Formulation and Process Considerations for Delayed Release Multiparticulates of Esomeprazole Magnesium

PURPOSE

Esomeprazole magnesium belongs to the family of proton pump inhibitors (PPIs) which inhibits gastric acid secretion.[1] The pharmaceutical dosage form is generally formulated as delayed release (DR) multiparticulates, either filled in capsules or compressed into disintegrating tablets. A DR formulation with multiparticulates offers design flexibility and clinical benefits, but requires relatively complex manufacturing processes as compared to tablets. In addition, quality assurance of multiparticulates may be complex and time consuming due to the challenges associated with reproducibility and uniformity within or among the batches.[2]

Esomeprazole has acceptable stability under alkaline conditions but rapidly degrades in acidic media.[1] An enteric coating is therefore applied to the dosage form in order to prevent drug degradation in the stomach. Esomeprazole drug release criteria have been reported as less than 10% drug loss after 2 hours in acid media (compendial acid phase, 0.1N HCl or non-compendial intermediate pH, acetate buffer, pH 4.5), followed by rapid release of the drug (not less than 80% of labeled amount) after 45 minutes in phosphate buffer, pH 6.8.[3&4]

The objective of this work was to investigate and establish an application process for Acryl-EZE®, aqueous acrylic enteric system, on an esomeprazole magnesium trihydrate (40 mg) multiparticulate system.

METHODS

Preparation of Delayed Release Multiparticulates

Sugar spheres were drug layered, seal-coated, and enteric coated in a fluid bed coater (MP-2/3, Wurster setup, Niro Inc., USA) using the ingredients shown in Table 1. Drug layering dispersion was prepared by dissolving a binder (hypromellose or HPMC) and a wetting agent (polysorbate 80) in water, followed by addition of drug. The drug dispersion was sieved through a 60-mesh screen (250 µm) to remove any aggregates (screen retains of 0.36% w/w and dispersion pH of 9.0). The seal-coat dispersion shown in Table 1 was prepared at 13% solids, passed through a 60-mesh screen (mesh retains of 0.27% w/w) and applied to the drug loaded beads to a weight gain of 44.5% w/w.5 The seal-coated beads were then enteric coated, using Acryl-EZE 93A19326 and triethyl citrate (TEC) as the plasticizer. The enteric coating composition was prepared at 20% solids and applied to a weight gain of 61.5% w/w. The dispersion was passed through a 60-mesh screen (mesh retains of 0.32% w/w) prior to application. Due to the small size of the beads, the spray rate, air flow, and product temperature were carefully monitored to ensure individual particle coating and to

minimize potential agglomeration or electrostatic charge (Table 2). The enteric coated beads (242.9 mg of beads containing 40 mg esomeprazole) were then encapsulated in gelatin shells (size 1) (Hawkins, USA), using an automatic bench top capsule filling machine (IN-CAP, Dott. Bonapace& C, Italy).

Table 1. Formulation of Esomeprazole Multiparticulates (40 mg Base)

Ingredients	Supplier	% w/w	mg/capsule
Sugar Spheres (45/60 mesh size; 250-355 µm)	Mutchler Inc. (NP Pharm), USA	16.43	39.91
Drug Layering			
Esomeprazole Magnesium Trihydrate	Kemprotec Ltd. (UK)	18.32	44.50
Hypromellose 2910 (HPMC, METHOCEL™, premium cellulose ether (E6-LV))	The Dow Chemical Company (USA)	7.33	17.80
Polysorbate 80 (Tween 80)	Croda (USA)	0.82	2.00
Seal-Coating			
Hydroxypropyl cellulose (Klucel LF)	Aqualon (USA)	6.43	15.63
Talc	Luzenac (USA)	11.61	28.20
Magnesium stearate	Mallinckrodt (USA)	0.99	2.40
Enteric Coating			
Acryl-EZE 93A19326	Colorcon (USA)	34.56	83.95
Triethyl citrate (TEC)	Morflex (USA)	3.47	8.43
Simethicone emulsion, USP	Dow Corning Corporation (USA)	0.04	0.09
Total		**100.00**	**242.91**

Table 2. Process Parameters Used for Drug Layering, Seal Coating, and Enteric Coating

Process Parameters	Drug Layering	Seal Coating	Acryl-EZE® 93A19326
Batch size (kg)	4.0	5.0	1.0
Inlet temperature (ºC)	67	72	72
Product temperature (ºC)	40	41	32
Outlet temperature (ºC)	35-40	35-40	35-40
Air flow (CMH)	250	250	100
Atomization pressure (bar)	2.5	2.5	2.5
Flow rate (g/min)	56	58	32

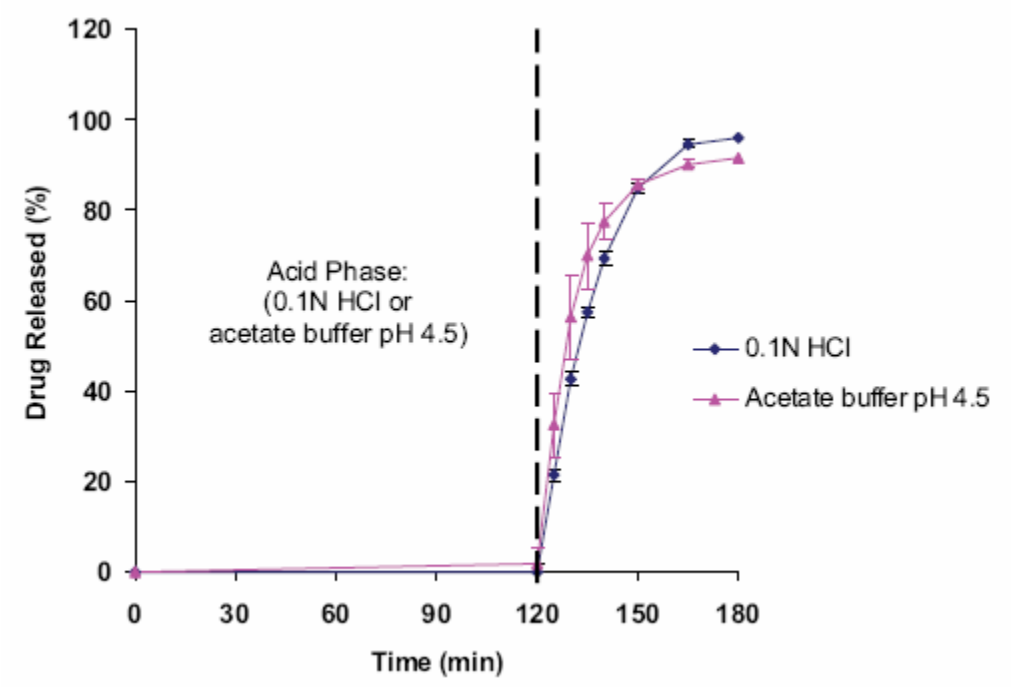
Evaluation of Esomeprazole Capsules

Capsules were evaluated for drug assay, total impurities using HPLC analysis, and drug release using UV spectroscopy. To evaluate the enteric protection, drug release was measured in a USP compliant bath, using apparatus II at 100 rpm (Varian, USA). Capsules were placed in 500 mL of acid media, either 0.1N HCl or acetate buffer, pH 4.5 for 2 hours, followed by dissolution testing in 900 mL phosphate buffer, pH 6.8. Capsules were packaged in HDPE bottles, with desiccant, and placed on stability at 30°C/65%RH and 40°C/75%RH conditions and evaluated as described above.

RESULTS

The values for drug assay and total impurities for esomeprazole capsules were determined as 100.2% and 1.0% (time zero), respectively. The release profiles of esomeprazole capsules are presented in Figure 1. The drug loss in either acid media (0.1N HCl or acetate buffer, pH 4.5) was equal to or less than 2% after 2 hours, followed by rapid release of the drug in phosphate buffer, pH 6.8. The values for t80% in buffer (pH 6.8) were less than 25 minutes for capsules pre-exposed to either acid phase. The results for 1 and 3 month stability testing revealed no significant change in drug assay (99.5 – 104.2%), total impurities (0.79 – 1.16%) and release profiles regardless of storage conditions.

Figure 1. Release Profiles of Delayed Release Esomeprazole Capsules (40 mg) in Acid Phase for 2 Hours Followed by Buffer Phase (n=6)



CONCLUSIONS

Esomeprazole magnesium trihydrate was loaded on small size (250-355 µm) sugar spheres, seal-coated and enteric coated using Acryl-EZE 93A19326. Capsules containing enteric coated esomeprazole multiparticulates showed excellent acid resistance (less than 2% in 0.1N HCl or acetate buffer pH 4.5) after 2 hours exposure to the media. In addition, $t_{80\%}$ in buffer (pH 6.8) was less than 25 minutes, complying with the desired drug release criteria. Key fluid bed coating process parameters such as spray rate, air flow, and product temperature were carefully monitored to avoid agglomeration and/or electrostatic charge.

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