

Application of a Fully Formulated Aqueous Enteric Coating System on Rabeprazole Sodium Tablets (20 mg)

OBJECTIVES

Rabeprazole sodium is a proton pump inhibitor used in treating Gastroesophageal Reflux Disease (GERD).¹ It is highly acid-labile and presents many formulation challenges. The objective of this study was to evaluate an aqueous enteric coating (Acryl-EZE®, aqueous acrylic enteric system) on rabeprazole tablet formulations. The enteric protection of these delayed release tablets was examined in a compendial acid phase and in an intermediate pH to better simulate the elevated gastric pH of the patients who are administered multiple doses of this drug.^{2&3} The dissolution specifications are <10% drug loss after 2 hours in acid phase, followed by >80% after 45 minutes in buffer phase.

METHODOLOGY

Preparation of Tablet Cores

Rabeprazole sodium tablets (Table 1) were prepared by wet granulating the drug, mannitol, magnesium oxide, L-HPC (one half) and HPC in a Vector Corp. high shear granulator using ethanol (impeller speed of 250 rpm, chopper speed of 1750 rpm).⁴ The wet mass was sieved through a 14-mesh screen (1.4mm) and dried in a Vector Corp. Flocoater FL-M-15 to achieve a product temperature of 30°C. Dried granules were blended with the rest of L-HPC and magnesium stearate in a V-blender. Density of the final granulation was measured with a tapped density tester. Tablets were manufactured on a Vector Corp. 16-station rotary press using 6.35 mm concave tooling at a compaction force of 16 kN. Physical properties of the tablets were determined using an Erweka tester.

Table 1. Rabeprazole Sodium Tablet Formulation

Material	Function	Supplier	% w/w	Mg/tablet
Rabeprazole Sodium	Active	Cadila Pharma India	13.70	20.0
Powdered Mannitol (Mannogem)	Filler	SPI Pharma Delaware, USA	27.40	40.0
Magnesium Oxide USP, Heavy (Marinco OH)	Filler/Buffering Agent	Rohm and Haas Massachusetts, USA	42.46	62.0
Low Substituted Hydroxypropylcellulose (L-HPC, LH-21)	Binder Disintegrant	Biddle Sawyer New York, USA	13.36	19.5
Hydroxypropylcellulose (Klucel LF)	Binder	Hercules Inc. Delaware, USA	2.05	3.0
Magnesium Stearate	Lubricant	Mallinckrodt New Jersey, USA	1.03	1.5
Total			100	146.0

Film Coating

The tablets were then subcoated organically using ethylcellulose/magnesium oxide (1:1%w/w) dispersion, followed by aqueous enteric coating with Acryl-EZE 93F19255. Both coating dispersions were prepared using low shear mixing (Table 2). Acryl-EZE is a fully formulated aqueous enteric coating system based on methacrylic acid copolymer Type C. The subcoat layer was applied at a 1.37% weight gain, followed by Acryl-EZE at various weight gains of 8.1, 10.1, 12.1 and 14.1% in a partially perforated coating pan (LDSC5, Vector Corp.). Table 3 lists the coating process parameters.

Table 2. Dispersion Preparation Parameters

Parameter	Subcoat Layer	Acryl-EZE
Dispersion Solids Content (%)	10	20
Theoretical Weight Gain (%)	1.37	8.1-14.1
Coating Application Level (mg/cm ²)	1.5	9.0-15.6
Powder (g)	Ethylcellulose – 20.55 Magnesium Oxide – 20.55 Total – 41.1	81
Deionized Water (g)	N/A	324
Absolute Alcohol (g)	369.9	N/A
Total Dispersion (g)	411	405
Dispersion Mixing Time (min)	60	25

Table 3. Coating Process Parameters for Subcoat Layer and Enteric Coating

Parameter	Subcoat Layer	Enteric Layer
Pan Volume (L)	3.75	1.3
Pan Charge (kg)	3.0	1.0
Inlet Temperature (°C)	48	63
Outlet Temperature (°C)	28	35
Fluid Delivery Rate (g/min)	14	12
Process Air Flow (CFM/CMH)	40/68	40/68
Pan Rotational Speed (rpm)	15	25
Atomization Air Pressure (psi/bar)	18.9/1.3	18.5/1.3

Acid Uptake Testing

The delayed release tablets of rabeprazole sodium were individually weighed and placed in either a compendial acid phase (0.1N HCl) or an intermediate pH (acetate buffer USP, pH 4.5) for 2 hours in a disintegration bath (Erweka ZT44), after which they were removed and inspected for bloating or discoloration. Tablets were dried using a tissue paper and reweighed. The percent weight difference, before and after exposure to acid, was reported as the acid uptake value.

Dissolution Testing

Drug release was measured in a USP dissolution bath (Varian Inc.), maintained at 37 ± 0.5°C, using apparatus II at 100rpm. Tablets were placed in 1000ml of either 0.1N HCl or acetate buffer (pH 4.5) for 2 hours, followed by phosphate buffer USP (pH 7.8). Drug release was measured using HPLC analysis.

RESULTS

The values of bulk and tapped density of the final granulation were 0.774 g/ml and 0.990 g/ml, respectively. Carr's compressibility index of the formulation was 21%, indicating a passable flow character.⁵ Physical properties of the uncoated tablets are listed in Table 4.

Table 4. Physical Properties of Uncoated Tablets (n=10)

Weight (mg)	144.50 ± 3.60
Breaking Force (kp)	9.30 ± 0.80
Diameter (mm)	6.31 ± 0.03
Thickness (mm)	3.44 ± 0.05
Friability (%)	0.34
Content Uniformity (%)	101.80 ± 2.90

Enteric coating trials yielded tablets without edge defects or surface imperfections. The acid uptake of the enteric coated tablets, at different weight gains, is listed in Table 5. Historically, values less than 10% have shown to correlate to acceptable dissolution performance (no drug release or degradation in the acid phase). Visual observation of the tablets after 2 hours in each acid medium yielded no signs of discoloration of the tablet or disintegration media.

Table 5. Acid Uptake for Delayed Release Tablets at Various Weight Gains in 0.1N HCl or Acetate Buffer (pH 4.5) (n=6)

	Acid Uptake (%)	
	0.1N HCl	Acetate Buffer pH 4.5
8.1% WG	4.35 ± 0.26	4.86 ± 0.52
10.1% WG	4.76 ± 0.28	5.01 ± 0.28
12.1% WG	3.81 ± 0.36	4.48 ± 0.23
14.1% WG	3.48 ± 0.26	4.03 ± 0.24

Table 6. t80% Values for Delayed Release Tablets of Rabeprazole Sodium in pH 7.8 After 2-hour Exposure to 0.1N HCl or Acetate Buffer (pH 4.5)

	T80% (min) in Phosphate Buffer (pH 7.8)	
	0.1N HCl	Acetate Buffer pH 4.5
8.1% WG	26.5	19.5
10.1% WG	28.5	20.0
12.1% WG	43.0	30.0
14.1% WG	39.5	32.5

Figure 1. Drug Release Profiles of Rabeprazole Sodium Tablets in 0.1 N HCl, Followed by Phosphate Buffer, pH 7.8

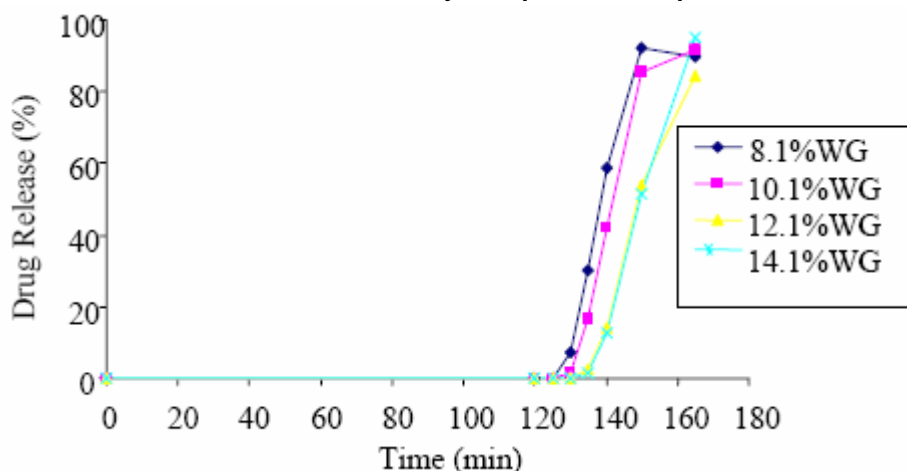
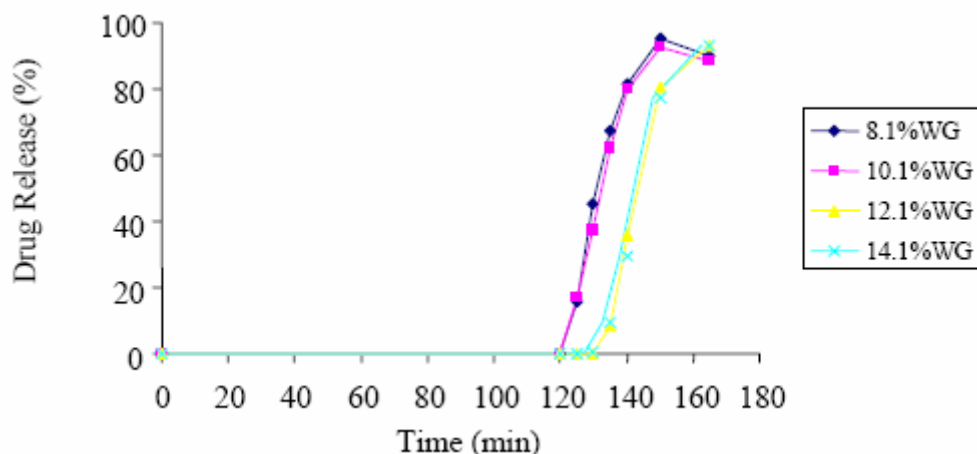


Figure 2. Drug Release Profiles of Rabeprazole Sodium Tablets in Acetate Buffer, pH 4.5, Followed by Phosphate Buffer, pH 7.8



CONCLUSIONS

A delayed release rabeprazole sodium tablet (20mg) was prepared using an organic subcoat and aqueous enteric coating. Acceptable enteric protection was achieved with Acryl-EZE independent of the acid media (0.1N HCl or acetate buffer, pH 4.5). Various weight gains of Acryl-EZE provided different drug release profiles in buffer phase, with higher weight gains resulting in slower release.

In all cases, <10% drug release was observed after 2 hours in both acid phases, followed by rapid drug release (>80%) after 45 minutes in pH 7.8.

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