

PHARMACY

Formulation, Optimization and Evaluation of Delayed Release Tablets of Esomeprazole Magnesium

Charu Jain¹, Pradeep Chauhan², Sandeep Jain², Bharat K. Tyagi²

¹Department of Pharmaceutics, Institute of Professional Studies, College of Pharmacy, Gwalior, Madhya Pradesh, India

²Institute of Professional Studies, College of Pharmacy, Gwalior, Madhya Pradesh, India

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Abstract

The objective of the current investigation was to formulate delayed release tablets of Esomeprazole that could control the release of the drug thereby reducing its dosing frequency and improving the bioavailability. The objective was accomplished by preparation of the matrix tablets using HPMC K4M, carbopol 940 and Eudragit RLPO as the matrix forming polymers. The angle of repose for all formulations was found to be within the range from 23°13 to 28°15. This indicates that good flow property of powder blend. The bulk density and tapped density values were found to be within the range from 0.54 to 0.60 and 0.63 to 0.71 respectively. The Hausner's ratio values were found to be within the range from 6.35 to 21.13. The friability of all formulation was in the range of 0.37% to 0.52% and the weight variation was in the range of 1.7 to 2.8 %. Swelling study was performed on all the formulation for 9 h and was found to be in the range of 1.32 to 5.22. The highest degree of swelling was achieved by F8 that contained equal concentration of HPMC K4M, carbopol 940 and Eudragit RLPO. The formulations F1, F2, F3 and F4 could not control the release for even up to 8 h. On the other hand, the formulation F5 was able to release almost 100% of the drug at the end of 10th whereas formulations F6 and F7 released 100% drug at the end of 11th hour.

Keywords: formulation; optimization; delayed release tablet; esomeprazole magnesium

1 Introduction

Drug delivery technologies are the formulation technologies that modify drug release profile, absorption, distribution and elimination for the benefit of improving product efficacy and safety, as well as patient convenience and compliance.

One would always like to have ideal drug delivery systems that will possess two main properties:

- It will be a single dose for the whole duration of treatment.
- It will deliver the active drug directly at the site of action.

Esomeprazole magnesium is a proton pump inhibitor (PPI) widely used in the treatment of gastroesophageal reflux disease (GERD), peptic ulcers, and other acid-related disorders. It suppresses gastric acid secretion by inhibiting the H⁺/K⁺-ATPase enzyme in gastric parietal cells. However, esomeprazole is susceptible to degradation in the acidic environment of the stomach; therefore, a delayed-release formulation is required to protect the drug and ensure its release in the intestine.

1.1 Plasma concentration–time profile

The plasma concentration–time profile is a graphical representation of the change in drug concentration in blood plasma with time after drug administration (Figure 1).

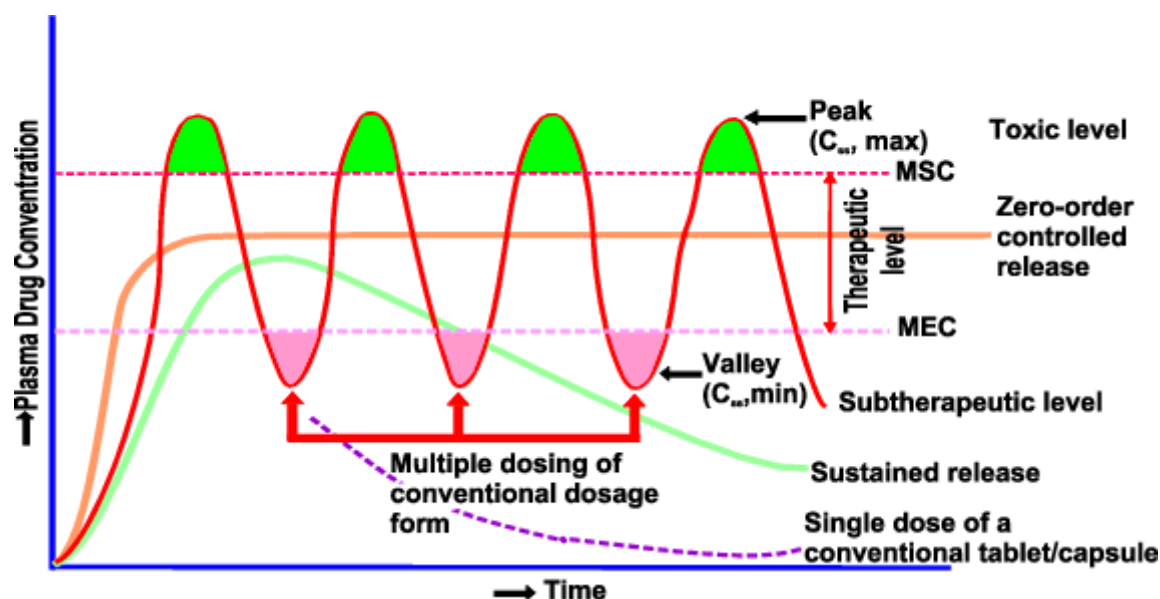


Figure 1. Plasma concentration–time profile.

1.2 Oral controlled-release formulations

Oral controlled-release formulations are pharmaceutical dosage forms designed to release a drug gradually over an extended period after oral administration. They maintain therapeutic drug concentrations in the blood for a prolonged duration, reduce dosing frequency, improve patient compliance, and minimize fluctuations in drug levels.

These formulations use mechanisms such as diffusion, dissolution, erosion, and osmosis to control drug release. Common examples include controlled-release tablets, capsules, matrix systems, and osmotic drug delivery systems.

1.2.1 Types of oral controlled-release formulations

Matrix systems. The drug is uniformly dispersed within a polymeric matrix. Drug release occurs through diffusion, polymer swelling, or erosion. Common polymers include hydroxypropyl methylcellulose (HPMC) and ethyl cellulose.

Reservoir systems. The drug core is surrounded by a rate-controlling polymeric membrane. The coating regulates drug release by controlling the movement of the drug into the surrounding gastrointestinal fluids.

Osmotic systems. These formulations use osmotic pressure to control drug delivery through a small opening in a semipermeable membrane. Drug release can be relatively consistent under suitable conditions.

Multilayer tablets. Different layers contain different drug quantities or release-controlling excipients. They may provide an initial dose followed by prolonged release or separate incompatible ingredients.

2 Materials and methods

2.1 Materials

The materials used and their sources are listed in Table 1.

Table 1. Materials and their sources.

S. no.	Item	Source of procurement
1	Esomeprazole	Gift Sample from Edmund Healthcare
2	HPMC K4M	Oxford Chemicals
3	Eudragit	Yarrow Pharmaceuticals
4	Carbopol 940	Oxford Chemicals
5	Methanol	Rankem
6	Ethanol	MSW Chemicals
7	Hydrochloric acid	Rankem
8	Magnesium Stearate	Oxford Chemicals
9	Sodium dihydrogen phosphate	Oxford Chemicals
10	Dipotassium hydrogen phosphate	Oxford Chemicals

2.2 Preformulation studies

2.2.1 *### organoleptic properties*

A small quantity of pure Esomeprazole powder was taken in a butter paper and viewed in well illuminated place to observe its color; the taste and odor were observed using tasting and smelling the drug.

2.2.2 *### solubility analysis*

Solubility of Esomeprazole was determined in water, methanol, ethanol, 0.1N hydrochloric acid. Solubility studies were performed by shaking small amount of Esomeprazole in test tubes containing the solvent and observing for undissolved particles (if any).

2.2.3 *### drug excipient compatibility studies by FT-IR*

IR spectra of drug, polymer and drug and polymers, individual excipients, drug and polymers and excipients were obtained using FT-IR. Spectra were recorded for pure drug, pure excipients, and physical mixture of drug and polymer, drug, polymer and excipients.

2.2.4 *### standard curve of Esomeprazole*

The maximum absorption of Esomeprazole was observed at 295 nm. The calibration curve was obtained using different concentrations of the drug at the above wavelength.

2.2.5 *### preparation of stock and standard solution*

The stock solution was freshly prepared by dissolving 100 mg of Esomeprazole in 10 ml of phosphate buffer pH 6.8 in a 100 ml volumetric flask and then made up the solution up to the mark using the same buffer for obtaining the solution of strength 1000 µg/mL (stock I). 10ml of this solution is diluted to 100 ml with pH 6.8 buffer to obtain a solution of strength 100 µg/mL (stock II).

2.2.6 ### preparation of various concentrations

10 ml stock solution was taken from stock II and volume made up to 100 ml by using pH 6.8 buffer to obtain 10µg/ml. From this solution withdraw 2, 4, 6, 8, 10 ml of solution into the 10 ml volumetric flask and volume made up to 10 ml by using pH 6.8 buffer to get the solutions of 2, 4, 6, 8, 10µg/ml.

2.3 Formulation of Esomeprazole delayed release tablets

A 2³ factorial approach was used for preparing eight formulations in various combinations of the matrix forming polymers. Each polymer (independent variable) was used as two levels, high and low or presence and absence (Table 2).

Table 2. Design of formulations.

Factor	Level	
	High (+)	Low (-)
HPMC K4M	10%	3.33%
Carbopol 940	10%	3.33%
Eudragit RLPO	10%	3.33%

The formulation of the matrix tablets was performed using direct compression method by employing HPMC K4M, carbopol 940 and Eudragit RL/PO as the matrix forming polymers (Table 3). Magnesium stearate was used as the lubricant in 2.5% concentration of total weight of the polymers and Esomeprazole.

The quantity of the drug, matrix forming polymers and all other excipients was accurately weighed and passed through sieve no. 22. The ingredients were mixed together manually using tumbling action in large poly bags. The powder blend was again passed through sieve no. 22 and mixed with magnesium stearate. The blend was evaluated for precompression parameters and compressed into 5 mm tablets using single punch tablet punching machine.

Table 3. Composition of matrix tablets.

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8
Esomeprazole	40	40	40	40	40	40	40	40
HPMC K4M	-	40	-	20	-	20	-	13.33
Carbopol 940	-	-	40	20	-	-	20	13.33
Eudragit RLPO	-	-	-	-	40	20	20	13.33
Magnesium stearate	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0

2.4 Evaluation of precompression blends

Angle of repose, Carr's Index, Bulk density, Tapped density and Hausner's ratio were determined to assess the flow ability of the prepared granules.

2.4.1 Angle of repose

Angle of repose was determined by using funnel method. Accurately weighed amount of blend was taken in funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just

touches the heap of the pile. The blends were allowed to flow through the funnel freely on to the surface. The diameter of powder cone was measured and the angle of repose was calculated using the following formula:

$$\tan \theta = \frac{h}{r}$$

Where, h is the height of the pile; θ is the angle of repose; and r is the radius of the heap

2.4.2 Bulk density

Bulk density is the ratio between a given mass of powder and its bulk volume. Apparent bulk density was determined by pouring the weighed granules into a graduated cylinder via funnel and measuring the volume. Density was calculated using the formula:

$$\rho_b = \frac{M}{V_b}$$

Where, ρ_b is the bulk density; M is the mass of the microspheres and V_b is the volume occupied by the microspheres.

2.4.3 Tapped density

Tapped density is the ratio between a given mass of powder and the constant or final volume of powder after tapping. It was determined by tapping a graduated cylinder containing a known mass of granules for a fix number of taps until the powder volume has reached a constant value. The tapped density was computed using the formula:

$$\rho_t = \frac{M}{V_t}$$

where ρ_t is the tapped density and V_t is the tapped volume.

2.4.4 Hausner's ratio

Hausner's ratio was calculated from the bulk and tapped density using the formula:

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

2.4.5 Percent compressibility (Carr's index)

Compressibility is an important measure that can be obtained from the bulk and tapped densities. The flow ability of the granules was measured by the application of compressibility index given by the equation:

$$I = \left(1 - \frac{V_f}{V_0}\right) \times 100$$

where V_f is the volume of the sample after tapping and V_0 is the volume before tapping.

2.5 Evaluation of delayed release tablets

The tablets were evaluated for in process and finished product quality control tests i.e. appearance, thickness, weight variation, hardness, friability, swelling index, dissolution study.

2.5.1 Hardness test

The hardness of the formulated tablets was tested using Monsanto type hardness tester. Three tablets from each batch of formulation were randomly taken and the force required to break the tablets was measured using hardness tester.

2.5.2 Friability test

The friability test of the formulations was performed using a Roche type friability test apparatus. Twenty tablets were initially weighed (W_{initial}) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (W_{final}). The percentage friability was then calculated by the formula.

$$\% \text{ Friability} = \frac{W_{\text{initial}} - W_{\text{final}}}{W_{\text{initial}}} \times 100$$

2.5.3 Weight variation test

20 tablets were randomly taken and weighed to calculate the average weight of the tablets. Each of these tablets was individually weighed and the difference from average weight was calculated. The percent weight variation was calculated to determine the deviation from the average weight.

2.5.4 Thickness

The thickness of randomly selected tablets from each batch of formulation was measured using a digital vernier caliper.

2.5.5 Drug content

Five tablets from each formulation were weighed to determine the average weight. These tablets were crushed in a mortar then the amount of powder equivalent to 10 mg of drug was dissolved in 0.1M HCl and volume was made up to 100 ml using 0.1M HCl. 10ml of the filtrate was made up to 100ml with 0.1M HCL. 10 μ g/ml solution was prepared from the above solution and analyzed for drug content.

2.5.6 In vitro dissolution

The USP type II paddle apparatus with a paddle speed of 50 rpm was used for dissolution testing for the formulated matrix tablets. The dissolution media used consisted of 900 mL of phosphate buffer pH 6.8 and distilled water. 5 mL of samples were collected at time points of every hour until 12 h and the media was replenished with the same volume of fresh media. The free drug concentration was estimated using a UV spectrophotometer at a wavelength of 295 nm.

2.5.7 Swelling index

One tablet from each formulation was kept in a Petri dish containing phosphate buffer pH 7.2. At the end of 2 h, the tablet was withdrawn, kept on tissue paper and weighed. The weighing was continued for every 2 hr, till the end of 9 h. The % weight gain by the tablet was calculated by formula

$$\text{S.I.} = \frac{M_t - M_0}{M_0} \times 100$$

where S.I. is the swelling index, M_t is the weight of the tablet at time t and M_0 is the weight of the tablet at time zero.

3 Results and discussion

3.1 Preformulation studies

3.1.1 Organoleptic properties

The organoleptic properties were observed using the sense organs. The results observed are reported in Table 4.

Table 4. Organoleptic properties of Esomeprazole.

Test	Specification	Observation
Color	White to off white	White
Odor	Odorless	Odorless
Taste	Bitter	Bitter
Appearance	Amorphous	Amorphous

3.1.2 Solubility analysis

Esomeprazole was found to be soluble in water and 0.1N HCl, slightly soluble in ethanol, methanol. Esomeprazole is reported to be class III drug according to the BCS classification and the freely soluble nature suggests similarly.

3.1.3 Calibration curve of Esomeprazole

The λ_{max} of esomeprazole in phosphate buffer pH 6.8 was observed to be 295 nm. Calibration curve of Esomeprazole was obtained by plotting absorbance at 295 nm in phosphate buffer pH 6.8 versus concentration ($\mu\text{g/ml}$) (Table 5 and Figure 2).

Table 5. Calibration curve data.

Concentration ($\mu\text{g/mL}$)	Absorbance
0	0
2	0.123
4	0.251
6	0.377
8	0.482
10	0.608

The linear regression analysis for the calibration curve was $\text{Abs} = 0.0606(\text{conc}) + 0.0038$, with a coefficient of determination (R^2) of 0.999.

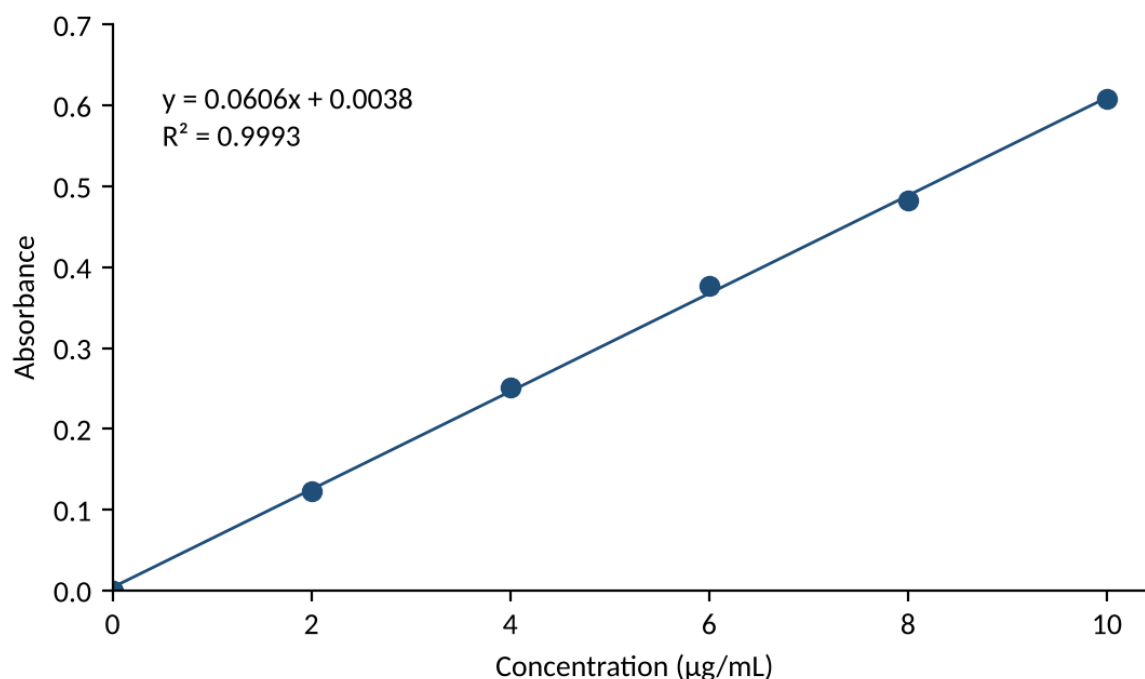


Figure 2. Calibration curve of Esomeprazole.

3.1.4 Drug-polymer compatibility study

The FTIR spectra of the pure drug and physical mixture of drug and excipient were recorded in between 400-4000 wave number (cm^{-1}).

The peak at 3669.22 cm^{-1} in the spectra of the pure Esomeprazole corresponds to N-H (stretching) (Figure 3). The peak at 1010.47 cm^{-1} could be assigned to S=O (stretching), the peak at 1164.99 cm^{-1} may be assigned for C-O-C (stretching). The drug and polymers employed were found to be compatible as similar peaks were observed in the physical mixture of drug and polymers with slight differences (Figure 4).

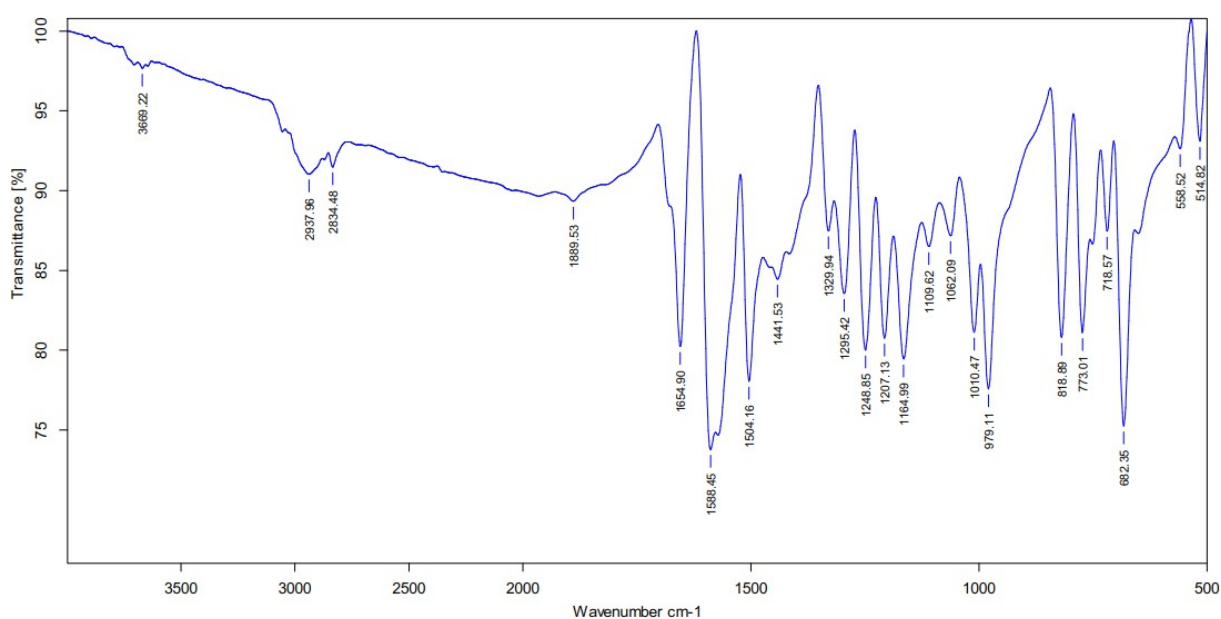


Figure 3. FTIR spectrum of Esomeprazole.

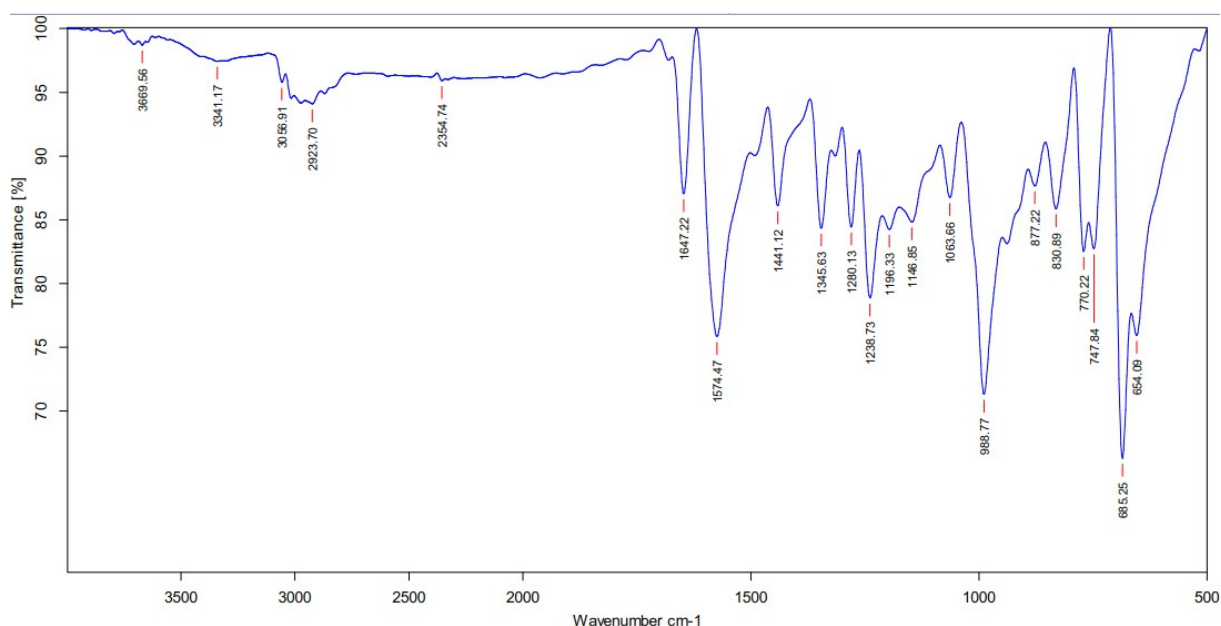


Figure 4. FTIR spectrum of the physical mixture (drug + polymers).

3.2 Precompression blend characterization

All these parameters indicate that the powder blend had good to fair flow property and is suitable for compression into tablets (Table 6). The compressibility index for formulations exhibited good compaction characteristics of the blends.

Table 6. Precompression characterization.

Formulation code	Angle of repose (°)	Bulk density (g/mL)	Tapped density (g/mL)	Carr's index (%)	Hausner's ratio
F1	27.61	0.58	0.65	10.77	1.12
F2	26.32	0.57	0.70	18.57	1.23
F3	27.23	0.54	0.64	15.63	1.19
F4	28.15	0.60	0.67	10.45	1.12
F5	27.34	0.59	0.63	6.35	1.07
F6	27.25	0.56	0.71	21.13	1.27
F7	26.13	0.56	0.63	11.11	1.13
F8	26.61	0.57	0.68	16.18	1.19

3.3 Evaluation of matrix tablets

The tablets were evaluated for appearance, thickness, hardness, weight variation, friability, swelling index, in vitro buoyancy and dissolution study (Tables 7 and 8).

Table 7. Quality parameters of delayed release tablets of Esomeprazole.

Formulation code	Thickness (mm)	Hardness (kg/cm ²)	Weight variation (%)	Friability (%)	Swelling index	Drug content (%)
F1	5.01	4.5	1.9	0.37	1.32	98.3

Formulation code	Thickness (mm)	Hardness (kg/cm ²)	Weight variation (%)	Friability (%)	Swelling index	Drug content (%)
F2	4.98	4.0	2.1	0.39	2.25	98.5
F3	5.01	4.0	2.1	0.51	2.42	98.4
F4	4.99	4.5	1.7	0.45	3.26	98.7
F5	4.98	4.5	2.3	0.44	3.37	98.5
F6	5.02	4.0	2.8	0.38	3.52	98.9
F7	5.01	4.5	2.5	0.52	4.58	98.7
F8	5.03	4.5	2.1	0.51	5.22	98.6

Table 8. Cumulative release of Esomeprazole from matrix tablets.

Time (h)	Cumulative release (%)							
	F1	F2	F3	F4	F5	F6	F7	F8
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	15.80	21.30	24.50	27.30	15.10	6.20	8.10	8.60
2	28.60	33.40	36.20	40.50	26.40	13.20	16.20	15.70
3	41.30	45.60	48.70	52.40	35.30	23.30	27.10	25.10
4	60.40	62.10	66.10	70.10	43.40	35.50	38.40	34.30
5	76.40	78.30	80.50	83.20	51.70	41.70	46.30	40.50
6	81.10	84.70	91.80	99.50	63.20	50.10	58.20	48.90
7	94.60	97.90	100.10	98.30	75.40	61.20	73.10	59.70
8	100.10	97.10	98.60	96.40	87.90	75.10	88.30	68.30
9	96.50	96.30	97.40	94.80	94.60	84.80	96.90	79.40
10	94.10	94.90	95.80	91.60	100.80	97.60	99.90	90.50
11	93.20	94.10	95.10	90.10	98.40	100.30	99.10	98.70
12	90.10	93.10	94.60	88.50	98.10	100.10	98.60	100.10

A plot of % cumulative drug release versus time for matrix tablet formulations is shown in Figures 5 and 6.

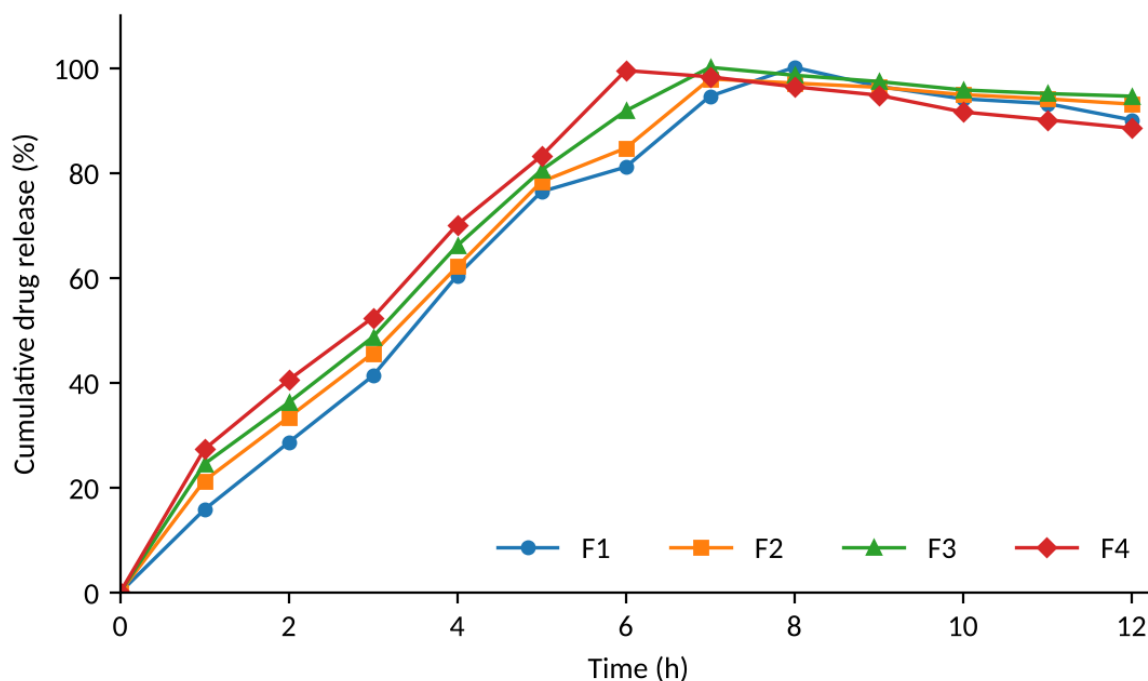


Figure 5. Release of Esomeprazole from formulations F1–F4.

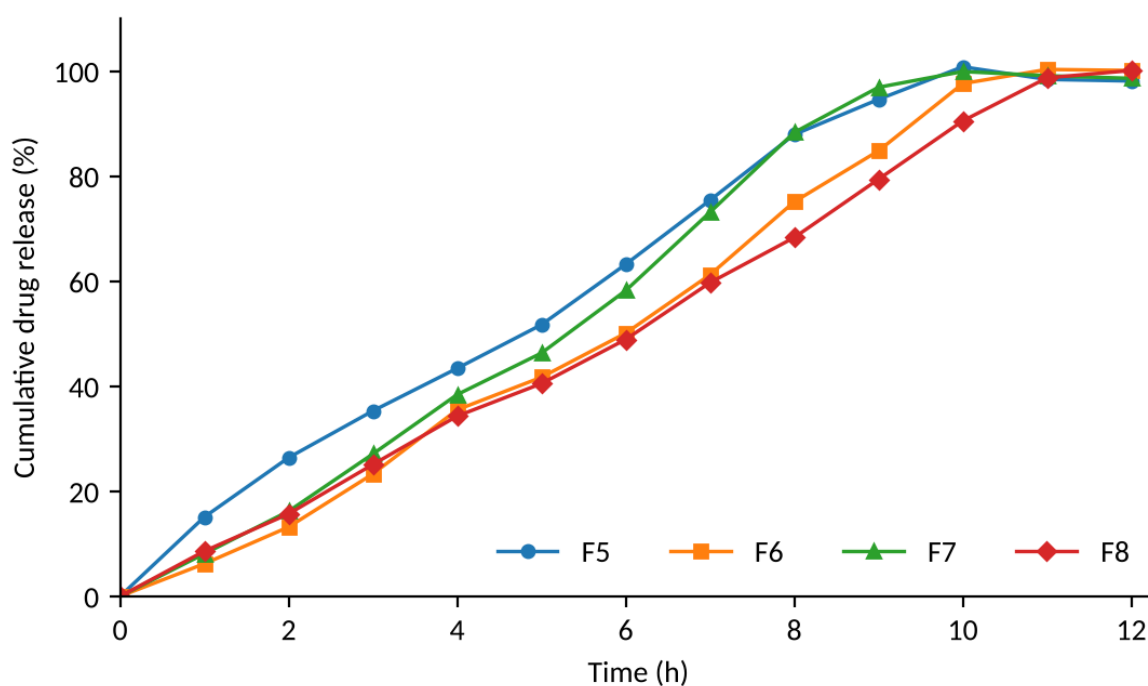


Figure 6. Release of Esomeprazole from formulations F5–F8.

4 Summary and conclusion

4.1 Summary

The objective of the current investigation was to formulate delayed release tablets of Esomeprazole that could control the release of the drug thereby reducing its dosing frequency and improving the

bioavailability. The objective was accomplished by preparation of the matrix tablets using HPMC K4M, carbopol 940 and Eudragit RLPO as the matrix forming polymers.

The precompression blend prepared was evaluated for the micromeritic properties in order to ascertain the compressibility characteristics of the blend. The angle of repose for all formulations was found to be within the range from 23°13 to 28°15. This indicates that good flow property of powder blend. The bulk density and tapped density values were found to be within the range from 0.54 to 0.60 and 0.63 to 0.71 respectively. The Hausner's ratio values were found to be within the range from 6.35 to 21.13.

The thickness of all formulation was ranged in between 4.98 to 5.03 mm. while the hardness of the formulations ranged from 4.0 kg/cm² and 4.5 kg/cm². The friability of all formulation was in the range of 0.37% to 0.52% and the weight variation was in the range of 1.7 to 2.8 %.

Swelling study was performed on all the formulation for 9 h and was found to be in the range of 1.32 to 5.22. The highest degree of swelling was achieved by F8 that contained equal concentration of HPMC K4M, carbopol 940 and Eudragit RLPO.

The formulations F1, F2, F3 and F4 could not control the release for even up to 8 h. On the other hand, the formulation F5 was able to release almost 100% of the drug at the end of 10th whereas formulations F6 and F7 released 100% drug at the end of 11th hour. The formulation F8, on the other hand was able to sustain the drug release for entire 12 hours of the study. The results lead to conclusion that the formulation F6, F7 and F8 were the best formulation that exhibited the desired sustained release, tablet qualities as well as the swelling properties that are desired by a matrix tablet.

4.2 Conclusion

The results obtained from the study indicate that use of HPMC K4M, carbopol 940 and Eudragit RLPO in equal ratio as the matrix forming substance could help in achieving sustained release over a longer duration and help in reducing the dose as well as frequency of administration of the medicaments. Further *in vivo* release studies are needed to support for the conclusion of the present investigation.

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