In Vitro Evaluation of an Enteric Coating System for Esomeprazole Delayed Release Multiparticulates for Administration Through Nasogastric Tube

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Introduction

Esomeprazole magnesium is the S-isomer of omeprazole. It is indicated for short-term suppression of gastric acid and the treatment of hyperacidity-associated disorders, including gastroesophageal reflux disease (GERD) and erosive esophagitis.1

Esomeprazole magnesium delayed release (DR) capsules are administered orally or delivered via a nasogastric (NG) tube for those patients who cannot swallow medications. NG tube is specifically designed for the administration of nutrition, or medicine to patients who have an underlying disease state that makes giving by the oral route difficult. For this procedure, the contents of capsules are emptied into water (dispersion medium) and then administered through a nasogastric (NG) tube. Many PPIs have an NG tube route of administration as one of the recommended dosing methods.

The objective of this study was to investigate the use of a fully formulated enteric system (Acryl-EZE® II, aqueous acrylic enteric system) to coat multiparticulates for NG administration.

Methods

Preparation of Delayed Release Multiparticulates

Suglets®, sugar spheres (PF001, 45/60 250-355 µm, Colorcon) were drug layered, seal-coated, and enteric coated in a GPCG 1.1 fluid-bed equipment (ACG Pharma Technologies) using the ingredients, shown in Table 1.

Table 1: Formulation of Esomeprazole Multiparticulates (40 mg)

Ingredients	%w/w	mg/capsule
Drug Layer		
Suglets PF001 (250/355 micron)	13.82	39.91
Esomeprazole magnesium trihydrate	15.41	44.5
Opadry HPMC-based, Clear	6.17	17.81
Polysorbate 80	0.69	2
Seal-coat		
Opadry HPMC-based, Clear	16.03	46.27
Enteric Coat		
Acryl-EZE II	42.22	121.89
Top-coat		
Acryl-EZE II	5.66	16.34
Total	**100.00**	**288.72**

The drug layering dispersion was prepared by dissolving a binder (Opadry® HPMC-based, clear) and a wetting agent (polysorbate 80, followed by addition of the drug in water at 17% w/w solids, then applied

to the substrate to a weight gain of 161.5% w/w. The drug dispersion was sieved through a 60-mesh screen (250 µm) to remove any aggregates (dispersion pH of 9 to 10) before application.
The seal-coat dispersion was prepared with an HPMC-based Opadry, at 7% w/w solids in water, and applied to the drug-loaded multiparticulates (MP) to a weight gain of 44.4% w/w.
Seal-coated MP were then enteric coated, using Acryl-EZE II. The enteric coating composition was prepared at 20% w/w solids and applied to a weight gain of 81% w/w. The dispersion was passed through a 60-mesh screen prior to application. The enteric coated MP were then top-coated to a weight gain of 6% w/w.

Evaluation of Esomeprazole DR Multiparticulates
MP were evaluated for assay content, and drug release using HPLC analysis. To evaluate the enteric performance, drug release was measured in a USP compliant dissolution bath, using apparatus II at 100 rpm (Electrolab, DT 800). MPs were placed in 300 mL of 0.1N HCl for 2 hours, followed by dissolution testing in 1000 mL phosphate buffer, pH 6.8.

Evaluating of Esomeprazole DR Multiparticulates through Nasogastric Tube
Esomeprazole DR MP (40 mg) were evaluated for “drug recovery” and “acid resistance recovery” test with NG tube. In this study, NG tube of size 8 French (Romsons Scientific & Surgical Industries) and 50 mL oral syringe (Dispovan, Hindustan Syringes & Medical Devices) was used (Figures 1 & 2) along with purified water as a dispersion medium having different pH values (5.6, 7.0 and 8.5). The pH of water media was adjusted with dilute sodium hydroxide solution.

Drug Recovery
Esomeprazole magnesium delayed release MP were transferred to a 50 mL oral syringe and suspended in 50 mL of dispersion medium (water with varying pH values). The syringe was shaken vigorously for 15 seconds before attaching to the NG tube. The syringe containing MP was held at approximately 45° angle and contents were then passed through the tube. The tube was flushed after drug delivery with 20 mL of water. The recovered MP that had passed through the NG tube were dissolved in tribasic sodium phosphate (pH 11.0) as the diluent and sonicated for 5 minutes for the complete dissolution of MP. The amount of esomeprazole magnesium recovered was determined following the USP monograph.

Figure 1: Nasogastric Tube Size 8 French

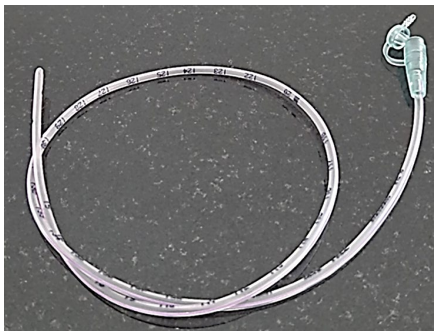


Figure 2: 50 mL Oral Syringe

Acid Resistance Recovery
The procedure used for acid resistance recovery was similar to that described in the drug recovery studies, except, after suspension in water, the esomeprazole MP were delivered through the oral syringe and NG tube directly into a dissolution jar containing 300 mL of 0.1N HCl. The dissolution test was performed using USP Apparatus II (Paddle) at 100 rpm, and after 2h the MP were carefully removed from the jar and processed for assay test using an HPLC method (similar to described in drug recovery test) to confirm the amount of esomeprazole released from the MP in acid stage dissolution. Similarly, the

buffer stage dissolution test was performed with a fresh sample of esomeprazole MP, except instead of removing the MP from the jar after 2h in acid stage (0.1 M HCl), the dissolution was continued with a pH 6.8 phosphate buffer by addition of 700 mL of 0.086 M dibasic sodium phosphate.

Microscopic Analysis of NG Tube with Multiparticulates

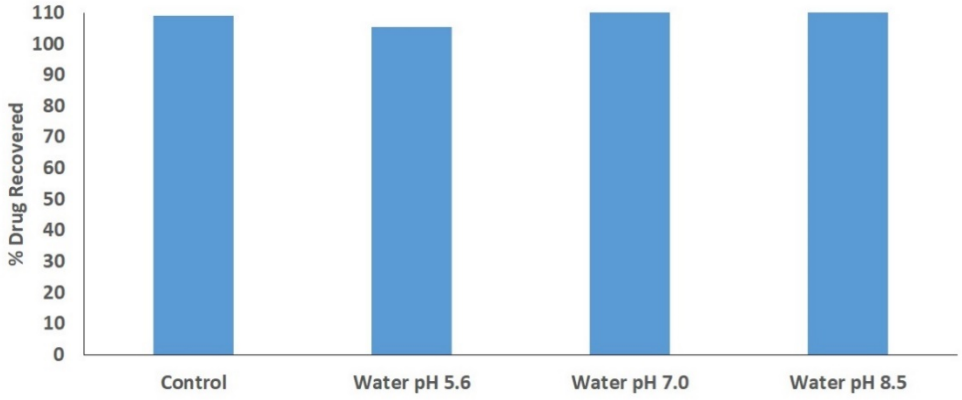
Microscopic analysis of NG tube with coated MP was performed using Leica stereo microscope (S8 APO), by placing multiparticulates in the NG tube to measure the internal diameter of the tube and overall space occupied by MP. Particle size distribution (PSD) of enteric coated MP was performed using a dynamic image analyzer (Camsizer P4, Microtrac Retsch) to determine the size range of MP.

Results

The coated multiparticulates did not adhere to the wall of the syringe or NG tube during the drug recovery and acid resistance recovery tests. The MP were intact after delivery through the NG tube irrespective of pH of water used as suspension medium.

Figure 3 shows values of drug recovery testing, indicating no significant difference in assay between MP before (without suspending in water and passing through NG tube, the control) and after suspending in water having different pH values and delivered through the NG tube.

Figure 3: Drug Recovery of 40 mg Esomeprazole DR Multiparticulates



The robustness of enteric coating with Acryl-EZE II was determined by performing an acid resistance recovery test. The release profiles of enteric coated esomeprazole MP, before and after passing through the NG tube are shown in Figure 4. The drug loss in acid media (0.1N HCl) was negligible after 2 hours, followed by the rapid release of the drug in phosphate buffer, pH 6.8 in all cases. The drug content and the drug release of enteric coated samples were not affected by pH of water or in transferring through the NG tube.

Figure 4: Release Profiles of 40 mg Esomeprazole DR Multiparticulates in Acid Phase for 2 h Followed by Buffer Phase (n=6)

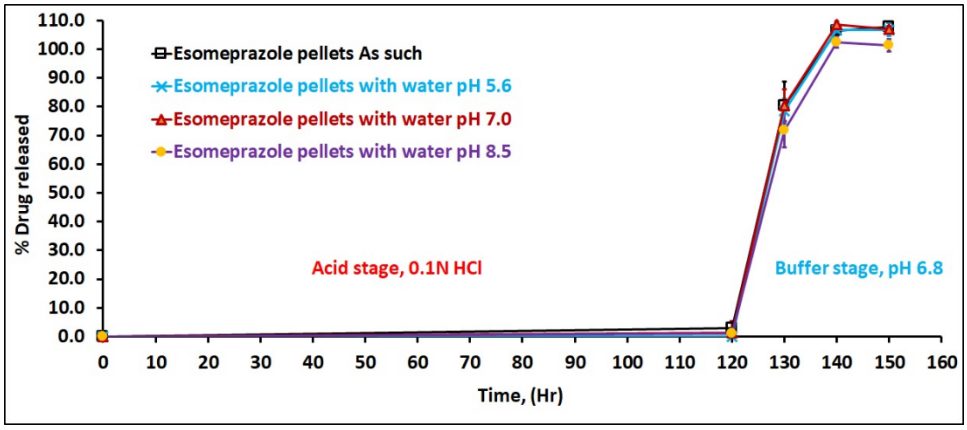


Figure 5 shows the dimensions of NG tube at various locations: start of the tube (1828 µm), middle (1811 µm) and end of tube (1341 µm x 2960 µm). The microscopic evaluation of samples in the NG tube and space occupied by MP are shown in Figure 6. PSD study using Camsizer P4 indicated that enteric coated MP have a size in the range of 547–732 µm (cumulative %distribution: Q3 10%: 547 µm, Q3 50%: 636 µm and Q3 90%: 732 µm). The above study suggests that esomeprazole DR MP prepared with starting substrate, Suglets with a size range of 250-355 µm and coated with Acryl-EZE II for enteric protection, have total size of ~700 µm and can smoothly pass through the NG tube.

Figure 5: Microscopic Images of Nasogastric Tube (Start, Middle and End of Tube)

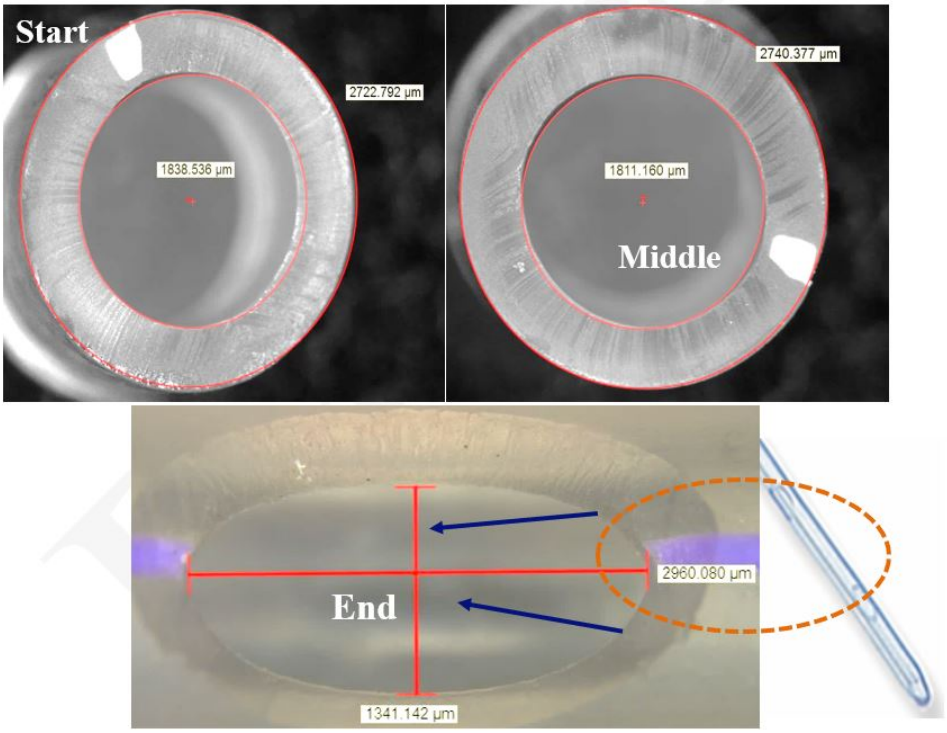
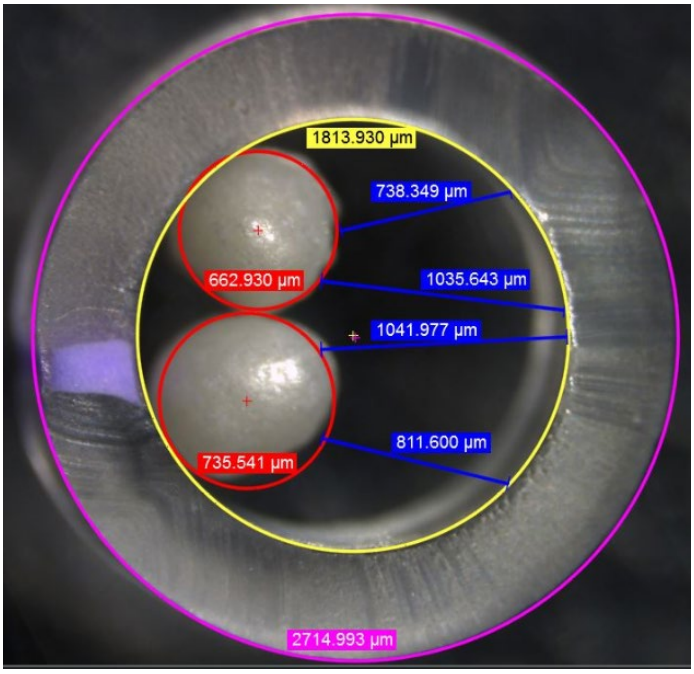


Figure 6: Microscopic Images of Nasogastric Tube with Coated Multiparticulates



- Outer diameter of NG Tubes (size FG080): ~ 2715 micron
- Inner diameter of NG Tubes (size FG080): ~ 1814 micron
- Size of enteric coated pellets (2 #): (662.9 + 735.5) = 1398 micron
- Free space after occupying 2 # pellets inside NG Tubes: 738 to 1042 micron

Conclusions

Acryl-EZE II was successfully used in the development of an enteric coated esomeprazole MP formulation. Coated multiparticulates complied with the USP in vitro acid resistance dissolution test for esomeprazole, and the integrity of samples was maintained after dispersion in water with different pHs when passing through the size 8 French nasogastric tube.

References

1. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/021153Orig1s008.pdf. Accessed 20th May 2020.

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