Investigation of Formulation and Analytical Challenges of Delayed Release Rabeprazole Sodium Tablets

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CRS

Poster Reprint 2020

Purpose

Rabeprazole sodium is a proton pump inhibitor (PPI) used to treat gastroesophageal reflux disease. It is a challenging drug due to its sensitivity to acid, moisture, heat and light. The purpose of this study was to investigate the formulation development, stability and enteric performance of rabeprazole sodium (Na) tablets coated with a hypromellose phthalate (HPMCP) based enteric coating system.

Methods

Rabeprazole Na granules (1.5 kg) were generated in a P/VAC-10 high shear granulator (Diosna Dierks & Söhne GmbH, DE) by dry blending rabeprazole Na, mannitol, magnesium oxide (MgO)-heavy, L-HPC and HPC followed by granulation with ethanol, using propeller and chopper speeds of 150 and 1500 rpm, respectively. The granules were dried in a vacuum oven for 12 hours. Two batches of dried granules were milled with a Comil (Quadro Engineering Corp, CA), blended with L-HPC in a V-Blender (Patterson Kelley) for 5 minutes, then further blended with magnesium stearate for 3 minutes. The final blend was compressed into 146 mg (containing 20 mg rabeprazole-Na) round deep concave tablets (6 mm diameter) using a Piccola 10-station rotary tablet press (Specialty Measurements Inc, USA). The composition of the core formulation is shown in Table 1.

Table 1. Core Formulation for Uncoated Rabeprazole Na Tablets

INGREDIENTS	Quantity (%w/w)	Quantity (mg/tablet)
Rabeprazole Na	13.70	20.00
Powdered Mannitol (Mannogem)	24.45	35.70
Magnesium Oxide USP, Heavy	42.46	61.99
L-HPC	13.36	19.51
HPC	5.00	7.3
Magnesium Stearate	1.03	1.50
Total	100	146

Rabeprazole Na tablets (1 kg) were coated to achieve 1.37% w/w weight gain with a seal-coat of ethylcellulose (ETHOCEL™ 20) with MgO-heavy at a 50:50 % w/w, in ethanol at 10% w/w solids content, using a Vector LDCS fitted with a 2.5 L perforated pan. An enteric coat was then applied to the seal-coated tablets, achieving 8.1% w/w weight gain at 10% w/w solids content in an 80:20% w/w ethanol: water solvent. Either a yellow-pigmented HPMCP based coating, plasticized with diacetylated monoglycerides (HPMCP+DM) as used in a marketed product, or a yellow-pigmented Opadry® Enteric coating system based on HPMCP and triethyl citrate as a plasticizer, were used. Coating process conditions are described in Table 2.

Table 2. Coating Process Conditions for Seal and Enteric Coating

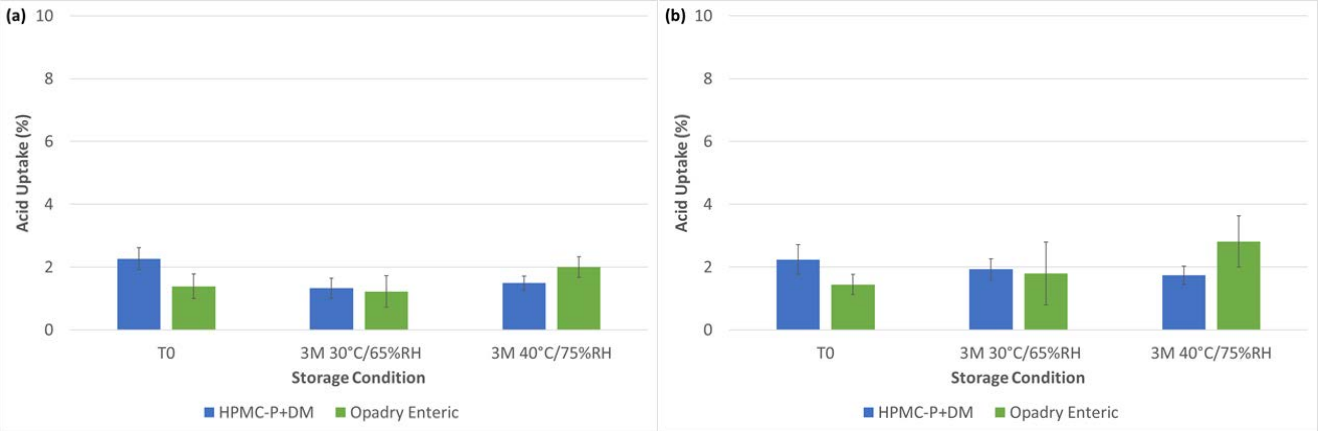
Parameter	Seal-Coat	HPMCP Enteric Coat
Batch Size (kg)	1.0	1.0
Solvent (%w/w)	100% Ethanol	80% Ethanol: 20% Water
Solids Content (%)	10	10
Inlet Temperature (°C)	37	40
Product Temperature (°C)	30	30
Spray Rate (g/min)	10	15
Air flow (cfm / m^3/hr)	75 / 127.4	75 / 127.4
Weight gain (%w/w)	1.37	8.1

Enteric coated tablets were stored in HDPE bottles, with 2 desiccants, for 3 months at 30°C/65% RH and 40°C/75% RH, then evaluated for appearance and enteric performance. The color change was measured using a Datacolor600. Non-compendial acid uptake of the coated tablets was determined after exposure to either 0.1N HCl or acetate buffer at pH 5.0 for 2 hours. Assay and impurity levels in the formulation were tracked during the stability using HPLC-UV (Waters Alliance) analysis. Drug release in 0.1N HCl followed by a Tris buffer at pH 8.0 were carried out, as described by US FDA[1]

Results

All coating trials were completed without any tablet-to-tablet or tablet-to-pan sticking. Tablets with both enteric coatings provided good enteric protection, as shown by the low acid uptake values in Figure 1. After storage for 3 months at 30°C/65% RH or 40°C/75% RH no tablet sticking in the bottle was observed, and the acid uptake remained low.

Figure 1. Acid Uptake After 2 Hours in (a) 0.1N HCl and (b) pH 5.0 Acetate Buffer for Enteric Coated Rabeprazole Na Tablets Before and After Storage



Analytical quantification of rabeprazole Na is challenging, due to its sensitivity to low and neutral pH media, e.g. 0.1N HCl, pH 5.0 acetate buffer or even in pH 8.0 tris buffer, turning yellow as it degrades. The addition of 30 µl of 5N sodium hydroxide to the HPLC collection vials (increasing pH to 11) could stabilize the rabeprazole Na and avoid further degradation during HPLC analysis. The high pH

environment has the potential to negatively impact the HPLC column if used continuously over a long time; however, no system suitability issues were observed during this study.

Rabeprazole assay after acid resistance testing in either 0.1N HCl, pH 5.0 acetate buffer remained consistent over the storage period (Figure 2). Similarly, the drug release profiles in pH 8.0 tris buffer after exposure to the acids were also consistent over 3 months of storage (Figure 3).

Figure 2. Acid Resistance After 2 Hours in (a) 0.1N HCl and (b) pH 5.0 Acetate Buffer for Enteric Coated Rabeprazole Na Tablets Before and After Storage

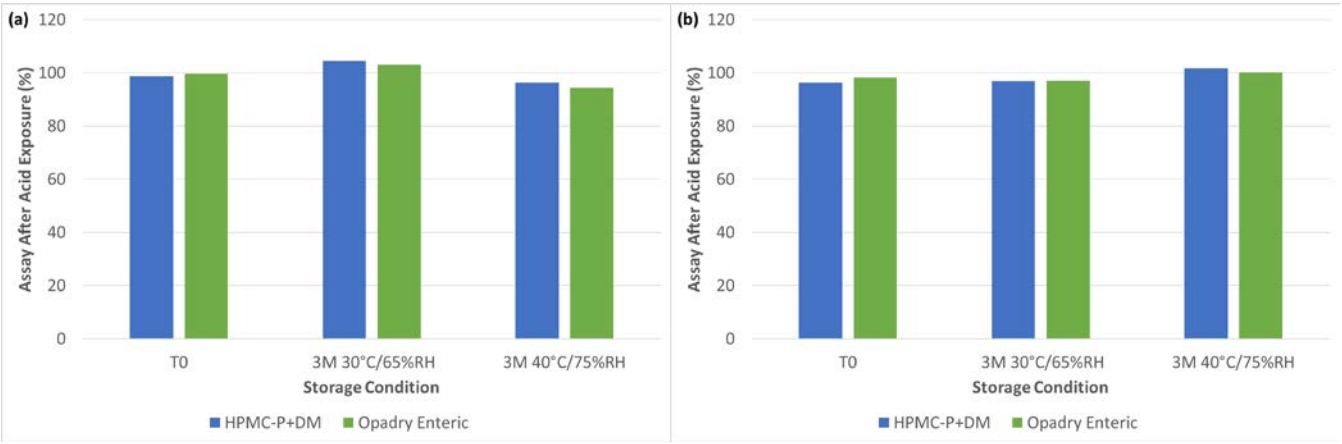
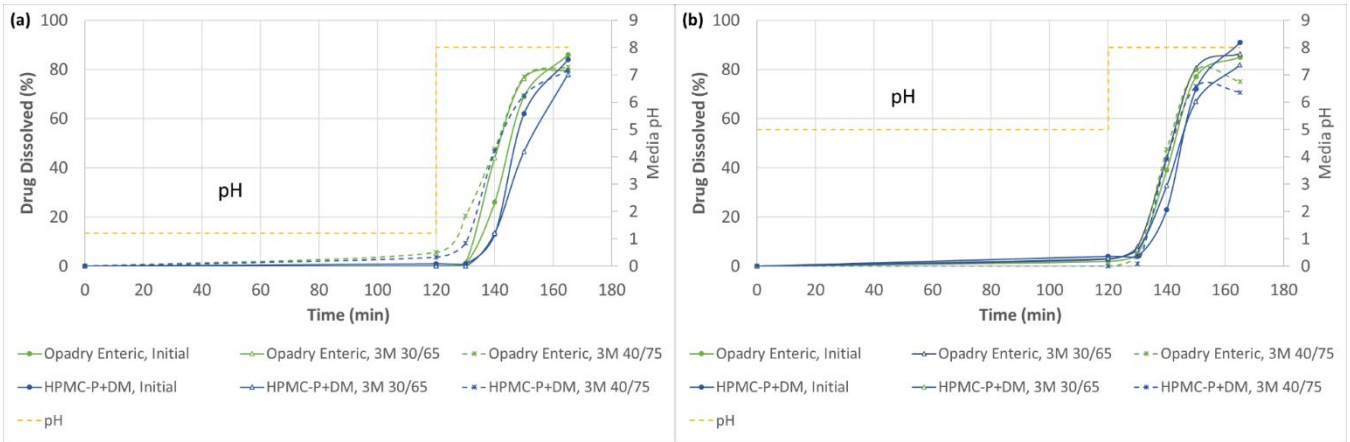
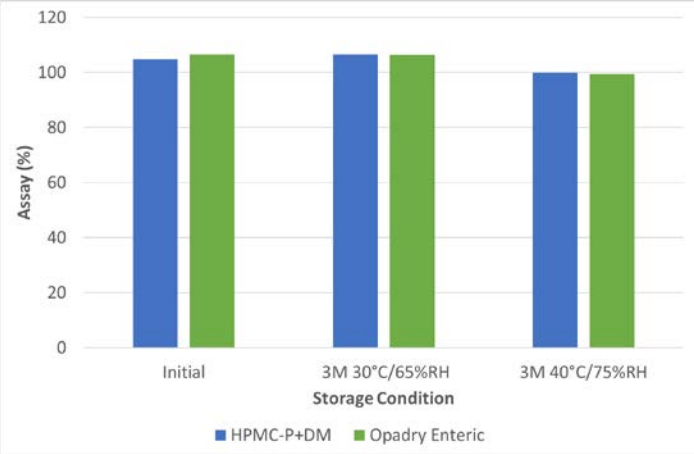


Figure 3. Dissolution Profile in (a) 0.1N HCl to pH 8.0 Tris Buffer and (b) pH 5.0 Acetate Buffer to pH 8.0 Tris Buffer for Enteric Coated Rabeprazole Na Tablets Before and After Storage



Rabeprazole Na assay was within specification (90-110%) before and after storage (Figure 4); however, there was a slight reduction in the assay for tablets stored for 3 months at 40°C/75% RH.

Figure 4. Assay of Enteric Coated Rabeprazole Na Tablets Before and After Storage



The reduction in assay corresponds with an increase of impurities (Figure 5). While an increase in impurities was observed for both formulations, a larger increase was observed with the tablets coated with enteric coating plasticized with diacetylated monoglycerides. This also corresponds to a significant increase in color change shown in Figure 6. Opadry Enteric had a lower level of impurities, less color change and remained within specification (DE < 3.0).

Figure 5. Total Impurities in Enteric Coated Rabeprazole Na Tablets Before and After Storage

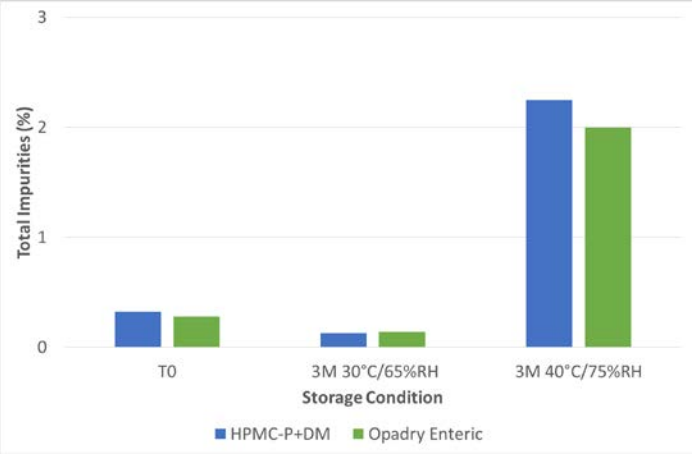
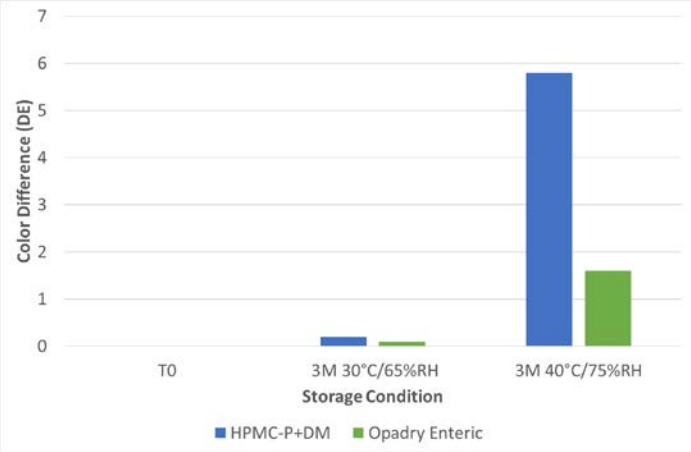


Figure 6. Color Change of Enteric Coated Rabeprazole Na Tablets Before and After Storage



Conclusions

HPMCP based coatings provided good enteric protection for rabeprazole Na tablets, before and after storage at accelerated conditions. The enteric coating plasticized with diacetylated monoglycerides, as used in a marketed product, showed a significant color change of the coating and greater levels of total impurities, yet had an acceptable enteric performance. The color change is believed to be due to the instability of the diacetylated monoglycerides. Opadry Enteric, the fully formulated enteric coating system based on HPMCP and triethyl citrate, demonstrated excellent enteric performance with no color change and can be successfully used in the formulation of challenging proton pump inhibitors.

References

1. US Department of Health and Human Services: Food and Drug Administration: Center for Drug Evaluation and Research. “Dissolution Methods”. https://www.accessdata.fda.gov/scripts/cder/dissolution/dsp_getallData.cfm. Accessed Jan 17, 2020.

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