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FORMULATION AND EVALUATION OF MUCOADHESIVE MICROSPHERES OF REBAMIPIDE

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ABSTRACT

The present study aimed to develop and evaluate chitosan-based mucoadhesive microspheres of rebamipide for sustained gastric drug delivery. Rebamipide-loaded microspheres were prepared using the ionotropic gelation method with sodium tripolyphosphate as a crosslinking agent. Preformulation studies confirmed the identity, purity, and suitability of the drug for formulation development. Six formulations were developed by varying polymer and crosslinker concentrations. The optimized formulation (F3) showed the highest percentage yield (76.65 ± 0.74%) and entrapment efficiency (76.65 ± 0.25%). Particle size analysis revealed nanosized microspheres (225.65 nm) with good stability, as indicated by a zeta potential of −35.65 mV. In vitro release studies demonstrated sustained drug release (98.12% over 12 h) compared to the plain drug. Release kinetics followed zero-order and Korsmeyer–Peppas models, indicating a non-Fickian diffusion mechanism. The results suggest that chitosan-based mucoadhesive microspheres are a promising system for improving the oral delivery of rebamipide.

INTRODUCTION

The advancement of novel drug delivery systems has become a key focus in pharmaceutical research to address the limitations of conventional dosage forms, particularly poor bioavailability and short residence time at the absorption site. Among these systems, mucoadhesive microspheres have gained considerable attention due to their ability to adhere to mucosal surfaces and provide prolonged and controlled drug release, thereby enhancing therapeutic efficacy.[1,4]

The oral route remains the most preferred mode of drug administration owing to its convenience and patient compliance. However, conventional oral formulations often fail to maintain adequate drug concentration at the absorption site because of rapid gastrointestinal transit and extensive first-pass metabolism. Microspheres, owing to their small size and high drug-loading capacity, serve as effective carriers; nevertheless, their clinical performance is frequently limited by insufficient mucosal retention.[4,6]

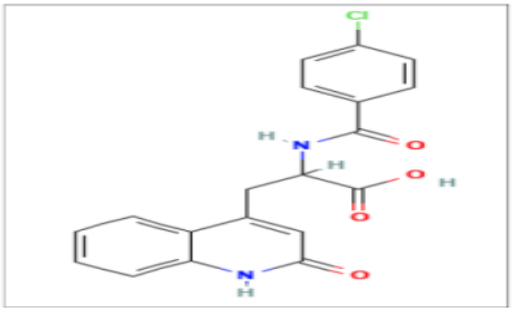
Mucoadhesive microspheres are designed by incorporating bioadhesive polymers into microspheric systems to improve residence time and drug absorption. These systems establish intimate contact with the mucus layer through interfacial interactions, resulting in enhanced bioavailability and site-specific drug delivery. The mechanism of mucoadhesion has been explained by several theories, including electronic, wetting, adsorption, diffusion, mechanical, and cohesive theories, which collectively describe polymer–mucin interactions.[6,9]

A wide range of natural and synthetic polymers such as chitosan, carbomers, hydroxypropyl methylcellulose, sodium alginate, and xanthan gum have been employed in the formulation of mucoadhesive microspheres. These polymers are selected based on their biocompatibility, adhesion strength, stability, and ability to control drug release. Owing to their advantages such as reduced dosing frequency, improved patient compliance, and enhanced therapeutic outcomes, mucoadhesive microspheres represent a promising strategy for targeted and controlled drug delivery applications.[9,12]

The selection of an appropriate mucoadhesive polymer plays a crucial role in the design and performance of mucoadhesive microspheres. Both natural and synthetic polymers have been employed based on their biocompatibility, non-toxicity, non-irritancy, stability, and adhesion properties. Commonly used polymers include chitosan, carbomers, hydroxypropyl methylcellulose, sodium alginate, xanthan gum, and polyvinyl alcohol. These polymers not only impart mucoadhesive properties but also influence drug release kinetics, swelling behavior, and formulation stability.[12,15]

The present study aims to formulate and evaluate mucoadhesive microspheres of **rebamipide**, a gastroprotective agent widely used in the management of gastric ulcers and mucosal injury, with the objective of enhancing its therapeutic efficacy and localized drug delivery. The study focuses on the development of a novel mucoadhesive drug delivery system capable of prolonging the residence time of rebamipide at the gastric mucosa, thereby enabling sustained drug release and improved bioavailability. Mucoadhesive microspheres will be prepared using appropriate natural or synthetic polymers possessing mucoadhesive properties. The formulated microspheres will be optimized and characterized for particle size, surface morphology, drug loading, encapsulation efficiency, and in vitro mucoadhesive behavior. Furthermore, the optimized formulation will be evaluated for in vitro drug release, stability, and compatibility under simulated gastric conditions.

Drug Name: Rebamipide
Chemical Name: 2-(4-chlorobenzoylamino)-3-[2-(1H)-quinolinon-4-yl] propionic acid
Molecular Formula: $C_{19}H_{15}ClN_2O_4$
Molecular Weight: ~370.78 g/mol
Category: Gastroprotective agent, anti-ulcer drug.



Description
Rebamipide is a gastroprotective drug primarily used for the treatment of gastric ulcers and mucosal lesions. It is a white to off-white crystalline powder, practically insoluble in water but soluble in organic solvents such as methanol and dimethyl sulfoxide. Rebamipide is known for its mucosal protective and anti-inflammatory properties.

Mechanism of Action
Rebamipide exerts its gastroprotective action by increasing endogenous prostaglandin production, enhancing mucus secretion, and improving mucosal blood flow. It also scavenges free radicals and suppresses inflammatory cytokines, thereby promoting healing of gastric mucosal damage and protecting against ulcer formation.[15,18]

Pharmacological Actions
- Enhances gastric mucus secretion
- Increases prostaglandin E_2 levels
- Exhibits antioxidant and anti-inflammatory activity
- Promotes epithelial regeneration and mucosal repair

Therapeutic Uses
- Treatment of gastric ulcers
- Management of gastritis and mucosal damage
- Protection against NSAID-induced gastric injury
- Used in ocular formulations for dry eye syndrome (topical use).

Pharmacokinetics
Rebamipide shows limited oral bioavailability due to poor aqueous solubility and rapid gastrointestinal transit. It undergoes minimal metabolism and is primarily excreted via feces. Its short gastric residence time necessitates frequent dosing in conventional dosage forms.

Preformulation Studies of Rebamipide
The preformulation studies of the active pharmaceutical ingredient (API), rebamipide, were conducted to evaluate its physicochemical properties and to assess its suitability for the development of mucoadhesive microspheres. The investigated parameters included organoleptic properties, solubility, loss on drying, melting point, UV–visible spectrophotometric analysis, and Fourier-transform infrared (FTIR) spectroscopy.

Organoleptic Properties
The organoleptic characteristics of rebamipide were evaluated by visual and sensory examination. Rebamipide appeared as a white, odorless, crystalline powder with a bitter taste, indicating acceptable characteristics for oral dosage form development.

Solubility Analysis

Solubility is a critical physicochemical property influencing drug absorption and bioavailability. The solubility of rebamipide was determined in various solvents based on the Indian Pharmacopoeia solubility classification. An accurately weighed quantity (5 mg) of the drug was added to 10 mL of different solvents and shaken at room temperature (21.0 ± 1.5 °C) until equilibrium was achieved. Rebamipide was found to be sparingly soluble in distilled water, 0.1 N HCl, and chloroform, while it exhibited good solubility in methanol, ethanol, and phosphate buffer (pH 7.4).

Loss on Drying

Loss on drying was determined to estimate the moisture content of the drug. Approximately 5 g of rebamipide was analyzed using an IR moisture balance at 100–105 °C until a constant weight was obtained. The percentage loss on drying was found to be 0.149 ± 0.005%, indicating low moisture content and good stability of the drug.

Melting Point

The melting point of rebamipide was determined using the open capillary method to assess purity and thermal behavior. The finely powdered drug was filled into a sealed capillary tube and heated gradually using a melting point apparatus. Rebamipide exhibited a melting point range of 290–292 °C, which was in close agreement with reported literature values, confirming its purity.

UV–Visible Spectrophotometric Analysis

The UV–visible absorption maximum (λmax) of rebamipide was determined using a double-beam UV spectrophotometer. A standard drug solution was prepared in methanol and scanned over the range of 200–400 nm. Rebamipide showed a λmax at 228 nm. A calibration curve was constructed in the concentration range of 5–25 µg/mL using 0.1 N HCl as the diluent. The method demonstrated good linearity with a correlation coefficient (R^2) of 0.998, indicating suitability for quantitative analysis.

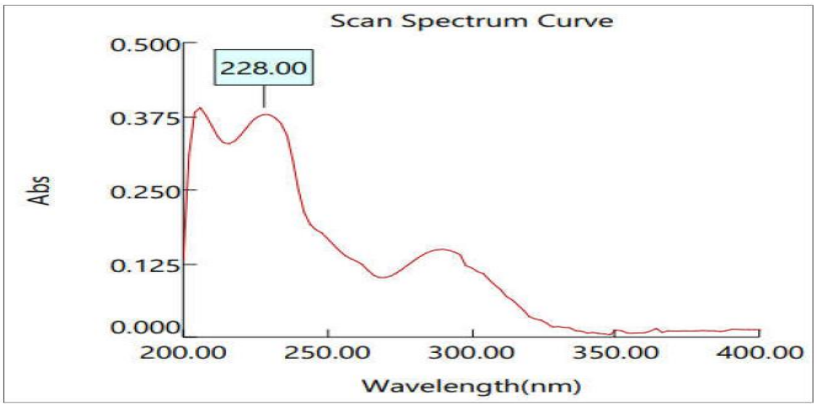


Fig. 1. UV–Visible Spectrophotometric Analysis.

FTIR Spectroscopy

FTIR spectroscopy was performed to identify characteristic functional groups and to confirm the chemical integrity of rebamipide. The drug was mixed with potassium bromide, and pellets were prepared using the KBr pellet method. The spectrum was recorded in the range of 400–2000 cm^{-1}. The FTIR spectrum exhibited characteristic peaks corresponding to –NH/–OH stretching, C=O stretching, aromatic C=C stretching, C–N stretching, and aromatic C–H bending, confirming the purity of the drug and absence of structural abnormalities.

Formulation of Chitosan Mucoadhesive Microspheres of Rebamipide

Chitosan mucoadhesive microspheres containing rebamipide were prepared by the ionotropic gelation technique using sodium tripolyphosphate (STPP) as a crosslinking agent. Briefly, a 1% w/v chitosan solution was prepared by dissolving chitosan in 5% v/v acetic acid under continuous stirring at room temperature. Rebamipide was dissolved in the chitosan solution, followed by dropwise addition of aqueous STPP solution under magnetic stirring. The system was stirred for 30 min to allow microsphere formation. The resulting microspheres were collected by filtration, washed with distilled water, air-dried for 24 h, and further oven-dried at 40 °C. Six formulations (F1–F6) were prepared by varying chitosan and STPP concentrations while maintaining a constant drug load (50 mg) to study the influence of polymer and crosslinker levels on microsphere characteristics.

Evaluation of Mucoadhesive Microspheres

Percentage Yield

The percentage yield of microspheres was calculated by weighing the dried product and comparing it with the total theoretical weight of drug and polymer.

Entrapment Efficiency

Entrapment efficiency was determined by dissolving accurately weighed microspheres in 0.1 N HCl, followed by centrifugation and filtration. The drug content in the supernatant was analyzed spectrophotometrically at 228

nm, and entrapment efficiency was calculated using standard calibration data.

Stability in Acidic Medium

The stability of chitosan microspheres in acidic conditions was assessed by incubating a 0.5% w/v microsphere suspension in 0.1 N HCl for 12 h. Sample transmittance was measured at 228 nm to evaluate polymer integrity and crosslinking efficiency.

Particle Size and Zeta Potential

Mean particle size and zeta potential were measured using photon correlation spectroscopy and electrophoretic mobility analysis, respectively, employing a Malvern particle size analyzer. Measurements were performed in distilled water at 25 °C.

Flow Properties

Flow characteristics were evaluated by determining bulk density, tapped density, Carr's compressibility index, and Hausner's ratio using standard methods to assess the handling and processing behavior of microspheres.

Surface Morphology

The surface morphology and shape of the optimized formulation were examined using scanning electron microscopy (SEM). Samples were gold-coated and scanned at an accelerating voltage of 10 kV to observe surface characteristics.

In Vitro Drug Release Studies

In vitro drug release studies were performed using a USP type I (basket) dissolution apparatus. Microspheres equivalent to 10 mg of rebamipide were placed in hard gelatin capsules and subjected to dissolution in 900 mL of 0.1 N HCl at 37 ± 0.2 °C with a stirring speed of 100 rpm. Samples were withdrawn at predetermined intervals, filtered, and analyzed spectrophotometrically at 228 nm. Fresh dissolution medium was used to maintain sink conditions.

Drug Release Kinetic Analysis

Release data were fitted to zero-order, first-order, Higuchi, and Korsmeyer–Peppas kinetic models to elucidate the mechanism of drug release. The release exponent (n) from the Korsmeyer–Peppas model was used to characterize the release mechanism as Fickian, non-Fickian, or case II transport.

Stability Studies

Stability studies of the optimized formulation (F3) were conducted for three months at refrigerated (4 °C) and room temperature (25–28 ± 2 °C) conditions. Stability was evaluated based on entrapment efficiency, particle size, and physical appearance. The formulation remained stable under refrigerated conditions but showed reduced stability at room temperature.

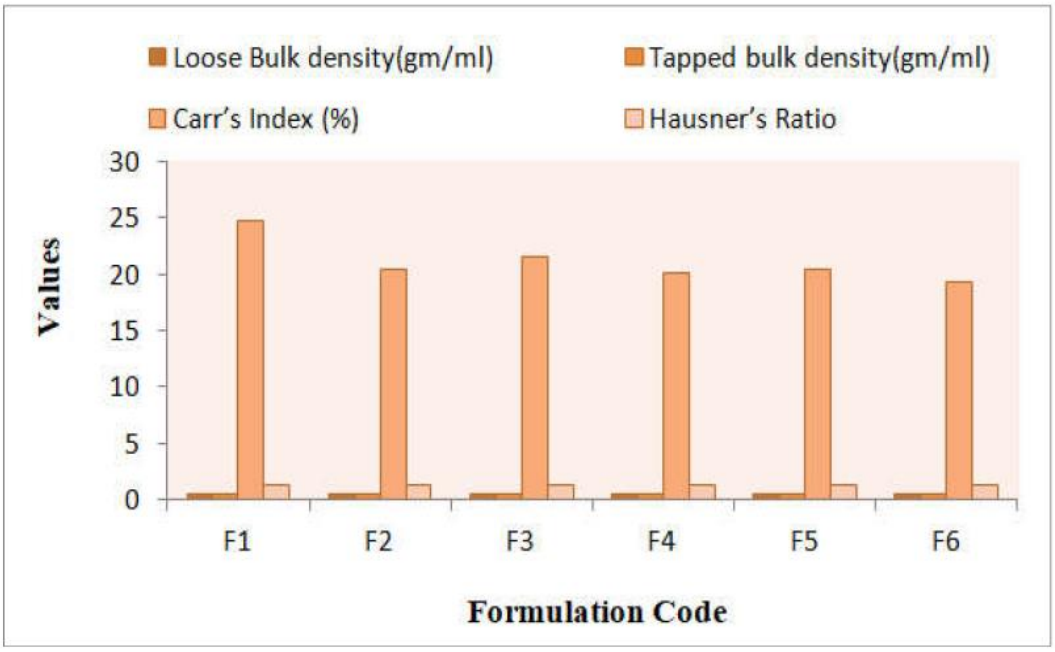


Fig.: Graph of Flow Properties of different microspheres formulations.

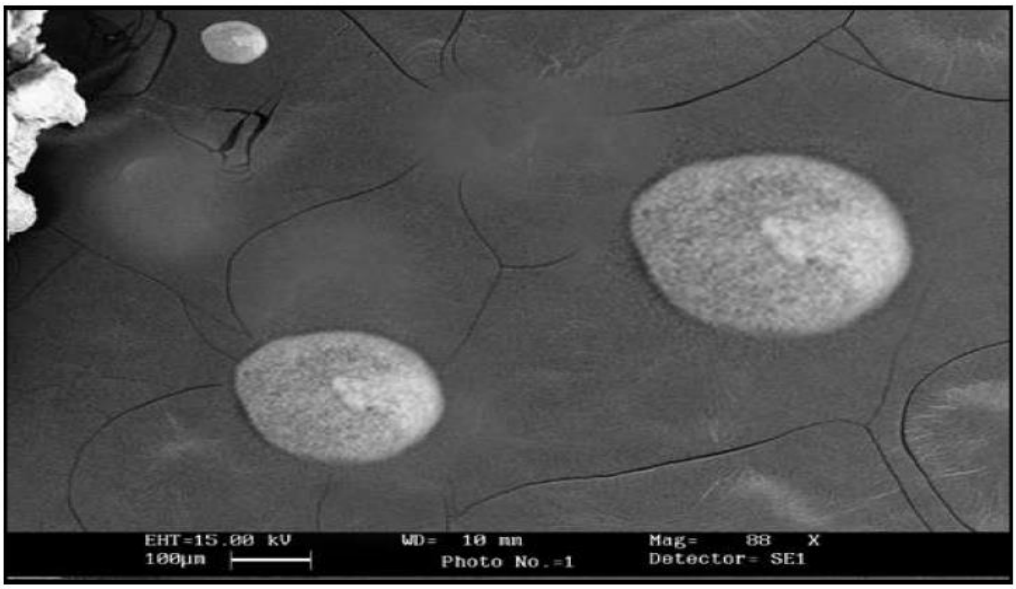


Fig: Scanning Electron Microscope of optimized formulation (F3).

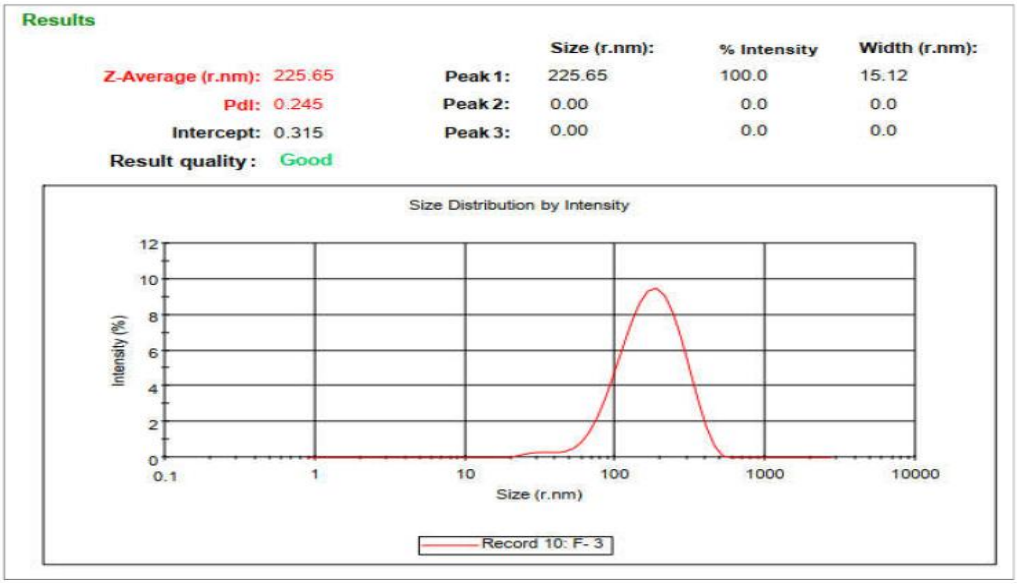


Fig.: Particle size data of chitosan microspheres (F3).

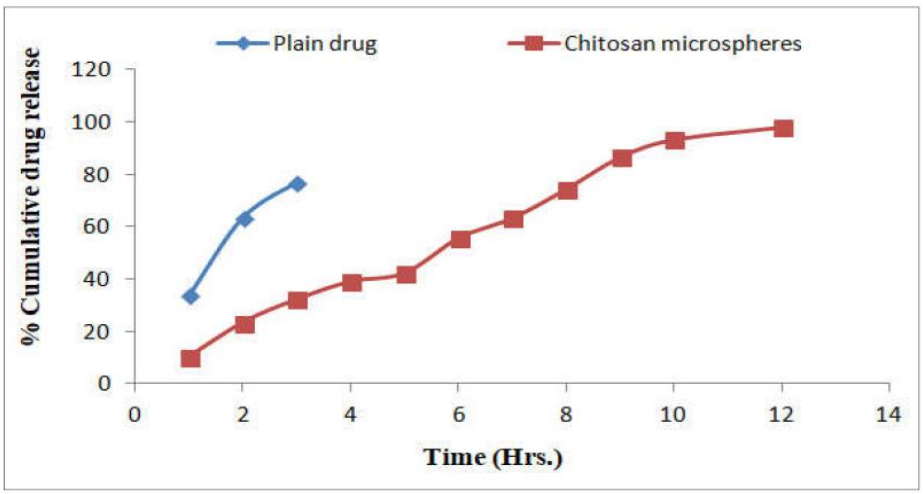


Fig: Graph of cumulative % release of Rebamipide from plain drug and chitosan microspheres.

Table: Characterization of stability study of optimized formulation of microspheres (F3)

Characteristic	Time (Month)		
	1 Month	2 Month	3 Month
Temperature	4.0 ± 0.2 °C / 25–28 ± 2 °C	4.0 ± 0.2 °C / 25–28 ± 2 °C	4.0 ± 0.2 °C / 25–28 ± 2 °C
Average Particle Size (nm)	225.65/ 315.65	211.75 / 320.45	213.20 / 325.85
% Entrapment Efficiency (%EE)	75.23 / 65.45	74.68 / 63.95	74.10 / 62.55
Physical Appearance	Normal / Normal	Normal / Normal	Normal / Slightly opaque

RESULT AND DISCUSSION

Rebamipide was systematically characterized for its organoleptic, physicochemical, and spectral properties to confirm its identity, purity, and suitability for formulation development. The drug was obtained as a white, odorless, crystalline powder with a bitter taste, in agreement with reported literature values. Solubility studies demonstrated that rebamipide is sparingly soluble in water, 0.1 N HCl, and chloroform, while showing good solubility in ethanol, methanol, and phosphate buffer (pH 7.4), indicating preferential solubility in polar solvents. The observed melting point (290–292 °C) closely corresponded to the reported standard range (288–290 °C), confirming the purity of the drug. Loss on drying was found to be 0.149 ± 0.005%, reflecting low moisture content and adequate stability under laboratory conditions.

UV spectrophotometric analysis showed a linear response in the concentration range of 5–25 µg/mL with a regression equation of $y = 0.034x - 0.013$ and a high correlation coefficient ($R^2 = 0.998$), indicating the suitability of the method for quantitative estimation. FTIR spectral analysis further confirmed the chemical identity of rebamipide through the presence of characteristic functional groups, including –NH/–OH stretching, C=O stretching, aromatic C=C stretching, C–N stretching, and aromatic C–H bending vibrations.

Rebamipide-loaded chitosan microspheres were successfully prepared using the ionotropic gelation technique with sodium tripolyphosphate as the crosslinking agent. Six formulations (F1–F6) were developed to investigate the effect of varying polymer and crosslinker concentrations on microsphere characteristics. The percentage yield ranged from 68.74 ± 0.55% to 76.65 ± 0.74%, with formulation F3 exhibiting the highest yield, suggesting an optimal polymer-to-crosslinker ratio. Entrapment efficiency varied between 65.58 ± 0.45% and 76.65 ± 0.25%, with F3 again showing superior encapsulation, attributed to efficient crosslinking and uniform microsphere formation.

Particle size analysis of the optimized formulation (F3) revealed an average particle size of 225.65 nm, indicating nanosized particles suitable for controlled drug delivery. The zeta potential of −35.65 mV suggested good colloidal stability due to sufficient electrostatic repulsion. Flow property evaluation demonstrated acceptable flow behavior, as indicated by Carr's index values of 19.22–24.78% and Hausner's ratio of 1.238–1.329, confirming suitability for further pharmaceutical processing. SEM analysis of formulation F3 revealed smooth, spherical, and uniformly distributed microspheres without surface defects, supporting the structural integrity of the formulation.

In vitro drug release studies conducted in simulated gastric fluid (pH 1.2) showed a sustained release pattern from chitosan microspheres compared to the plain drug. The optimized formulation (F3) achieved a controlled release of 98.12% over 12 h, whereas the plain drug exhibited rapid release, exceeding 70% within the first 3 h. This sustained release behavior highlights the effectiveness of the chitosan matrix in prolonging drug release. Release kinetics analysis indicated that the formulation followed zero-order kinetics ($R^2 = 0.9817$) and best fit the Korsmeyer–Peppas model ($R^2 = 0.989$), suggesting a non-Fickian diffusion mechanism involving both diffusion and polymer relaxation.

Stability studies of the optimized formulation (F3) conducted over three months at refrigerated and room temperature conditions demonstrated no significant changes in particle size, entrapment efficiency, or physical appearance. Although slight opacity was observed at room temperature after three months, the formulation remained stable overall.

In conclusion, rebamipide-loaded chitosan microspheres prepared by ionotropic gelation represent a promising sustained-release oral delivery system. The optimized formulation (F3) exhibited high entrapment efficiency, good physicochemical stability, and effective controlled drug release, indicating its potential to enhance bioavailability and therapeutic efficacy of rebamipide in the management of gastric mucosal disorders.

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