

Investigation of a Modified USP Disintegration Test Method for Enteric Coated Tablets

INTRODUCTION

Proton pump inhibitors (PPIs) are substituted benzimidazoles and are generally administered as enteric coated tablets or multiparticulates that pass through the stomach intact and are absorbed in the proximal small bowel. The enteric coating protects the PPIs – which are acid labile – as they pass through the stomach; and start to dissolve at higher pH media in the proximal intestine.

During the formulation and development of these enteric coated dosage forms, testing of the enteric performance is routinely performed using the standard USP disintegration test 2. The USP disintegration test measures the protection provided due to the enteric coat by exposing the tablet to a 0.1N HCl acid media (pH 1.2, which is thought to be similar to the gastric pH in a healthy volunteer). While this test method may be appropriate for general enteric performance, the *in vivo* stomach pH for patients may be significantly different. This is especially the case for patients who are on multiple dose regimen of PPIs. As a result of drug action, the gastric acid secretion will be reduced, with a subsequent elevation in gastric pH 3-5. Miner et al 6 have reported patients with gastric pH as high as 6. In addition, all PPIs in the market undergo significant degradation in media below pH 5. Therefore, it is important to assess performance of enteric coated PPI dosage forms in media resembling the gastric conditions of these patients.

This study utilized a modified USP disintegration test method to investigate the impact of elevated pH conditions (using a variety of buffer compositions) on placebo and Omeprazole (PPI) tablets, coated with Acryl-EZE®, aqueous acrylic enteric system, or Eudragit L30D-55.

METHODS AND MATERIALS

Placebo tablets (0.95 cm diameter, 325 mg weight, normal convex) comprising of lactose (Fast-Flo), microcrystalline cellulose (Emcocel 90M), Starch 1500®, partially pregelatinized maize starch, Mg-stearate (Mallinckrodt), and Cab-O-Sil M5 were prepared by direct compression. A candidate PPI tablet formulation (0.64 cm diameter, 115 mg weight, normal convex) comprising Omeprazole 20mg (Medelom), maltose (Advantose 100, SPI Pharma), Starch 1500, Mg-stearate, and Cab-O-Sil were prepared by direct compression.

Tablet hardness in all cases were greater than 10 kP and friability was less than 0.1% w/w. The placebo and Omeprazole 20 mg tablets were seal coated with Opadry®, complete film coating system, YS-1-7027 at 4% weight gain (WG). Acryl-EZE 93F19255 powder was reconstituted in water, 20% w/w solid dispersion, and coated to 12% WG onto 1 kg of the placebo or Omeprazole 20 mg tablets in an O'Hara LabCoat I. The coating process conditions used are shown in Table 1.

Table 1. Acryl-EZE 93F19255 Coating Parameters

Average Parameter Value	
Inlet Air Temp (C)	37-40
Product Temp (C)	30
Exhaust Air Temp (C)	32
Fluid Delivery Rate (g/min)	9-10
Atomizing Air Pressure (psi)	15
Pattern Air Pressure (psi)	15
Inlet Air Volume (cfm)	125
Pan Rotation (rpm)	20

Tablets were also coated with Eudragit L30D-55 to 12%w/w WG using Degussa recommended procedures and conditions.

Acid Uptake Testing

Enteric coated tablets (n=6) were weighed individually and placed in a USP disintegration bath containing buffers of varying composition and pH for 2 hours at 37°C. After the enteric test, the tablets were removed, excess surface moisture was eliminated and the tablets were reweighed. The difference in the weights was reported as percent acid uptake.

RESULTS AND DISCUSSIONS

The percent acid uptake by the enteric coated tablets after direct exposure to 0.1N HCl (pH 1.2), USP phthalate, (pH 3.0 and pH 4.0), and USP acetate, (pH 3.0 and pH 4.5) were measured. To ensure complete enteric coating dissolution, the disintegration time of coated tablets in phosphate buffer of pH 6.0 and 6.8 was also measured. The acid uptake results for the placebo tablets are shown in Figure 1 and those for the Omeprazole 20 mg tablets are shown in Figure 2.

Figure 1. Acid Uptake Results for Placebo Cores Coated with 12% WG Enteric Polymer

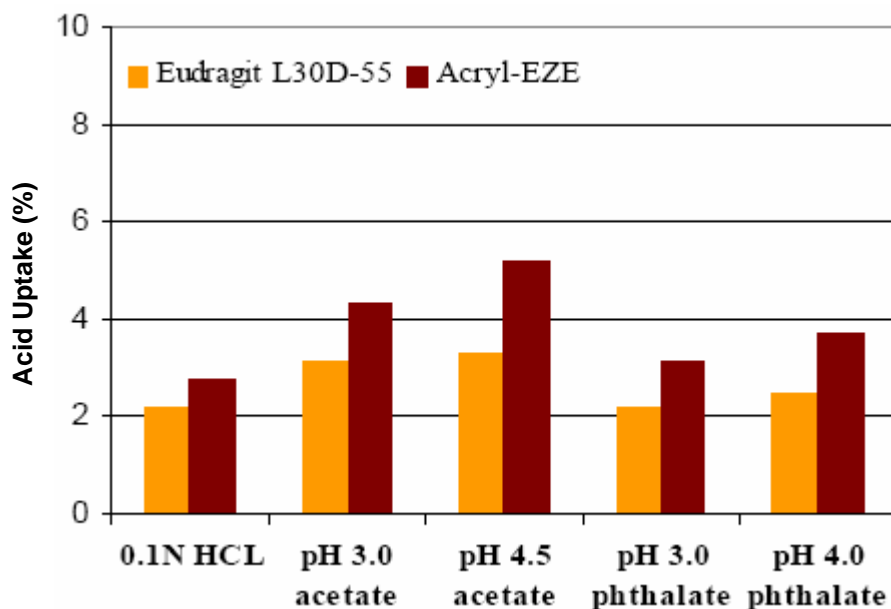
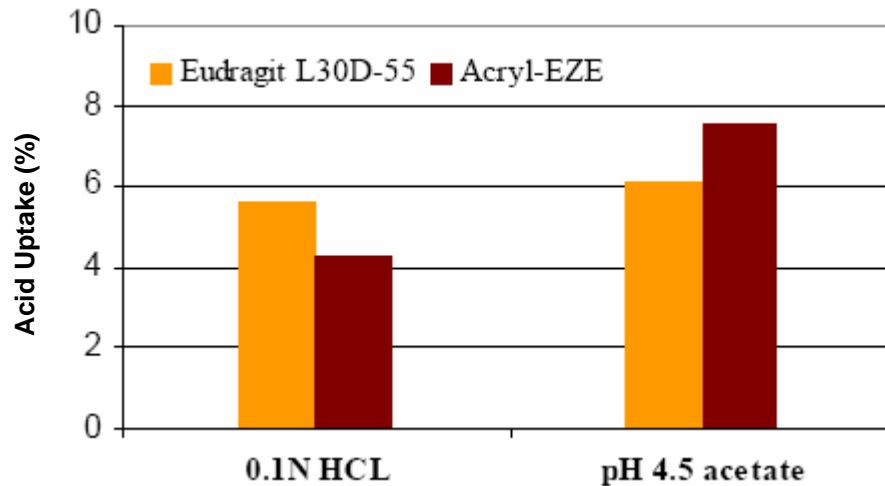


Figure 2. Acid Uptake Results for the Omeprazole 20mg Tablets Coated with 12% WG Enteric Polymer



Previous data has shown that media uptake of 10% or less, correlates to sufficient enteric protection for the drug product, without any signs of bloating or rupture of the tablet coating.

Acryl-EZE is a one-step polymer system that is based on the Eudragit L100-55 polymer (spray dried version of Eudragit L30D-55). The solubilization pH for both polymers (Eudragit L30D-55 and L100-55) is around pH 5.5. Placebo and Omeprazole 20mg tablets coated with Acryl-EZE or Eudragit L30D-55 and exposed to pH 6.0 and pH 6.8 phosphate buffer disintegrated within 30 minutes. This was expected since the media pH is above the solubilization pH for the enteric systems and rapid dissolution of the enteric film is expected to occur.

CONCLUSIONS

Modification of the USP disintegration test method may be required to test the performance of enteric coated proton pump inhibitors, during the development of these products. One such modification is to assess enteric performance at elevated pH media. Testing of the enteric dosage forms at intermediate pHs may also provide information that would be important in achieving bioequivalence. This in turn may help cost containment by reducing the iterations of clinical testing necessary for achieving bioequivalent formulations.

Placebo and Omeprazole 20mg tablets coated with Acryl-EZE 93F19255 and Eudragit L30D-55, provided good enteric protection at intermediate pH media, resulting in low percent acid uptake and rapid disintegration at phosphate buffers pH 6.0 and 6.8.

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