The Influence of Intermediate pH Gastric Media (*In Vitro*) on the Performance of Delayed Release Proton Pump Inhibitor Dosage Forms

INTRODUCTION

The pharmacological effect from the therapeutic category of medicaments known as proton pump inhibitors (PPI's) is to elevate the pH of the gastric environment. The pH level in vivo is above what is typically specified in *in vitro* compendial monographs for delayed release dosage forms.[1]

The objective of this study was to investigate the enteric performance of aqueous enteric-coated tablet formulations containing proton pump inhibitors (PPI's) in bio-relevant media, which better simulates the gastric environment of a patient on a multiple dose regimen of PPI's.

METHODS AND MATERIALS

Tablet Formulations

Direct compression formulations of two common PPI's (Formulation 1, Omeprazole and Formulation 2, Pantoprazole Sodium) were prepared as outlined in Tables 1 and 2.

Table 1. Formulation 1 – Omeprazole

Material	Supplier	% w/w	mg/tablet
Omeprazole	Medilom	17.39	20.000
Crystalline maltose (Advantose 100)	SPI Pharma	66.61	76.600
Pregelatinized starch (Starch 1500®)	Colorcon	15.00	17.250
Colloidal silicon dioxide (Cab-o-sil M5)	Cabot Corp.	0.50	0.575
Magnesium stearate	Mallinckrodt	0.50	0.575
	Total	100.00	115.00

Table 2. Formulation 2 – Pantoprazole Sodium

Material	Supplier	% w/w	mg/tablet
Pantoprazole sodium	Cadila Pharma	25.00	45.00
Crystalline maltose (Advantose 100)	SPI Pharma	23.00	41.40
Pregelatinized starch (Starch 1500)	Colorcon	40.00	72.00
Sodium bicarbonate	Church and Dwight	5.50	9.90
Crospovidone	ISP Corporation	4.00	7.20
Colloidal silicon dioxide (Cab-o-sil M5)	Cabot Corp.	1.00	1.80
Stearic acid	CK Witco	1.00	1.80
Magnesium stearate	Mallinckrodt	0.50	0.90
	Total	100.00	180.00

Blending and Compaction

Colloidal silicon dioxide and Starch 1500 were hand sieved through a 25 mesh (0.71 mm) screen prior to placement into an 8 quart V-shaped blender. The remaining materials (except magnesium stearate) were charged into the blender and mixed for 10 minutes. Finally the magnesium stearate was added and blended for an additional 3 minutes.

115 mg tablets (Formulation 1) or 180 mg tablets (Formulation 2) were manufactured using an instrumented 10 station rotary tablet press (Piccola, Riva, Argentina), fitted with ¼ inch (6.35 mm, Formulation 1) or 9/32 inch (7.14 mm, Formulation 2) standard concave tooling at a turret speed of 30 rpm and compaction force of 10 kN. Tablet diameter, thickness, weight uniformity and breaking force values were determined using an automatic tester (MultiCheck, Erweka, USA).

Aqueous Coating Trials

Coating dispersions for the seal coat (Opadry®, complete film coating system, 03K19229) and for the enteric coat (Acryl-EZE®, aqueous acrylic enteric system, 93F19255) were prepared using low shear mixing as outlined in Table 3.

Table 3. Dispersion Preparation Parameters

Parameter	Opadry	Acryl-EZE
Dispersion solids content (%)	12	20
Theoretical weight gain (%)	4	12
Powder weight (g)	40	120
Deionized water weight (g)	293	480
Total dispersion weight (g)	333	600
Dispersion mixing time (min)	60	25

Tablets (2.5 kg) were coated in a side-vented coating pan (Compu-Lab, Thomas Engineering, USA) utilizing a 15" pan insert and (1) JAU spraying nozzle.

The seal layer (Opadry 03K19229) was applied at a theoretical weight gain (wg) of 4%. Following application of the seal layer a 12% weight gain of Acryl-EZE 93F19255 was applied as the enteric layer. The 12% weight gain samples were then submitted for disintegration and dissolution analysis. The process parameters used for both coating steps are outlined in Table 4.

Table 4. Coating Process Parameters

Parameter	Seal Layer	Enteric Layer
Pan Charge (kg)	1.0	1.0
Inlet Temperature (ºC)	75	55
Outlet Temperature (ºC)	51	40
Product Bed Temperature (ºC)	44	33
Fluid Delivery Rate (g/min)	18	18
Process Air Flow (cfm/cmh)	125/213	125/213
Pan Rotational Speed (rpm)	20	20
Atomization Air Pressure (psi/bar)	20/1.4	20/1.4
Pattern Air Pressure (psi/bar)	20/1.4	20/1.4

Disintegration Testing – Percent Acid Uptake

Enteric coated tablets were individually weighed (n=6) and reciprocated for 2 hours in either 0.1N HCl or pH 4.5 acetate buffer in a USP compliant disintegration apparatus. The percent acid uptake for a tablet was calculated according to Equation 1.

Equation 1:

Percent Acid Uptake = [(Tf - Ti)/Ti] x 100

Tf = Tablet weight final (mg)

Ti = Tablet weight initial (mg)

Dissolution Testing

Drug release was measured in a USP compliant dissolution bath (Varian, USA) using apparatus I (basket method) at 100 rpm.

Acid Phase - Six tablets were subjected to two hours exposure in the dissolution bath. At the end of this time the tablets were removed and assayed for the percent drug remaining. An additional six tablets were again subjected to two hours in 0.1N HCl or pH 4.5 acetate buffer followed by immediate transfer to a dissolution bath containing phosphate buffer, pH 7.8 (Colorcon Method). The criterion for drug release was not more than 10 percent drug loss after 2 hours in 0.1N HCl or pH 4.5 acetate buffers.

Buffer Phase - Samples were withdrawn from the dissolution vessels at 5, 10, 15, 20, 25, 30, 35 and 45 minute intervals. The percent drug release was measured via HPLC (Waters Symmetry C18, 75 x 4.6 mm, 3.5 micron column) at a UV wavelength of 280 nm. The criterion for drug release was not less than 80% drug dissolved after 45 minutes in pH 7.8 phosphate buffer (Colorcon Method).

RESULTS AND DISCUSSION

Tablet Physical Properties

Properties of the uncoated tablets are shown in Table 5. The formulations had good flow resulting in low weight variation. Tablets with mechanical strength (breaking force) suitable for additional coating unit operations were manufactured.

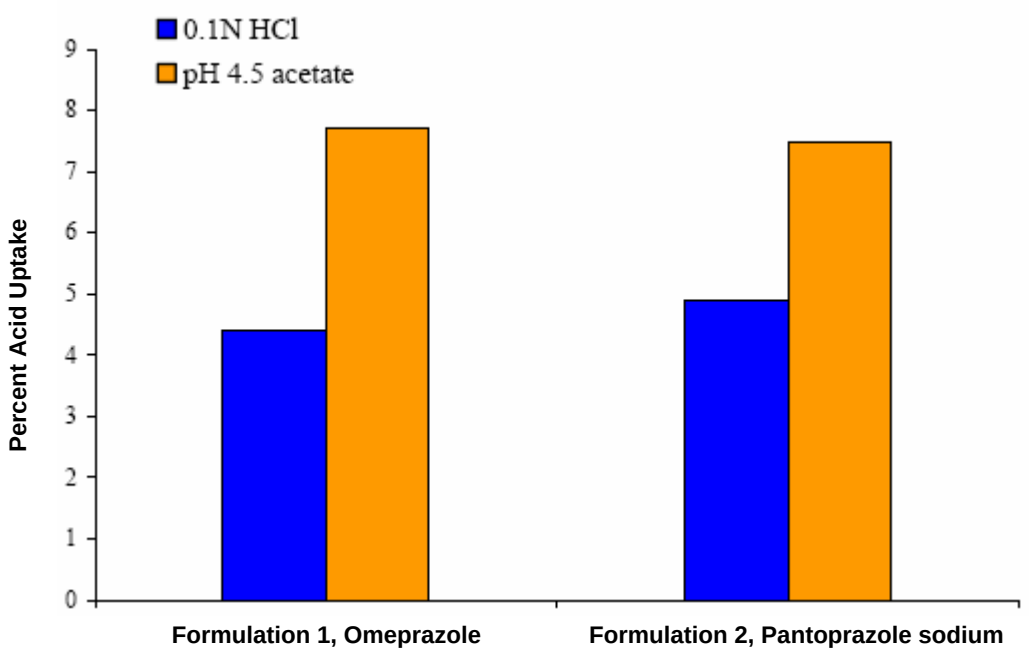
Table 5. Physical Properties for Un-Coated Tablets

Tablet Properties	Formulation 1 Omeprazole	Formulation 2 Pantoprazole sodium
Weight (mg)	115.6 ± 4.3	175.1 ± 4.2
Breaking force (kp)	11.4 ± 0.9	6.0 ± 0.9
Diameter (mm)	6.04 ± 0.02	6.81 ± 0.02
Thickness (mm)	3.34 ± 0.09	4.12 ± 0.69

Percent Acid Uptake for Enteric Coated Tablets

The percent acid uptake for the enteric coated tablets is shown in Figure 1. Historically, values less than 10 percent acid uptake have shown to correlate to acceptable dissolution performance. Visual observation of the tablets after 2 hours in each media yielded no signs of disintegration, cracking, softening, or degradation.

Figure 1. Percent Acid Uptake



Delayed Release Dissolution

Drug release profiles for the enteric coated formulations fulfilled the criteria outlined in the objectives (<10% release or degradation) when utilizing 0.1N HCl or pH 4.5 acetate buffers as the "acid phase". Visual observation showed no signs of degradant in the dissolution vessel and HPLC chromatograms yielded no degradant peaks for the assayed tablets. The results in Figures 2 and 3 show the release of drug from enteric coated tablets that were first subjected to 2 hours in 0.1N HCl or 2 hours in pH 4.5 acetate buffer followed by transfer into pH 7.8 phosphate buffer.

Drug release for each sample met the criteria outlined in this study, i.e. not less than 80% dissolved after 45 minutes in buffer, pH 7.8.

Figure 2. Formulation 1 – Omeprazole

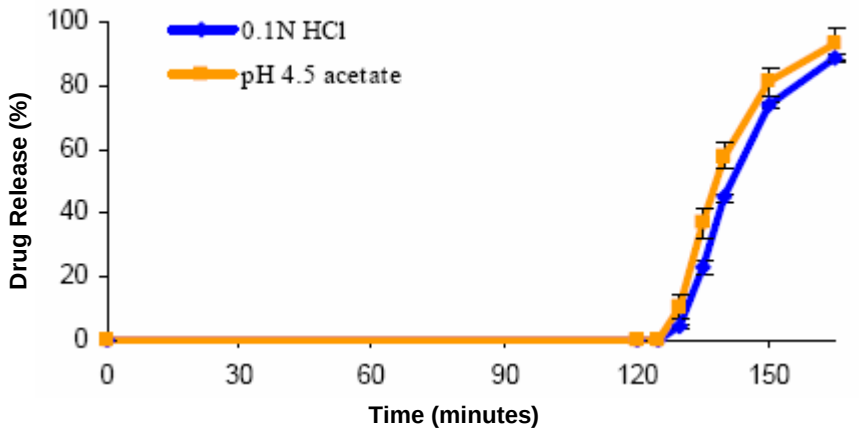
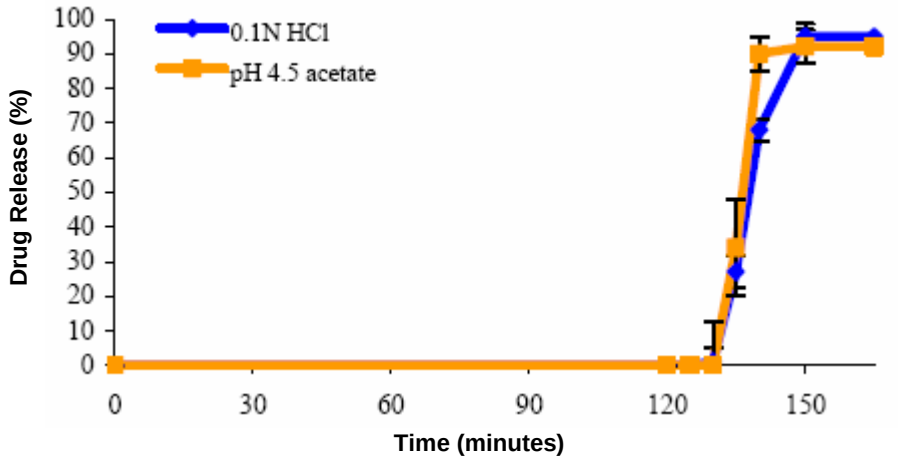


Figure 3. Formulation 2 – Pantoprazole Sodium



CONCLUSIONS

• Delayed release, direct compression formulations can be successfully prepared for omeprazole and pantoprazole sodium.

• Enteric protection and suitable drug release were obtained independent of the media (0.1N HCl or acetate buffer, pH 4.5) utilized to simulate different gastric environmental conditions.

Reprint of poster presented at AAPS – Nov 2005. Authors: Kurt A. Fegely, Cara J. Young, Pankaj R. Rege, and Ali R. Rajabi-Siahboomi.

REFERENCES

1. Bruley des Varannes S. et al., “Effect of low-dose rabeprazole and omeprazole on gastric acidity: results of a double blind randomized, placebo-controlled, three way Cross over study in healthy subjects”, Aliment Pharmacol Ther., 2004 Oct 15; 20(8) 899-907.

For more information, contact your Colorcon representative or call:

North America **+1-215-699-7733**
Europe/Middle East/Africa **+44-(0)-1322-293000**
Asia Pacific **+65-6438-0318**
Latin America **+54-11-4552-1565**

You can also visit our website at **www.colorcon.com**