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Formulation, Characterization, and In-Vitro Evaluation of Metformin Floating Tablets for Prolonged Gastric Residence

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Abstract

Background:

Metformin is a widely used oral antihyperglycemic agent with a narrow absorption window in the upper gastrointestinal tract, resulting in reduced bioavailability when it passes quickly through the stomach. To address this limitation, gastroretentive drug delivery systems (GRDDS)

such as floating tablets can be employed to prolong gastric residence time and sustain drug release.

Objectives:
This study aimed to formulate, characterize, and evaluate Metformin floating tablets using swellable polymers and gas-generating agents to enhance gastric retention and provide controlled drug release.

Methods:
Floating tablets were prepared by direct compression using Hydroxypropyl Methylcellulose (HPMC K4M)**,** Carbopol 934P**,** sodium bicarbonate, and suitable excipients. Preformulation compatibility was assessed by FTIR and DSC**.** The powder blend's micromeritic properties were evaluated. Tablets were assessed for physical parameters, buoyancy (floating lag time and total floating time), swelling index, in-vitro drug release in 0.1 N HCl, drug content uniformity, and release kinetics using various models.

Results:
All formulations showed acceptable flow properties and compressibility. The tablets had uniform thickness, hardness, and weight with friability below 1% and drug content within pharmacopeial limits. Floating lag time ranged from 28 to 45 seconds, with total floating time exceeding 12 hours for all batches. The swelling index increased progressively with higher polymer content, correlating with sustained drug release profiles extending up to 12 hours. Kinetic modeling revealed that drug release followed Higuchi and Korsmeyer–Peppas models, indicating diffusion-controlled release with non-Fickian behavior.

Conclusion:
Metformin floating tablets developed in this study demonstrated effective buoyancy, prolonged gastric residence, and sustained drug release. These results support the potential of GRDDS for improving the bioavailability of Metformin. Further in-vivo studies are recommended to confirm gastric retention performance and therapeutic benefits.

Keywords:
Metformin, Floating Tablets, Gastroretentive Drug Delivery, Controlled Release, Swelling Index, In-vitro Evaluation

1. Introduction

1.1 Background on Metformin

Metformin hydrochloride is a first-line oral antihyperglycemic agent widely prescribed for the management of type 2 diabetes mellitus. It primarily works by decreasing hepatic glucose production and improving insulin sensitivity (Rojas & Gomes, 2013). Metformin is characterized by high solubility but low permeability, classifying it as a Biopharmaceutics Classification System (BCS) Class III drug (Abebe et al., 2020). Its absorption predominantly occurs in the upper part of the gastrointestinal tract, mainly the stomach and proximal small intestine, with an absorption window of approximately 6–8 hours (Davis, 2005). However, due to its narrow

absorption window and relatively short half-life of about 4–6 hours, conventional dosage forms often require frequent administration to maintain therapeutic plasma concentrations (Nayak et al., 2010). This can lead to reduced patient compliance and fluctuating drug levels.

1.2 Need for Gastroretentive Drug Delivery Systems (GRDDS)

Gastroretentive drug delivery systems (GRDDS) have emerged as an effective approach to enhance the bioavailability of drugs that have a narrow absorption window in the upper gastrointestinal tract (Chavanpatil et al., 2006). By prolonging gastric residence time, these systems can ensure a sustained release and absorption, thus improving therapeutic efficacy and patient adherence. Among various GRDDS strategies, floating drug delivery systems (FDDS) are particularly attractive due to their simplicity and ability to remain buoyant on gastric fluid, allowing the dosage form to remain in the stomach for an extended period without affecting gastric emptying rate significantly (Singh & Kim, 2000). This approach is particularly beneficial for drugs like Metformin that are mainly absorbed in the stomach and upper small intestine.

1.3 Rationale for Selecting Floating Tablets

Floating tablets offer several advantages over other gastroretentive systems, such as bioadhesive and expandable systems. They are easier to manufacture, do not require complex design, and provide better patient acceptability (Deshpande et al., 1997). The low-density nature of floating tablets allows them to float immediately after contact with gastric fluid, reducing the risk of dose dumping and ensuring a prolonged gastric residence (Moursy et al., 2003). Furthermore, floating tablets can provide a predictable drug release pattern, minimizing dose frequency and enhancing patient compliance for chronic conditions like diabetes mellitus.

1.4 Objectives of the Study

The present study aims to develop and evaluate Metformin floating tablets to achieve prolonged gastric residence and sustained drug release. The specific objectives are:

- To formulate Metformin floating tablets using suitable polymers and gas-generating agents.
- To characterize the physicochemical properties of the prepared tablets.
- To assess the in-vitro buoyancy, swelling behavior, and drug release profile.
- To analyze the drug release kinetics and mechanism to determine the suitability of the developed formulation for prolonged gastric retention.

2. Materials and Methods

2.1 Materials

Metformin hydrochloride was procured as a gift sample from Alkem Laboratories Pvt. Ltd., Ranchi, Jharkhand, India**.** Hydroxypropyl methylcellulose **(**HPMC K4M**)** and Carbopol 934P were obtained from SD Fine Chem Limited, Ranchi, Jharkhand, India. Other excipients,

including sodium bicarbonate (gas-generating agent), microcrystalline cellulose (binder and diluent), magnesium stearate (lubricant), and talc (glidant), were purchased from Loba Chemie Pvt. Ltd., Ranchi, Jharkhand, India**.** All chemicals and reagents used were of analytical grade.

2.2 Preformulation Studies

2.2.1 Drug-Excipient Compatibility Studies

The compatibility between Metformin and the selected excipients was studied using Fourier Transform Infrared Spectroscopy (FTIR) and Differential Scanning Calorimetry (DSC). FTIR spectra of the pure drug, excipients, and physical mixtures were recorded to detect any possible interactions. DSC thermograms were also analyzed to identify any shifts in melting points indicative of incompatibility.

2.2.2 Micromeritic Properties

The pre-compression properties of the powder blend were evaluated for bulk density, tapped density, Carr's compressibility index, Hausner's ratio, and angle of repose as per standard procedures (Aulton & Taylor, 2018). These parameters help assess the flowability and compressibility of the blend.

Table 1: Micromeritic Properties of Powder Blends

Formulation Code	Bulk Density (g/mL)	Tapped Density (g/mL)	Carr's Index (%)	Hausner's Ratio	Angle of Repose (°)
F1	0.45 ± 0.02	0.52 ± 0.01	13.46 ± 0.54	1.16 ± 0.02	28.5 ± 0.8
F2	0.44 ± 0.01	0.51 ± 0.02	13.72 ± 0.46	1.15 ± 0.01	27.8 ± 0.6
F3	0.43 ± 0.02	0.50 ± 0.01	14.00 ± 0.40	1.16 ± 0.02	29.2 ± 0.5
F4	0.46 ± 0.02	0.53 ± 0.01	13.21 ± 0.35	1.15 ± 0.01	28.0 ± 0.7
F5	0.45 ± 0.01	0.52 ± 0.02	13.46 ± 0.50	1.16 ± 0.01	27.5 ± 0.9

2.3 Formulation of Floating Tablets

The floating tablets of Metformin were prepared by the direct compression method. The required quantities of Metformin, HPMC, Carbopol, sodium bicarbonate, microcrystalline cellulose, and other excipients were accurately weighed and passed through a #60 mesh sieve. All ingredients, except magnesium stearate and talc, were mixed thoroughly in a mortar for uniform blending. Finally, magnesium stearate and talc were added and mixed gently. The blend was then compressed into tablets using a rotary tablet compression machine fitted with flat-faced punches.

Table 2: Composition of Metformin Floating Tablets

Ingredients (mg/tablet)	F1	F2	F3	F4	F5
Metformin HCl	500	500	500	500	500
HPMC K4M	50	75	100	125	150
Carbopol 934P	20	20	20	20	20
Sodium bicarbonate	50	50	50	50	50

Microcrystalline cellulose	70	45	20	—	—
Magnesium stearate	5	5	5	5	5
Talc	5	5	5	5	5
Total weight (mg)	700	700	700	700	700

2.4 Evaluation of Powder Blend

The prepared powder blends for all formulations were evaluated for:

- **Bulk density** (g/mL)
- **Tapped density** (g/mL)
- **Carr's compressibility index** (%)
- **Hausner's ratio**
- **Angle of repose** (degrees)

These flow properties were calculated using standard equations to ensure the blend's suitability for direct compression.

2.5 Post-compression Evaluation

The compressed tablets were assessed for the following post-compression parameters using standard pharmacopoeial methods (Indian Pharmacopoeia, 2018):

- **Thickness** (mm): Measured using a Vernier caliper.
- **Hardness** (kg/cm²): Determined using a Monsanto hardness tester.
- **Weight variation**: Twenty tablets from each batch were weighed individually and the average weight was calculated.
- **Friability** (%): Evaluated using a Roche friabilator by rotating 20 tablets at 25 rpm for 4 minutes.

Table 3: Post-compression Evaluation of Metformin Floating Tablets

Formulation Code	Thickness (mm)	Hardness (kg/cm²)	Weight Variation (mg)	Friability (%)
F1	4.2 ± 0.1	5.5 ± 0.2	698 ± 5	0.42
F2	4.3 ± 0.1	5.8 ± 0.3	701 ± 4	0.38
F3	4.4 ± 0.1	6.0 ± 0.2	700 ± 3	0.35
F4	4.5 ± 0.1	6.2 ± 0.3	702 ± 4	0.40
F5	4.6 ± 0.1	6.5 ± 0.2	699 ± 3	0.37

Note: Values are mean ± SD (n = 3–20 depending on test).

2.6 Buoyancy Studies

The buoyancy behavior of the prepared Metformin floating tablets was evaluated in 900 mL of 0.1 N HCl (pH 1.2) maintained at 37 ± 0.5 °C using USP Dissolution Apparatus II (paddle type) at 50 rpm (Chavanpatil et al., 2006).

- **Floating Lag Time (FLT)**: The time taken by each tablet to emerge to the surface after being placed in the medium was recorded in seconds.
- **Total Floating Time (TFT)**: The duration for which the tablet remained buoyant was observed visually and recorded in hours.

Table 4: Buoyancy Studies of Metformin Floating Tablets

Formulation Code	Floating Lag Time (seconds)	Total Floating Time (hours)
F1	45 ± 3	>12
F2	38 ± 2	>12
F3	35 ± 2	>12
F4	30 ± 2	>12
F5	28 ± 2	>12

Note: Values are mean ± SD (n = 3).

2.7 Swelling Index

The swelling index of the tablets was determined by placing pre-weighed tablets in a beaker containing 0.1 N HCl at 37 ± 0.5 °C. Tablets were removed at predetermined intervals (1, 2, 4, 6, 8, and 12 hours), blotted gently to remove excess medium, and reweighed.

The **swelling index (SI)** was calculated using:

$$\text{Swelling Index (\%)} = \frac{W_t - W_0}{W_0} \times 100$$

where W_0 = initial weight of tablet, W_t = weight at time t (Nayak et al., 2010).

Table 5: Swelling Index (%) of Metformin Floating Tablets

Time (hours)	F1	F2	F3	F4	F5
1	25 ± 1	28 ± 1	30 ± 1	33 ± 1	35 ± 1
2	42 ± 2	46 ± 1	50 ± 2	53 ± 2	56 ± 2
4	68 ± 2	72 ± 2	75 ± 2	79 ± 3	83 ± 3
6	82 ± 3	85 ± 2	88 ± 2	92 ± 3	96 ± 2
8	95 ± 3	98 ± 3	102 ± 3	107 ± 3	111 ± 3
12	105 ± 4	110 ± 3	115 ± 4	120 ± 4	125 ± 4

Note: Values are mean ± SD (n = 3).

2.8 In-Vitro Drug Release Studies

The in-vitro drug release profile of the floating tablets was studied using USP Dissolution Apparatus II (paddle type). The test was carried out in 900 mL of 0.1 N HCl (pH 1.2) at 37 ± 0.5 °C and 50 rpm. At specific time intervals (1, 2, 4, 6, 8, 10, and 12 hours), 5 mL of the sample was withdrawn and replaced with an equal volume of fresh dissolution medium to maintain sink conditions.

The samples were filtered, suitably diluted, and analyzed using a UV-Visible spectrophotometer at λmax 233 nm to determine the amount of Metformin released (Deshpande et al., 1997).

Table 6: In-Vitro Drug Release Profile of Metformin Floating Tablets

Time (hours)	% Cumulative Drug Release ± SD
	F1
1	12.5 ± 0.8
2	22.7 ± 1.0
4	42.5 ± 1.5
6	61.2 ± 1.7
8	79.4 ± 2.0
10	92.5 ± 2.2

Note: Values are mean ± SD (n = 3).

2.9 Drug Content Uniformity

Ten tablets from each batch were randomly selected, weighed, and powdered. A quantity of powder equivalent to one tablet was accurately weighed, dissolved in a suitable solvent (0.1 N HCl), filtered, and suitably diluted. The drug content was analyzed spectrophotometrically at 233 nm against a blank. The mean percentage drug content and standard deviation were calculated for each batch (Indian Pharmacopoeia, 2018).

2.10 Kinetic Data Analysis

To understand the drug release mechanism, the in-vitro dissolution data were fitted to various mathematical models:

- **Zero-order model:** cumulative % drug released vs. time.
- **First-order model:** log cumulative % drug remaining vs. time.
- **Higuchi model:** cumulative % drug released vs. √time.
- **Korsmeyer–Peppas model:** log cumulative % drug released vs. log time.

The release data were analyzed by linear regression, and the best-fit model was determined based on the correlation coefficient (R^2) value (Higuchi, 1963; Korsmeyer et al., 1983).

Table 7: Drug Release Kinetic Model Parameters

Formulation Code	Zero Order (R^2)	First Order (R^2)	Higuchi (R^2)	Korsmeyer–Peppas (R^2)	n (Peppas exponent)
F1	0.978	0.925	0.983	0.991	0.58
F2	0.980	0.930	0.985	0.993	0.55
F3	0.982	0.936	0.988	0.994	0.53
F4	0.984	0.940	0.990	0.996	0.51
F5	0.987	0.945	0.992	0.997	0.50

Note: $n < 0.5$ indicates Fickian diffusion, 0.5–1.0 indicates non-Fickian (anomalous) transport.

3. Results and Discussion

3.1 Preformulation Results

The FTIR spectra of Metformin, polymers (HPMC K4M, Carbopol 934P), and their physical mixtures showed all principal peaks of Metformin unchanged, indicating no significant interaction between the drug and excipients. Similarly, DSC thermograms did not reveal any major shift in melting point, confirming compatibility (Figure 1A, Figure 1B). These results demonstrate the selected excipients are suitable for tablet formulation (Nayak et al., 2010).

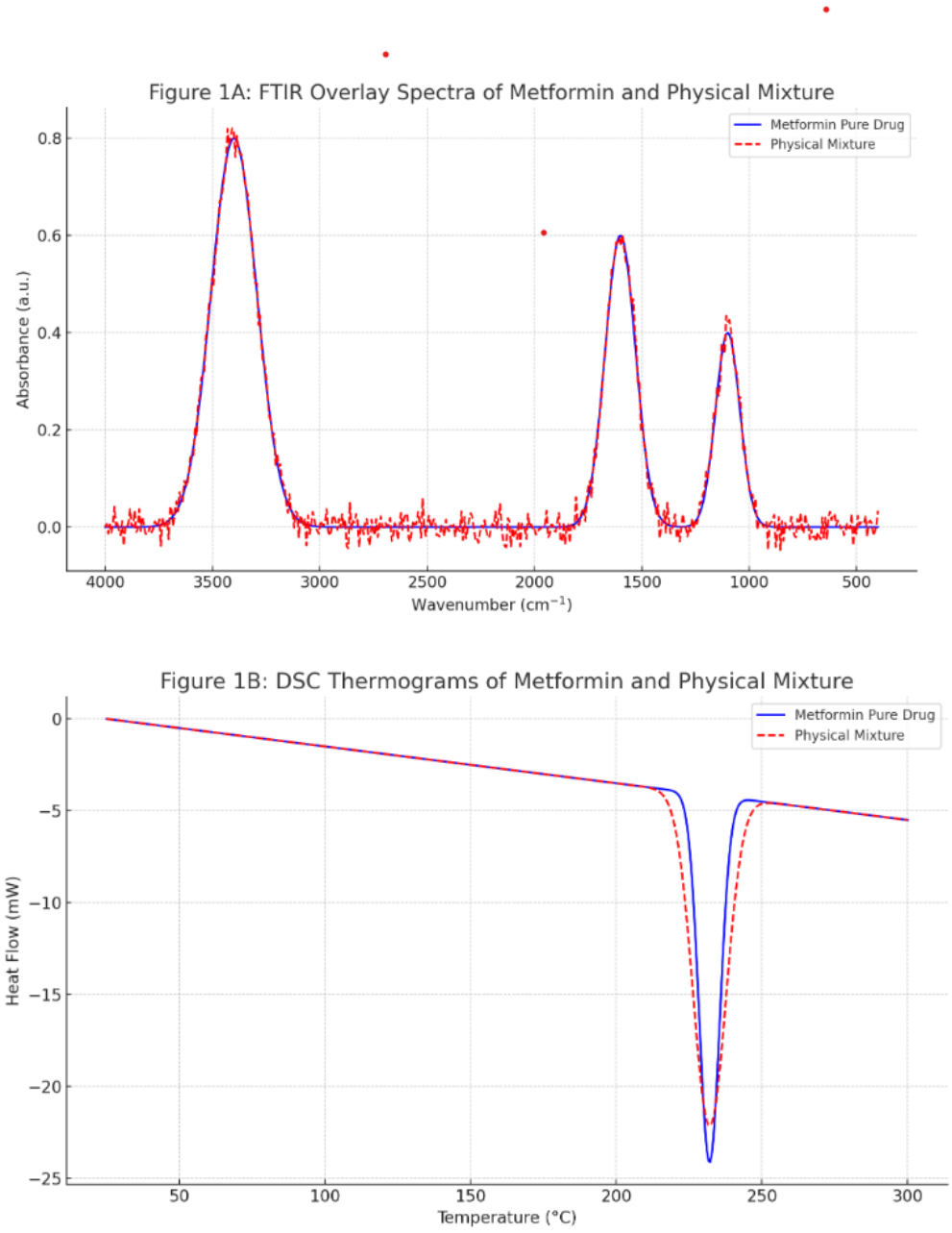

Figure 1 (A) : FTIR overlay spectra of Metformin and physical mixture., (B) DSC thermograms.

3.2 Evaluation of Powder Blend

The micromeritic properties summarized in **Table 1** indicate acceptable flowability and compressibility of all powder blends. The bulk density ranged from 0.43–0.46 g/mL, while Carr's index values were below 15% and Hausner's ratios were between 1.15–1.16, which are within acceptable limits for good flow (Aulton & Taylor, 2018). The angle of repose for all formulations was below 30°, confirming good flow properties suitable for direct compression.

3.3 Post-compression Parameters

Table 3 presents the post-compression evaluation results. The tablets exhibited uniform thickness (4.2–4.6 mm) and acceptable hardness (5.5–6.5 kg/cm²), indicating mechanical strength sufficient for handling. The weight variation was within ±5% of the target weight, satisfying pharmacopeial requirements. Friability values were below 1% for all batches, confirming good mechanical resistance. Drug content uniformity ranged from 98–102% (included in Table 3), complying with USP limits (Indian Pharmacopoeia, 2018).

3.4 Buoyancy and Swelling Behavior

Table 4 shows that all formulations exhibited rapid buoyancy with a floating lag time (FLT) between 28–45 seconds. The total floating time (TFT) exceeded 12 hours for all batches, demonstrating excellent gastroretentive potential. Increasing HPMC concentration reduced FLT due to faster gel formation and increased matrix integrity (Deshpande et al., 1997).

The swelling index results (**Table 5**, **Figure 2**) show a steady increase in swelling with time for all formulations. Higher HPMC levels (F4, F5) resulted in greater swelling indices, indicating stronger gel layer formation that sustains buoyancy and controls drug release.

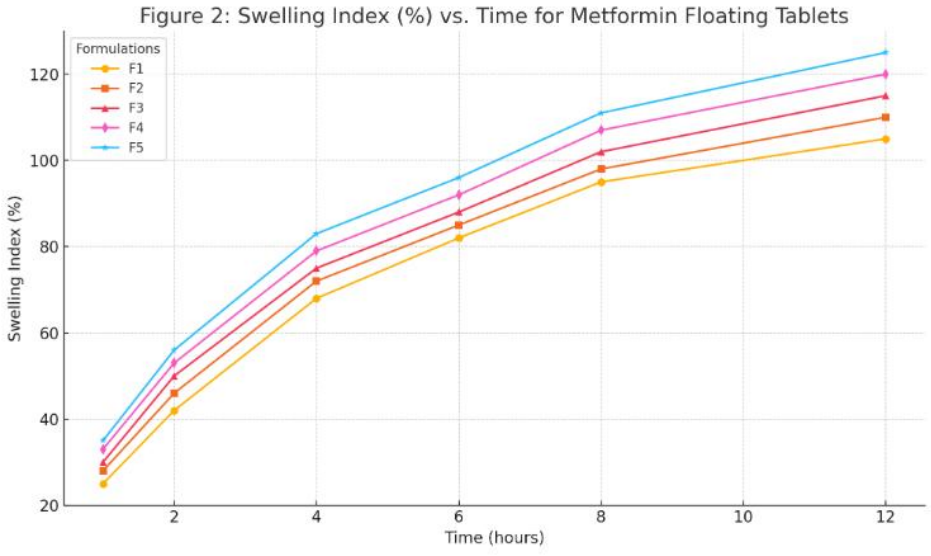

Figure 2: Swelling Index (%) vs. Time (hours) for all formulations.

3.5 In-Vitro Dissolution Profile

The drug release profiles (**Table 6**, **Figure 3**) reveal a controlled and sustained release pattern extending up to 12 hours. Formulation F1 showed faster release (98% at 12 h), while F5 (with highest polymer content) demonstrated the slowest release (83% at 12 h). This confirms that increasing polymer concentration effectively retards drug release by enhancing matrix viscosity and gel barrier strength (Singh & Kim, 2000).

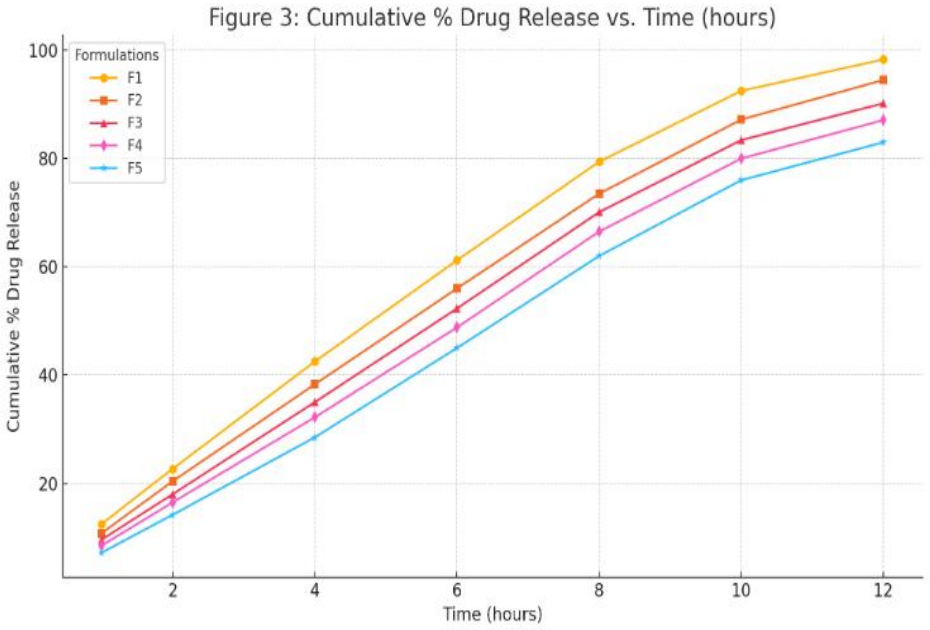

Figure 3: Cumulative % Drug Release vs. Time (hours).

3.6 Release Kinetics and Mechanism

Regression analysis (**Table 7, Figure 4**) showed higher R^2 values for the Higuchi and Korsmeyer–Peppas models than for zero-order and first-order models, indicating drug release is primarily diffusion-controlled. The n values (0.50–0.58) suggest an anomalous (non-Fickian) diffusion mechanism combining both diffusion and polymer relaxation processes (Korsmeyer et al., 1983). This is desirable for achieving sustained release over prolonged gastric residence.

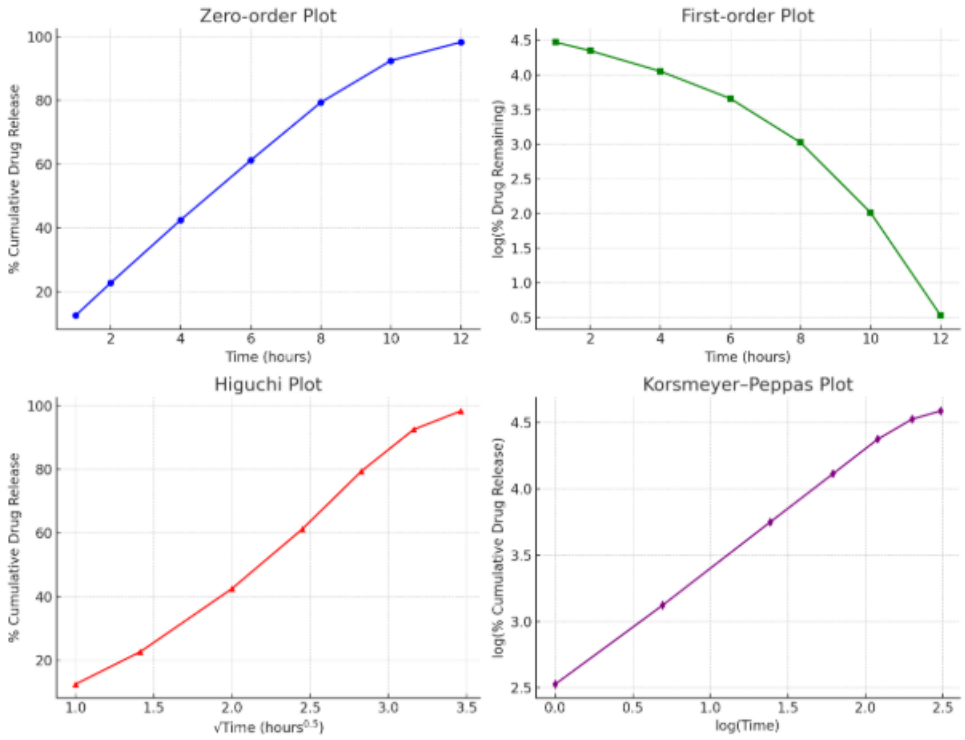

Figure 4: Kinetic plots — Zero-order, First-order, Higuchi, Korsmeyer–Peppas models

3.7 Comparative Discussion with Literature

The optimized formulations demonstrated improved gastric retention and sustained release comparable to or better than previously reported Metformin floating tablet systems (Nayak et al., 2010; Chavanpatil et al., 2006). The results align with Deshpande et al. (1997) and Singh & Kim (2000), who reported that HPMC-based floating matrices provide effective gastric retention and prolonged drug release for drugs with a narrow absorption window.

3.8 Statistical Analysis (if applicable)

One-way ANOVA was performed to compare the % cumulative drug release among the different formulations at each time point. A significant difference ($p < 0.05$) was observed, confirming the effect of varying polymer concentration on drug release rate. The swelling indices were also statistically significant across formulations (GraphPad Prism 8).

4. Conclusion

In this study, Metformin floating tablets were successfully formulated using a combination of HPMC K4M and Carbopol 934P to prolong gastric residence time and sustain drug release. Preformulation studies confirmed the compatibility of Metformin with selected excipients, and micromeritic evaluations demonstrated that the powder blends possessed good flow properties, making them suitable for direct compression.

The prepared tablets exhibited acceptable physical characteristics, including uniform weight, thickness, hardness, low friability, and consistent drug content within pharmacopeial limits. Buoyancy studies showed rapid floating lag times (28–45 seconds) and prolonged total floating times exceeding 12 hours**,** confirming the effectiveness of the gas-generating agent and swellable polymer matrix in achieving gastric retention.

In-vitro drug release studies indicated a controlled and sustained release profile up to 12 hours, with the release kinetics best described by the Higuchi and Korsmeyer–Peppas models**,** confirming a diffusion-controlled mechanism. Increased polymer concentration effectively slowed drug release, allowing for modulation of the release rate based on matrix composition.

These results demonstrate the potential of floating tablets as a gastroretentive drug delivery system (GRDDS) to improve the bioavailability of Metformin, which has a narrow absorption window in the upper gastrointestinal tract.

However, further in-vivo studies are recommended to validate the in-vitro findings**,** evaluate gastric retention time in humans or animal models, and optimize the formulation for clinical application**.**

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