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Formulation and Characterization of the Esomeprazole Microsponge Loaded *in-situ* Gel

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Abstract

Background: This study investigates establishing a novel therapeutic approach to treating peptic ulcers that uses an *in-situ* gel microsponge incorporating esomeprazole. Microsponges carrying esomeprazole magnesium, ethyl cellulose, and Eudragit RS-100 were developed via a quasi-emulsion solvent diffusion technique. **Methods:** Five formulations were developed and analyzed for entrapment efficiency, drug content, yield, and particle size. **Results:** From all the five formulations, the F3 formulation showed the maximum results in terms of high drug content (85.24%), entrapment efficacy (85.67 %), particle size (8.36$\pm$0.43 μm), and production yield (87.35%). Then the microsponges were incorporated with the Poloxamer 188 to form *in-situ* gel. The formulation (F3) demonstrated appropriate viscosity (38cps), gelling time (11.95$\pm$0.56 sec), and gelling capacity (++). The in-vitro drug release profile revealed that formulation F3 exhibited an extended drug release rate (92.18%). Stability studies indicated minimal changes in particle size (8.36$\pm$0.43) and entrapment efficiency (85.67) over three months. **Conclusion:** This innovative Esomeprazole-loaded microsponge *in- situ* gel formulation is promising to enhance drug delivery, prolong drug release, and improve patient compliance in peptic ulcer therapy.

Keywords: Microsponge; Esomeprazole; Gastric; Peptic Ulcer; In-situ gel

1 Introduction

Gastric disorders are prevalent medical conditions affecting millions of individuals worldwide. These disorders are characterized by a range of symptoms, including heartburn, nausea, vomiting, and bloating. the years, various drug systems have been developed to manage these symptoms.

Ulcers are characterized histologically as a part of the mucosa of the GI tract through the muscularis mucosae into the submucosa or more inside part of the GI tract mucous membrane. The ulcer can affect any part of the gastrointestinal tract contact with more secretion of acid peptic juices. The gastric ulcer is generalized

into Aphthous ulcers, Esophageal ulcers, and Peptic ulcers based on their affected area in the gastrointestinal tract in the mouth, throat, and stomach or the duodenum separately.[1,2] Peptic ulcers are chronic, frequently develop lesions that happen in any part of the gastrointestinal tract due to the greater amount of secretion of acid peptic juices. Peptic ulcers develop in several parts of the gastrointestinal tract (GIT) which are exposed to gastric acid and pepsin, for example, the stomach and duodenum. Peptic ulcers are generally induced in rodents by physiological, pharmacological, or other surgical medicines that have etiological significance for stimulation of peptic ulcers. A few models are referenced in the following which are utilized tentatively for testing or assessing against peptic ulcer action of medications.[3]

A variety of cutting-edge techniques are being used in modern medicine to treat peptic ulcers. These techniques include state-of-the-art procedures including biological therapies, probiotics and gut microbiome modification, personalized medicine, nanotechnology, and treatments based on certain biomarkers. Mucoadhesive drug delivery systems are one of these progressive techniques that represent a progressive change in the treatment landscape for gastric illnesses. They provide more accurate and efficacious treatment approaches that can greatly improve patient outcomes and general well-being. The application of these cutting-edge techniques denotes a breakthrough in the sector and gives patients suffering from stomach health problems hope for more effective and focused treatment alternatives.[4]

Gastroretentive drug delivery system is a novel pathway in pharmaceutical products. The systems are provided to retain the dosage forms in the gastrointestinal tract for a prolonged period before it reaches its absorption site, slowly releasing the drug and long of retention in the stomach, consequently increasing bioavailability, reducing drug wastage, and drugs are highly soluble at less pH condition, but drugs are less soluble at high pH condition. The aim of the study is the integration of microsponges with the mucoadhesive *in-situ* gels. These gels are basically in liquid form before installation but after installation, it undergoes gelation in the stomach and thus slowly release the medicament. The advantages of *in-situ* gels are that they can be easily administered, cause a reduction in the frequency of dosing, and increase patient compliance.[5]

Esomeprazole is a proton pump inhibitor used to treat GERD, reduce the risk of NSAID-associated gastric ulcers, eradicate H. pylori, and treat conditions causing gastric acid hypersecretion. Esomeprazole is a compound that inhibits gastric acid secretion and is indicated in the treatment of gastroesophageal reflux disease (GERD), the healing of erosive esophagitis, and H. pylori eradication to reduce the risk of duodenal ulcer recurrence. Esomeprazole belongs to a new class of antisecretory compounds, the substituted benzimidazoles, that do not exhibit anticholinergic or H2 histamine antagonistic properties, but that suppress gastric acid secretion by specific inhibition of the H+/K+ ATPase at the secretory surface of the gastric parietal cell. By doing so, it inhibits acid secretion into the gastric lumen. This effect is dose-related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus.[6]

Market expansion, technology breakthroughs, and changing medical procedures have all fueled recent developments in studying esomeprazole active pharmaceutical ingredients (APIs). The market for esomeprazole API has grown significantly in the last several years. The global market for esomeprazole sodium API was estimated to be worth USD 1.2 billion in 2023 and is expected to increase at a compound yearly growth rate (CAGR) of 6.2% to reach USD 2.1 billion by 2032. Comparably, the market for esomeprazole magnesium API was estimated to be worth USD 800 million in 2023 and is expected to grow at a compound annual growth rate (CAGR) of 4.5% to reach USD 1.2 billion by 2032. The increased incidence of gastrointestinal illnesses and the growing need for efficient proton pump inhibitors are the main drivers of this growth. With businesses concentrating on creating more effective and tailored treatments to improve patient outcomes, the growing market has also increased spending on pharmaceutical research and development. To enhance the efficacy and safety profiles of esomeprazole formulations, these initiatives involve investigating innovative drug delivery methods and combination treatments.[7] Research on esomeprazole has also been in the incorporation of digital health technology. Esomeprazole is now more widely available to patients thanks to new distribution channels brought about by the growth of telemedicine and internet pharmacies. Pharmaceutical companies employ these technologies to create more potent formulations and draw in investors hoping to profit from the expanding industry. Digital health systems also make remote patient monitoring possible, giving medical professionals real-time access to data on medication compliance and treatment effectiveness. This integration improves patient outcomes by facilitating faster interventions and personalized treatment plans.[7] An additional significant factor influencing the market for esomeprazole APIs is regulatory developments. Regulatory organizations such as the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) are revising their recommendations to maintain the safety, efficacy, and quality of esomeprazole APIs. The incorporation of expensive analytical methods like mass spectrometry and high-performance liquid chromatography (HPLC) for better quality control is one of the recent initiatives aimed at adhering to these changing requirements. To ensure that new esomeprazole products are safe and effective for patient utilization, pharmaceutical companies are prompted by these regulatory changes to invest in research that satisfies the most recent criteria. These developments in technology, research, and regulatory compliance are all contributing to the future growth of esomeprazole APIs

as the market keeps expanding.[8]

The research aims to formulate the gastroretentive microsponges of esomeprazole and incorporate them into the *in-situ*gels. Esomeprazole-loaded microsponges were formulated by using ethyl cellulose and Eudragit RS -100 polymer. Both polymers are produced for the extended release of the drug so that the drug remains longer period into the stomach and effectively treats the peptic ulcer. The microsponges are then loaded into an *in-situ* gel which reduces the frequency of dosing of drug and thus helps in better patient compliance.

2 Materials and Methods

2.1 Materials

Esomeprazole Magnesium was obtained from Dhamtec Pharma and Consultants (Maharashtra India) Dichloromethane Pure (Methylene Chloride) was purchased from Central Drug House (India). Acetone AR/ACS (2-Propanone, Dimethyl ketone) was obtained from Central Drug House (India). Paraffin Liquid Light (Petrolatum Liquid) was bought from Central Drug House (India). Ethyl cellulose and Eudragit RS 100 were obtained from Central Drug House (India). Hexane was purchased from Central Drug House (India).

2.2 Methods

2.2.1 *Preparation of Esomeprazole microsponges*

The method used to prepare microsponges was the Quasi-emulsion solvent diffusion method. For the preparation of internal phase polymers ethyl cellulose and Eudragit RS-100 were dissolved in dichloro methane and Acetone (1:1). Then Esomeprazole Magnesium was added to the polymeric solution, and after that, the mixture was kept for 5 min sonication. Light liquid paraffin was used as the external phase. Then the external phase is placed in the magnetic stirrer continuously stirring at 4000 RPM. With the help of a syringe internal phase containing the drug is added dropwise into the external phase with continuous stirring (at 4000 RPM). Due to diffusion, the organic phase is evaporated, and the drug: polymer mixture gets solidified in an external phase, which is collected through filtration and then dried at room temperature for 24 hours and finally stored in desiccators.[9]

2.2.2 *Design of experiment*

Five formulations (F1–F5) were fabricated using two different polymers. The design is mentioned in Table 1.

2.2.3 *Evaluation of microsponges*

- **Determination of Absorption maxima (λ_{max}):** Absorption maxima is generally carried out to determine the purity of the drug as well as find the maximum λ_{max} of Esomeprazole. Standard stock solution (6μg/ml and 8 μg/ml) of Esomeprazole Magnesium was prepared in distilled water and pH1.2 acidic buffer. Then the solution was scanned at 400 to 200 nm in a UV-visible spectrophotometer (Lab India).[10]
- **Fourier transform infrared spectroscopy (FT-IR):** FT-IR is a simple, quick, and inexpensive analytical technique employed to anticipate drug-excipient interaction. This analysis has been carried out using the potassium bromide pellet technique. The FT-IR of Esomeprazole and Esomeprazole with different polymers was taken and homogeneously combined with 200 mg potassium bromide. Then the mixture was compressed using a mechanical die press. It was captured using Shimadzu's Fourier transform infrared spectrometer (Japan) with a frequency range of 4,000 to 450 cm^{-1}.[11]
- **Practical size by optical microscopy:** particle size was determined by using optical microscopy. 150 particles were measured, and the mean particle was determined.
- **Product yield:** The product yield of the esomeprazole microsponges was calculated by using the formula:

$$\text{Product yield} = \frac{\text{Total microsponges formed}}{\text{Total amount of drug and excipients}}$$

- **Drug content (DC) and entrapment efficiency (EE):** 50 mg esomeprazole microsponges were weighed and dissolved in 5 ml methanol. The sample was placed in a centrifuge for 10 min at 4500 rpm. The supernatant layer was collected, and the absorbance was determined at 302 nm. The % drug content and entrapment efficiency were calculated.[12]

$$\%\ \text{Drug Content} = \frac{\text{Amount of Esomeprazole in microsponge}}{\text{Weighed amount of microsponge}} \times 100$$

$$\%\ \begin{matrix}\text{Entrapment}\\ \text{Efficiency}\end{matrix} = \frac{\begin{matrix}\text{Amount of Esomeprazole}\\ \text{in microsponge}\end{matrix}}{\begin{matrix}\text{Theoretical amount of esomeprazole}\\ \text{in microsponge}\end{matrix}} \times 100$$

- **Microsponges surface morphology :** The surface morphology of the esomeprazole microsponges was determined by scanning electron microscopy (SEM).[13]

2.3 Development of Esomeprazole loaded microsponges *in-situ* gels

The calculated amount of Poloxamer 188 (35%w/v) was introduced to distilled water by mixing. The mixture was exposed at 4°C in a refrigerator overnight until the whole polymer swelled. Once a clear viscous solution is formed,

Table 1. Formulation chart of Esomeprazole loaded Microsponges using Ethyl Cellulose and Eudragit RS-100

Formulation Code	Esomeprazole Magnesium (mg)	Ethylcellulose (mg)	Eudragit RS 100 (mg)	Dichloromethane (ml)	Acetone (ml)	Paraffin Liquid Light (ml)
F1	40	400	-	10	10	250
F2	40	300	100	10	10	250
F3	40	200	200	10	10	250
F4	40	100	300	10	10	250
F5	40	-	400	10	10	250

the weighed quantity of microsponges is introduced to the solution. The solution formed was put under sonication for 1 min to form a gel.

2.3.1 *Evaluation of microsponge-loaded gel*

- **pH determination:** The pH of the esomeprazole-loaded *in-situ* gel was determined with the help of a digital pH meter. The average reading of the pH was recorded.
- **Rheological behavior determination:** The rheology of the esomeprazole-loaded *in-situ* gel was at 50 rpm using a Brookfield Viscometer. The readings were taken in triplicates.[14]
- **In-vitro gelling capacity:** The method for determination of in-vitro gelling capacity involves the use of a fresh drop of esomeprazole-loaded i*n-situ* gel in a vial that contains 2 ml phosphate buffer pH 7.4 at 37°C. The time duration for gelation was noted down. The different grades were given according to gelling capacity.[15]
- **In vitro drug release study of esomeprazole-loaded microsponges *in-situ* gel:** In-vitro release test was carried out in 50 ml of acidic buffer (pH 1.2) in Franz Diffusion cell. A semi-permeable membrane (Himedia) was used for the study. 0.5 g of microsponge gel was taken and put on the cell. At a regular interval (1 to 24 hours)the sample was taken and analyzed at 302 nm in a spectrophotometer. Kinetic analysis was carried out for the determination of the order of reaction (using BIT software). The release data was put into kinetic models to find out the mechanism of drug release.[16]
- **Stability Study:** In stability studies the microsponge gel was stored at 40°C and 75% RH for three months. The two parameters mean particle size and entrapment efficiency were evaluated.[17]

3 Results and Discussion

- **Determination of Absorption maxima (λ_{max}):** Absorption maxima of Esomeprazole Magnesium in distilled water and 1.2 acidic buffer was found to be 302nm which shows that the API was pure. The absorption maximum was obtained at 302 nm as shown in Figure 1.

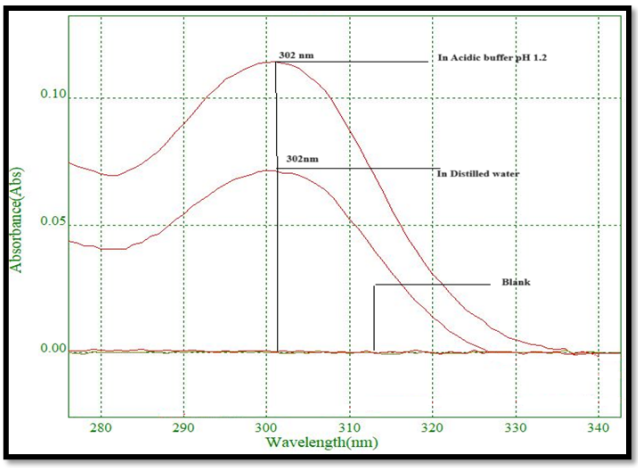

Fig 1. UV Absorption maxima of Esomeprazole Magnesium in Distilled water and 1.2 acidic buffer

- **Fourier Transform Infrared Spectroscopy (FT-IR):** FT-IR spectroscopy studies were conducted to assess potential interactions between esomeprazole and the polymers ethyl cellulose and Eudragit RS 100 in the microsponge formulation. The FT-IR spectra of pure esomeprazole, ethyl cellulose, and Eudragit RS 100 were examined within a frequency range of 4,000–450 cm^{-1}, utilizing Shimadzu's Fourier transform infrared spectrometer (Japan). The FT-IR spectrum of pure esomeprazole exhibited characteristic vibrational peaks corresponding to key functional groups. Specifically, peaks for O-H stretching, C-H stretching, and C=O stretching frequencies were identified at 3,209.36 cm^{-1}, 3,100.14 cm^{-1}, and 1,739.19 cm^{-1}, respectively. Additionally, symmetric, and asymmetric stretching vibrations of N=O were observed at around 1,471.91 $cm^{-1}$and 1,354 cm^{-1}, respectively. Other significant peaks included those attributed to C-C stretching (1,427.33 cm^{-1}), C-O stretching (1,264.51–1,185.80 cm^{-1}), and C-N stretching (1,073.40 cm^{-1}). The FT-IR spectrum of ethyl cellulose displayed characteristic peaks indicative of its molecular structure. Notable absorptions included stretching vibrations of

O-H (2,940.81 cm^{-1}), C=O (1,698.01 cm^{-1}), and –CH2 (1,450.88 cm^{-1}), as well as bending vibrations of C-H (1,162.12 cm^{-1}). Similarly, the FT-IR spectrum of Eudragit RS 100 revealed distinctive peaks corresponding to its functional groups. Noteworthy absorptions comprised stretching vibrations of O-H (2,940.81 cm^{-1}), C=O (1,698.01 cm^{-1}), and –CH2 (1,450.88 cm^{-1}), along with bending vibrations of C-H (1,162.12 cm^{-1}). Upon analyzing the FT-IR spectrum of the esomeprazole microsponge formulation containing ethyl cellulose and Eudragit RS 100, it was observed that the primary peaks corresponding to esomeprazole remained consistent. Importantly, there were no discernible shifts in peak positions in the presence of the polymers, indicating the absence of significant interactions between esomeprazole and the encapsulating agents.

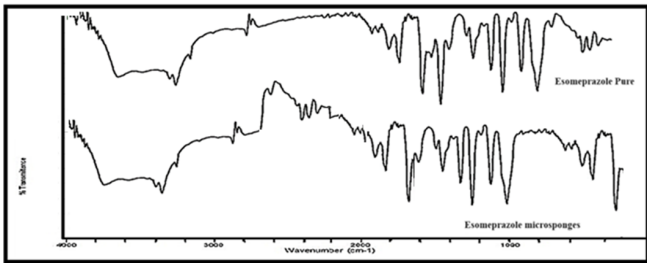

Fig 2. FTIR of Esomeprazole Magnesium pure and Formulation

- **Particle size:** The prepared microsponge varies from 6.24±0.27 to 8.36±0.43μm. The F3 formulation consists of the maximum particle size when ethyl cellulose and Eudragit RS 100 are equal. The particle size of all formulations lies in the range of 10μm.
- **Product yield:** The production yield of the esomeprazole microsponges varies from 76.89% to 87.35% as shown in Table 2. The maximum value was found to be 87.35% for F3 which contains an equal proportion of polymers.
- **Entrapment efficiency:** The percentage entrapment efficiency usually varies from 75.98% to 85.67 %. F3 formulation showed the maximum entrapment efficacy (85.67 %) while the minimum was 75.98% for F1. The entrapment efficiency can be associated with the porous structure of microsponges. The porous nature of microsponges favors high entrapment efficiency. The drug content and % entrapment efficiency depend on the drug to polymer concentration. The higher value of the drug-to-polymer ratio favors high drug content and entrapment efficiency.
- **Drug Content**: The drug content was found maximum for Formulation F3 which was 85.24%. The high percentage of drug content was due to the porous structure of microsponges which favors the maximum drug loading. The high drug loading leads to increased drug content of the formulation.

Table 2. Esomeprazole microsponges results

Formulation Code	Mean Particle Size (μm)	Production yield (%)	Entrapment efficiency (%)	Drug Content (%)
F1	7.67±0.35	78.74	76.43	75.98
F2	7.78±0.57	81.34	78.67	78.04
F3	8.36±0.43	87.35	85.67	85.24
F4	6.24±0.27	76.89	75.98	74.23
F5	7.47±0.31	84.68	79.29	77.87

Fig 3. A: Particle size, B: % Production yield, C: % Entrapment Efficiency, D: % Drug Content

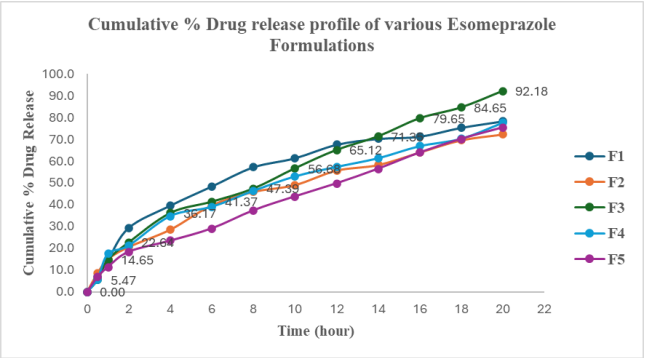

Fig 4. Cumulative % Drug release of Esomeprazole microsponges

- **Microsponges surface morphology :** The scanning electron microscopy of microsponges shows that

they are round with porous surfaces. The formed microsponges were found uniform and spherical.

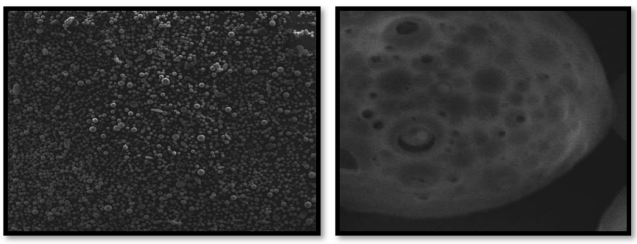

Fig 5. Scanning electron microscopy of prepared nanosponges

- **Evaluation of Gel loaded Microsponges :** The different parameters were evaluated for esomeprazole-loaded microsponges *in-situ* gel, including viscosity, gelling capacity, and gelling time determination and stability studies. The results of esomeprazole-loaded microsponges *in-situ* gel are shown in Table 3.
- **Rheological behavior :** The viscosity was determined with the help of a Brookfield viscometer. The viscosity helps to enhance the residence time of formulation in the targeted site. The viscosity of the gel was found in between 30-39 cps. The esomeprazole-loaded microsponges *in-situ* gel formulation must have adequate viscosity so that it remains for a longer time in the stomach.
- **Gelling capacity and gelling time:** The ideal *in-situ* system is the one that gelled on exposure to body temperature. The maximum gelling time was found to be 11.95±0.56 sec for F3 formulation. The gelling time is low for the formulation having low entrapment efficiency (75.98%).

Table 3. Evaluation of *in-situ* gels-loaded microsponges

Formulation code	Viscosity (cps)	Gelling capacity	Gelling time (sec)
F1	33	++	8.54±0.34
F2	35	++	9.54±0.87
F3	38	++	11.95±0.56
F4	35	++	7.56±0.58
F5	37	++	8.95±0.64

- **In vitro Release of esomeprazole-loaded microsponges *in-situ* gel Formulations:** The in-vitro release study of microsponges loaded *in-situ* gel was conducted in Franz Diffusion cell. The release data was calculated for all the formulations and the results are shown in Table 4. From the study, it was found that the formulation F3 has a greater rate of drug release due to an equal concentration of polymer. The release data was put under different mathematical models to find out the release mechanism. The data is subjected to kinetic models like zero order, first order, Higuchi's, and Korsmeyer Peppas. When the data is plotted between time vs drug release the best-fit model was found to be Korsmeyers Peppas as it shows the high range of linearity. The value of n is found to be 0.7464 which shows an Anomalous transport mechanism.

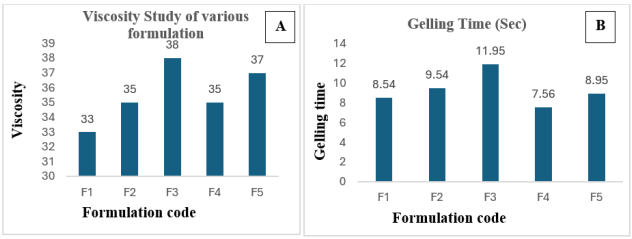

Fig 6. Viscosity of formulations, B: Gelling time of different formulations

Table 4. In-Vitro Drug Release Kinetic Data

	Formulation code				
	F1	F2	F3	F4	F5
Cumulative % drug release after 20 hours	78.33	72.27	92.18	77.54	75.37
Zero-order	0.8779	0.9461	0.9875	0.9394	0.9878
First order	0.9704	0.9911	0.9499	0.9862	0.9810
Higuchi	0.9383	0.9257	0.9338	0.9281	0.9226
Korsmeyers Peppas	0.9548	0.9951	0.9956	0.9545	0.9914
Hix. Crow.	0.9456	0.9826	0.9880	0.9802	0.9916

- **Stability studies:** The stability studies of the prepared microsponges were conducted and the results are shown in Table 5. From the studies, it was found that there were no changes occurred in entrapment efficiency and mean particle size of formulations during the storage period.

Table 5. Stability study of formulation after three months

Formulation code	Mean particle size (μm)	% Entrapment Efficiency
F1	7.62±0.32	76.37
F2	7.75±0.58	77.97
F3	8.33±0.37	85.27
F4	6.21±0.23	75.45
F5	7.37±0.21	79.12

4 Conclusion

Esomeprazole-loaded microsponge *in-situ*gel was successfully prepared by the quasi-emulsion solvent diffusion method. The microsponge-loaded *in-situ* gel was subjected to different evaluation parameters. From the results, it was found that the microsponges were successfully prepared and spherical. The size of the microsponges was found up to 10μm which is suitable for a gastroretentive drug delivery system. The most optimized formulation was found to be F3 due to its satisfactory results in particle size, drug content, entrapment efficiency, and viscosity. Lastly, it was concluded that the formulation would reduce the frequency of dosing, and provide sustained action so that the drug remains longer period of the time in the stomach treat the ulcer effectively, and improve patient compliance.

References

1) Di Natale MR, Athavale ON, Wang X, Du P, Cheng LK, Liu Z, et al. Functional and anatomical gastric regions and their relations to motility control. *Neurogastroenterology & Motility*. 2023;35(9):e14560. Available from: https://dx.doi.org/10.1111/nmo.14560.
2) Varghese C, Carson DA, Bhat S, Hayes TCL, Gharibans AA, Andrews CN, et al. Clinical associations of functional dyspepsia with gastric dysrhythmia on electrogastrography: A comprehensive systematic review and meta-analysis. *Neurogastroenterology & Motility*. 2021;33(12):e14151. Available from: https://dx.doi.org/10.1111/nmo.14151.
3) Chen YC, Malfertheiner P, Yu HT, Kuo CL, Chang YY, Meng FT, et al. Global Prevalence of Helicobacter pylori Infection and Incidence of Gastric Cancer Between 1980 and 2022. *Gastroenterology*. 2024;166(4):605–619. Available from: https://dx.doi.org/10.1053/j.gastro.2023.12.022.
4) Qin Y, Lao YH, Wang H, Zhang J, Yi K, Chen Z, et al. Combatting Helicobacter pylori with oral nanomedicines. *Journal of Materials Chemistry B*. 2021;9(48):9826–9838. Available from: https://dx.doi.org/10.1039/d1tb02038b.
5) Das S, Kaur S, Rai VK. Gastro-retentive drug delivery systems: a recent update on clinical pertinence and drug delivery. *Drug Delivery and Translational Research*. 2021;11(5):1849–1877. Available from: https://dx.doi.org/10.1007/s13346-020-00875-5.
6) An G. Pharmacokinetics and Pharmacodynamics of GalNAc-Conjugated siRNAs. *Journal of Clinical Pharmacology*. 2023;64(1):45–57. Available from: https://doi.org/10.1002/jcph.2337.
7) Richter JE, Kahrilas PJ, Johanson J, Maton P, Breiter JR, Hwang C, et al. Esomeprazole Study Investigators. Efficacy and safety of esomeprazole compared with omeprazole in GERD patients with erosive esophagitis: a randomized controlled trial. *American Journal of Gastroenterology*. 2001;96(3):656–665. Available from: https://doi.org/10.1111/j.1572-0241.2001.3600_b.x.
8) Kidholm K, Jensen LK, Johansson M, Montori VM. Telemedicine and the assessment of clinician time: a scoping review. *International Journal of Technology Assessment in Health Care*. 2024;40(1):e3. Available from: https://dx.doi.org/10.1017/s0266462323002830.
9) El-Kimary EI, Ragab MAA. Recent Analytical Methodologies for the Determination of Omeprazole and/or Its Active Isomer Esomeprazole in Different Matrices: A Critical Review. *Critical Reviews in Analytical Chemistry*. 2022;52(1):106–130. Available from: https://dx.doi.org/10.1080/10408347.2020.1791042.
10) Biharee A, Bhartiya S, Yadav A, Thareja S, Jain AK. Microsponges as Drug Delivery System: Past, Present, and Future Perspectives. *Current Pharmaceutical Design*. 2023;29(13):1026–1045. Available from: https://dx.doi.org/10.2174/1381612829666230404082743.
11) Chandra SM, Dharan SS, Ajikumar A. Formulation and evaluation of gastroretentive floating microballoons containing selected anti-ulcer drug. *Journal of Pharmaceutical Sciences and Research*. 2021;13(1):49–63. Available from: https://search.proquest.com/openview/ccb25b5dcd6bfc7662c24a7f0fa50efc/1?pq-origsite=gscholar&cbl=54977#:~:text=formulation%20of%20floating%20MICROBALLOONS%3A,the%20ratio%20of%201%3A1.
12) Abdelsamie M, Zahran F, Hussine AA, Shaker O, Al-mahallawi AM. Clinical and biochemical assessment of the effect of topical use of coenzyme Q10 versus topical corticosteroid in management of symptomatic oral lichen planus: randomized controlled clinical trial. *BMC Oral Health*. 2023;23(1):506. Available from: https://dx.doi.org/10.1186/s12903-023-03206-5.
13) Rajput D, Rajput D, Masih P. Microsponge Based Drug Delivery System: A Futuristic Approach In Disease Diagnosing And Management. *Journal of Population Therapeutics and Clinical Pharmacology*. 2022;29(02):284–303. Available from: https://www.jptcp.com/index.php/jptcp/article/view/4054.
14) Farhadnejad H, Mortazavi SA, Jamshidfar S, Rakhshani A, Motasadizadeh H, Fatahi Y, et al. Montmorillonite-Famotidine/Chitosan Bio-nanocomposite Hydrogels as a Mucoadhesive/Gastroretentive Drug Delivery System. *Iranian Journal of Pharmaceutical Research*. 2022;21(1):e127035. Available from: https://dx.doi.org/10.5812/ijpr-127035.
15) Butola M, Bhatt V, Nainwal N, Jakhmola V, Dobhal K, Ale Y. Preparation and Evaluation of Polymer Fused Metformin Hydrochloride Sustained Release Tablet. *Indian Journal of Pharmaceutical Education and Research*. 2023;57(3):711–717. Available from: https://dx.doi.org/10.5530/ijper.57.3.86.
16) Shailaja P, Ashok KS. A Promising Oral Drug Delivery System of Microsponges: A Brief Review. *Research Journal of Pharmacy and Technology*. 2022;15(9):4319–4324. Available from: https://dx.doi.org/10.52711/0974-360x.2022.00725.
17) He Y, Majid K, Maqbool M, Hussain T, Yousaf AM, Khan IU, et al. Formulation and characterization of lornoxicam-loaded cellulosic-microsponge gel for possible applications in arthritis. *Saudi Pharmaceutical Journal*. 2020;28(8):994–1003. Available from: https://dx.doi.org/10.1016/j.jsps.2020.06.021.