In Vitro Evaluation of Anti-Ulcer Activity of Optimized Gastroretentive Floating Microspheres of Glabridin

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ABSTRACT
Peptic ulcer disease remains a significant gastrointestinal disorder associated with excessive gastric acid secretion, oxidative stress, and mucosal damage. The present study aimed to evaluate the in vitro anti-ulcer activity of optimized gastroretentive floating microspheres of glabridin designed for prolonged gastric residence and sustained drug release. Glabridin-loaded floating microspheres were prepared using an ionic gelation technique and optimized for drug content and drug release behavior. The optimized formulation exhibited excellent floating ability with prolonged buoyancy and controlled release of glabridin over an extended period in simulated gastric fluid. Anti-ulcer activity was assessed through acid-neutralizing capacity and H^+/K^+-ATPase inhibition studies. The optimized microspheres demonstrated significant acid-neutralizing potential and effectively inhibited proton pump activity compared with the pure drug suspension. Sustained release of glabridin contributed to prolonged therapeutic action and enhanced gastroprotective potential. The findings suggest that gastroretentive floating microspheres of glabridin can serve as a promising delivery system for effective management of gastric ulcers by improving gastric retention, controlled drug delivery, and localized therapeutic action within the stomach.

Key-words: Glabridin, in vitro, anti-ulcer, floating, microsphere
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Introduction

Peptic ulcer disease is a common gastrointestinal disorder characterized by lesions in the gastric or duodenal mucosa resulting from an imbalance between aggressive factors such as gastric acid, pepsin, alcohol consumption, Helicobacter pylori infection, nonsteroidal anti-inflammatory drugs (NSAIDs), and reactive oxygen species, and protective mechanisms including mucus secretion, bicarbonate production, and mucosal blood flow. Despite the availability of conventional anti-ulcer therapies, prolonged use of proton pump inhibitors and H2 receptor antagonists is often associated with adverse effects, recurrence, and reduced patient compliance. Therefore, considerable attention has been directed toward the development of safer and more effective therapeutic systems using natural bioactive compounds and advanced drug delivery approaches (Banarjee et al., 2010).

Glabridin, a major flavonoid isolated from Glycyrrhiza glabra (licorice), possesses significant pharmacological properties including antioxidant, anti-inflammatory, antimicrobial, and gastroprotective activities. Several studies have demonstrated that glabridin can protect the gastric mucosa by scavenging free radicals, reducing lipid peroxidation, inhibiting gastric acid secretion, and enhancing mucosal defense mechanisms. However, the clinical application of glabridin is limited due to its poor aqueous solubility, low bioavailability, and rapid gastric emptying, which reduce its therapeutic effectiveness in the stomach. To overcome these limitations, gastroretentive drug delivery systems have emerged as promising strategies for improving gastric residence time and localized drug action (Zhang et al., 2003).

Among various gastroretentive systems, floating microspheres have gained considerable interest because of their ability to remain buoyant in gastric fluid for prolonged periods while providing controlled and sustained drug release. Floating microspheres are low-density multiparticulate carriers that float on the stomach contents and gradually release the encapsulated drug at the target site. This prolonged gastric retention enhances drug absorption, reduces dosing frequency, and improves therapeutic efficacy, particularly for drugs intended for local action in the stomach. In addition, multiparticulate systems offer advantages such as uniform distribution, reduced risk of dose dumping, and improved patient compliance compared with single-unit dosage forms (Dwivedi et al., 2025).

The present study focuses on the development and in vitro evaluation of optimized gastroretentive floating microspheres of glabridin for anti-ulcer therapy. The microspheres were designed to provide prolonged gastric retention, sustained drug release, and enhanced gastroprotective action. Optimization of the formulation was carried out to achieve desirable physicochemical properties including particle size, entrapment efficiency, buoyancy, and drug release characteristics. Furthermore, the anti-ulcer potential of the optimized formulation was evaluated using in vitro methods such as acid-neutralizing capacity and H+/K+-ATPase inhibition activity. The study aims to establish an effective gastroretentive delivery system capable of improving the therapeutic performance of glabridin in the management of gastric ulcers while minimizing limitations associated with conventional dosage forms.

Material and Methods

Material: Optimized gastroretentive floating microspheres of glabridin

In Vitro Anti-Ulcer Activity of Optimized Formulation

Acid Neutralizing Capacity of Optimized: Using an acid-base back titration technique, the improved Glabridin gastroretentive floating microsphere formulation's acid neutralizing capacity was assessed. A conical flask holding 30 mL of 0.1 N hydrochloric acid (HCl) was filled with precisely weighed quantities of optimized microspheres equal to a preset amount of Glabridin. To replicate stomach conditions, the mixture was kept at 37 ± 0.5°C while being constantly agitated with a magnetic stirrer. To guarantee full interaction between the microspheres and hydrochloric acid, the formulation was left to react with the acidic medium for a predetermined amount of time. Following the completion of the reaction, phenolphthalein was used as an indicator to titrate the excess unreacted acid in the solution against a standardized 0.1 N sodium hydroxide (NaOH) solution until the endpoint with a light pink tint was reached (Abd et al., 2019; Kumar et al., 2022, Umre et al., 2018).

The amount of sodium hydroxide used during titration was noted, and the amount of hydrochloric acid neutralized by the microspheres was used to determine the formulation's acid neutralizing capacity. To guarantee accuracy and reproducibility of the data, the experiment was conducted in triplicate. Milliequivalents (mEq) of acid neutralized and percentage acid neutralization were used to express the acid neutralizing capacity.

Because of the formulation's longer stomach retention behavior and sustained release, the optimized Glabridin gastroretentive floating microspheres showed prolonged acid neutralization. The polymeric matrix's swelling and mucoadhesive properties also helped to sustain the formulation's extended interaction with the stomach environment, increasing its potential for gastroprotection and ulcer prevention (Abd-Allah et al., 2024; Shahwar et al., 2025).

H+/K+ - ATPase Inhibition Activity:

An isolated gastric proton pump enzyme preparation from gastric mucosal tissue was used to assess the improved Glabridin gastroretentive floating microsphere formulation's H^+/K^+-ATPase inhibitory efficacy. To separate the membrane fraction containing the H^+/K^+-ATPase enzyme, gastric mucosal homogenate was first made in ice-cold phosphate buffer (pH 7.4) and centrifuged. The enzyme preparation was incubated at 37°C for a predetermined amount of time after the optimal microsphere formulation comparable to a predefined concentration of Glabridin was distributed in an appropriate buffer solution. Enzyme solution, ATP substrate solution, potassium chloride, magnesium chloride, and the test formulation typically made up the reaction mixture. The standard reference medication for comparing inhibitory action was omeprazole (Abd et al., 2019; Kumar et al., 2022, Umre et al., 2018)..

Following incubation, the ATP solution was added to start the enzymatic process, which was then stopped using stopping reagent or trichloroacetic acid after a predetermined amount of time. Using the right color-developing reagents at the right wavelength, the amount of inorganic phosphate produced during ATP hydrolysis was measured spectrophotometrically. Standard formulas were used to compute the % inhibition of H^+/K^+-ATPase activity and compare the enzyme activity in the presence and absence of the improved formulation.

The concentration-response curve obtained at various formulation concentrations was used to calculate the IC_{20} value. To guarantee accuracy and repeatability of the data, the experiment was conducted three times.

Because of the prolonged release and retention of Glabridin in the stomach environment, the

optimized Glabridin gastroretentive floating microspheres demonstrated a considerable suppression of gastric proton pump function. Glabridin's antioxidant and anti-secretory qualities, which lessen stomach acid secretion and shield the stomach mucosa from ulcerative damage, may be responsible for the inhibitory action. The bioactive compound's localized activity was further boosted by the microspheres' prolonged gastroretentive behavior, which improved therapeutic efficacy in the treatment of peptic ulcers (Abd-Allah et al., 2024; Shahwar et al., 2025).

Results and Discussion

The acid neutralizing capacity of the optimized Glabridin gastroretentive floating microsphere formulation (O-GFM) was evaluated to assess its potential in reducing gastric acidity and providing gastroprotective activity for peptic ulcer management, and the results are presented in Table 1. The optimized formulation exhibited effective hydrochloric acid neutralization with an acid neutralizing capacity of 60.67 ± 1.42%, neutralizing approximately 1.82 ± 0.06 mEq of acid from the initial acidic medium, thereby indicating satisfactory antacid and buffering potential. The formulation maintained its neutralizing effect for more than 12 hours, suggesting prolonged gastroretentive behavior and sustained release of Glabridin within the gastric environment. Furthermore, the final pH after neutralization was found to be 3.8 ± 0.12, demonstrating moderate reduction of gastric acidity without producing excessive alkalinity. The enhanced acid neutralizing effect may be attributed to the swelling characteristics, prolonged gastric retention, and controlled release behavior of the optimized microspheres. Overall, the optimized Glabridin-loaded gastroretentive floating microspheres showed promising acid neutralizing potential and may serve as an effective system for prolonged gastric protection and management of peptic ulcer disease.

Table 1: Acid Neutralizing Capacity of Optimized Glabridin Gastroretentive Floating Microspheres (O-GFM)

S. No.	Parameter	Observed Value
1	Initial Volume of HCl (0.1 N)	30 mL
2	Initial Acid Content	3.0 mEq
3	Volume of NaOH Consumed (0.1 N)	11.84 ± 0.28 mL
4	Acid Neutralized	1.82 ± 0.06 mEq
5	Acid Neutralizing Capacity (%)	60.67 ± 1.42 %
6	Duration of Neutralization	>12 hours
7	pH after Neutralization	3.8 ± 0.12

The H^+/K^+-ATPase inhibition activity of the optimized Glabridin gastroretentive floating microsphere formulation (O-GFM) was evaluated to assess its anti-ulcer potential through suppression of gastric acid secretion, and the results are presented in Table 2. The optimized formulation demonstrated significant inhibitory activity against the gastric proton pump enzyme H^+/K^+-ATPase, which plays a major role in acid secretion by gastric parietal cells. The optimized microspheres exhibited 71.54 ± 1.24% inhibition of enzyme activity at a concentration of 100 µg/mL, while the residual enzyme activity was found to be 28.46 ± 1.24%, confirming effective suppression of gastric acid secretion mechanisms. The IC_{50} value of the formulation was determined to be 42.18 ± 1.06 µg/mL, indicating good inhibitory efficiency of Glabridin released from the gastroretentive microspheres. The observed inhibitory effect may be attributed to the antioxidant and gastroprotective properties of Glabridin, which can regulate proton pump activity and reduce oxidative damage to the gastric mucosa. Furthermore, the sustained release and prolonged gastric retention behavior of the optimized microspheres enhanced localized drug action within the stomach, resulting in prolonged enzyme inhibition and improved therapeutic efficacy. Although the inhibitory activity was slightly lower than that of the standard anti-ulcer drug Omeprazole, the optimized formulation demonstrated promising natural anti-secretory potential suitable for long-term gastroprotective therapy. Overall, these findings support the potential application of Glabridin gastroretentive floating microspheres as an effective controlled-release herbal formulation for the management of peptic ulcer disease and gastric hyperacidity.

Table 2: H^+/K^+-ATPase Inhibition Activity of Optimized Glabridin Gastroretentive Floating Microspheres (O-GFM)

S. No.	Parameter	Observed Value
1	Concentration Tested	100 µg/mL

2	Control Enzyme Activity	100 %
3	Residual Enzyme Activity	28.46 ± 1.24 %
4	Percentage Inhibition	71.54 ± 1.24 %
5	IC_{50} Value	42.18 ± 1.06 µg/mL
6	Standard Drug Used	Omeprazole
7	Percentage Inhibition of Standard	84.36 ± 1.42 %

Conclusion

The optimized gastroretentive floating microspheres of Glabridin demonstrated significant anti-ulcer potential through effective acid neutralization and inhibition of H^+/K^+-ATPase activity. The formulation exhibited prolonged gastric retention, sustained drug release, and enhanced gastroprotective action, indicating its promising application as a controlled-release herbal delivery system for the management of peptic ulcer disease.

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