RESEARCH PAPER

# Development and Characterization of Gastro-Resistant Pellets of Esomeprazole Magnesium Trihydrate

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**ABSTRACT**
The objective of the study was to develop and evaluate the delayed release pellets of esomeprazole magnesium trihydrate. It is a proton pump inhibitor that suppresses the gastric acid. The drug is an acid labile drug i.e., degraded in stomach pH so it is formulated as a delayed release dosage form by employing suitable enteric coating polymers to absorb in intestinal pH. The formulation process was carried out in fluidized bed coater by suspension layer technique by using methacrylic acid copolymer (type C).The dissolution studies of the optimized formula (E5) show effective drug release and it follows first order kinetics indicated a super case II transport. FTIR studies prove that there is no incompatibility between the drug and excipients. The SEM studies were conducted to know the surface morphology and coating thickness. The optimized formulation (E5) demonstrated robust similarity with innovator. Accelerated stability studies indicated that storage conditions were excellent.

**Keywords**: *Delayed release, enteric coating, fluid bed processor, pellets, esomeprazole magnesium trihydrate*
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## INTRODUCTION

Esomeprazole magnesium trihydrate is belongs to BCS class-II drug having low solubility and high permeability and it belongs to pharmacological class of compounds called proton pump inhibitors[1], it suppresses the gastric acid secretion from the parietal cells[2,3]. The proton pump is highly unstable at pH of gastric environment and stable at intestinal pH (6.0-7.4). To overcome the stability and solubility problems, several polymers such as ethyl / methyl cellulose, methyl/ ethyl acrylate co-polymers (eudragit L-30 D55 series), HPMC phthalates[4] , ethyl cellulose acetates were used for the enteric film coating process of proton pump inhibitors and eudragit L-30 D55 and hydroxyl propyl cellulose-L (HPC-L) and talc are recommended to produce shape of the spheres and rapid dissolution.

Chemically esomeprazole, is a di-(S)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl] sulfinyl]-1H-benzimidazole magnesium salt trihydrate. Esomeprazole inhibits the $H^+/K^+$ ATPase pump at the surface of the gastric parietal cell, by acting specifically on the proton pump and it blocks the final stage of the acid production and reduces the gastric acidity [6].

The objective of the present study was to formulate and evaluate the esomeprazole magnesium trihydrate delayed release pellets by using suspension layer technique with fluid bed processor for the treatment of peptic ulcers. Pellatization technique is employed to overcome the solubility, dissolution and bioavailability problems associated with the hydrophobic drugs [7].

## MATERIALS AND METHODS

### Materials

Analytical grade materials were used in study.

### Methods

**Formulation of delayed release Esomeprazole magnesium trihydrate Pellets** [13-17]

The suspension layering technique includes the following steps.

**Screening (or) selection of inert core:** Required quantity of sugar spheres were sifted through mesh #60. Meshes #60 passed sugar spheres were sifted through mesh #80 and retains were collected.

**Preparation of drug layer pellets:** Sodium hydroxide (NaOH) was dissolved in small quantity of water in a stainless-steel container and dissolve polysorbate 80 and hydroxyl propyl cellulose-L (HPC-L) in another container with continuous stirring, esomeprazole was added to this

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solution, followed by talc and NaOH solution with continuous stirring. Weighed quantity of Sugar pellets were loaded into the product bowl of the fluid bed coater (FBC) which is pre warmed with temperature 45± 10°C and continued until bed temperature reached to 30± 5°C,then dispersion of esomeprazole solution was sprayed onto sugar spheres at inlet temperature 45± 5 °C and bed temperature of 40 ± 3 °C. Weight was gained after completion of drug loading, then drug loaded pellets were dried for NLT 15 minutes with low fluidization temperature of 35 ± 5 °C. Then drug loaded pellets were screened through 425 microns (ASTM # 40 sieve) and 250 microns (ASTM #60 sieves).

**Table No:1** Formulation of delayed release Esomeprazole magnesium trihydrate Pellets

| S. No. | INGREDIENTS (mg/unit) | DRUG COATING | | | | SUB COATING | | | ENTERIC COATING | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | D1 | D2 | D3 | D4 | S1 | S2 | S3 | E1 | E2 | E3 | E4 | E5 |
| 1 | Sugar Spheres #60/#80 | 14 | 14 | 14 | 14 | - | - | - | - | - | - | - | - |
| 2 | Esomeprazole magnesium trihydrate | 47.6 | 47.6 | 47.6 | 47.6 | - | - | - | - | - | - | - | - |
| 3 | Drug Coated Pellets D4 | - | - | - | - | 70 | 70 | 70 | - | - | - | - | - |
| 4 | Sub coated pellets S2 | - | - | - | - | - | - | - | 91.1 | 91.1 | 91.1 | 91.1 | 91.1 |
| 5 | Hypromellose 5cps | 5 | - | - | 4 | 30 | - | - | - | - | - | - | - |
| 6 | Eudragit L30 D55 | - | - | - | - | - | - | - | - | 36.4 | 45.5 | 54.6 | 61.6 |
| 7 | HPMC HP55 | - | - | - | - | - | - | - | 81.9 | - | - | - | - |
| 8 | Hydroxy propyl cellulose (HPC-L) | - | 6 | 4 | - | - | 9.6 | 13 | - | - | - | - | - |
| 9 | Polysorbate 80 | 2 | 2 | 4 | 4 | - | - | - | 0.82 | 0.2 | 0.5 | 0.8 | 1.2 |
| 10 | Sodium Hydroxide | 0.2 | 0.2 | 0.2 | 0.2 | - | - | - | - | - | - | - | - |
| 11 | Triethyl citrate | - | - | - | - | - | - | - | 24.6 | 10.9 | 13.6 | 16.4 | 18.5 |
| 12 | Talc | - | - | - | - | 7 | 11 | 4.3 | 16.4 | 7.3 | 9.1 | 10.9 | 9.2 |
| 13 | Magnesium Stearate | - | - | - | - | 7 | 1.1 | 4.3 | - | - | - | - | - |
| 14 | Glyceryl mono stearate | - | - | - | - | - | - | - | - | 1.8 | 2.3 | 2.7 | 3.1 |
| 15 | Ethanol (mL) | 385 | - | - | - | 182 | - | - | - | - | - | - | - |
| 16 | Acetone (mL) | 165 | - | - | - | - | - | - | - | - | - | - | - |
| 17 | Purified water(mL) | - | 322 | 322 | 322 | 82 | 191 | 191 | 550 | 400 | 450 | 500 | 450 |

**Preparation of Barrier Coating pellets:** Weighed quantities of HPC-L, talc, and magnesium stearate were taken and passed through the sieve no # 60 separately. HPC-L was dissolved in required quantity of water under continues stirring then magnesium stearate and talc was added to the HPC-L solution under continues stirring, weighed quantity of drug loaded pellets into the product bowl of the FBC bowl and pre warmed with temperature 50 ± 5°C continued until bed temperature reaches to 40± 3°C. Then the HPC-L dispersion was sprayed onto sugar spheres at inlet temperature 50±5°C and bed temperature of 40 ± 3°C, and Parameters were recorded for every 15 minutes after spraying was started. Weight was gained after completion of barrier coating , the pellets were dried for NLT 15 minutes with low fluidization temperature of 35 ± 5 °C. Barrier coated pellets were screened through 425 microns (ASTM # 40 sieve) and 250 microns, retentions were discarded on ASTM 40 sieve and fines were passed through ASTM # 60 sieve.

**Preparation of Enteric Coating pellets:** Required amount of water was taken in a clean stainless-steel container and then Triethyl citrate, Tween 80, Talc were added to the water under continues stirring, then eudragit-L30 D55 was added to the solution of under continues stirring. And weighed quantity of barrier coated pellets were loaded into the product bowl of the FBC bowl which is pre warmed with temperature 50± 5°C continued until bed temperature reached to 40±5°C. Then the dispersion was sprayed onto sugar spheres at inlet temperature 50±5 °C and bed temperature of 40±5°C. Parameters were recorded for every 15 minutes after spraying was started. Then weight was gained after completion of enteric coating dispersion, then enteric coated pellets were dried for NLT 15 minutes with low fluidization temperature of 35 ± 5 °C. The enteric coated pellets were screened through 600 microns (ASTM # 30 sieve) and 250 microns (ASTM #60 sieves), retentions were discarded on ASTM 30 sieve and fines were passed through ASTM # 60 sieve, then sifted enteric coated pellets were collected and stored in a suitable container with double lined LDPE kept in triple laminated Aluminium bags with 100g of silica gel desiccant in between every bag.

**Characterization of Pellets** [21]

**Scanning electronic microscopy (SEM) studies**[23]

Surface morphology of enteric coated pellets was determined by SEM (Scanning electron microscopy) analysis. Scanning electron microscopy (SEM) is a technique of choice for measuring the shape and surface smoothness of the pellets to support visually the other qualitative and quantitative results.

**Fourier Transform Infrared (FTIR) Studies**[24]**:** FTIR studies were done to detect the possible interactions between the drug and excipients. The prepared samples were analysed for FTIR spectroscopic studies to determine the interaction between drug and carrier. For the FTIR Study samples were prepared with potassium bromide as a disc , then spectra were recorded Perkin Elmer, RXi FTIR system. The scanning range was 4000 to 400 $cm^{-1}$ and the resolution was $2cm^{-1}$

**Evaluation of Delayed Release Formulations (Enteric Coated Pellets)**[25]

**Assay:** Assay was determined by using HPLC (waters) was carried out under isocratic conditions using Hypersil, BDS $C_{18}$ column (150× 4.6mm internal diameter) 5µm particulate size at 20 to 25°C, injection volume 20µl, mobile phase was phosphate buffer pH (7.4) and methanol 50:50 v/v, flow rate at 1.5ml/min and chromatogram monitored at 302nm. Then chromatograms and peak responses were noted.

***In Vitro* Dissolution Studies**[28]**:** Dissolution studies were carried out in dissolution apparatus Electro lab (TDT – 08 L) for the formulated batches of pellets(E1 to E5) by using the 300ml of 0.1N HCl using USP-II paddle type at a speed of 100rpm at temperature of 37±0.5ºC for 2 hrs. After 2 hrs 0.1N HCl was discarded and transferred into 1000ml of sodium phosphate buffer, pH 6.8 and run at 100 rpm for specified time at the temperature of 37±0.5ºC. Then 10ml of samples were withdrawn sample was filtered through 0.45µm membrane. 5ml of the filtered sample solution was immediately transferred into test tubes containing 1ml of 0.25N NaOH in a test tube at the time interval of 10,20,30,45 and 60 mins. Then the collected samples were analyzed by using HPLC method. 20 µl of dissolution medium, standard solution (5 times) and sample solution was filtered through 0.45µm membrane filter and then they were separately injected at a flow rate of 1.5ml/min at the wave length of 302nm at ambient temperature into HPLC column (Hypersil BDS, $C_{18}$, 4.6 X 150 mm internal diameter, 5µm) for 10min. The chromatograms and peak responses were noted.

**Stability Studies** [28]

As per ICH guidelines, the samples for stability analysis must be exposed to an environment of 40˚C ± 2˚C / 75% ± 5% RH for a period of 6 months. As per the standard protocol the samples must be analyzed at 0, 1, 2, 3 and 6 months' time points. Accelerated stability studies were performed for the final optimized formulation. Samples are analyzed at 1, 2, 3 months time points.

**RESULTS AND DISCUSSION**

Formulation of delayed release Esomeprazole magnesium trihydrate Pellets were prepared by three steps. Initially**,** Drug coating was given to sugar spheres by using suspension layering technique. The four formulations were developed with sugar spheres with different concentrations of binders (HPMC and HPC-L), and solubilizer (polysorbate 80). Then, the drug coated pellets were analyzed for the amount of drug bound over the sugar spheres.

In Formulation D1 contain HPMC (7.3%) and D2 contain HPC-L (8.6%) with polysorbate 80 (2.9%) in non-aqueous systems shows that the amount of the drug coated was 70% and 80% respectively. The *in vitro* drug release in pH 6.8 phosphate buffer in 30min were shown 94.5% and 95.1% for formulation D1 and D2 respectively. From this result formulation D2 was considered to be better than D1. To improve the amount of drug to be coated on to the sugar spheres, further formulation D3 were designed with decreased binder HPC-L (5.7%) with increased polysorbate 80 (5.7%) concentration and using aqueous system. D3 formulation was observed to be 90% drug loading but incomplete drug release (85.1%) was observed. Further D4 formulation were designed with 5.7% concentrations of HPMC and polysorbate 80. Hence, formulation D4 was found to have drug coating of 98% and process problems were not observed during coating and drug releases in buffer stage were observed. From the above formulations, it was concluded that 5.7% hydroxy propyl methyl cellulose and 5.7% polysorbate 80 was an optimized binder concentration for drug coating.

The main aim of sub coating is to protect the drug coated pellets from enteric coating and environmental conditions. In S1 and S3 formulations, yield was found to be low. Consequently these formulations not shown improved protection for drug coated pellets. In S2 formulation HPC-L, talc and magnesium stearate concentrations were optimum for better film formation, there by better protection was obtained to drug coated pellets. In this formulation S2 yield was found to be high compared with S1 and S3.

In enteric coating, HPMCP enteric polymer coating was given to E1 formulation, due to the high viscosity of polymer very harder film was formed when compared with formulation E2-E5 contain different concentrations of eudragit L30 D55 (Methacrylic acid copolymer type C polymer i.e. 30% aqueous). So, methacrylic acid copolymer (type C) selected as furthered enteric coated formulations. Plasticizer plays major role in enteric film formation, triethyl citrate (TEC) was found to have good film forming capacity. Plasticizer concentration was optimized at 30% of dry polymer weight. TEC was a superior and more suitable plasticizer for eudragit dispersion, resulting in a more uniform and continuous coating that reduced plasticizer leaching. Polysorbate 80 plays major role in the drug release in buffer stage polysorbate 80 concentration was optimized at 2% of dry polymer weight.

**Scanning electronic microscopy (SEM) studies:** Scanning electron microscopy of optimized formulation (E5) of enteric coated pellets was shown in Fig.1(A), the pellets were found to be discrete, uniform and spherical in shape and coating layers of optimized formulation (E5) and Innovator (Nexium) were shown in Fig.1of image B and C. the thickness of the three coating layers were

shown in Table.2 On compares with innovator, the formulation (E5) shows more or less identical thickness values in drug loading, barrier and enteric coating layers.

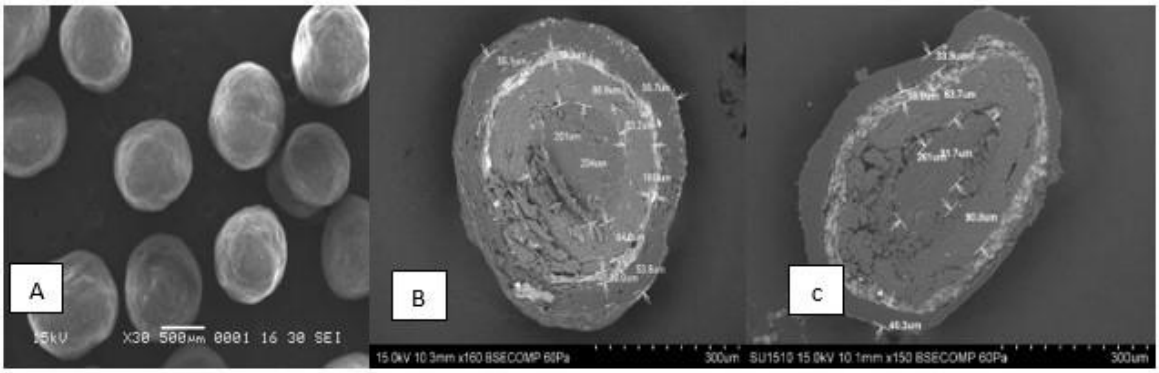


**Figure No.1:** (A) SEM image of optimized formulation (E5) Esomeprazole DR Pellets, (B) Coating Layer of (E5) and (C) Coating Layer of Innovator (Nexium)

**Table.2:** Thickness of coated pellets(from SEM studies)

| S. No | Stage | Innovator | E5 Formulation |
|---|---|---|---|
| 1 | Drug layering thickness | 60 - 65 µm | 63 - 70 µm |
| 2 | Barrier thickness | 16 - 20 µm | 18 - 20 µm |
| 3 | Enteric Coating thickness | 33 - 41 µm | 53 - 57 µm |

**Fourier Transform Infrared (FTIR) Studies**

Pure Esomeprazole magnesium Trihydrate spectra showed sharp characteristic peaks at 3068cm$^{-1}$ (N-H, Stretching), 2995cm$^{-1}$ ($OCH_3$ stretch), 1573cm$^{-1}$(C=C Aromatic ring, stretch), 1cm$^{-1}$(C=N, Stretch), 1473 cm$^{-1}$ ($CH_2$ Bending) 1199 cm$^{-1}$ (C-H Stretch), and 637 cm$^{-1}$ (S-O Bending). These peaks are also prominent in the FTIR spectra's and were shown in Fig.2. This indicates that there is no interaction between the drug and excipients from both physical observation and FT-IR studies.

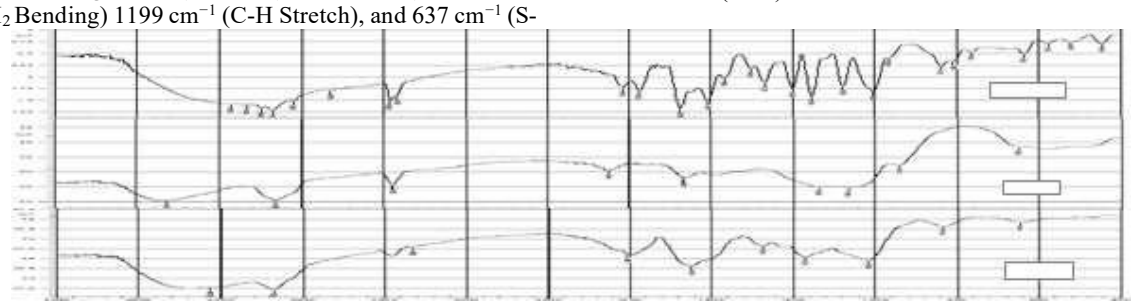


**Figure No.2:** FTIR spectra Pure Esomeprazole magnesium trihydrate and its Enteric coated pellets (E5)

**Assay:** The assay values for all enteric coated formulations (E1, E2, E3, E4 and E5) were found to be within acceptable limits and were shown in Table:3

**Table.3:** Assay of Enteric Coated Pellets

| S.No | Formulatio No. | ASSAY(%) | ACID RESISTANCE (%) |
|---|---|---|---|
| 1 | E1 | 99.8±0.02 | 79.0±0.04 |
| 2 | E2 | 101.5±0.11 | 80.9±0.23 |
| 3 | E3 | 101.5±0.13 | 87.0±0.55 |
| 4 | E4 | 101.2±0.34 | 99.2±0.12 |
| 5 | E5 | 99.7±0.42 | 99.7±0.15 |
| 7 | Innovator | 99.6 ±0.01 | 99.9±0.01 |

***In vitro* dissolution studies:** The study was carried out by using USP Dissolution apparatus -II, revealed that in the acidic medium E1 and E2 formulations had higher than the acceptable range, where as E3,E4 and E5 were within the acceptable range and both E5 and the innovator formulation (Nexium) showed 13% of drug release. E1-E4 formulations showed 98% of drug release in buffer medium, whereas E5 released 100% of drug in 30min due to efficient amount of Eudragit L30,D55 and polysorbate 80. The percentage of drug release in buffer medium is better than acidic medium. Dissolution profile of formulation E5 was compared with innovator product

(Nexium), which is shown in Fig.3. and the kinetic release profiles of delayed release pellets of esomeprazole magnesium trihydrate of all formulations were showed in Table.4. Dissimilarity factor (f1 = 9.85) and similarity factor (f2= 54.62) during the comparison of dissolution profiles of E5 & innovator product, indicated no significant difference between two formulations. Hence E5 formulation was found to be optimized.

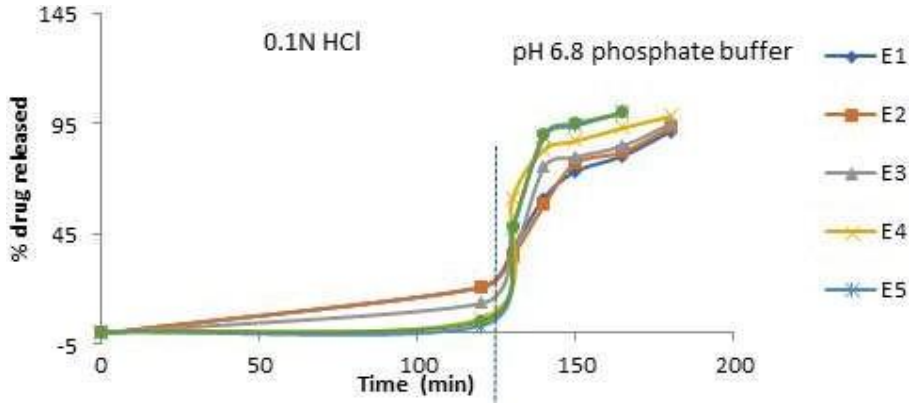


**Figure No.3:** *In vitro* dissolution profile of Enteric coated pellets (E1-E5) with Innovator in acid and buffer stage

**Table No.4:** Correlation coefficient (r) values in the analysis of release data as kinetic model

| Formulation | Zero order $R^2$ | First order $R^2$ | Higuchi $R^2$ | Krosmeyer Peppas | |
|---|---|---|---|---|---|
| | | | | $R^2$ | n |
| E1 | 0.839 | 0.983 | 0.984 | 0.931 | 1.120 |
| E2 | 0.857 | 0.981 | 0.980 | 0.942 | 1.131 |
| E3 | 0.778 | 0.952 | 0.935 | 0.934 | 1.145 |
| E4 | 0.663 | 0.969 | 0.909 | 0.884 | 1.140 |
| E5 | 0.849 | 0.967 | 0.947 | 0.941 | 1.276 |
| INNOVATOR | 0.841 | 0.964 | 0.944 | 0.939 | 1.277 |

**Stability studies**

The Accelerated Stability studies were conducted for optimized formulation (E5) according to ICH guidelines. There were no significant changes in color, assay, and percentage drug release in acid stage and buffer stage during the period of 3 months at 40°C/75% RH of the optimized formulation E5.

## CONCLUSION

Esomeprazole magnesium trihydrate is an acid labile drug i.e., degraded in stomach pH so, the formulation of delayed release pellets of esomeprazole magnesium trihydrate were developed by enteric coating process varying the composition of drug loading, barrier coating, and enteric coating. It was prepared by the suspension layer technique by using fluidized bed dryer using enteric coating polymer such as meth acrylic acid copolymer (type C). It formulated as delayed release dosage form using entering coating to absorb in intestine pH and bioavailability improved by palletization technique. The dissolution profile of formulation (E5) contains the efficient amount of talc, hydroxyl propyl cellulose-L, eudragit L30 D55 leads to effective release of drug in 40min in phosphate buffer pH 7.4., which is similar to innovator product. FTIR studies proved that there is no incompatibility between drug and excipients. SEM image illustrate surface morphology of the pellets. The study concluded that the E5 formulation revealed great similarity with innovator and the accelerated stability study result found to be storage conditions were excellent.

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**Conflict of interest:**

The authors declared no conflict of interest.

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