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Vineet Joshi

College of Pharmacy, Shivalik
Campus, Dehradun,
Uttarakhand, India

Dheeraj Kumar

College of Pharmacy, Shivalik
Campus, Dehradun,
Uttarakhand, India

Rohit Kumar Trivedi

College of Pharmacy, Shivalik
Campus, Dehradun,
Uttarakhand, India

Semwal Amit

College of Pharmacy, Shivalik
Campus, Dehradun,
Uttarakhand, India

Corresponding Author:

Vineet Joshi

College of Pharmacy, Shivalik
Campus, Dehradun,
Uttarakhand, India

Formulation and characterization of the esomeprazole magnesium enteric coated tablet

Vineet Joshi, Dheeraj Kumar, Rohit Kumar Trivedi and Semwal Amit

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Abstract

Gastric ulcers are a common gastrointestinal condition often treated with proton pump inhibitors like Esomeprazole Magnesium. However, stability issues in the gastric environment necessitate advanced drug delivery systems. This study focuses on developing an enteric-coated tablet of Esomeprazole Magnesium using ethyl cellulose as the coating polymer, aiming to enhance gastric stability and therapeutic efficacy. The formulation was prepared using the wet granulation method and evaluated against a marketed formulation. FT-IR spectroscopy confirmed the absence of drug-excipient interactions. Physical parameters of the tablets were within pharmacopeial limits. *In vitro* drug release studies demonstrated a sustained release from the laboratory formulation compared to the marketed product. The area under the curve (AUC) and similarity factor ($f_2 = 53.53$) were calculated to assess bioavailability. Drug release followed Peppas-Korsmeyer kinetics ($R^2 = 0.9664$), indicating diffusion and erosion mechanisms. Results suggest that the formulated enteric-coated Esomeprazole tablet is a viable alternative to commercial products, offering comparable release characteristics and improved formulation stability.

Keywords: Gastric ulcer, enteric-coated tablet, bioavailability, drug release kinetics

Introduction

Gastric ulcer is the most common disorder of the upper digestive tract. The prevalence of gastric ulcers is 2.4% in the Western population, and annual incidence rates range from 0.10% to 0.19%. In certain regions of Mainland China, the prevalence of gastric ulcer is as high as 6.07% in the general population, and 22.5% of patients with gastrointestinal symptoms have gastric ulcer. Higher incidence usually occurs in people who smoke, use nonsteroidal anti-inflammatory drugs (NSAIDs), or consume alcohol (Khan, Dar, & Mir, 2023) ^[10]. The recurrence rate is as high as 60%. Gastric ulcers have a significant economic impact. Average annual medical costs are \$23819 for a gastric ulcer in the United States. In South Korea, the annual medical costs for gastric ulcer range from \$959.6 to \$2553.10. Although some studies have demonstrated that *Helicobacter pylori* (*H. pylori*) eradication therapy is cost-effective, a more systematic study indicated that there was no significant cost difference per subject between eradication therapy and placebo (Jaiswal, Rai, Wal, Wal, & Singh, 2021) ^[8]. Although conventional regimens are effective, their side effects are often inevitable and limit clinical utility. However, both clinical and experimental studies have demonstrated that herbal medicines exhibit therapeutic benefits for gastric ulcers with fewer side effects. Moreover, the cost of herbal medicine for gastric ulcers is only about one-sixth of that of Western medicine (Laucirica, Iglesias, & Calvet, 2023) ^[11]. The role of treatment with proton pump inhibitors for patients with active or recent ulcer bleeding is controversial. If given in an adequate dose by continuous intravenous infusion, proton pump inhibitors can maintain intragastric pH at 6 or above (Clarke *et al.*, 2022) ^[3]. Those levels of pH, peptic activity are minimized, platelet function is optimized, and fibrinolysis is inhibited; these effects should help to stabilize clot formation over an ulcer. Although proton pump inhibitors are already widely used for ulcer bleeding, intravenous therapy may have been overused and given inappropriately for patients at low risk. (Csiki *et al.*, 2021) ^[4] Extended-Release formulations are usually designed to reduce dose frequency and maintain relatively constant or flat plasma drug concentration. This helps avoid the side effects associated with

high concentration. Such coatings are variously referred to as enteric coatings. (Loh, Enose, & Garg, 2022) ^[13] An enteric coating is a protective layer that controls the medication in the digestive system, where it is absorbed. The word "Enteric" indicates the small intestine; therefore, enteric coating prevents the release of the drug before it reaches the small intestine. (Patil, Tambe, Shirsat, & Patil, 2021) ^[15] A tablet that has a special outer covering layer, which was designed to dissolve in the small intestine and has an alkaline pH of about 7-9. So, most of the currently used enteric coatings are weak acids which remain undissociated in the low pH environment, but they readily get ionized when the pH rises above. An enteric coating is a barrier that controls the location of oral medication in the digestive system, where it is absorbed. The enteric-coated polymers remain unionized at low pH, and therefore, remain insoluble. But as the pH increases in the GIT, the acidic functional groups are capable of ionization, and the polymer swells or becomes soluble in the intestinal fluid. (Ghube, Khade, & Bhosale, 2020; Thakkar, 2023) ^[6, 17] "In the present research work, an enteric-coated tablet formulation of Esomeprazole Magnesium has been developed to enhance its stability and therapeutic efficacy. The prepared formulation is evaluated and compared with a commercially available marketed formulation in terms of bioavailability, to assess its *in vivo* performance and potential for improved clinical outcomes."

Materials and Methods

Materials

Esomeprazole Magnesium was obtained from Dhamtec Pharma and Consultants (Maharashtra, India) Ethanol was

purchased from Central Drug House (India). Mannitol was obtained from Central Drug House (India). Starch, Magnesium stearate was bought from Central Drug House (India). Ethyl cellulose was obtained from Central Drug House (India).

Methods

Preparation of Esomeprazole Magnesium Enteric Coated Tablet

Esomeprazole magnesium Enteric Coated Tablet was prepared by the Wet Granulation method. All Excipients were accurately weighed and passed through a sieve number 22 (Except Talc and Magnesium Stearate). Mannitol, fenugreek seeds, and the drug were transferred into an air-filled polybag and mixed by shaking it for 5 minutes. Then the mixture was transferred into a mortar and pestle. Starch was dissolved in chloroform, and a paste (5%) was made for the mixture. The prepared solution was slowly added to the mortar, then the mixture was triturated, and the granules were formed. Granules were dried in a hot air oven for 5 minutes at 60°C. After half drying granules passed through sieve no. 22. Then these granules were completely dried in an oven. Sieve no. 22, 44, and the collectors were taken; dried granules were transferred to sieve no. 22, and these sieves were shaken. Fine and coarse powder was collected. 70% coarse and 30% fine powder were taken and lubricated with talc and magnesium stearate. Finally, the granules were compressed in the form of tablets by using single-station rotary compression machines. Then, tablets are coated with ethyl cellulose (as an enteric coating agent) using a coating pan (Kadam, Yadav, & Landge, 2020; Lee, Kim, Kim, Ro, & Na, 2023) ^[9, 12].

Table 1: formulation design of enteric-coated esomeprazole magnesium tablet

Name of Ingredient	Quantity of Ingredient	
	Laboratory Formulation 1	Marketed Formulation 2 (NEXPRO-40)
Esomeprazole magnesium	20mg	-----
Mannitol	120mg	-----
Fenugreek seeds	35mg	-----
Starch paste (In Chloroform)	q. s	-----
Talc	2.5mg	-----
Magnesium Stearate	2.5mg	-----
Ethyl cellulose	15% Solution in Ethanol	-----

Evaluation of Esomeprazole Magnesium Enteric Coated Tablet

- Determination of Absorption maxima ($\lambda_{\max}$):** Absorption maxima are generally carried out to determine the purity of the drug as well as find the maximum $\lambda_{\max}$ of Esomeprazole. Standard stock solutions (6µg/ml and 8 µg/ml) of Esomeprazole Magnesium were prepared in distilled water and a pH 1.2 acidic buffer. Then the solution was scanned at 400 to 200 nm in a UV-visible spectrophotometer (Lab India) (Ruikar *et al.*, 2020) ^[16].
- 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. (Deepika, Vishnu, & Rao, 2021) ^[5]

- General appearance:** Tablets were assessed for their general appearance.
- Hardness:** 10 tablets of each formulation were selected randomly, and the hardness of tablets was measured by using the Monsanto hardness tester.
- Weight variation:** 10 tablets were accurately weighed individually, and the average weight was calculated. Percent weight variation was calculated by this formula

$$\% \text{weight variation} = \frac{\text{Average weight} - \text{Initial weight}}{\text{Average weight}} \times 100$$

- Thickness:** The Thickness of tablets is determined by using the vernier caliper scale.
- In vitro drug release study:** A USP-type II dissolution apparatus was used for the *in vitro* drug release study. The Enteric Coating Tablet was transferred to the 900

mL dissolution medium (0.1N HCl) for 2 hours. The dissolution apparatus was operated at 75 rpm, and the temperature was set at 37°C. Samples were taken at 0.5, 1, 1.5, and 2-hour intervals. After two hours, the dissolution medium was replaced with pH 6.8 phosphate buffers. The temperature was maintained at 37 °C, and the apparatus was operated at 75 rpm. Samples were taken at 2.5, 3, 3.5, 4.5, 5, 5.5, and 6-hour intervals (Gopaiah *et al.*, 2020; Parihar, Prajapati, Patel, & Paliwal, 2023) [7, 14].

3. **Drug release kinetics:** The mechanism of drug release and rate kinetics were evaluated by plotting the *in vitro* release data in various kinetic models.
- **Zero-order kinetics:** when the rate of reaction is independent of the concentration.

- **First-order kinetics:** When the reaction rate depends on the first power of the concentration of a single reactant.
- **Higuchi kinetics:** Drug release was proportional to the square root of time. This indicates that drug release is diffusion-controlled. (Askarizadeh, Esfandiari, Honarvar, Sajadian, & Azdarpour, 2023; Cheng, Qin, Acevedo, Jiang, & Shi, 2020) [1, 2]

Results and Discussion

- **Determination of Absorption maxima ($\lambda_{\max}$):** Absorption maxima of Esomeprazole Magnesium were obtained at 301 nm in distilled water and 296 nm in 0.1 N HCl, which shows that the API was pure, as shown in Figure 1.

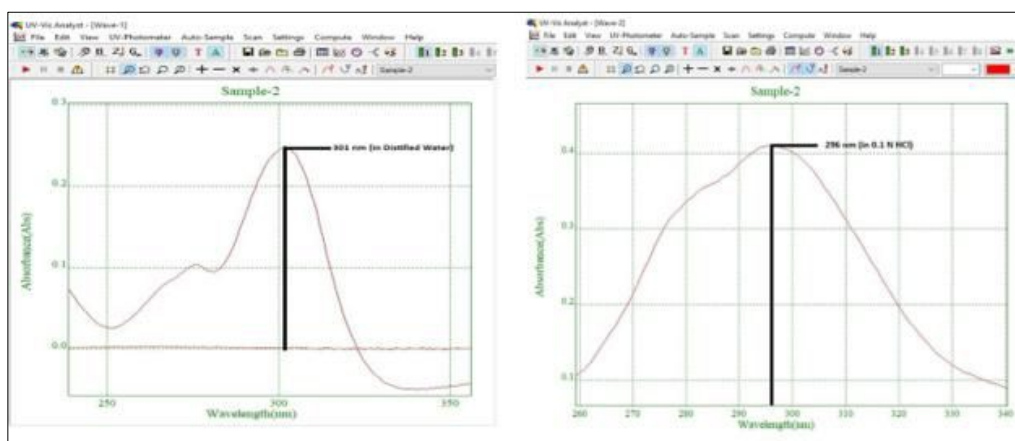


Fig 1: UV Absorption maxima of Esomeprazole Magnesium in Distilled water and 1.2 acidic buffer

- **Fourier Transform Infrared Spectroscopy (FT-IR):** FT-IR spectroscopy studies were conducted to assess potential interactions between Esomeprazole and the polymer Ethyl Cellulose, along with other excipients used in the formulation. The FT-IR spectra of pure Esomeprazole, Ethyl Cellulose, and formulation excipients were examined within a frequency range of 4,000-450 cm^{-1} using a Shimadzu Fourier Transform Infrared Spectrometer (Japan). The FT-IR spectrum of pure Esomeprazole exhibited characteristic vibrational peaks corresponding to its key functional groups. Notably, O-H stretching was observed at 3,209.36 cm^{-1} , C-H stretching at 3,100.14 cm^{-1} , and C=O stretching at 1,739.19 cm^{-1} . Additionally, symmetric and asymmetric N=O stretching vibrations were recorded at 1,471.91 cm^{-1} and 1,354 cm^{-1} , respectively. Other significant

peaks included 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, including O-H stretching at 2,940.81 cm^{-1} , C=O stretching at 1,698.01 cm^{-1} , -CH₂ bending at 1,450.88 cm^{-1} , and C-H bending vibrations at 1,162.12 cm^{-1} . Upon analysis of the FT-IR spectrum of the Esomeprazole formulation containing Ethyl Cellulose and other excipients, it was observed that the principal characteristic peaks of Esomeprazole remained unchanged. No significant shifts in peak positions were detected, suggesting the absence of chemical interactions between Esomeprazole and the polymer or excipients used in the formulation.

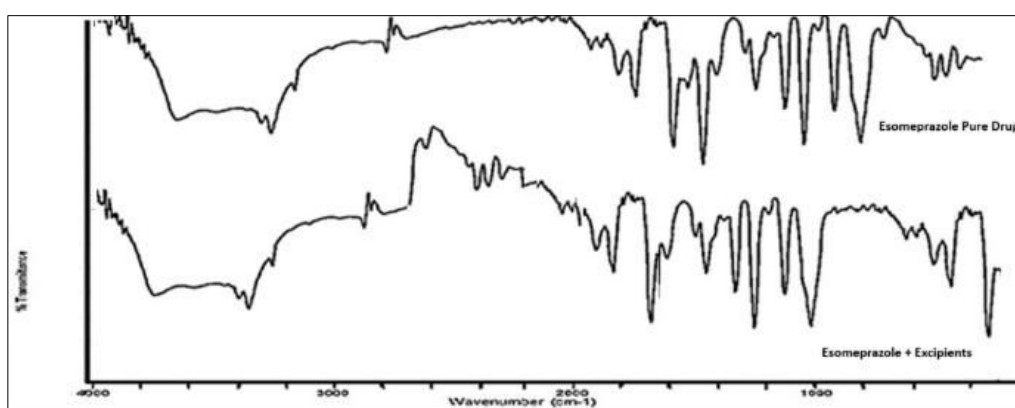


Fig 2: FTIR of Esomeprazole Magnesium Pure and Formulation

- **Tablet Evaluation:** Enteric coating tablet of Esomeprazole magnesium was formulated and evaluated. Both formulations have hardness, thickness, friability, and weight variation (before coating) within acceptable limits. Tablets were found to be satisfactory as per Indian pharmacopeia tolerance limit and both formulations were subjected to various parameters and the result obtained was within the range.

Table 2: Physical evaluations of tablets.

Parameters	Laboratory Formulation 1	Marketed Formulation 2
Thickness	4.0mm	3.8mm
Hardness	8.1kg/cm ²	8.5kg/cm ²
Friability	0.8% (before coating)	-----
Avg. weight	179.12mg (before coating)	-----

- **In-vitro drug release of the Laboratory Formulation:** *In-vitro* release of esomeprazole studies is shown in Table 3. A Dissolution study of each formulation was conducted by using 0.1N HCl for the first 2 hours. After two hours of dissolution, the media were replaced with phosphate buffer, pH 6.8. A graph was plotted between

% drug release versus time (Fig. 1). The *in vitro* data were fitted to different kinetic models by using BITSTAT software. The results (Table 4) revealed that the formulation prepared alone followed the first-order release kinetics with a correlation coefficient.

Table 3: *In vitro* release of esomeprazole magnesium in laboratory studies

Time (Hr.)	Avg % Drug Release Laboratory Tablet	Avg % Drug Release of Marketed Tablet
0	0.00	0.00
0.5	0.45	0.15
1	0.89	0.53
1.5	3.65	1.23
2	4.23	2.65
2.5	15.86	16.76
3	28.98	32.46
3.5	42.34	56.37
4	59.77	78.49
4.5	73.56	87.29
5	86.12	96.21
5.5	91.21	98.32
6	94.32	98.39

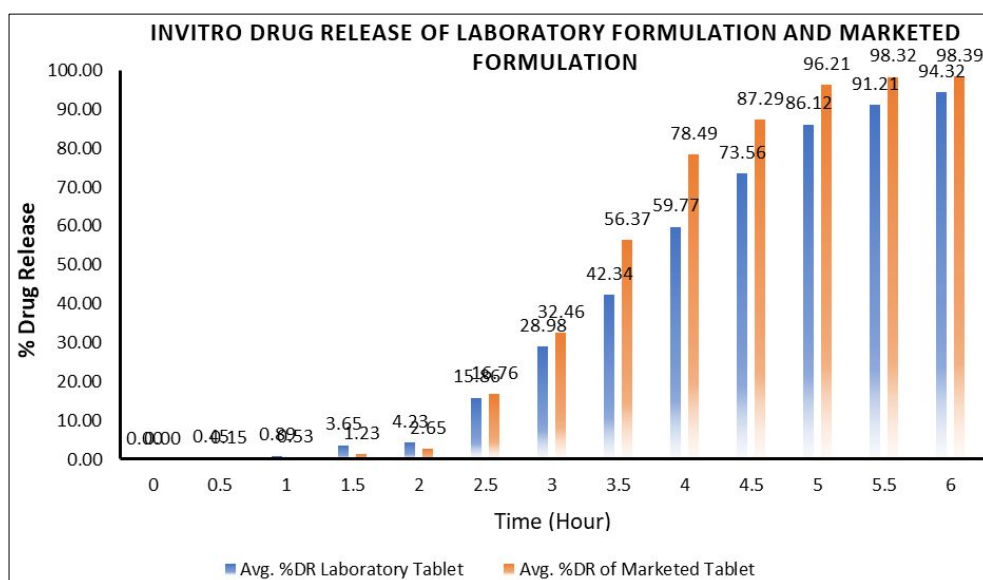


Fig 3: Drug release Kinetics model of formulation 1

- **Comparative study of Laboratory Formulation and Marketed Formulation:** Based on the dissolution data, the bioavailability of the laboratory-developed formulation was compared with the marketed formulation by calculating the similarity factor (f_2).

AUC (Area Under Curve) Comparison: The area under the drug release curve (AUC) was calculated using the trapezoidal rule:

- Laboratory Formulation: 227.10
- Marketed Formulation: 259.92

Similarity Factor: The similarity factor (f_2) was used to compare the dissolution profiles of two drug products. It was calculated by using the following formula:

$$f_2 = 50 \times \log_{10} \{ [1 + (1/n) \sum (R_t - T_t)^2]^{-0.5} \times 100 \}$$

Where:

n = number of time points

R_t = % drug release of reference (marketed) product at time t

T_t = % drug release of test (laboratory) product at time t

Number of time points (n) = 13

$$\sum (R_t - T_t)^2 = 926.2101$$

$$f_2 = 50 \times \log_{10} \{ [1 + (1/13) \times 926.2101]^{-0.5} \times 100 \}$$

$$= 50 \times \log_{10} \{ (1 + 71.2469)^{-0.5} \times 100 \}$$

$$= 53.53$$

The similarity factor (f_2) between the dissolution profiles of the laboratory and marketed formulations was calculated to be 53.53. An f_2 value between 50 and 100 suggests that the two formulations exhibit similar drug release characteristics. In this case, an f_2 value of over 50 indicates that the laboratory formulation has a comparable dissolution profile to the marketed formulation, although it is not identical.

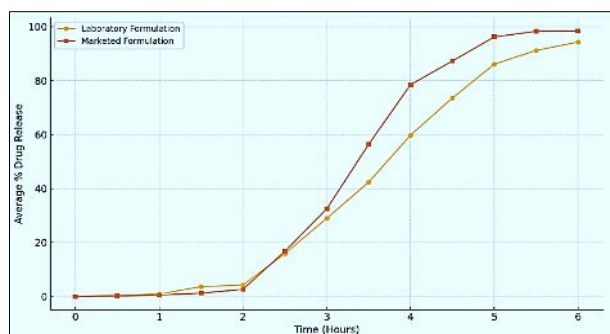


Fig 4: Drug Release Profile of Laboratory Formulation and Marketed Formulation

- **Drug release kinetics:** The drug release kinetics best fitted the Peppas-Korsmeyer model ($R^2 = 0.9664$), suggesting an anomalous transport mechanism involving both diffusion and erosion, which aligns with the behavior expected from enteric-coated systems.

Table 4: Drug release Kinetics model of Laboratory formulation

kinetic release study of esomeprazole enteric-coated tablet						
Time (hr)	Avg % DR	Zero	1st order	Matrix	Peppas	Hix.crow.
0	0.00	0.00	0.00	0.00	0.00	0.00
0.5	0.45	9.38	9.79	7.08	0.22	15.63
1	0.89	18.77	18.63	10.01	1.19	29.54
1.5	3.65	28.15	26.60	12.26	3.24	41.83
2	4.23	37.54	33.79	14.16	6.57	52.60
2.5	15.86	46.92	40.28	15.83	11.38	61.95
3	28.98	56.31	46.13	17.34	17.83	69.98
3.5	42.34	65.69	51.40	18.73	26.07	76.80
4	59.77	75.07	56.16	20.02	36.21	82.49
4.5	73.56	84.46	60.46	21.23	48.40	87.17
5	86.12	93.84	64.33	22.38	62.73	90.93
5.5	91.21	103.23	67.82	23.47	79.32	93.88
6	94.32	112.61	70.97	24.52	98.27	96.10
model fitting (r^2 value)		0.9321	0.8319	0.9509	0.9664	0.8825
Best fit model		Peppas Korsmeyer				

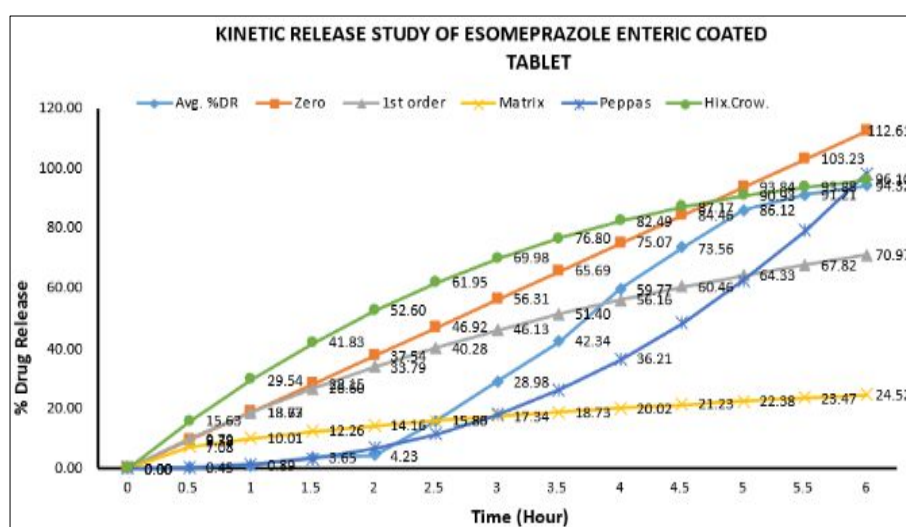


Fig 5: Kinetic release study of esomeprazole magnesium enteric-coated tablet

Conclusion

The present study successfully formulated and evaluated an enteric-coated tablet of Esomeprazole Magnesium aimed at improving drug stability and achieving a sustained release profile. Using ethyl cellulose as the enteric polymer and employing the wet granulation technique, the formulation was optimized and compared with a marketed product to assess its pharmaceutical performance.

Physicochemical evaluations—including tablet hardness, thickness, and weight variation—confirmed that the formulation met pharmacopeial standards. FT-IR spectroscopy showed no significant interactions between the drug and excipients, confirming the compatibility of the formulation components.

In vitro drug release studies revealed a gradual and extended drug release pattern from the laboratory formulation. Bioavailability comparison using AUC showed values of 227.10 for the laboratory formulation and 259.92 for the marketed one, indicating substantial release efficiency. The similarity factor ($f_2 = 53.53$) further demonstrated that both formulations have comparable dissolution profiles.

Kinetic modeling showed the best fit with the Peppas-Korsmeyer model, suggesting a release mechanism governed by both diffusion and erosion. This is ideal for

maintaining consistent therapeutic levels and minimizing side effects.

Overall, the developed formulation offers a promising, cost-effective alternative to marketed Esomeprazole products, with comparable drug release characteristics and enhanced stability. Further *in vivo* and scale-up studies are recommended to support commercial viability.

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