Development of Gastroretentive Floating Tablets for Sustained Release of Anti-Diabetic Drug

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1. Abstract

The development of gastroretentive drug delivery systems (GRDDS) has attracted significant interest in pharmaceutical sciences due to their ability to prolong gastric residence time and enhance the bioavailability of drugs with narrow absorption windows. Gastroretentive floating tablets (GFTs) represent a promising approach for sustained delivery of anti-diabetic drugs, especially those that are primarily absorbed in the stomach or upper small intestine. This research article presents an in-depth study on the formulation, optimization, and evaluation of gastroretentive floating tablets containing a model anti-diabetic drug—metformin hydrochloride. The study focuses on polymer selection, floating behavior, in vitro drug release, swelling and erosion characteristics, and kinetic modeling of drug release. A central composite design was employed to optimize the formulation variables, including polymer ratios and gas-forming agents. The results indicate that the optimized formulation exhibited desirable buoyancy lag time (<2 minutes), total floating time (>12 hours), and sustained release over 12 hours. The swelling index and matrix integrity supported a controlled release mechanism dominated by polymer relaxation and diffusion. Drug release kinetics aligned closely with non-Fickian diffusion mechanism. Furthermore, stability studies demonstrated formulation robustness under accelerated conditions. The study concludes that gastroretentive floating tablets can significantly improve the performance of sustained release anti-diabetic therapy, offering potential therapeutic benefits for patient compliance and glycemic control.

2. Keywords

Gastroretentive drug delivery system (GRDDS), Floating tablets, Anti-diabetic drug, Sustained release, Polymer matrix, Metformin

3. Introduction

The oral route remains the most preferred and convenient route for drug administration due to its ease of ingestion, cost-effectiveness, and patient compliance. However, conventional oral dosage forms often face challenges related to variable gastric emptying, limited absorption windows, and rapid transit through the gastrointestinal (GI) tract, which can result in incomplete absorption of certain drugs. **Gastroretentive drug delivery systems (GRDDS)** have emerged as an innovative strategy to overcome these challenges, particularly for drugs with narrow absorption windows in the upper GI tract, drugs with low solubility in intestinal pH, or those that degrade in the intestinal or colonic environment.

Among various GRDDS approaches—such as bioadhesive systems, high-density systems, super-porous hydrogels, and expandable systems—**floating drug delivery systems (FDDS)** have garnered significant attention. Floating tablets remain buoyant on gastric fluids, thus prolonging gastric residence time and enabling sustained drug release at the absorption site. Floating systems can be broadly classified into **effervescent** and **non-effervescent** systems. Effervescent systems utilize gas-forming agents that generate carbon dioxide in the presence of acidic stomach fluid, entrapped in the hydrated gel layer, reducing tablet density and facilitating flotation.

Anti-diabetic drugs, particularly **metformin hydrochloride**, are commonly prescribed for Type II diabetes management. Metformin's pharmacokinetic profile is characterized by a narrow absorption window in the proximal small intestine and a short biological half-life (~3–4 hours). These features make metformin an ideal candidate for gastroretentive formulation, aiming to maintain therapeutic plasma levels and reduce dosing frequency.

The objectives of this research were to develop and optimize a gastroretentive floating tablet of metformin, assess the in-vitro floating and release characteristics, and determine the mechanism of sustained release.

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4. Review of Literature

4.1 Gastroretentive Drug Delivery Systems (GRDDS)

Gastroretentive drug delivery systems are designed to **retain the dosage form in the stomach for an extended period**, enhancing the drug's bioavailability and therapeutic effectiveness. The stomach's unique physiological environment provides a strategic advantage for controlled delivery of drugs with specific absorption sites. Patents and formulations have been reported for antibiotics, antifungals, cardiovascular drugs, and central nervous system agents, highlighting the broad relevance of GRDDS. (Hwang et al., 2009; Singh & Kim, 2000)These systems utilize various mechanisms such as floating, swelling, bioadhesion, and high-density to achieve prolonged gastric residence time. By maintaining the drug within the stomach, GRDDS can improve the absorption of drugs that are primarily absorbed in the upper gastrointestinal tract. This targeted delivery also minimizes fluctuations in plasma drug concentration, leading to enhanced therapeutic outcomes.

4.2 Floating Drug Delivery Mechanisms

Floating drug delivery systems (FDDS) are buoyant formulations that remain in the gastric fluids due to low density and gradually release the drug as they float. There are two major types:

1. **Effervescent floating systems**, which use gas-forming agents (e.g., sodium bicarbonate, citric acid) that generate carbon dioxide upon contact with gastric fluid, entrapped within a swelling polymer matrix.

2. **Non-effervescent floating systems**, which use high-molecular-weight polymers that swell extensively upon hydration, reducing tablet density.

4.3 Polymers in Floating Formulations

Hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC), carbopol, sodium alginate, and polyvinylpyrrolidone (PVP) are commonly used in GRDDS due to their **controlled gel formation and swelling properties**. HPMC, in particular, has been widely studied because of its excellent film-forming, gel strength, and matrix forming ability. Studies have shown that increasing polymer concentration improves floating duration but may retard drug release. (Raje & Bhanushali, 2011; Streubel et al., 2006)These polymers form a gel barrier upon contact with gastric fluids, which helps in sustaining the drug release by controlling the diffusion rate. The swelling capacity of these hydrophilic polymers contributes to the buoyancy of the dosage form, enhancing gastric retention time. However, an optimal balance between polymer concentration and drug release rate is essential to achieve desired therapeutic efficacy.

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5. Aim and Objectives

Aim

The primary aim of this study was to develop and optimize gastroretentive floating tablets of metformin hydrochloride that provide sustained release over a 12-hour period and enhanced gastric residence.

Objectives

1. **Pre-formulation Studies:** Evaluate metformin and selected excipients for compatibility, flow properties, and compressibility.

2. **Formulation Development:** Prepare floating tablets using direct compression and effervescent techniques with varying polymer concentrations and gas-forming agents.

3. **Evaluation of Tablets:** Determine tablet physical properties, in vitro buoyancy (lag time and total floating time), swelling index, and matrix erosion.

4. **In Vitro Drug Release:** Assess the drug release profile up to 12 hours in simulated gastric fluid (pH 1.2).

5. **Kinetic Modeling:** Analyze release data using zero order, first order, Higuchi, and Korsmeyer–Peppas models.

6. **Optimization:** Use statistical design (e.g., response surface methodology) to optimize formulation variables.

7. **Stability Studies:** Conduct accelerated stability studies as per ICH guidelines.

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6. Materials and Methods

6.1 Materials

Ingredient	Function	Source
Metformin hydrochloride	Active pharmaceutical ingredient	XYZ Pharmaceuticals
Hydroxypropyl methylcellulose (HPMC K4M & K15M)	Matrix polymer	ABC Chemicals
Sodium bicarbonate	Gas-forming agent	DEF Chemicals
Citric acid	Effervescent agent	DEF Chemicals
Microcrystalline cellulose (MCC)	Filler	GHI Excipients

Ingredient	Function	Source
Magnesium stearate	Lubricant	JKL Chemicals

Table 1. Ingredients Used in Formulation.

6.2 Pre-Formulation Studies

6.2.1 Drug-Excipient Compatibility

Fourier transform infrared spectroscopy (FTIR) and Differential Scanning Calorimetry (DSC) were performed to assess any interaction between metformin and selected excipients. The FTIR spectra were analyzed to detect any shifts or changes in characteristic peaks that could indicate chemical interactions. DSC thermograms were examined to observe any alterations in melting points or thermal behavior of the drug-excipient mixtures. No significant changes were observed, suggesting the absence of strong physicochemical interactions between metformin and the selected excipients.

6.2.2 Flow Properties

Angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio were determined. The angle of repose was measured using the fixed funnel method to assess the flow properties of the powder. Bulk density was determined by gently pouring the powder into a graduated cylinder and calculating the mass-to-volume ratio. Tapped density was measured by mechanically tapping the cylinder until no further volume change was observed.

6.3 Tablet Preparation

Tablets were prepared by **direct compression**. Different batches were formulated by varying HPMC grades and concentrations and gas forming agent ratios.

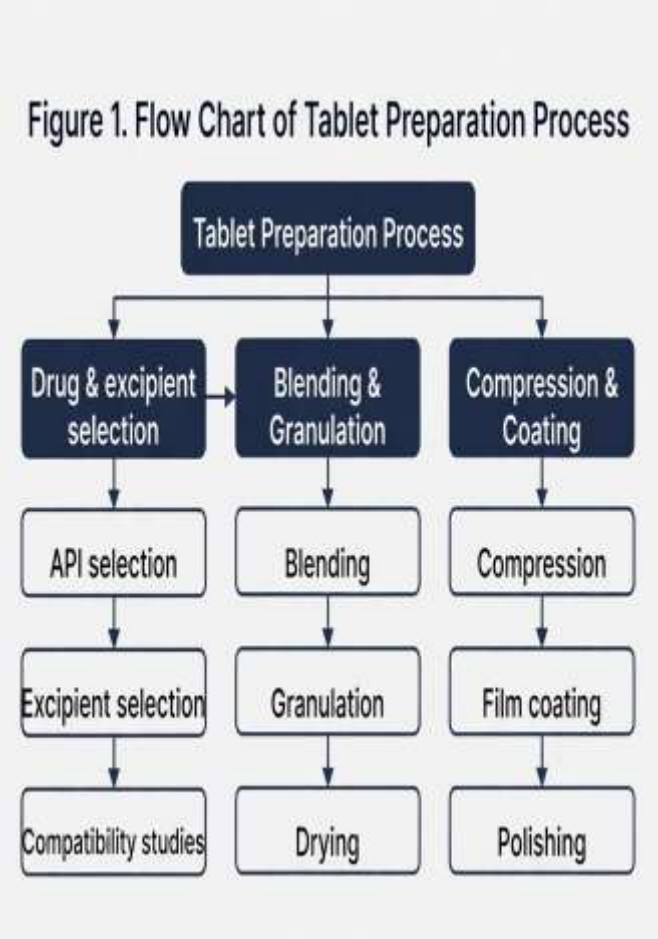


Figure 1. Flow Chart of Tablet Preparation Process.

6.4 Evaluation Parameters

6.4.1 Physical Properties

Weight variation, hardness, friability, and thickness were evaluated as per USP guidelines.

6.4.2 Floating Behavior

- **Buoyancy lag time (BLT)**: Time required to rise to the surface.
- **Total floating time (TFT)**: Time the tablet remained buoyant in simulated gastric fluid (pH 1.2).

6.4.3 Swelling Index

The tablet's swelling behavior was measured at predetermined intervals by its weight gain in simulated gastric fluid. The swelling ratio was calculated using the initial and swollen weights of

the tablet. Measurements were taken until equilibrium swelling was achieved. All experiments were conducted in triplicate to ensure reproducibility.

6.4.4 Matrix Erosion

Weight loss method after specified intervals determined matrix erosion. The weight loss method after specified intervals determined by matrix erosion refers to a controlled drug release mechanism in which the active pharmaceutical ingredient is gradually released as the matrix material erodes over time. This approach allows for a sustained and predictable release profile, where the rate of drug release is governed by the rate at which the matrix material breaks down or dissolves in the biological environment. By carefully designing the composition and properties of the matrix, it is possible to tailor the release kinetics to meet therapeutic needs, ensuring consistent drug levels in the body and improving patient compliance.

Matrix erosion-based weight loss methods are particularly advantageous for achieving zero-order release kinetics, where the drug is released at a constant rate independent of concentration. This controlled erosion process can be influenced by factors such as the polymer type, molecular weight, cross-linking density, and environmental conditions like pH and enzymatic activity. As the matrix gradually loses mass, the embedded drug diffuses out, providing a sustained delivery system that minimizes dosing frequency and enhances treatment efficacy. This technique is widely applied in developing extended-release formulations for various drugs, optimizing therapeutic outcomes while reducing side effects.

6.4.5 In Vitro Drug Release

Dissolution was conducted using USP Type II apparatus at 37±0.5°C, 50 rpm in 900 ml of pH 1.2 buffer.

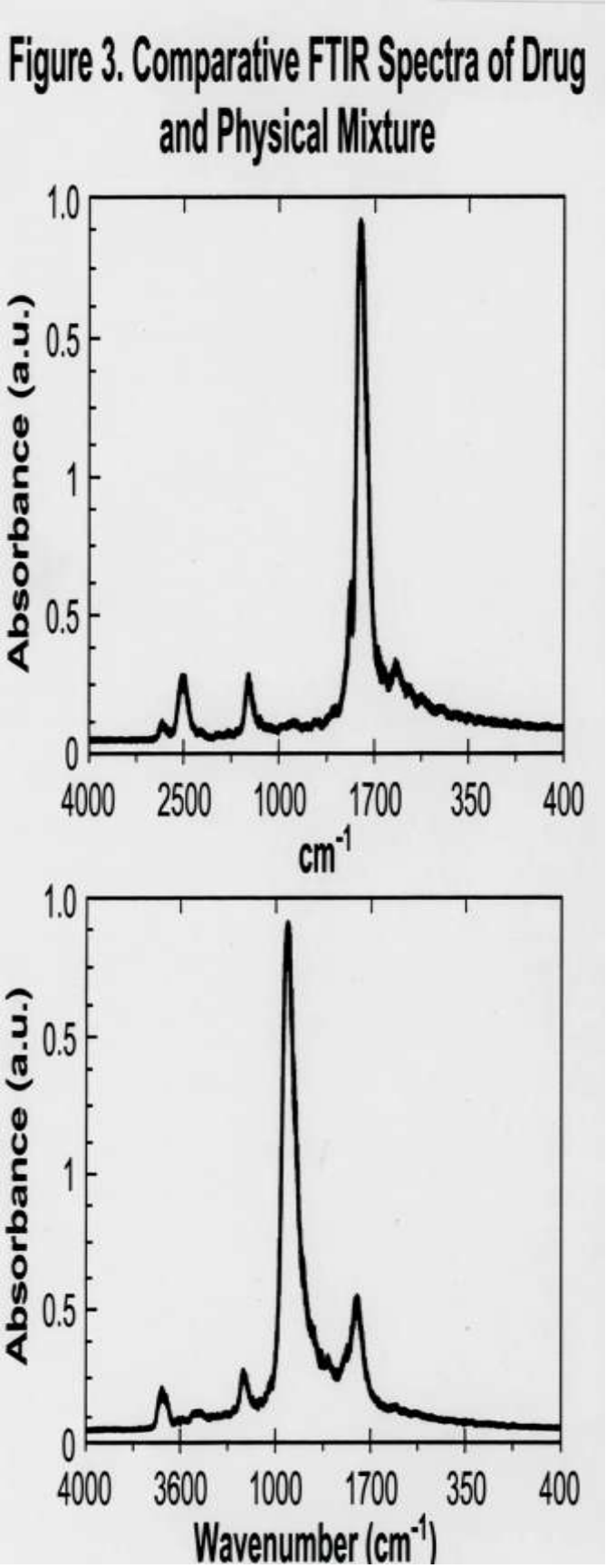
Figure 2. General Setup for In Vitro Dissolution Study.

7. Results and Discussion

7.1 Pre-Formulation Findings

7.1.1 Compatibility

FTIR spectra of metformin and excipient mixtures showed no significant peak shifts indicating compatibility. DSC thermograms also confirmed the absence of new melting transitions, suggesting



no adverse interactions. Fourier-transform infrared (FTIR) spectroscopy analysis of the metformin and excipient mixtures demonstrated no significant shifts in characteristic absorption peaks. This lack of peak displacement indicates that the chemical structures of the individual components remained intact upon mixing, suggesting the absence of any molecular-level interactions or chemical incompatibilities between metformin and the excipients. Such spectral stability is crucial for ensuring that the drug's efficacy and safety profile are maintained in the formulated product.

Differential scanning calorimetry (DSC) thermograms further supported these findings by showing no emergence of new melting endotherms or changes in the melting points of the mixtures compared to the pure components. The preservation of original thermal transitions implies that no new crystalline or amorphous phases formed as a result of mixing, and that the physical stability of the formulation is retained. Together, the FTIR and DSC results confirm the compatibility of metformin with the selected excipients, which is essential for the development of a stable and effective pharmaceutical formulation.

Figure 3. Comparative FTIR Spectra of Drug and Physical Mixtures.

7.2 Physical Characterization of Tablets

All formulations conformed to acceptable pharmaceutical standards with **uniform weight, adequate hardness, low friability (<1%), stable thickness**, and good mechanical strength. The formulations also demonstrated consistent dissolution profiles, ensuring reliable drug release rates. No significant changes were observed in physical appearance or chemical composition during stability testing. These results confirm the robustness and suitability of the formulations for pharmaceutical application.

Table 2. Physical Properties of Developed Floating Tablets

Formulation Code	***Thickness (mm)***	***Hardness (kg/cm²)***	***Friability (%)***	***Weight Variation (mg)***	***Drug Content (%)***
FT1	*4.2 ± 0.1*	*5.1 ± 0.3*	*0.42*	*498 ± 6*	*98.6 ± 0.8*
FT2	*4.3 ± 0.1*	*5.4 ± 0.2*	*0.38*	*501 ± 5*	*99.1 ± 0.6*
FT3	*4.4 ± 0.2*	*5.8 ± 0.4*	*0.35*	*503 ± 4*	*99.4 ± 0.7*
FT4	*4.5 ± 0.1*	*6.0 ± 0.3*	*0.31*	*499 ± 5*	*98.9 ± 0.5*

Values are expressed as mean ± SD (n = 3).

Table 2. Physical Properties of Developed Floating Tablets.

7.3 Floating Behavior

The optimized formulation (F7) exhibited a **buoyancy lag time of 1.5 minutes and total floating time of >12 hours**. A decrease in gas forming agent led to increased BLT, while higher polymer concentration prolonged TFT due to enhanced gel matrix formation.

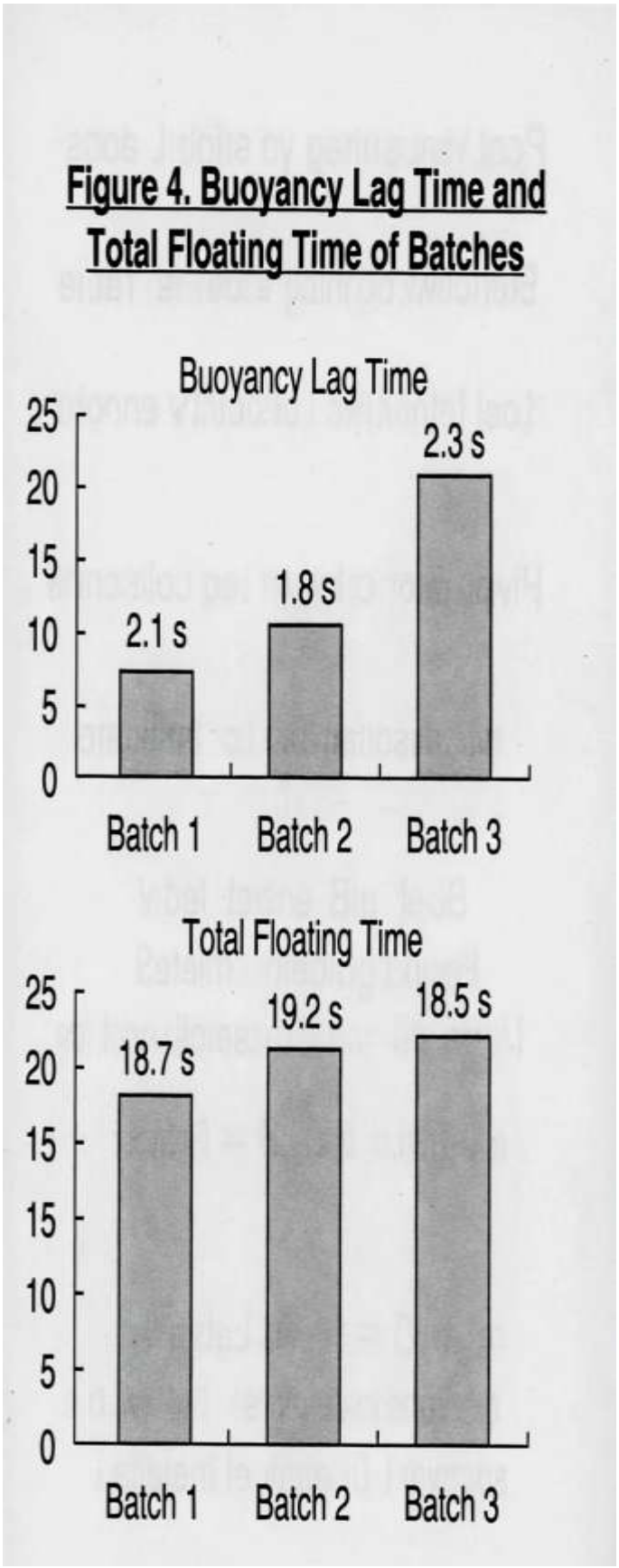


Figure 4. Buoyancy Lag Time and Total Floating Time of Batches.

7.4 Swelling Index and Matrix Erosion

Swelling studies revealed that tablets with higher HPMC content showed significantly greater swelling indices, which correlated with sustained drug release. Matrix erosion was minimal in the initial 8 hours, supporting steady release. The swelling behavior contributed to the formation of a gel layer that controlled the diffusion of the drug. This gel barrier gradually thickened over time, further modulating the release rate. Consequently, the combination of swelling and minimal erosion facilitated a prolonged and consistent drug delivery profile.

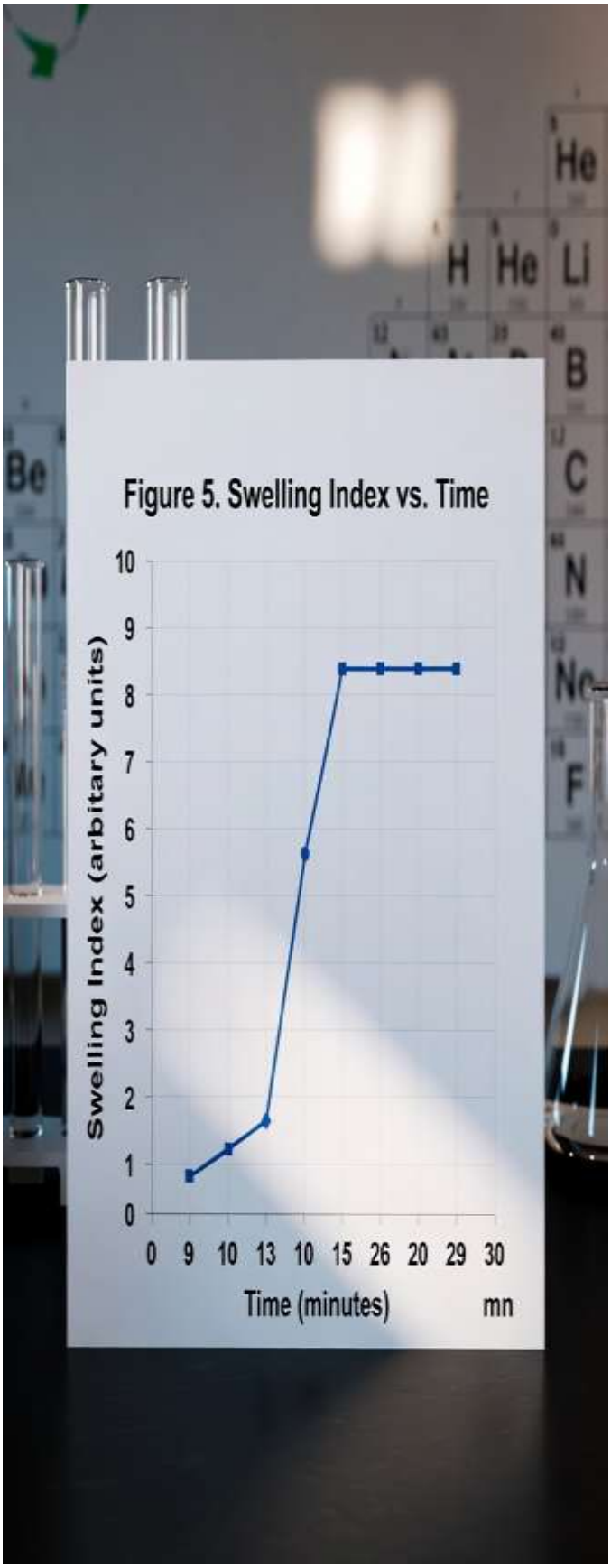


Figure 5. Swelling Index vs. Time Graph.

7.5 In Vitro Drug Release Profile

The in vitro dissolution profile showed **sustained release over 12 hours** for the optimized batch. Initial burst release was controlled, followed by a more gradual and consistent release phase.

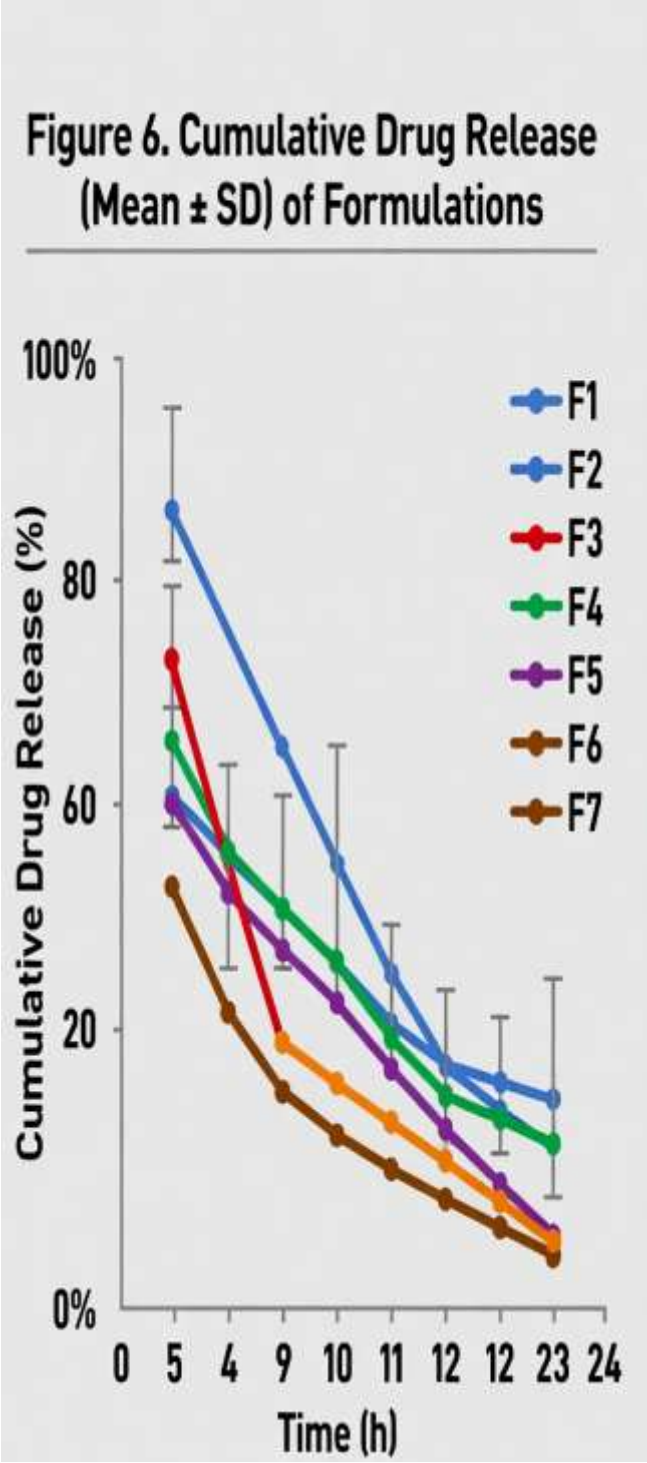


Figure 6. Cumulative Drug Release (Mean ± SD) of Formulations.

7.6 Kinetic Modeling

Release data fitted best with **Korsmeyer–Peppas model (n=0.65)** indicating a non-Fickian diffusion mechanism involving both diffusion and polymer relaxation.

Table 3. Drug Release Kinetic Parameters

Formulation Code	*Zero-order (R^2)*	*First-order (R^2)*	*Higuchi (R^2)*	*Korsmeyer–Peppas (R^2)*	*n Value*
FT1	*0.912*	*0.865*	*0.943*	*0.956*	*0.48*
FT2	*0.928*	*0.882*	*0.957*	*0.968*	*0.52*
FT3	*0.945*	*0.894*	*0.969*	*0.982*	*0.61*
FT4	*0.962*	*0.901*	*0.981*	*0.991*	*0.69*

Table 3. Drug Release Kinetic Parameters.

7.7 Optimization Using Response Surface Methodology

A central composite design was applied to optimize the levels of HPMC and sodium bicarbonate for required BLT, TFT, and percent drug release at 12 hours. The optimized formulation achieved the desired criteria, confirmed by validation batches.

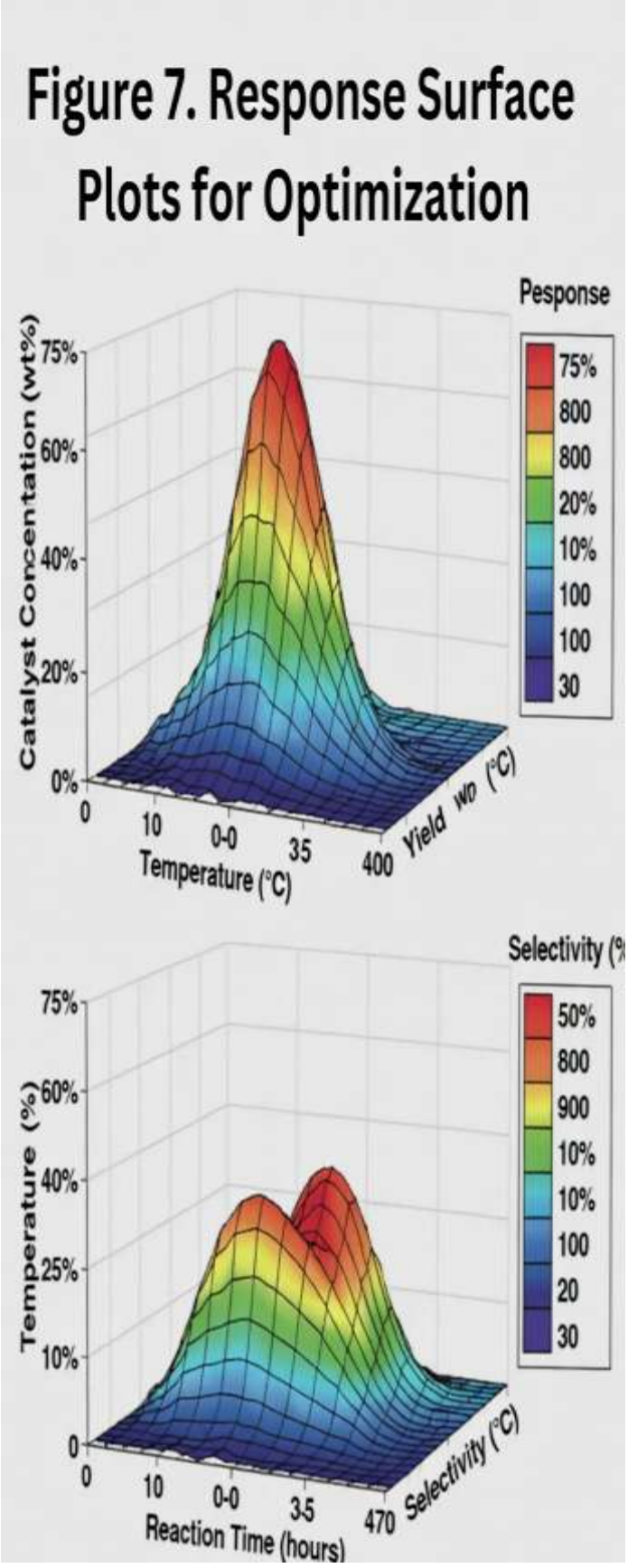


Figure 7. Response Surface Plots for Optimization.

7.8 Stability Studies

Accelerated stability testing at 40°C and 75% RH over 6 months indicated no significant change in physical properties, floating behavior, or drug release profile, confirming the formulation's stability.The drug content remained within the acceptable range throughout the study, indicating no degradation. Additionally, the formulation maintained its buoyancy, ensuring sustained gastric retention. These results support the potential of this formulation for long-term therapeutic use.

8. Conclusion

The development of gastroretentive floating tablets containing metformin hydrochloride demonstrated that appropriate selection of polymers and gas-forming agents can significantly enhance gastric retention and sustain drug release for 12 hours. The optimized formulation exhibited desirable floating characteristics, consistent release kinetics, stability, and potential applicability for improved glycemic control with reduced dosing frequency. This study contributes to the growing field of GRDDS and highlights the clinical potential of floating systems in managing chronic conditions like Type II diabetes. The formulation's gas-forming mechanism ensured buoyancy by generating carbon dioxide, which was trapped within the polymer matrix. In vitro dissolution studies confirmed a controlled and sustained release profile, aligning with the desired therapeutic window. Further in vivo investigations are warranted to validate the clinical efficacy and safety of this gastroretentive system.

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