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Review

Formulation and in Vitro Characterization of Floating Tablets of Doxofylline

[1*]Selora Agasti, [1]Rakesh Kumar Parida

[1*]*Associate Professor*, [1]*M.Pharma Student*
[1]*Department of Pharmaceutics, Indira Gandhi Institute of Pharmaceutical Sciences, Bhubaneswar, Odisha, Pin:751015*

*Author for Correspondence: Selora Agasti
Email: seloraagasti@gmail.com

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Abstract

Doxofylline is a novel methylxanthine derivative widely used in the management of bronchial asthma and chronic obstructive pulmonary disease (COPD); however, its short biological half-life necessitates frequent dosing, which may compromise patient compliance. The present study aimed to develop and evaluate gastro-retentive floating tablets of doxofylline to prolong gastric residence time and achieve sustained drug release. Floating tablets were prepared by the direct compression method using hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC K4M) and xanthan gum in varying concentrations, along with sodium bicarbonate and citric acid as gas-generating agents. A total of nine formulations (DXFT1–DXFT9) were developed and evaluated for pre-compression parameters, post-compression characteristics, in vitro buoyancy, swelling behavior, drug content, and in vitro dissolution studies. All formulations exhibited acceptable flow properties and complied with pharmacopeial limits for weight variation, hardness, friability, and drug content. In vitro dissolution studies demonstrated sustained drug release over 12 hours, with formulation DXFT7 showing the most desirable performance, releasing 99.12% of doxofylline at 12 hours along with the shortest floating lag time (8 seconds) and the highest swelling index (90.12%). Drug release kinetics revealed that most formulations followed zero-order release with diffusion-controlled mechanisms, as confirmed by Higuchi and Korsmeyer–Peppas models. Stability studies of the optimized formulation (DXFT7) indicated no significant changes in drug content or buoyancy parameters over three months. Overall, the study concludes that gastro-retentive floating tablets of doxofylline can be successfully formulated to provide prolonged gastric retention and sustained drug release, thereby improving therapeutic efficacy and patient compliance.

Keywords: Sustained drug release, Drug release kinetics, Buoyancy studies, Direct compression

Introduction

Oral drug delivery systems remain the most favored method of administration owing to their convenience, patient adherence, cost-effectiveness, and the simplicity of large-scale production. But physiological factors like different times for the stomach to empty, short times for the stomach to stay full, and narrow absorption windows often limit how well traditional oral dosage forms work. These limitations can cause drugs to not be fully absorbed and not be as available to the body, especially for drugs that are mostly absorbed in the stomach or the upper part of the small intestine.[1]

To address the shortcomings of traditional oral dosage forms, gastro-retentive drug delivery systems (GRDDS) have been created to extend the duration of dosage forms in the stomach. GRDDS allow drugs to be released continuously at the desired site of absorption by staying in the stomach for a long time.[2] This can greatly improve drug bioavailability and therapeutic efficacy while lowering the number of doses needed. Drugs that are better absorbed in the stomach or the upper part of the small intestine, as well as drugs that are more stable in acidic conditions, benefit from long gastric retention.[3] Floating drug delivery systems (FDDS) have gotten a lot of attention as a way to keep drugs in the stomach because they are easy to make, work well, and are reliable. FDDS are made to have a lower density than stomach fluids, which lets them float on top of the stomach contents without changing the normal process of emptying the stomach.[4] These systems slowly release the drug in a controlled way while floating, which keeps the plasma drug levels steady and makes it easier for patients to follow their treatment.[5]

Floating tablets are a type of gastroretentive drug delivery system that usually use a mix of hydrophilic polymers and gas-generating agents to stay afloat in the stomach while releasing drugs in a controlled way. The hydrophilic polymers in the tablet quickly absorb water and swell when they come into contact with gastric fluid. This creates a thick gel layer around the tablet that protects it and controls how the drug spreads.[6] At the same time, the gas-generating agents, which are usually carbonates or bicarbonates, react with the acidic stomach environment to make carbon dioxide, which gets trapped in the gel matrix. The gas that is trapped inside the tablet makes it less dense overall, which lets it float on the contents of the stomach for a long time.[7] This longer time in the stomach increases the bioavailability of drugs, especially those that dissolve better in acidic conditions or are unstable, poorly absorbed, or quickly broken down in the intestines. Floating tablets are a good way to improve therapeutic outcomes.[8]

Doxofylline is a new methylxanthine derivative that is commonly used to treat bronchial asthma and chronic obstructive pulmonary disease (COPD). Doxofylline is a better choice than theophylline because it relaxes the airways, has a better safety record, fewer drug interactions, and fewer side effects on the heart and central nervous system. Even though doxofylline has these benefits, it has a short biological half-life, which means that patients need to take it often to keep therapeutic plasma levels, which could make it harder for them to follow their treatment plan.[9]

Changes in the amount of drug in the blood can greatly reduce the effectiveness of treatment and make it harder for patients to stick to their medication, especially for long-term conditions that require long-term medication. To solve this problem, creating a gastro-retentive floating tablet of doxofylline is a useful and new way to do it. It increases the time the dosage form stays in the stomach and makes it easier for the drug to be released over time.[10] The tablet stays in the stomach for a long time because it floats on the stomach contents. This makes sure that doxofylline is always available at the best place for it to be absorbed. This extended presence improves drug absorption, slows down the clearing of drugs from the body, and keeps plasma drug levels from changing too much. The formulation keeps therapeutic concentrations steady for a long time, which means that patients don't have to take their medicine as often, which makes it easier for them to follow their treatment plan and leads to better clinical outcomes.[11]

Consequently, this study seeks to develop and assess floating tablets of doxofylline utilizing hydrophilic polymers and a gas-generating agent. The formulated tablets underwent extensive in vitro characterization, encompassing physicochemical assessment, buoyancy analysis, drug content quantification, in vitro dissolution testing, and release kinetic modeling, to evaluate their efficacy as a gastro-retentive drug delivery system.[12]

Material:

All pharmaceutical-grade chemicals and excipients were procured from reputed suppliers in the Hyderabad region. Doxofylline was obtained from Aurobindo Pharma Ltd.; HPMC K15M from Colorcon Asia Pvt. Ltd.; sodium bicarbonate from Loba Chemie Pvt. Ltd.; citric acid (anhydrous) from S.D. Fine Chemicals (SDFCL); Carbopol 934P from Lubrizol Advanced Materials; PVP K30 from BASF India Ltd.; and microcrystalline cellulose (MCC PH 102) from Signet Chemical Corporation, Hyderabad.

Methodology

Development of Floating Tablets of Doxofylline

By using different amounts of polymer, we made floating tablets of Doxofylline using the direct compression method. To get the right particle size and make sure they mixed well, the raw materials were put through a no. 60 mesh sieve. To make a uniform blend, the weighed amounts of Doxofylline, polymer(s) (like HPMC K4M and Xanthan gum), binder Povidone K-30, diluent (MCC), and gas-generating agents (sodium bicarbonate and citric) were mixed well in a glass mortar and pestle. After that, 1% w/w magnesium stearate was added to the powder mixture to make it slippery. The final blend was made into tablets using a single-punch tablet compression machine (Cadmach, Ahmedabad, India) and the direct compression method.[13]

Table No: 1 Formulation Table for Floating Tablet of Doxofylline

Ingredients(mg)	**DXFT 1**	**DXFT 2**	**DXFT 3**	**DXFT4**	**DXFT 5**	**DXFT 6**	**DXFT 7**	**DXFT 8**	**DXFT 9**
Doxofylline	400	400	400	400	400	400	400	400	400
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
Xanthan Gum	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 (mg)	700	700	700	700	700	700	700	700	700

DXFT= Doxofylline Floating Tablet

Evaluation of Doxofylline Floating Tablets

Post compression parameters:

The prepared tablets were evaluated for quality control tests like weight variation, hardness, thickness, friability and content uniformity.[14]

Weight variation:

Ten tablets were selected randomly from each batch and weighed individually, calculating the average weight and comparing the individual tablet weight to the average. From this; percentage weight difference was calculated and then checked for USP specifications.[15]

Hardness and friability:

Hardness of tablet was determined by Monsanto hardness Tester. Ten tablets were randomly picked from each batch and analyzed for hardness. The mean and standard deviation were also calculated. Friability test was done by Roche friabilator. Ten tablets were weighed and were subjected to the combined effect of attrition and shock by utilizing a plastic chamber that revolve at 25 rpm dropping the tablets at distance of 6 in. with each revolution. Operated for 100 revolutions, the tablets were de-dusted and reweighed. The percentage friability was calculated.[16]

In vitro buoyancy studies:

The in vitro buoyancy was evaluated by measuring the floating lag time (FLT), following the method described by Rosa et al. Tablets were placed in a 250 ml beaker containing 200 ml of 0.1 N HCl. The time required for the tablet to rise to the surface and float was recorded as the Floating Lag Time (FLT), while the duration the tablet remained buoyant was recorded as the Total Floating Time (TFT).[17]

In vitro Dissolution Studies:

For the in vitro dissolution studies, a United States Pharmacopeia (USP) type II (paddle) apparatus was used, set to a rotational speed of 100 rpm. The dissolution medium consisted of 900 ml of 0.1 N HCl, maintained at a temperature of 37°C ± 0.5°C. At specified intervals over a 12-hour period, 10 ml samples were withdrawn from the dissolution apparatus and replaced with pre-warmed fresh dissolution medium. These samples were filtered

using Whatman filter paper, diluted to an appropriate concentration with 0.1 N HCl, and their absorbance was measured with a UV spectrophotometer.[18]

Drug Release Kinetics:

To establish the order and mechanism of drug release, dissolution data of the optimized batches were fitted to four different kinetics models, namely, zero order model, first order model, Higuchi model and Korsmeyer peppas model. The model for best it was predicted from the value of R^2. For an ideal it, value of R^2 was 1. Hence, the model which gives the R^2 values nearest to 1 describe the order drug release. Zero order drug release and followed Higuchi model describing drug release from polymeric matrix.[19,20]

Results & Discussion

FTIR Study of Pure Doxofylline

FTIR spectroscopy of doxofylline exhibited (**Fig:1**) characteristic absorption peaks that confirmed its molecular structure and functional group integrity. Distinct C–H stretching vibrations were observed at 2956.1 cm^{-1}, 2923.3 cm^{-1}, and 2852.4 cm^{-1}, indicating the presence of aliphatic methyl and methylene groups. A prominent sharp peak at 1732.4 cm^{-1} was attributed to carbonyl (C=O) stretching, confirming ester or lactone functionalities within the xanthine nucleus. Bending vibrations of CH_2 and CH_3 groups were observed at 1462.2 cm^{-1} and 1375.3 cm^{-1}, respectively. Several absorption bands in the region of 1240.3–1018.2 cm^{-1} correspond to C–O stretching vibrations, suggesting the presence of ether and alcohol linkages associated with the dioxolane ring. Additionally, a characteristic CH_2 rocking vibration at 720.4 cm^{-1} further confirmed the presence of aliphatic chains. Overall, the FTIR spectral data confirmed the identity and purity of doxofylline, indicating its suitability for formulation development and compatibility studies.

Pre compression study of Floating Tablet of Doxofylline

Pre-compression evaluation of the floating tablet formulations of doxofylline demonstrated (**Table:2**) acceptable flow and compressibility characteristics across all batches. Carr's Index(**Fig.2b**) values ranged between 9.8% and 15.8%, indicating excellent to good flow properties suitable for direct compression. The angle of repose(**Fig.2a**) values (22.5°–29.4°) confirmed good powder flow, with DXFT7 showing the most favourable result (22.5°). Hausner ratios(**Fig.2c**) varied from 1.09 to 1.19, further supporting the conclusion that the blends possessed adequate packing ability and minimal interparticle friction. Collectively, these parameters validate that the prepared blends were free-flowing and compressible, ensuring uniform die filling and consistent tablet weight during compression. Among the formulations, DXFT7 exhibited the best overall pre-compression characteristics, making it the most promising candidate for robust floating tablet development.

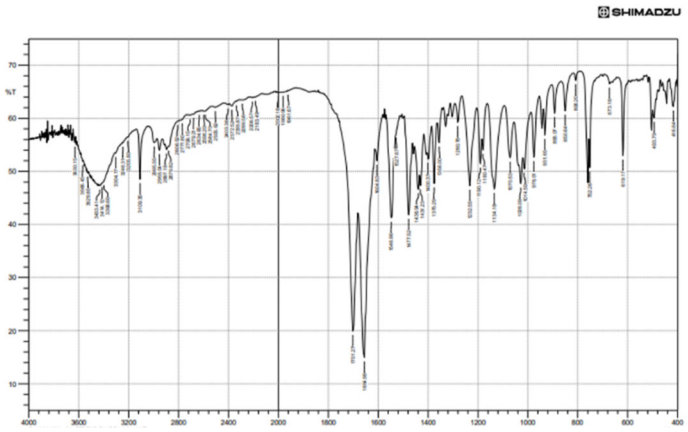

Figure No: 1 FTIR of Pure Doxofylline

Table No: 2 Pre compression Results of Floating Tablet of Doxofylline

Formulation	Carr's Index	Angle of Repose	Hausner Ratio
DXFT1	10.2	29.4º	1.13
DXFT2	15.7	28.4º	1.18
DXFT3	12.6	26.9º	1.16
DXFT4	11.7	27.5º	1.15
DXFT5	15.8	28.4º	1.15
DXFT6	11.8	26.9º	1.16
DXFT7	9.8	22.5º	1.09
DXFT8	12.3	25.4º	1.16
DXFT9	11.7	29.4º	1.19

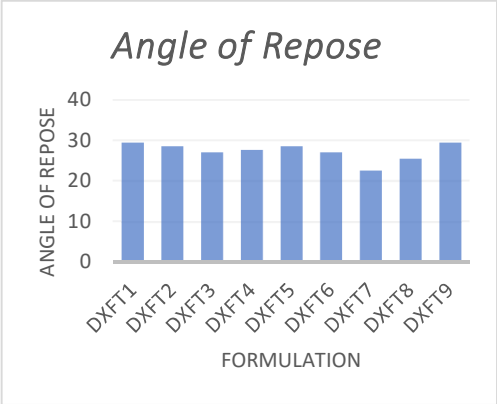

Figure No: 2a Angle of Repose

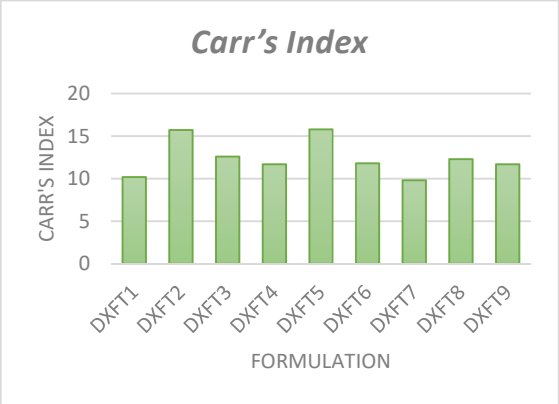

Figure No: 2b Carr's Index

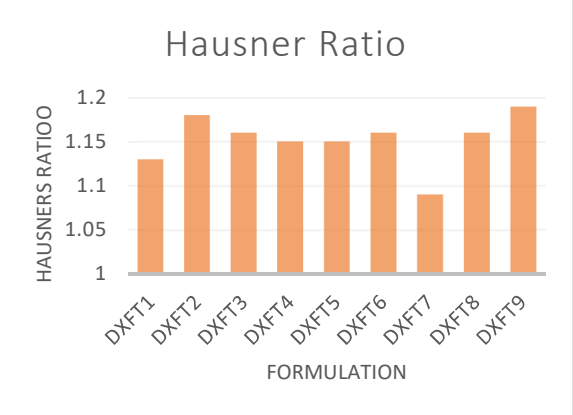

Figure No: 2c Hausner Ratio

Post Compression results of Doxofylline Floating Tablet

Post-compression evaluation of the floating tablets of doxofylline confirmed that all formulations complied (Table:3) with pharmacopeial limits for weight variation, hardness, friability, and drug content, ensuring their suitability for direct compression. Tablet weights(**Fig.3a**) remained consistent (699–702 mg), indicating uniform die filling. Hardness values(**Fig.3b**) ranged from 4.8–5.5 kg/cm², providing adequate mechanical strength for handling while maintaining matrix integrity for buoyancy. Friability values(**Fig.3c**) were below 1% (0.18–0.33%), demonstrating excellent resistance to abrasion. Drug content(**Fig.3d**)was within acceptable limits (95–105%) for most batches, with DXFT7 showing the highest assay (99.72%), while DXFT2 exhibited lower content (90.83%), suggesting blend uniformity issues. Overall, the results validate the robustness of the formulations, with DXFT7 emerging as the most promising batch due to its optimal balance of mechanical strength, low friability, and high drug content.

Table No:3 Post Compression results of Doxofylline Floating Tablet

Formulation	Weight variation(mg)	Hardness(kg/cm^2	Friability(%)	Drug content (%)
DXFT1	700	5.5	0.32	96.23
DXFT2	702	5.2	0.20	90.83
DXFT3	701	5.4	0.26	98.65
DXFT4	702	4.8	0.33	98.85
DXFT5	700	5.0	0.24	98.12
DXFT6	701	4.9	0.29	95.64
DXFT7	701	5.1	0.18	99.72
DXFT8	699	4.8	0.23	97.45
DXFT9	700	5.1	0.29	96.73

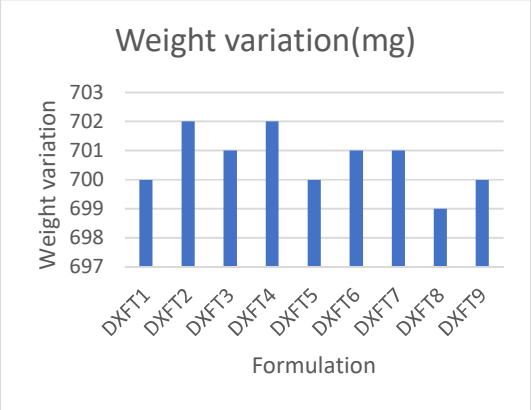

Figure No: 3a Weight variation(mg)

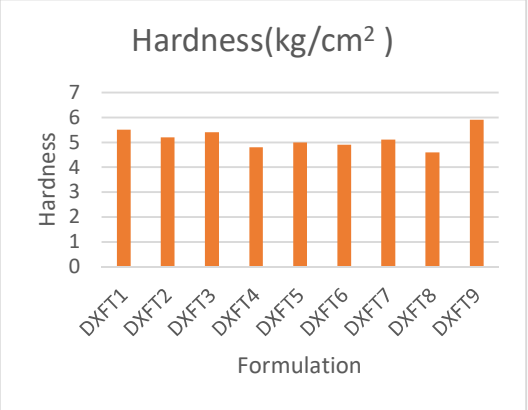

Figure No: 3b Hardness (kg/cm^2)

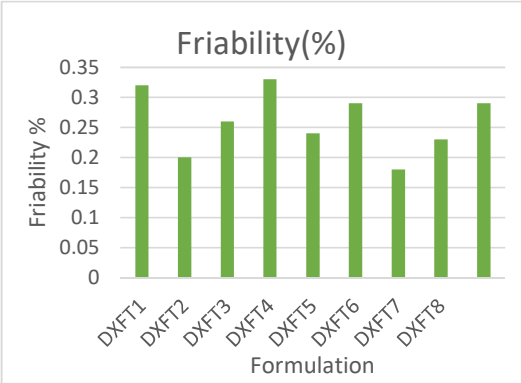

Figure No: 3c Friability (%)

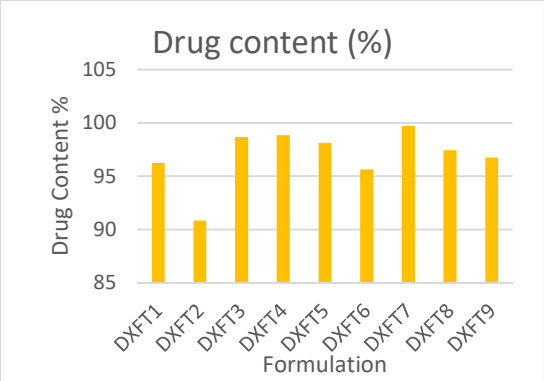

Figure No: 3d Drug content (%)

In-vitro buoyancy Results of Floating Tablets of Doxofylline

In vitro buoyancy tests of the floating doxofylline tablets showed that all of the formulations had longer gastric retention times, with total floating times of more than 12 hours (**Table :4**). This shows that the matrix system works to keep the tablets floating. The time it took for the floatation to start varied from 8 to 23 seconds, which shows that it happened quickly in most batches. DXFT7 had the shortest lag time (8 seconds), which means it trapped gas better and hydrated the matrix better. DXFT6 had the longest lag time (23 seconds), which means it released CO_2 more slowly or formed a gel more slowly. The other batches (DXFT1–5, DXFT8–9) had lag times of 10 to 14 seconds, which is fine for gastro retentive dosage forms. Overall, the results show that the tablets have the right buoyancy properties. DXFT7 is the most promising formulation because it has a short lag time and stays afloat for more than 12 hours.

Table No: 4 In-vitro buoyancy Results of Floating Tablets of Doxofylline

Formulation	Floating Lag time(seconds)	Total floating time (hours)
DXFT1	14	>12
DXFT2	13	>12
DXFT3	10	>12
DXFT4	14	>12
DXFT5	13	>12
DXFT6	23	>12
DXFT7	8	>12
DXFT8	11	>12
DXFT9	10	>12

Swelling Index % for Floating Tablets of Doxofylline

Swelling index studies of the floating tablets of doxofylline showed (**Table : 5**) that the polymeric system could form a gel over 12 hours by getting more hydrated and expanding the matrix. At 0 minutes, all formulations showed very little swelling, but this increased steadily over time. Moderate swelling (around 10–49%) was seen between 30 and 120 minutes, which showed that the gel layer was starting to form and the skin was getting hydrated. After 240–360

minutes, swelling indices went up a lot (52–71%), which helped keep the matrix strong and buoyant. The highest swelling was seen at 720 minutes, with values between 75% and 90%. This shows that the gel was able to hold water and stay strong. The swelling index for DXFT7 (90.12%) was the highest among the batches, which means it had better hydration and matrix stability. DXFT8, on the other hand, had a lower swelling index (75.11%). These results show that the formulations kept their structural integrity and swelling behavior, which are both important for long-term gastric retention. DXFT7 was the best candidate for controlled drug release and gastro-retentive performance.

Table No: 5 Swelling Index % for Floating Tablets of Doxofylline

Time (min)	**DXFT1**	**DXFT2**	**DXFT3**	**DXFT4**	**DXFT5**	**DXFT6**	**DXFT7**	**DXFT8**	**DXFT9**
0	0	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
30	10	10.22	10	12.11	12.11	12.11	9.14	9.18	10.27
60	21	22	21	24.77	24.77	24.77	15.24	16.24	18.24
90	34	36	34	38.11	38.11	38.11	21.33	22.33	28.33
120	47	48	47	49.01	49.01	49.01	32.11	36.11	39.11
240	52	54	52	65	65	65	47.11	49.11	51.11
360	67	68	67	71.33	71.33	71.33	51.33	53.33	58.33
540	72	76	72	82.11	82.11	82.11	62.11	42.11	67.11
720	81	83	82	86.31	86.31	86.31	90.12	75.11	79.11

In vitro Release Profile for Doxofylline Floating Tablets

In-vitro release studies of the floating tablets of doxofylline demonstrated (**Table: 6 & 7**) sustained drug release over 12 hours across all formulations, confirming the effectiveness of the polymeric matrix system in controlling release. For DXFT1–DXFT5, initial release at 0.5 h ranged between 10.22–16.12%, followed by a gradual increase to 92.31% (DXFT1), 89.31% (DXFT2), 90.13% (DXFT3), 89.74% (DXFT4), and 91.22% (DXFT5) at 12 h. These batches showed consistent release kinetics, with DXFT1 and DXFT5 achieving higher cumulative release, while DXFT2 and DXFT4 exhibited slightly slower profiles, likely due to polymer concentration differences.For DXFT6–DXFT9, release patterns also indicated sustained delivery, with initial release at 0.5 h ranging from 8.12% (DXFT6) to 22.57% (DXFT7). By 12 h, cumulative release reached 86.75% (DXFT6), 99.12% (DXFT7), 80.31% (DXFT8), and 91.22% (DXFT9). Among these, DXFT7 showed the most rapid onset and nearly complete release (99.12%), reflecting optimal polymer hydration and matrix erosion, while DXFT8 demonstrated comparatively slower release (80.31%), suggesting stronger gel barrier formation. Overall, all formulations maintained controlled release beyond 12 hours, with variations attributable to polymer type and concentration. DXFT7 emerged as the most promising batch, combining minimal lag time, high swelling index, and near-complete drug release, while DXFT1 and DXFT5 also showed favorable sustained profiles. These findings validate the floating matrix design for gastro-retentive delivery of doxofylline, ensuring prolonged gastric residence and controlled therapeutic release.

Table No: 6 In vitro Release Profile for Doxofylline Floating Tablets (DXFT1 to DXFT5)

Time	DXFT1	DXFT2	DXFT3	DXFT4	DXFT5
0	0	0	0	0	0
0.5	10.22	16.12	10.23	13.14	15.95
1	21.32	22.57	20.44	19.84	22.42
2	34.91	38.15	29.26	25.23	31.38
3	46.12	48.23	39.48	29.56	41.42
4	51.27	53.21	48.84	36.28	52.61
6	63.01	61.21	62.02	61.17	68.12
8	72.38	72.25	78.64	77.58	76.23
10	88.11	80.33	80.24	79.44	85.28
12	92.31	89.31	90.13	89.74	91.22

Table No: 7 In vitro Release Profile for Doxofylline Floating Tablets(DXFT6 to DXFT9)

Time	DXFT6	DXFT7	DXFT8	DXFT9
0	0	0	0	0
0.5	8.12	22.57	9.84	11.62
1	11.94	38.15	18.24	19.68
2	21.2	48.23	23.86	28.74
3	31.74	53.21	25.66	32.75
4	48.76	61.21	47.68	43.84
6	53.47	78.25	58.24	57.32
8	66.78	86.33	68.66	69.68
10	72.84	92.39	72.78	86.32
12	86.75	99.12	80.31	91.22

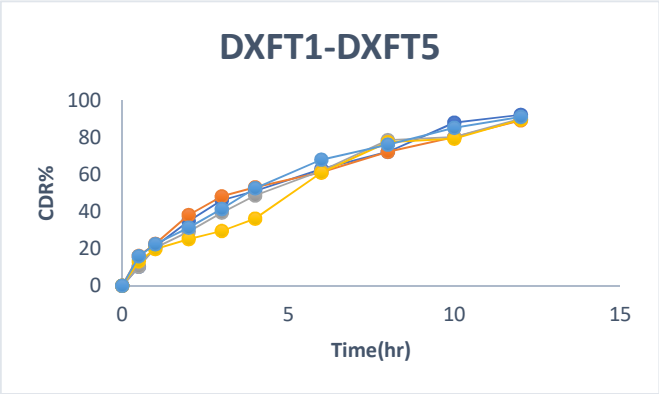

Figure No: 4a Drug Release of DXFT1-DXFT5

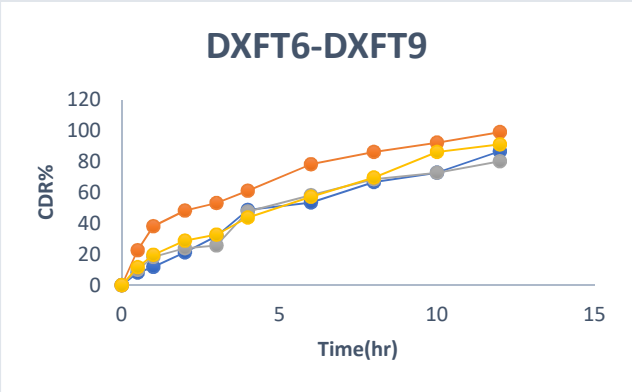

Figure No: 4b Drug Release of DXFT6-DXFT9

Release kinetics Study of Doxofylline Floating Tablets

Release kinetics analysis revealed that the floating tablets of doxofylline predominantly followed (**Table:8**) zero-order and diffusion-controlled release mechanisms. High correlation coefficients for zero-order kinetics (r^2 = 0.96–0.99) confirmed sustained, concentration-independent drug release, while good fitting to the Higuchi model (r^2 = 0.91–0.98) indicated diffusion through the hydrated polymeric matrix as a major release pathway. Excellent correlation with the Korsmeyer–Peppas model (r^2 ≈ 0.99 for most formulations) further suggested a combined mechanism of diffusion and polymer relaxation/erosion. Formulations DXFT1 and DXFT7 showed near-perfect zero-order release (r^2 = 0.99), whereas DXFT2 and DXFT8 exhibited greater diffusion- and concentration-dependent behavior. DXFT9 showed comparatively lower correlation with the Peppas model (r^2 = 0.90), indicating some variability in its release mechanism. Overall, DXFT7 emerged as the optimized formulation due to its consistent release behavior and excellent kinetic fit.

Table No: 8 Release kinetics Study of Doxofylline Floating Tablets

Formulationcode	r^2			
	Zero	First	Higuchi	Korsmeyer& Peppas
DXFT1	0.99	0.89	0.91	0.96
DXFT2	0.93	0.82	0.98	0.99
DXFT3	0.98	0.89	0.92	0.99
DXFT4	0.98	0.91	0.95	0.99
DXFT5	0.96	0.76	0.95	0.99
DXFT6	0.97	0.91	0.95	0.99
DXFT7	0.99	0.94	0.95	0.99
DXFT8	0.95	0.98	0.96	0.99
DXFT9	0.92	0.97	0.96	0.90

Conclusion

Floating tablets of doxofylline (DXFT1–DXFT9) were formulated using the direct compression method. Based on the outcomes of floating lag time and total floating time, HPMC K4M and xanthan gum were chosen for the creation of the optimized floating tablet, with HPMC K4M selected as the hydrophilic polymer that changes the rate of release, as previous studies have shown. We checked all of the prepared formulations for physicochemical properties like weight variation, hardness, friability, thickness, and drug content. They all met the standards set by the pharmacopeia. All batches had good floating properties, like floating lag time and total floating time. All formulations were tested for drug release in vitro in 0.1 N HCl. The batch that released the most drug over 12 hours was chosen for optimization. The kinetic analysis of drug release showed that most formulations had zero-order release behavior. Formulation DXFT7 performed the best of all the batches. It had the best drug content, a short floating lag time of about 10 seconds, and a maximum cumulative drug release of 99.12% after 12 hours.

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