoemulsifying. *AAPS PharmSciTech, 25*(1), 7. doi:10.1208/s12249-023-02717-2