

FORMULATION AND CHARACTERIZATION OF GASTRORETENTIVE MICROBALOONS OF POLYPHENOLS KEMPFEROL FOR ANTIULCER ACTIVITY

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Abstract

Kaempferol is a naturally occurring flavonoid possessing antioxidant, anti-inflammatory, and anticancer activities; however, its clinical application is limited due to poor aqueous solubility, low oral bioavailability, and rapid elimination. The present study aimed to develop and evaluate gastroretentive floating microballoons of Kaempferol for prolonged gastric residence and sustained drug release. Floating microballoons were prepared by the solvent evaporation technique using hydroxypropyl methylcellulose (HPMC), xanthan gum, and guar gum in different concentrations. The prepared formulations were evaluated for percentage yield, drug entrapment efficiency, floating lag time, percentage buoyancy, particle size, zeta potential, in vitro drug release, release kinetics, and accelerated stability. Among the six formulations, F6 demonstrated the highest percentage yield ($82.12 \pm 0.18\%$), drug entrapment efficiency ($81.15 \pm 0.22\%$), and buoyancy ($95 \pm 3\%$) with a floating lag time of 50 ± 2 seconds. The optimized formulation exhibited sustained drug release of 99.12% over 12 hours and followed the Korsmeyer–Peppas kinetic model ($R^2 = 0.9976$), indicating diffusion-controlled release. Accelerated stability studies performed at $40 \pm 2^\circ\text{C}/75 \pm 5\% \text{ RH}$ for three months showed no significant changes in physicochemical properties, drug content, or dissolution profile. The results indicate that the developed Kaempferol-loaded floating microballoons provide effective gastroretention and sustained drug release, offering a promising approach to enhance the oral bioavailability and therapeutic efficacy of Kaempferol.

Keywords: Kaempferol, Floating microballoons, Gastroretentive drug delivery, Solvent evaporation, HPMC, Xanthan gum, Guar gum, Sustained release, Drug entrapment, Buoyancy.

How to cite this article: Neha Kumari Rajkumari Lodhi* Dr. Satish Nayak. FORMULATION AND CHARACTERIZATION OF GASTRORETENTIVE MICROBALOONS OF POLYPHENOLS KEMPFEROL FOR ANTIULCER ACTIVITY. Int J Drug Deliv Technol. 2026;16(84s):1834-1839. DOI: 10.25258/ijddt.16.84s.187.

Introduction

Peptic ulcer disease (PUD) is one of the most common gastrointestinal disorders, characterized by erosion of the gastric or duodenal mucosa due to an imbalance between aggressive factors, such as gastric acid, pepsin, *Helicobacter pylori* infection, nonsteroidal anti-inflammatory drugs (NSAIDs), and oxidative stress, and the protective mechanisms of the gastric mucosal barrier (Jaiswal et al., 2021).

Despite the availability of proton pump inhibitors, H_2 -receptor antagonists, and antibiotic therapy, long-term treatment is often associated with adverse effects, drug resistance, frequent dosing, and recurrence of ulcers. Therefore, there is a growing interest in developing novel drug delivery systems and natural therapeutic agents that can provide sustained gastroprotective effects with improved patient compliance (Chand et al., 2024).

Polyphenols have gained considerable attention due to their diverse pharmacological activities, including antioxidant, anti-inflammatory, antimicrobial, and gastroprotective properties. Among them, Kaempferol is a naturally occurring flavonol widely distributed in fruits, vegetables, tea, and medicinal plants (Rana et al., 2022).

Kaempferol has been reported to possess potent antioxidant and free radical scavenging activity, inhibit inflammatory mediators, reduce oxidative stress, and protect the gastric mucosa from ulcerative damage. Experimental studies have demonstrated that Kaempferol exerts antiulcer effects by enhancing mucosal defense mechanisms, suppressing gastric acid secretion, reducing lipid peroxidation, and promoting tissue repair. However, its therapeutic application is limited because of poor aqueous solubility, low oral bioavailability, rapid metabolism, and short residence time in the gastrointestinal tract (Repetto and Llesuy, 2002).

Gastroretentive drug delivery systems (GRDDS) have emerged as an effective strategy to improve the oral bioavailability of drugs that are preferentially absorbed in the stomach or upper gastrointestinal tract or require prolonged gastric residence for optimal therapeutic action (Tripathi et al., 2019).

These systems remain buoyant on gastric fluids, thereby extending gastric retention time, maintaining the dosage form in the stomach, and providing controlled drug release. Floating microballoons, also known as hollow microspheres, are one of the most promising gastroretentive multiparticulate systems.

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Owing to their low density and hollow internal cavity, they float on gastric contents for prolonged periods without affecting gastric emptying, resulting in enhanced drug absorption, reduced dosing frequency, and improved therapeutic efficacy (Mishra et al., 2025).

The selection of suitable polymers plays a crucial role in determining the performance of floating microballoons. Hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC), xanthan gum, and guar gum are widely employed because they form a hydrated gel barrier that controls drug diffusion, improves buoyancy, and enhances matrix integrity. The combination of these polymers can produce stable floating microballoons with high drug entrapment efficiency and sustained drug release characteristics (Iglesias et al., 2020).

Based on these considerations, the present study was undertaken to formulate and characterize gastroretentive floating microballoons of the polyphenol Kaempferol using the solvent evaporation technique. The developed formulations were evaluated for percentage yield, drug entrapment efficiency, floating lag time, buoyancy, particle size, zeta potential, in vitro drug release, release kinetics, and accelerated stability. The objective of this study was to develop an optimized gastroretentive delivery system capable of prolonging gastric residence, providing sustained drug release, and enhancing the antiulcer potential and oral bioavailability of Kaempferol.

Material and Methods

Material

Kaempferol was used as the model drug. Hydroxypropyl methylcellulose (HPMC), xanthan gum, and guar gum were employed as matrix-forming polymers. Ethanol and dichloromethane (DCM) were used as organic solvents, while Tween 80 served as the surfactant. Distilled water was used as the external aqueous phase for the preparation of floating microballoons. All chemicals and reagents used in the study were of analytical grade.

Methods

Formulation of Kaempferol loaded microballoons

Floating microballoons containing Kaempferol with a central hollow cavity were prepared by the solvent evaporation technique as reported by Yadav and Kumar (2011) and Senthil et al. (2016). Accurately weighed quantities of Kaempferol, HPMC, Xanthan Gum, and Guar Gum were dissolved in a mixture of ethanol and dichloromethane (DCM) in a 1:1 ratio at room temperature to obtain a uniform polymeric solution. The prepared solution was slowly introduced into 250 mL of distilled water containing 0.01% Tween 80 under continuous stirring using a propeller-type agitator at 300 rpm. The temperature

was maintained at 40°C for 1 hour to facilitate evaporation of the volatile organic solvents and formation of hollow microballoons.

The formed microballoons were separated by filtration, washed thoroughly with distilled water to remove residual surfactant, and dried under vacuum to obtain free-flowing floating microballoons. Different concentrations and combinations of polymers were used to prepare various formulations in order to study their effect on the characteristics of the microballoons. The composition of different formulations is presented in Table 1.

Table 1: Formulations of the floating microballoons prepared

S. N o.	Formulat ion Code	Kaempfe rol (mg)	HPM C (mg)	Xanth an Gum (mg)	Gu ar Gu m (mg)
1.	F1	25	100	25	-
2.	F2	25	100	50	-
3.	F3	25	100	75	-
4.	F4	25	150	25	10
5.	F5	25	150	50	20
6.	F6	25	150	75	30

Evaluation of microballoons

Percentage Yield

The prepared microballoons with a size range of 1µm to 1000µm were collected and weighed from different formulations. The measured weight was divided by the total amount of all non-volatile components which were used for the preparation of the microballoons (Azza and Marwa, 2015).

% Yield

$$= \frac{\text{Actual weight of product}}{\text{Total weight of drug and polymer}} \times 100$$

Drug Entrapment

The various formulations of the Floating microballoons were subjected for drug content. 10 mg of Floating microballoons from all batches were accurately weighed and crushed (Kumar, 2011). The powder of microballoons were dissolved in 10 ml 0.1 N HCl and centrifuge at 1000 rpm. This supernatant solution is then filtered through whatmann filter paper No. 44. After filtration, from this solution 0.1 ml was taken out and diluted up to 10 ml with 0.1 N HCl. The percentage drug entrapment was calculated using calibration curve method.

Floating behavior

Ten milligrams of the floating microballoons were placed in 0.1 N HCl (100 mL). The mixture was stirred at 100 rpm in a magnetic stirrer (Swami and Saraf, 2011). After 10 h, the layer of buoyant microsphere was pipetted and separated by filtration. Particles in the sinking particulate layer were separated by filtration. Particles of both types were dried in desiccators until a constant weight was obtained. Both the fractions of microballoons were weighed and buoyancy was determined by the weight ratio of floating particles to the sum of floating and sinking particles.

$$\text{Percent buoyancy} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Measurement of mean particle size

The mean size of the microballoons was determined by Photo Correlation Spectroscopy (PCS) on a submicron particle size analyzer (Malvern Instruments) at a scattering angle of 90°. A sample (0.5mg) of the microballoons suspended in 5 ml of distilled water was used for the measurement (Joshi and Jaimini, 2013).

Determination of zeta potential

The zeta potential of the drug-loaded microballoons was measured on a zeta sizer (Malvern Instruments) by determining the electrophoretic mobility in a micro electrophoresis flow cell. All the samples were measured in water at 25°C in triplicate (Saneshan and Kanth, 2013).

Shape and surface characterization of microballoons by scanning electron microscopy (SEM)

From the formulated batches of microballoons, formulations (F3) which showed an appropriate balance between the percentage releases were examined for surface morphology and shape using scanning electron microscope Jeol Japan 6000 (Amrutha *et al.*, 2015). Sample was fixed on carbon tape and fine gold sputtering was applied in a high vacuum evaporator. The acceleration voltage was set at 10KV during scanning. Microphotographs were taken on different magnification and higher magnification (200X) was used for surface morphology.

In-vitro release studies

The *in vitro* drug release rate from Floating microballoons was carried out using the USP type I (Electro Lab.) dissolution assembly. A weighed amount of floating microballoons equivalent to 100 mg drug were dispersed in 900 ml of 0.1 N HCl (pH=1.2) maintained at $37 \pm 0.5^\circ\text{C}$ and stirred at 55rpm. One ml sample was withdrawn at predetermined intervals and filtered and equal volume of dissolution medium was replaced in the

vessel after each withdrawal to maintain sink condition. The collected samples analyzed spectrophotometrically at 265nm to determine the concentration of drug present in the dissolution medium.

Drug release kinetic data analysis

Several kinetic models have been proposed to describe the release characteristics of a drug from matrix. The following three equations are commonly used, because of their simplicity and applicability. Equation 1, the zero-order model equation (Plotted as cumulative percentage of drug released vs time); Equation 2, Higuchi's square-root equation (Plotted as cumulative percentage of drug released vs square root of time); and Equation 3, the Korsmeyer-Peppas equation (Plotted as Log cumulative percentage of drug released vs Log time).

Stability studies for optimized formulation

The optimized Kaempferol-loaded floating microballoon formulation (F6) was subjected to accelerated stability studies according to ICH Q1A(R2) guidelines. The formulation was stored in airtight HDPE containers at $40 \pm 2^\circ\text{C}$ and $75 \pm 5\%$ RH for 3 months. Samples were evaluated initially and after storage for appearance, colour, drug content, assay, pH, and *in vitro* drug release. The results obtained after storage were compared with the initial values to assess the physicochemical stability of the optimized formulation.

Results and Discussion

Kaempferol-loaded floating microballoons were successfully prepared by the solvent evaporation technique using HPMC, xanthan gum, and guar gum as release-retarding polymers. The prepared formulations exhibited satisfactory percentage yield, drug entrapment efficiency, buoyancy, and sustained drug release characteristics. The influence of polymer concentration and composition on the physicochemical properties of the microballoons was systematically evaluated.

The percentage yield of all formulations ranged from $68.85 \pm 0.45\%$ to $82.12 \pm 0.18\%$ (Table 2). An increase in polymer concentration resulted in a gradual improvement in production yield. Formulation F6 exhibited the highest percentage yield ($82.12 \pm 0.18\%$), indicating that the combined use of higher concentrations of HPMC, xanthan gum, and guar gum enhanced the structural integrity of the microballoons during solvent evaporation. Similar findings have been reported for floating multiparticulate systems where higher polymer content reduced material loss and improved process efficiency.

Drug entrapment efficiency also showed a progressive increase with increasing polymer concentration (Table 3). The entrapment efficiency

increased from $67.45 \pm 0.32\%$ for F1 to $81.15 \pm 0.22\%$ for F6. The improved entrapment observed in F6 may be attributed to the increased viscosity of the polymeric solution, which minimized drug diffusion into the external aqueous phase during preparation. Higher polymer concentration also promoted the formation of compact polymeric matrices capable of retaining a greater amount of Kaempferol within the hollow microballoons.

Floating behavior is one of the critical quality attributes of gastroretentive dosage forms. As shown in Table 4, floating lag time decreased from 74 ± 5 seconds for F1 to 50 ± 2 seconds for F6, whereas percentage buoyancy increased from $76 \pm 8\%$ to $95 \pm 3\%$. The superior floating performance of F6 indicates efficient formation of hollow internal cavities during solvent evaporation. The presence of xanthan gum and guar gum along with HPMC contributed to lower density and enhanced matrix strength, allowing the optimized microballoons to remain buoyant for prolonged periods. High buoyancy ensures prolonged gastric residence time, which is advantageous for improving the oral bioavailability of poorly soluble compounds such as Kaempferol.

The particle size distribution of the optimized formulation (Figure 1) demonstrated uniformly distributed spherical microballoons with an average particle size suitable for oral multiparticulate drug delivery. Uniform particle size contributes to reproducible drug release, improved flow characteristics, and enhanced gastric retention. The optimized formulation also exhibited an appropriate zeta potential (Figure 2), indicating sufficient electrostatic stability of the dispersed microballoons. Adequate surface charge minimizes particle aggregation and improves storage stability.

The in vitro drug release profiles (Table 5) demonstrated that polymer concentration markedly influenced the release characteristics of Kaempferol. Formulations containing lower polymer concentrations (F1–F3) released the drug rapidly, achieving almost complete release within 6–10 hours. In contrast, formulations containing higher concentrations of HPMC, xanthan gum, and guar gum (F4–F6) exhibited sustained drug release over an extended period. The optimized formulation F6 released only 18.65% drug during the first 30 minutes and gradually achieved 99.12% cumulative release at 12 hours, indicating excellent controlled-release behavior. The sustained release can be attributed to the formation of a thicker gel barrier and longer diffusion pathway produced by the hydrophilic polymer matrix.

Drug release kinetic analysis (Table 6) demonstrated that formulation F6 exhibited the highest correlation

coefficient for the Korsmeyer–Peppas model ($R^2 = 0.9976$) followed closely by the Higuchi model ($R^2 = 0.9962$). These findings suggest that drug release primarily occurred through diffusion from the hydrated polymer matrix with simultaneous polymer relaxation and erosion. The comparatively lower correlation coefficient observed for the first-order model indicates that drug release was not concentration dependent. The release mechanism therefore represents anomalous (non-Fickian) transport, which is commonly observed in hydrophilic polymer-based sustained-release systems. Accelerated stability studies performed for three months at $40 \pm 2^\circ\text{C} / 75 \pm 5\%$ RH demonstrated excellent stability of the optimized formulation (Table 7). No significant changes were observed in appearance, colour, drug content, assay, dissolution profile, or pH after storage. Drug content decreased only slightly from $99.12 \pm 0.24\%$ to $98.76 \pm 0.31\%$, while cumulative drug release remained almost unchanged ($96.84 \pm 0.42\%$ initially versus $95.96 \pm 0.38\%$ after storage). These results indicate that the optimized floating microballoons possess good physicochemical stability and are suitable for long-term storage without significant degradation or performance loss.

Table 2: Percentage yield for different formulation of Kaempferol floating microballoons

S. No.	Formulation	Percentage Yield*
1.	F1	68.85 ± 0.45
2.	F2	71.32 ± 0.32
3.	F3	74.28 ± 0.36
4.	F4	76.45 ± 0.44
5.	F5	79.65 ± 0.32
6.	F6	82.12 ± 0.18

*Average of three determinations

Table 3: Drug entrapment for different formulations

S. No.	Formulation	Drug Entrapment (% w/w)*
1.	F1	67.45 ± 0.32
2.	F2	69.23 ± 0.45
3.	F3	72.46 ± 0.33
4.	F4	74.58 ± 0.45
5.	F5	78.32 ± 0.36
6.	F6	81.15 ± 0.22

*Average of three determinations

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Table 4: Percentage Buoyancy and floating lag time of floating microballoons

Formulation	Floating Lag Time (Sec.)	Percentage Buoyancy (%)
F1	74±5	76±8
F2	69±6	81±6
F3	66±8	84±4
F4	60±7	88±2
F5	58±3	90±3
F6	50±2	95±3

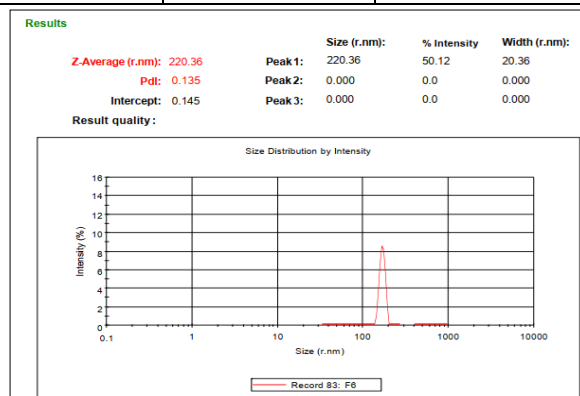


Figure 1: Particle size data of optimized microballoons formulation F6

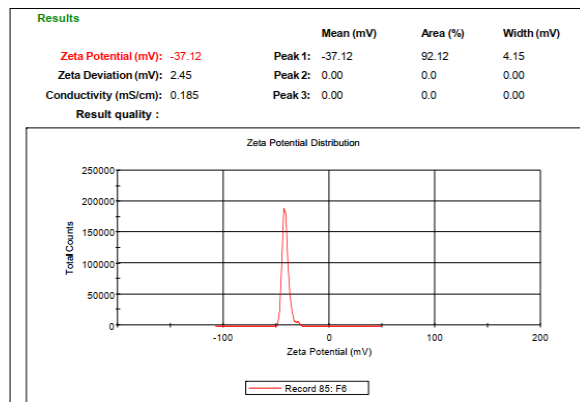


Figure 2: Zeta potential data of floating microballoons F6

Table 5: Release Study data of formulation F1-F6

Time (Hrs)	Percentage Drug Release					
	F1	F2	F3	F4	F5	F6
0.5	42.6	38.4	34.8	30.2	26.4	18.6
	5	5	5	5	5	5
1	64.8	58.6	54.3	48.8	40.2	24.8

	5	5	2	5	5	5
2	82.2	74.6	69.8	62.4	54.6	36.4
	5	5	5	5	5	5
4	94.6	88.4	82.6	76.8	68.8	52.2
	5	5	5	5	5	5
6	99.2	96.4	91.6	86.2	79.4	64.8
	5	5	5	5	5	5
8	-	99.1	96.4	92.6	88.6	76.4
		5	5	5	5	5
10	-	-	99.1	98.2	94.2	88.6
			8	5	5	5
12	-	-	-	99.0	98.8	99.1
				5	5	2

Table 6: Comparative study of regression coefficient for selection of optimized Formulation F6

Release Kinetics	Zero order	First order	Higuchi	Korsmeyer
R ²	0.9866	0.7997	0.9962	0.9976

Table 7: Results of Stability studies

Stability Parameters	Initial	After 3 Months (40±2° C / 75±5% RH)	Observation
Appearance	Uniform, smooth formulation	No significant change	Stable
Colour	Characteristic	No change observed	Stable
Drug Content	99.12 ± 0.24	98.76 ± 0.31	No significant

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(%)			difference
Assay (%)	98.95 ± 0.18	98.52 ± 0.27	Within acceptable limits
Dissolution / Drug Release (%)	96.84 ± 0.42	95.96 ± 0.38	Negligible change
pH	6.8 ± 0.05	6.7 ± 0.04	Stable
Physical Stability	No phase separation/cracking	No change observed	Stable

Conclusion

The present study successfully developed Kaempferol-loaded floating microballoons using the solvent evaporation technique. The optimized formulation (F6) exhibited high percentage yield, good drug entrapment efficiency, excellent buoyancy, and sustained drug release for up to 12 hours. The formulation followed the Korsmeyer–Peppas release model and remained stable under accelerated storage conditions. These findings suggest that the developed floating microballoons are a promising gastroretentive drug delivery system for improving the oral bioavailability and therapeutic efficacy of Kaempferol.

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