RESEARCH PAPER

Formulation and Evaluation of Mucoadhesive Microspheres Loaded with Antiulcer Drug

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Abstract

The present study aimed to develop and evaluate gastro-retentive mucoadhesive microspheres of esomeprazole for the effective management of *Helicobacter pylori*-associated gastric ulcer. Gastro-retentive drug delivery systems (GRDDS) are designed to prolong the residence time of dosage forms in the stomach, thereby enhancing local drug availability, improving therapeutic efficacy, and minimizing dosing frequency. Mucoadhesive microspheres of esomeprazole were prepared using an emulsification cross-linking technique with hydroxypropyl methylcellulose (HPMC), chitosan, and Acrycoat S100 at different polymer ratios. The prepared formulations were characterized for drug-excipient compatibility, percentage yield, micromeritic properties, particle size, drug content, entrapment efficiency, drug loading, swelling index, in vitro drug release, and release kinetics. Fourier-transform infrared (FTIR) spectroscopy confirmed the absence of significant drug-polymer interactions, indicating good compatibility between esomeprazole and the selected excipients. Among all the formulations, formulation EM8 containing HPMC and Acrycoat S100 exhibited the most desirable sustained drug release profile, extending up to 12 h with controlled release characteristics. The optimized formulation demonstrated excellent mucoadhesive properties and prolonged drug release, suggesting its potential as a promising gastro-retentive delivery system for the sustained treatment of *H. pylori*-associated gastric disorders.

Keywords: Esomeprazole, Gastro-retentive drug delivery system, Mucoadhesive microspheres, HPMC, Chitosan, Acrycoat S100, Sustained release.

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Introduction

Peptic ulcer disease (PUD) is a common gastrointestinal disorder characterized by the formation of ulcers in the gastric or proximal duodenal mucosa. The major etiological factors responsible for PUD include infection with *Helicobacter pylori* and prolonged use of non-steroidal anti-inflammatory drugs (NSAIDs). *H. pylori* colonizes the gastric mucosa and induces chronic inflammation, resulting in mucosal injury and ulcer formation. Although *H. pylori* infection is highly prevalent worldwide, only a small proportion of infected individuals develop clinically significant peptic ulcers, indicating the involvement of bacterial virulence factors, host immune responses, and environmental influences.

The clinical manifestations of peptic ulcer disease include epigastric pain, abdominal discomfort, nocturnal pain, nausea, reduced appetite, and weight loss. Eradication of *H. pylori* remains the cornerstone of ulcer management, requiring adequate local drug concentrations in the gastric environment for prolonged periods. However, conventional oral dosage forms often exhibit limited therapeutic efficacy because of rapid gastric emptying, resulting in insufficient gastric residence time and reduced drug availability at the site of infection.

Gastro-retentive drug delivery systems (GRDDS) have emerged as an effective strategy to overcome these limitations by prolonging gastric residence time and facilitating sustained drug release in the stomach. Such systems enhance local drug concentration, improve bioavailability, reduce dosing frequency, and increase patient compliance. Various approaches have been explored to achieve gastric retention, including floating systems, expandable systems, high-density systems, magnetic systems, and mucoadhesive drug delivery systems.

Floating drug delivery systems (FDDS), also known as hydrodynamically balanced systems, possess a bulk density lower than that of gastric fluids, enabling them to remain buoyant in the stomach for extended periods without significantly affecting gastric emptying. Their prolonged gastric residence facilitates continuous drug release in the upper gastrointestinal tract, making them particularly suitable for drugs with a narrow absorption window, poor intestinal stability, or local

gastric action.

Mucoadhesive drug delivery systems offer an additional advantage by adhering to the gastric mucosal surface through interactions with mucus glycoproteins. This intimate contact prolongs the residence time of the dosage form at the target site and enhances drug absorption. The combination of floating and mucoadhesive properties provides synergistic benefits by simultaneously increasing gastric retention and maintaining close contact with the gastric mucosa, thereby improving therapeutic outcomes against *H. pylori* infection.

Microspheres are free-flowing spherical particulate systems, generally ranging from 1 to 1000 µm in diameter, that have attracted considerable attention as controlled drug delivery carriers. Their small size, large surface area, high encapsulation efficiency, and ability to provide sustained drug release make them suitable for gastro-retentive applications. Polymer-based mucoadhesive microspheres can effectively control drug release while maintaining prolonged contact with the gastric mucosa.

Considering these advantages, the present study was undertaken to formulate and evaluate gastro-retentive mucoadhesive microspheres of esomeprazole using HPMC, chitosan, and Acrycoat S100. The developed microspheres were characterized for their physicochemical properties, drug entrapment efficiency, swelling behavior, and in vitro drug release performance to identify an optimized formulation capable of providing sustained gastric drug delivery for improved management of *H. pylori*-associated peptic ulcer disease.

Materials and Methods

Materials

Esomeprazole was procured from Yarrow Chemicals, India. Hydroxypropyl methylcellulose (HPMC), chitosan, and Acrycoat S100 were obtained from Nice Chemicals, India. Petroleum ether, light liquid paraffin, Span 80, Tween 80, glutaraldehyde, potassium bromide, methanol, hydrochloric acid, and all other analytical-grade reagents and solvents were used as received without further purification.

Methods

Preformulation Studies

Organoleptic Evaluation: The organoleptic characteristics of esomeprazole, including colour, appearance, texture, and odour, were examined visually and recorded to assess the physical identity and quality of the drug.

Microscopic Examination: The morphology of esomeprazole powder was evaluated using a phase-contrast microscope. A small quantity of the drug was uniformly spread on a clean glass slide and observed under appropriate magnification to determine the particle shape and surface characteristics.

Determination of Melting Point: The melting point of esomeprazole was determined using the capillary tube method. A small quantity of the drug was packed into a sealed capillary tube and placed in a digital melting point apparatus. The temperature at which complete melting occurred was recorded.

Solubility Study: The solubility of esomeprazole was evaluated in different solvents, including distilled water, methanol, and glacial acetic acid, following pharmacopeial procedures. An accurately weighed quantity of drug was added to the respective solvent, and solubility was determined based on complete dissolution. The drug was classified as very soluble, freely soluble, soluble, sparingly soluble, slightly soluble, or very slightly soluble according to standard pharmacopeial criteria.

Fourier Transform Infrared (FTIR) Spectroscopy: Drug-excipient compatibility was investigated using FTIR spectroscopy. Physical mixtures of esomeprazole and individual excipients were prepared in a 1:1 ratio and stored in airtight containers for one month. Samples were mixed with potassium bromide, compressed into pellets, and scanned over the spectral range of 4000–500 cm^{-1}. The obtained spectra were compared with that of pure esomeprazole to identify any significant changes in characteristic absorption peaks indicative of chemical interaction.

Determination of λmax: The maximum absorption wavelength (λmax) of esomeprazole was determined using a UV–Visible spectrophotometer. A standard solution of the drug in 0.1 N hydrochloric acid was scanned over the wavelength range of 200–400 nm, and the wavelength showing maximum absorbance was selected for subsequent quantitative analysis.

Preparation of Calibration Curve: A primary stock solution of esomeprazole was prepared in 0.1 N hydrochloric acid. Appropriate aliquots were diluted to obtain concentrations of 2, 4, 6, 8, and 10 µg/mL. The absorbance of each solution was measured at the predetermined λmax, and a calibration curve was constructed by plotting absorbance against concentration.

Preparation of Mucoadhesive Microspheres: Method of Preparation of Mucoadhesive Microspheres

Mucoadhesive microspheres containing esomeprazole were prepared by the emulsion solvent evaporation technique. The compositions of different formulations (EM1–EM8) are presented in the table above. Initially, 100 mg of esomeprazole was accurately weighed and dissolved or uniformly dispersed in a suitable organic solvent system containing HPMC along with either

chitosan or Acrycoat S100 according to the formulation composition. HPMC was kept constant at 100 mg in all formulations, whereas the amount of chitosan (500 or 1000 mg) or Acrycoat S100 (500 or 1000 mg) was varied. Chitosan-containing formulations were prepared by dissolving chitosan in 1% (v/v) acetic acid before mixing with the drug-polymer solution, while Acrycoat S100 formulations were prepared by dissolving the polymer in ethanol–acetone (1:1) or another suitable organic solvent. The resulting polymeric solution was slowly added dropwise into 100 mL of liquid paraffin containing Span 80 (5 or 10 mL, as specified in the formulation table) under continuous stirring using a mechanical stirrer at 1000–1200 rpm. Stirring was continued for 3–4 hours at room temperature to allow complete evaporation of the organic solvent, resulting in the formation of discrete mucoadhesive microspheres. The formed microspheres were collected by filtration and washed repeatedly with n-hexane or petroleum ether to remove residual liquid paraffin and excess surfactant. The washed microspheres were then dried at room temperature for 24 hours followed by drying in a hot-air oven at 40°C until a constant weight was obtained. The dried microspheres were stored in airtight containers over a desiccant until further characterization.

Table No.1: Formulation of mucoadhesive microspheres

F. Code	HPMC (mg)	Chitosan (mg)	Acrycoat S100 (mg)	Span 80
EM1	100	500	0	5
EM2	100	1000	0	5
EM3	100	0	500	5
EM4	100	0	1000	5
EM5	100	500	0	10
EM6	100	1000	0	10
EM7	100	0	500	10
EM8	100	0	1000	10

Evaluation:

Particle Size Analysis: The mean particle size of the prepared mucoadhesive microspheres was determined using an optical microscope (BEM-21, Besto Microscope, India) equipped with a calibrated ocular micrometer and stage micrometer. Approximately 200–300 microspheres were randomly selected from each formulation, and their diameters were measured under suitable magnification. The average particle size was calculated by taking the arithmetic mean of the measured particle diameters.

Micromeritic Properties: The flow and packing characteristics of the prepared mucoadhesive microspheres were evaluated by determining their micromeritic properties, including bulk density, tapped density, Carr's compressibility index, Hausner's ratio, true density, and angle of repose. Bulk and tapped densities were determined using standard graduated cylinder methods, while the angle of repose was measured by the fixed funnel method. Carr's compressibility index and Hausner's ratio were calculated using the measured bulk and tapped density values to assess the flowability of the microspheres.

Percentage Yield: The percentage yield of the prepared mucoadhesive microspheres was determined to evaluate the efficiency of the formulation process. After preparation, the microspheres were collected, dried to a constant weight, and accurately weighed. The practical yield obtained was compared with the theoretical weight of all formulation components used during preparation. The percentage yield was calculated using the following equation:

$$\text{Percentage Yield (\%)} = \frac{\text{Actual weight of microspheres}}{\text{Theoretical weight of formulation components}} \times 100$$

Drug Entrapment Efficiency: The drug entrapment efficiency of the microspheres was determined by estimating the amount of esomeprazole encapsulated within the polymeric matrix. Microspheres equivalent to 100 mg of esomeprazole were accurately weighed and finely powdered using a glass mortar and pestle. The powdered sample was transferred into a 100 mL volumetric flask containing 0.1 N hydrochloric acid (HCl) and allowed to stand for 24 h with occasional shaking to ensure complete extraction of the drug. The resulting solution was filtered through Whatman filter paper. An aliquot of 1 mL of the filtrate was diluted to 25 mL with 0.1 N HCl and analyzed using a UV–Visible spectrophotometer (Shimadzu UV-1800, Japan) at a wavelength of 262 nm. The drug entrapment efficiency was calculated using the following equation:

$$\text{Drug Entrapment Efficiency (\%)} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100$$

Swelling Study: The swelling behavior of the prepared mucoadhesive microspheres was evaluated in 0.1 N hydrochloric acid (pH 1.2) to simulate gastric conditions. Accurately weighed microspheres (50 mg) from each formulation were immersed in the dissolution medium and allowed to swell for 24 h at room temperature. At predetermined intervals, the swollen microspheres were carefully removed, gently blotted with filter paper to eliminate excess surface moisture, and immediately weighed using a digital analytical balance. The swelling index was calculated using the following equation:

$$\text{Swelling Index (\%)} = \frac{W_t - W_0}{W_0} \times 100$$

where:

- W_t= Weight of swollen microspheres at time *t*
- W_0= Initial weight of dry microspheres

In Vitro Mucoadhesion Study: The mucoadhesive properties of the prepared microspheres were evaluated using the falling liquid film technique. Fresh sheep gastric mucosa was obtained from a local slaughterhouse within 1 h of animal sacrifice and thoroughly rinsed with isotonic saline solution to remove adhering mucus and debris. A mucosal section measuring approximately 4 × 2 cm was carefully mounted onto a clean glass slide. Approximately 50 mg of accurately weighed microspheres were uniformly distributed over the surface of the mucosal tissue. The assembly was placed in a desiccator maintained at approximately 90% relative humidity for 15 min to facilitate interaction between the microspheres and the mucosal surface. Subsequently, the glass slide was fixed at an inclination of 45°. A reservoir containing prewarmed 0.1 N hydrochloric acid (pH 1.2) maintained at 37 ± 0.5°C was positioned above the mounted tissue. The dissolution medium was allowed to flow continuously over the mucosal surface at a rate of 1 mL/min for 5 min using a peristaltic pump. At the end of the experiment, the microspheres detached from the mucosal surface were collected, dried, and weighed. The percentage of mucoadhesion was calculated using the following equation:

$$\text{Mucoadhesion (\%)} = \frac{W_i - W_d}{W_i} \times 100$$

where:

- W_i= Initial weight of microspheres applied
- W_d= Weight of microspheres detached after washing

A higher percentage value indicated stronger mucoadhesive properties of the microspheres.

Result and discussion:

The micromeritic characteristics of the prepared mucoadhesive microspheres are summarized in Table 2. The mean particle size of the formulations ranged from 237.13 ± 3.65 µm (EM3) to 250.34 ± 3.67 µm (EM5), indicating successful preparation of microspheres with relatively uniform size distribution. The bulk density varied between 0.32 ± 0.018 and 0.42 ± 0.011 g/cm³, while tapped density ranged from 0.38 ± 0.017 to 0.47 ± 0.012 g/cm³. The calculated Carr's index values ranged from 10.63 ± 0.13% to 15.90 ± 1.07%, indicating good to excellent flow characteristics of all formulations. Similarly, the angle of repose was found between 24.25 ± 1.23° and 31.02 ± 2.18°, confirming satisfactory flowability suitable for further pharmaceutical processing. The percentage yield of the prepared microspheres ranged from 86.12 ± 2.46% (EM1) to 92.87 ± 2.54% (EM8), demonstrating the efficiency and reproducibility of the emulsification-solvent evaporation technique. Drug entrapment efficiency varied from 83.30 ± 1.73% to 88.70 ± 1.29%, with formulation EM8 exhibiting the highest encapsulation efficiency, followed closely by EM6 (87.41 ± 1.11%) and EM4 (87.17 ± 1.05%). The high encapsulation efficiencies indicate effective incorporation of esomeprazole within the polymeric matrix. The degree of swelling differed markedly among the formulations depending on polymer composition. The lowest swelling index was observed with EM1 (1.31 ± 0.22), whereas EM6 exhibited the highest swelling index (26.31 ± 2.22), followed by EM2 (21.12 ± 4.22). Formulation EM5 showed an intermediate swelling value (7.21 ± 1.22), while the remaining formulations displayed comparatively low swelling indices (1.32–1.76). These findings indicate that the type and concentration of polymer significantly influenced the hydration and swelling behavior of the prepared mucoadhesive microspheres. Overall, all formulations exhibited satisfactory micromeritic properties, high production yield, efficient drug entrapment, and acceptable flow characteristics, making them suitable candidates for gastro-retentive drug delivery.

The UV spectrum of esomeprazole in simulated gastric fluid (pH 1.2) was recorded over the wavelength range of 200–400 nm. The drug exhibited a distinct absorption maximum (λmax) at 262.0 nm, which was selected as the analytical wavelength for subsequent quantitative estimations (Figure 1). The sharp and well-defined absorption peak confirmed the suitability of the selected wavelength for spectrophotometric analysis. A calibration curve of esomeprazole was constructed in simulated gastric

fluid (pH 1.2) at 262.0 nm (Figure 2). The absorbance increased linearly with increasing drug concentration, indicating good compliance with Beer–Lambert's law over the selected concentration range. The standard curve demonstrated excellent linearity, validating the method for quantitative estimation of esomeprazole during formulation and in vitro drug release studies. The Fourier Transform Infrared (FTIR) spectra of pure esomeprazole and its physical mixture with formulation excipients are presented in Figure 3. The characteristic absorption peaks of esomeprazole were retained in the physical mixture without any significant shift, disappearance, or appearance of new peaks. These observations indicate the absence of any chemical interaction between esomeprazole and the selected excipients, confirming their compatibility for the preparation of mucoadhesive microspheres. The zero-order release plots of formulations EM1–EM8 are presented in Figure 4. The plots demonstrated a nearly linear relationship between cumulative drug release and time, indicating sustained release characteristics of the prepared mucoadhesive microspheres. The release profiles suggested that the polymer composition effectively controlled drug diffusion and prolonged drug release over the study period.

Discussion: The micromeritic evaluation demonstrated that the prepared esomeprazole-loaded mucoadhesive microspheres possessed suitable characteristics for gastro-retentive drug delivery. Particle sizes ranging from 237.13 ± 3.65 to 250.34 ± 3.67 µm indicated uniform microsphere formation by the emulsification–solvent evaporation method, while the narrow size distribution supports consistent drug loading and controlled release. Bulk density, tapped density, Carr's index (<16%), and angle of repose (<35°) confirmed good flowability and packing properties, indicating suitability for further pharmaceutical processing. Percentage yield (86.12–92.87%) reflected the efficiency and reproducibility of the preparation method, whereas drug entrapment efficiency (83.30–88.70%) demonstrated effective incorporation of esomeprazole within the polymeric matrix. Higher polymer concentrations enhanced encapsulation by minimizing drug diffusion during emulsification. Swelling studies revealed that formulations containing higher levels of HPMC and chitosan, particularly EM6 and EM2, exhibited greater hydration, which is expected to improve mucoadhesion and sustain drug release. UV spectrophotometric analysis established 262.0 nm as the λmax of esomeprazole in simulated gastric fluid, with the calibration curve showing excellent linearity for accurate drug estimation. FTIR studies confirmed the absence of significant drug–excipient interactions, indicating compatibility and preservation of drug stability. The zero-order release profiles demonstrated sustained and controlled drug release, attributable to the hydrated polymeric matrix formed by HPMC, chitosan, and Acrycoat S100, which effectively regulated drug diffusion. Overall, the results indicate that the prepared microspheres possessed excellent physicochemical properties, high encapsulation efficiency, satisfactory compatibility, and prolonged drug release. Among the formulations, EM6 and EM8 exhibited the most favorable characteristics, suggesting their potential as promising gastro-retentive delivery systems for improving the therapeutic efficacy of esomeprazole in the treatment of *Helicobacter pylori* infection.

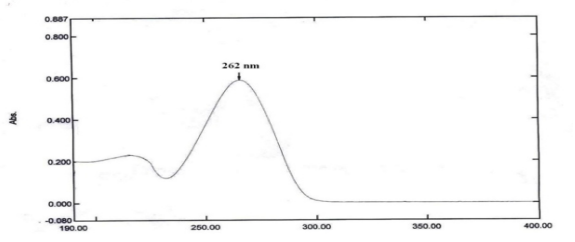

Figure 1: UV absorption maxima of drug in simulated gastric fluid (pH 1.2) at λmax 262.0 nm

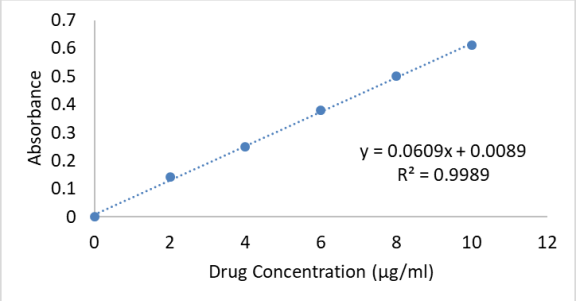

Figure 2: Standard Curve of drug in simulated gastric fluid (pH 1.2) at 262.0 nm

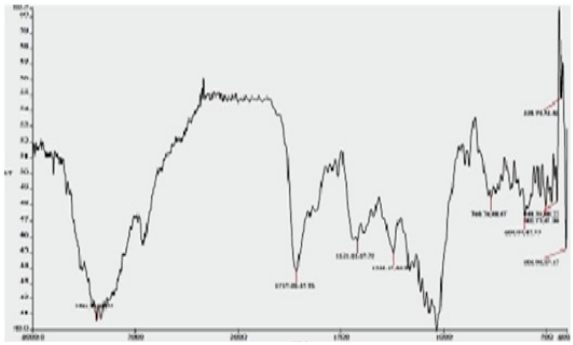

Figure 3: FTIR spectra of esomeprazole with excipient

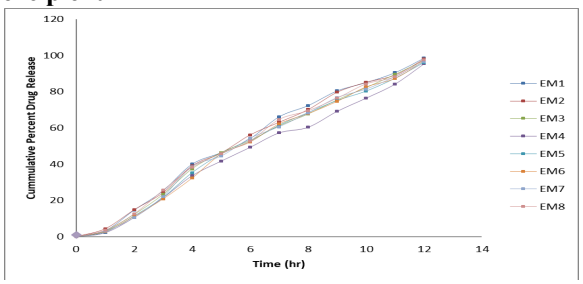

Figure 4: Zero-order plots of mucoadhesive microsphere of esomeprazole (EM1 – EM8)

Table 2: Micromeritic properties of prepared mucoadhesive microspheres

F. Code	Mean particle size[b] (µm)	Bulk density[a] (g/cm^3)	Tapped density[a] (g/cm^3)	Carr's index[a] (%)	Angle of repose[a] (Θ°)	Percentage yield	Percent entrapment	Degree of swelling
EM1	246.12 ±2.11	0.37± 0.021	0.44± 0.021	15.90 ±1.07	25.12 ±1.60°	86.12 ±2.46	83.3± 1.73	1.31 ±0.22
EM2	244.42 ±3.25	0.34± 0.012	0.41± 0.015	12.48 ±0.01	30.58 ±2.58°	91.85 ±2.46	86.4± 1.21	21.12 ±4.22
EM3	237.13 ±3.65	0.36± 0.028	0.42± 0.007	14.28 ± 0.25	25.22 ±1.16°	87.56 ±1.41	83.45 ±1.89	1.32 ±0.25
EM4	241.16 ±2.16	0.35± 0.011	0.42± 0.011	12.16 ±0.01	31.02 ±2.18°	92.85 ±2.58	87.17 ±1.05	1.73 ±0.54
EM5	250.34 ±3.	0.42± 0.0	0.47± 0.0	10.63 ±0.	24.25 ±1.	87.56 ±2.	84.1± 1.6	7.21 ±1.
	67	11	12	13	23°	41	8	22
EM6	248.14 ±2.47	0.41± 0.014	0.46± 0.014	14.23 ±1.25	28.11 ±1.21°	92.87 ±2.01	87.41 ±1.11	26.31 ±2.22
EM7	248.93 ±3.92	0.40± 0.017	0.45± 0.012	11.11 ±0.97	24.91 ±1.20°	87.95 ±2.48	84.7± 2.13	1.34 ±0.64
EM8	246.28 ±4.38	0.32± 0.018	0.38± 0.017	11.14 ± 0.15	28.45 ±1.56°	92.87 ±2.54	88.7± 1.29	1.76 ±0.62

Conclusion:

There are different types of ulcers and the most common are peptic ulcer. There is no single cause has been found for ulcers. Ulcers are mostly caused by an infection with a type of bacteria called *Helicobacter pylori*. Peptic ulcer will get worse if not treated. Treatment may include medicines to reduce stomach acids or to kill *H.pylori.* The development of formulation in the form of mucoadhesive would be an ideal approach to delivery such drug. Here the formulated floating mucoadhesive microsphere containing esomeprazole prepared with varying ratio of chitosan, HPMC and acrycoat S100 produce prolong the gastric retention and maximize drug release to the specific site by mucoadhesion on gastric fluid and adhering to the mucous layer in the treatment of peptic ulcer.

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