"Development and Evaluation of Gastroretentive Drug Delivery System for Quercetin: A Novel Approach for Enhancing Efficacy in Antidiabetic Therapy"

Vaibhav K. Khatal, Meena K. Jagtap* (Associate Professor)

Satara College of Pharmacy, Satara.

Abstract

Diabetes mellitus is a chronic metabolic disorder that requires effective long-term management strategies. Quercetin, a natural flavonoid with strong antioxidant and antidiabetic properties, suffers from poor solubility, low oral bioavailability, and rapid metabolism, limiting its therapeutic potential. To overcome these challenges, a gastroretentive drug delivery system (GRDDS) of quercetin was developed and evaluated. Floating matrix tablets were prepared using different grades and concentrations of hydroxypropyl methylcellulose (HPMC K4M and K100M) along with sodium bicarbonate as a gas-generating agent. The formulations were assessed for physicochemical properties, floating behavior, swelling index, drug content, and in vitro drug release kinetics. Results showed that optimized formulations achieved a floating lag time of less than 10 minutes and sustained buoyancy for up to 12 hours, ensuring prolonged gastric residence. Among the developed batches, formulations containing HPMC K4M demonstrated controlled and extended drug release following zero-order kinetics, with swelling contributing significantly to the release mechanism as per Korsmeyer-Peppas analysis. The optimized system successfully addressed quercetin's bioavailability limitations, potentially enhancing its antidiabetic efficacy by maintaining steady plasma concentrations and improving patient compliance. This study highlights GRDDS as a promising strategy for effective delivery of quercetin and similar bioactive compounds with absorption challenges.

Keywords

Quercetin; Gastroretentive drug delivery system (GRDDS); Floating matrix tablets; Antidiabetic therapy; Bioavailability enhancement; HPMC (Hydroxypropyl methylcellulose); Sodium bicarbonate; Sustained release.

Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from impaired insulin secretion, insulin resistance, or both. It has emerged as a major global health challenge, with approximately 537 million adults affected worldwide, a number projected to rise to 643 million by 2030. The disease not only imposes a substantial economic burden but also leads to serious complications such as cardiovascular diseases, neuropathy, nephropathy, and retinopathy. Despite the availability of conventional antidiabetic therapies, their effectiveness is often limited by poor bioavailability, frequent dosing, adverse effects, and patient non-compliance.

Quercetin, a naturally occurring flavonoid present in fruits and vegetables, has attracted significant attention due to its antioxidant, anti-inflammatory, and antidiabetic properties. Preclinical studies have demonstrated its ability to improve insulin sensitivity, lower blood glucose levels, and protect pancreatic β-cells from oxidative damage. However, quercetin's therapeutic application is hindered by poor aqueous solubility, extensive first-pass metabolism, and low oral bioavailability.

Gastroretentive drug delivery systems (GRDDS) have emerged as a promising approach to overcome these limitations. By prolonging the gastric residence time and enabling controlled release in the stomach, GRDDS enhance drug absorption within the upper gastrointestinal tract. Floating drug delivery systems, in particular, improve bioavailability and sustain drug release by maintaining buoyancy in gastric fluids.

Materials and Methods

Materials: Quercetin was selected as the model drug due to its proven antidiabetic and antioxidant activity. Hydroxypropyl methylcellulose (HPMC K4M and HPMC K100M) were employed as release-retarding polymers, while sodium bicarbonate served as the gas-generating agent to impart buoyancy. Dicalcium phosphate was used as a channeling agent, magnesium stearate as a lubricant, talc as a glidant, and lactose monohydrate as a filler. All other chemicals and reagents used were of analytical grade.

Preformulation Studies: Preliminary studies included evaluation of quercetin's organoleptic properties, solubility, melting point, and compatibility with excipients by Fourier Transform Infrared (FTIR) spectroscopy. Powder flow properties such as bulk density, tapped density, compressibility index, Hausner's ratio, and angle of repose were assessed to determine suitability for direct compression.

Formulation of Floating Matrix Tablets: Floating tablets of quercetin were prepared by the direct compression method. Different concentrations (20%, 30%, and 40%) of HPMC K4M and HPMC K100M were combined with sodium bicarbonate and excipients in varying ratios to prepare six formulations (F1–F6). The powders were blended uniformly, lubricated, and compressed into tablets using a single-punch tablet compression machine.

Table no. 1: Formulation of Floatig Matrix Tablets Of Qurecetin

Ingredients/ Formulations	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Quercetin	**100**	**100**	**100**	**100**	**100**	**100**
HPMC K 100 M	**35**	**70**	**105**	**---**	**---**	**---**
HPMC K 4 M	**---**	**---**	**---**	**35**	**70**	**105**
Sodium bicarbonate	**35**	**35**	**35**	**35**	**35**	**35**
Dicalcium Phosphate	**17.5**	**17.5**	**17.5**	**17.5**	**17.5**	**17.5**
Magnesium.Stearate	**3.5**	**3.5**	**3.5**	**3.5**	**3.5**	**3.5**
Lactose monohydrat	**205.5**	**170.5**	**135.5**	**205.5**	**170.5**	**135.5**
Talc	**3.5**	**3.5**	**3.5**	**3.5**	**3.5**	**3.5**
Total (mg)	**400**	**400**	**400**	**400**	**400**	**400**

Evaluation of Granules and Tablets

- *Granules:* Pre-compression parameters such as bulk density, tapped density, Carr's index, and angle of repose were measured.

- *Tablets:* Post-compression parameters including tablet diameter, thickness, hardness, friability, and weight variation were assessed according to IP standards. Uniformity of drug content was evaluated by UV spectrophotometry at 314 nm.

Floating Behavior: Floating lag time (FLT) and total floating time (TFT) were determined by placing the tablets in 0.1N HCl (pH 1.2) at 37 ± 0.5 °C using USP type II dissolution apparatus.

In Vitro Dissolution Studies: Drug release studies were carried out in 900 mL of 0.1N HCl (pH 1.2) at 37 ± 0.5 °C using USP type II (paddle) apparatus at 50 rpm. Samples were withdrawn at predetermined intervals, filtered, and analyzed spectrophotometrically at 314 nm.

Kinetic Modeling: The release data were fitted to various kinetic models, including Zero-order, First-order, Higuchi, and Korsmeyer-Peppas models, to elucidate the drug release mechanism.

Swelling Index: Swelling behavior of the formulations was studied by measuring the weight of tablets at predetermined intervals after immersion in 0.1N HCl, and the swelling index was calculated.

Results

Preformulation Studies: FTIR spectra confirmed no significant chemical interaction between quercetin and selected excipients, indicating compatibility. Quercetin exhibited characteristic peaks corresponding to functional groups without any noticeable shifts in the drug–excipient mixture. Powder blends showed good flow properties with Carr's index values within acceptable limits, making them suitable for direct compression.

Physicochemical Evaluation of Tablets: All formulations (F1–F6) complied with pharmacopeial limits for weight variation, hardness, thickness, and friability (<1%). Drug content uniformity ranged from 96% to 99%, confirming consistency across batches.

Floating Behavior: All tablets demonstrated rapid buoyancy with a floating lag time (FLT) of less than 10 minutes. The total floating time (TFT) extended beyond 12 hours, ensuring prolonged gastric retention. Formulations containing higher polymer concentrations showed longer floating duration and greater matrix stability.

Table no.2: Physicochemical evaluation

Formulation	Weight variation	Drug Content % ±S.D. (n=3)	Hardness (Kg/cm^2) ±S.D.(n=10)	Floting Lag Time (min.)	Floating Time(h) (n=3)	Swelling index ±S.D. (n=3)
F1	401±5.7	99.85±1.20	4.1±0.08	6±0.55	12±0.24	0.771±0.01
F2	399±6.2	101.30±2.10	4.5±0.08	5.66±0.24	12±0.17	0.7310±0.03
F3	400 ± 5.0	100.75±1.75	4.2±0.08	5.33±0.23	12±0.03	0.9495±0.01
F4	398±5.8	98.55±1.50	4.3±0.16	9.66±0.17	11±0.05	1.5026±0.06
F5	402±6.1	102.10±1.90	4.1±0.12	9.66±1	11±0.22	1.0453±0.01

F6	399±5.9	99.20±2.05	4.3±0.08	9.66±0.24	11±0.21	0.6215±0.03

In Vitro Drug Release

Cumulative drug release varied depending on polymer grade and concentration.

- Formulations with HPMC K100M (F1–F3) exhibited slower release due to high viscosity and stronger gel layer formation, sustaining drug release up to 12 hours.
- Formulations with HPMC K4M (F4–F6) showed relatively faster drug release, but still maintained controlled release over 10–12 hours.
- Among all, F5 (30% HPMC K4M) achieved optimal release, balancing floating ability with sustained drug release (≈ 92% release at 12 hours).

Table no. 2: Cumulative percentage Drug release from Formulation F1-F6

Time(h)	%Drug release ± S.D.(n=3)					
	F1	F2	F3	F4	F5	F6
0	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000
0.5	0.629±0.016	1.258±0.108	1.415±0.015	2.594±0.078	0.471±0.02	0.629±0.014
1	1.651±0.050	1.336±0.095	2.122±0.020	6.681±0.200	4.087±0.08	1.105±0.032
2	8.646±0.150	6.445±0.534	6.524±0.025	17.057±0.512	15.327±0.20	8.647±0.146
3	17.06±0.251	12.03±0.918	11.397±0.011	28.533±0.857	27.668±0.21	17.449±0.271
4	22.87±0.351	13.76±1.008	12.262±0.011	35.449±1.064	35.764±0.21	23.109±1.155
5	28.87±0.851	15.80±1.155	12.498±0.015	44.646±1.339	43.861±0.25	28.532±1.427
6	41.74±0.751	23.74±1.836	18.943±0.050	59.109±1.778	57.537±0.21	39.615±1.381
7	54.47±1.505	31.76±2.003	25.389±0.035	73.886±2.218	72.158±0.25	50.698±1.521
8	68.7±1.658	40.72±2.795	32.620±0.017	90.078±2.702	87.720±0.30	63.985±0.719

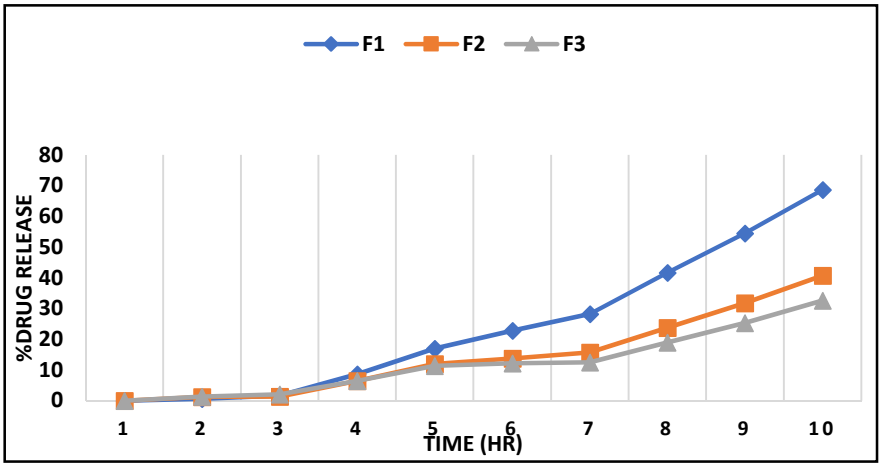

Fig.no. 1: in vitro release profile of Quercetin from formulation F1, F2 And F3 containing 20%,30 and 40% HPMC K100M Respectively.

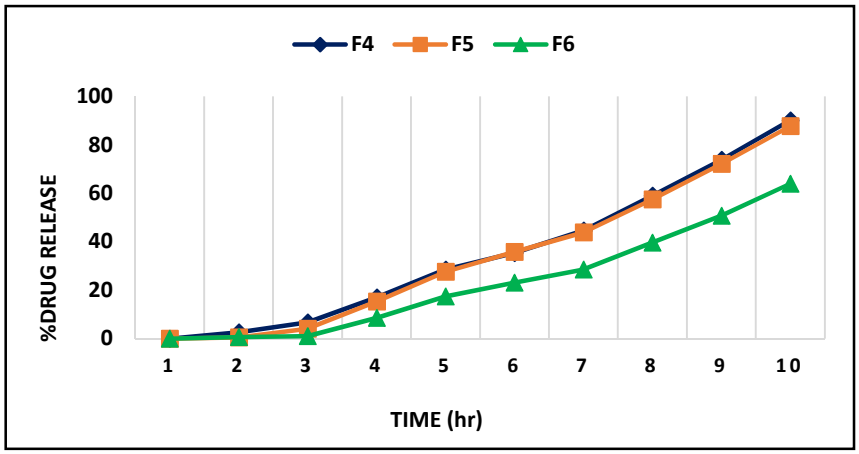

Fig.no.2: in vitro release profile of Quercetin from formulation F4, F5 And F6 containing 20%,30 and 40% HPMC K4M Respectively.

Kinetic Modeling

The drug release followed zero-order kinetics in optimized formulations, with high correlation coefficients ($R^2 > 0.98$). Korsmeyer-Peppas modeling indicated a non-Fickian (anomalous) diffusion mechanism, suggesting that both diffusion and polymer relaxation governed the drug release.

Table no. 3. Kinetic treatment of matrix floating tablet (10 mm dimeter)

Formulation code	Zero order		First Order		Korsemeyer- Peppas			Best Fit
	R^2	k_0	R^2	k_1	R^2	K_{kp}	n	
F1	0.9363	7.269	0.8754	0.092	0.9949	2.401	1.604	Peppas
F2	0.9376	4.286	0.9090	0.049	0.9824	1.649	1.522	Peppas
F3	0.9445	3.495	0.9266	0.039	0.9655	1.912	1.331	First Order
F4	0.9786	10.209	0.9010	0.148	0.9956	6.190	1.275	Zero-order, Peppas
F5	0.9757	9.951	0.9012	0.143	0.9959	5.763	1.301	Peppas
F6	0.9510	6.906	0.8993	0.087	0.9974	2.806	1.493	Peppas

Among the six formulations (F1–F6), Formulations F4 and F5 demonstrated the most desirable dissolution characteristics for a gastroretentive drug delivery system of Quercetin.

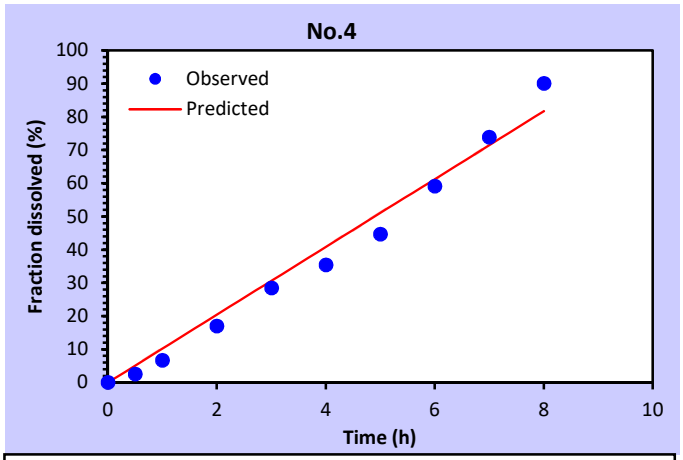

Fig.no.3 : Zero-order kinetic modeling of F4

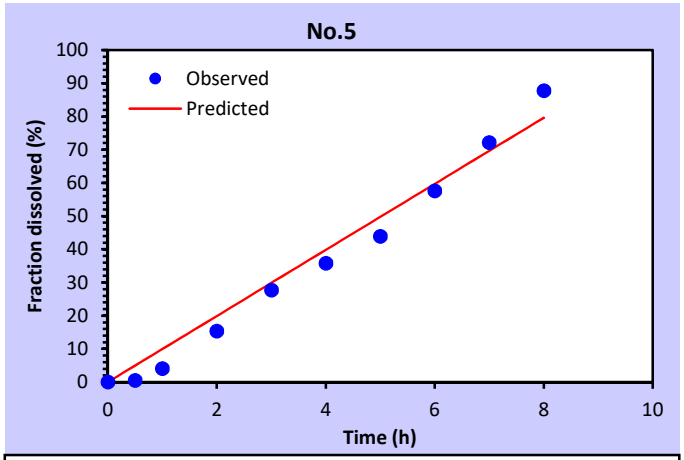

Fig.no.4: Zero-order kinetic modeling of F5

Zero-order kinetic modeling indicated that F4 (R^2 = 0.9928, MSC = 3.4823) and F5 (R^2 = 0.9936, MSC = 3.3667) followed near zero-order release, ensuring a constant drug release rate over 8 hours, which is essential for sustained gastric retention and improved bioavailability.

The Korsmeyer-Peppas model showed n values of 1.275 (F4) and 1.301 (F5), indicating polymer relaxation and swelling contributed to drug release. This behavior is suitable for a

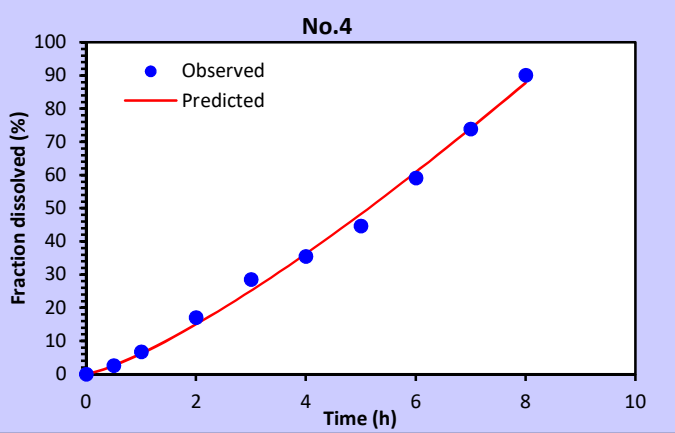

Fig.no.5: Korsmeyer-Peppas Model Modeling of F4

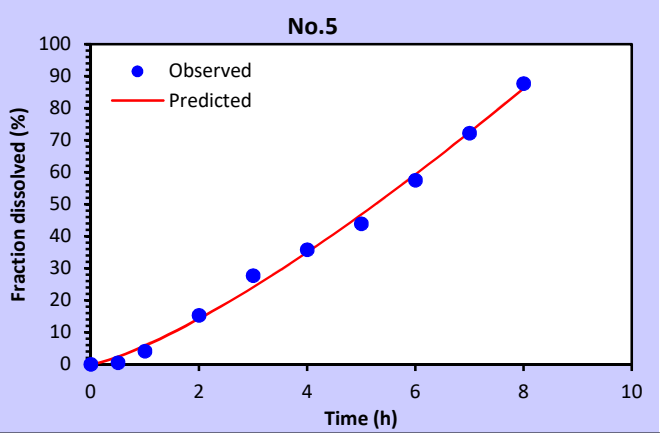

Fig.no.6: Korsmeyer-Peppas Model Modeling of F5

floating GRDDS as it maintains buoyancy and prolongs gastric residence. In contrast, Higuchi and First-order models showed relatively lower correlation, confirming that diffusion or concentration-dependent release was not predominant. Therefore, F4 and F5 can be considered optimized formulations for sustained release and therapeutic efficacy of Quercetin in antidiabetic therapy.

The Formulations F4 and F5 provided prolonged and controlled release of Quercetin up to 8 hours, fulfilling the primary objective of enhancing bioavailability by maintaining gastric retention and sustaining release. Zero-order kinetics ensures steady drug plasma levels, minimizing fluctuations and improving therapeutic efficacy in diabetes management. The Korsmeyer-Peppas model confirmed that polymeric behavior (HPMC K4M and HPMC K 100M) played a significant role in controlling the release mechanism.

Swelling Index

The swelling studies revealed that tablets containing higher polymer concentrations exhibited greater swelling capacity, which contributed to extended drug release and buoyancy.

Conclusion

The present study successfully developed and evaluated gastroretentive floating matrix tablets of quercetin to enhance its oral bioavailability and antidiabetic efficacy. All formulations showed acceptable physicochemical characteristics, rapid buoyancy, and prolonged gastric retention. Among them, the optimized formulation with HPMC K4M (30%) provided sustained drug release for up to 12 hours, following zero-order kinetics with a non-Fickian diffusion mechanism. The results demonstrate that gastroretentive drug delivery is a promising strategy to overcome quercetin's solubility and bioavailability limitations, potentially improving its therapeutic effectiveness in the management of diabetes mellitus.

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