OPADRY®Enteric

Poster Reprint

Acryl-Based Coating System

Comparative Evaluation of Enteric Film Coatings Applied in Organic Solvents

PURPOSE

Delayed release (DR) film coated products are among the most complex dosage forms to develop. Challenges arise in designing a quality film coating that can prevent drug release and ingress of gastric fluids under specified pH as well as pH conditions influenced by fed state and concurrent medicine use, eg, proton pump inhibitors (PPI).[1] In addition, rapid release of the drug in the higher pH regions of the small intestine is required. Many enteric polymers and formulated enteric coating systems are commercially available for both aqueous and organic applications. The purpose of this work was to carry out comparative evaluations of the acid-resistance and pH dependent solubility of four organic solvent coated enteric film coating systems.

METHODS

Tablet Coating

Placebo tablets (10 mm standard convex; 330 mg), were seal-coated to 3% weight gain (WG) in a side-vented 15” coating pan (O’Hara Labcoat I) using a clear, HPMC-based Opadry complete film coating system, reconstituted at 10% solids in purified water. These seal-coated tablets were then coated using film coating solutions formulated from various enteric polymers. Coating formulations (Tables 1 and 2) were based on polyvinyl acetate phthalate (PVAP) and methacrylic acid copolymers (MAC). The coating dispersions were reconstituted at 10% solids in a hydro-alcoholic solvent system (isopropanol: water) and coated to 12% WG. Coated tablet samples were taken after 5% theoretical weight gain (WG), and again after increments of 1% WG up to 12% WG. The coating process parameters used are listed in Table 3.

Table 1. Enteric Film Coatings Evaluated

Enteric Film Coating System	**Enteric Polymer** **Trade Name / Manufacturer**	**Coating Solvent** **IPA: Water**
Opadry Enteric (PVAP- based) Coating System Polymer: Polyvinyl acetate phthalate, NF	Phthalavin, Colorcon Inc.	80:20
Opadry Enteric (L100-based) Coating System Polymer: Methacrylic acid copolymer Type A, NF	Eudragit L100, Evonik Industries	88:12
Opadry Enteric (L100-55-based) Coating System Polymer: Methacrylic acid copolymer Type C, NF	Eudragit L100-55, Evonik Industries	88:12
ChromaTeric (MAE 100P-based) Coating System Polymer: Methacrylic acid-ethyl acrylate copolymer Type B, EP	Kollicoat MAE 100P, BASF	88:12

Table 2. Enteric Film Coating Compositions

Qualitative Enteric Film Coating Compositions			
Opadry Enteric (PVAP-based)	**Opadry Enteric (L100-based)**	**Opadry Enteric (L100-55-based)**	**ChromTeric (MAE 100P-based)**
PVAP	Eudragit L100	Eudragit L100-55	Kollicoat MAE 100P
Titanium dioxide	Titanium dioxide	Titanium dioxide	Titanium dioxide
Talc	Talc	Talc	Talc
Triethyl citrate	Triethyl citrate	Triethyl citrate	Triethyl citrate
Purified stearic acid		Collodial silicon dioxide	Collodial silicon dioxide

Table 3. Coating Process Parameters (15" O'Hara Labcoat I)

Parameter	***Enteric Coating Formulation***			
	Opadry Enteric (PVAP-based)	***Opadry Enteric (L100-based)***	***Opadry Enteric (L100-55-based)***	***ChromTeric (MAE 100P-based)***
Placebo charge (g)	1000	1000	1000	1000
Airflow (m^3/h)	210	200	211	211
Product temperature (°C)	36-38	30-31	28-29	29-30
Fluid delivery rate (g/min)	6-8	13-15	15-18	15-17
Pan speed (rpm)	20	18	20	20
Pattern air pressure (bar)/(psi)	2.5	2.1-2.2	1.6-2.1	2.0-2.3
	36	30-32	23-30	29-33
Atomization air pressure (bar)/(psi)	2.0	2.0-2.2	1.8-2.0	2.0-2.2
	29	29-32	26-29	29-32
Coating weight gain (%)	12*	12*	12*	12*
Coating solids content (%)	10	10	10	10

*Samples pulled at 5, 6, 7, 8, 9, 10, 11, and 12% WG

Tablet Testing

Assessment of Acid Uptake

Acid uptake (AU) evaluations provide an indication of the ability of the coating to protect the active from the effects of gastric fluid. Placebo tablets (n=6) of each of the enteric coating weight gains were individually weighed and reciprocated for 2 hours in the test media [0.1 N HCl; USP standard acetate buffer solutions (pH 4.5, 5.1 and 5.5)] in a USP 31 disintegration test apparatus at 37° ± 2°∞C. At the end of this time interval, the tablets were removed from the disintegration bath and inspected for any defects (bloating or swelling). Any excess surface moisture was gently blotted dry using a paper towel, and the tablets were reweighed individually. The percent (%) acid uptake for a tablet was calculated according to Equation 1.

Generally, less than 10% acid uptake has been predictive of acceptable enteric protection and dissolution performance for tablets.

Equation 1

$$AU\ (\%) = [(Tf - Ti)/Ti] \times 100$$

AU (%): Percent acid uptake

Tf: Final tablet weight (mg)

Ti: Initial tablet weight (mg)

Disintegration Testing

Placebo tablets that were observed to be physically intact following the acid uptake test in 0.1 N HCl were then reciprocated in the disintegration test apparatus using pH 6.8 phosphate buffer maintained at 37° ± 2°C as the immersion fluid. The time taken for all of the tablets to disintegrate completely was recorded.

RESULTS

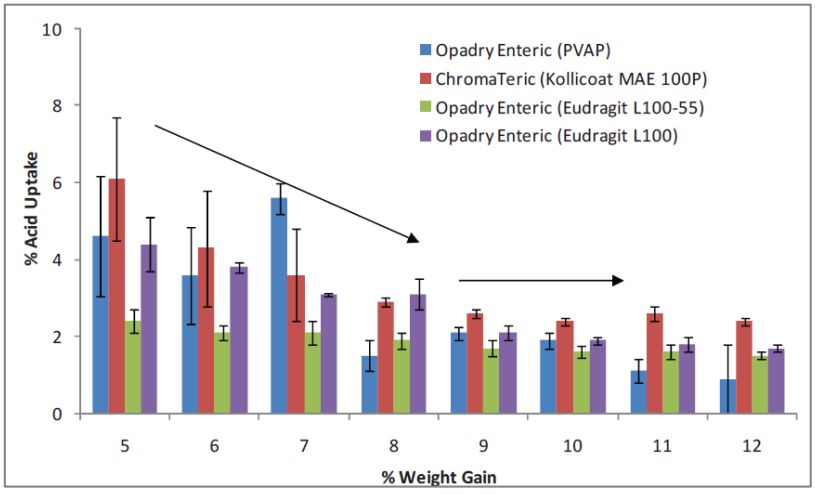
Assessment of Acid Uptake

Effect of Testing Medium pH on Acid Uptake

In 0.1N HCl

The effect of coating weight gain (film thickness) on acid-resistance of coated placebo tablets in 0.1 N HCl (pH 1.2) is shown in Figure 1. All the enteric polymers investigated in this study exhibited low (ie, less than 6%) acid uptake in 0.1 N HCl across the entire range of coating weight gains evaluated.

Figure 1. Acid Uptake of Placebo Tablets in 0.1 N HCl

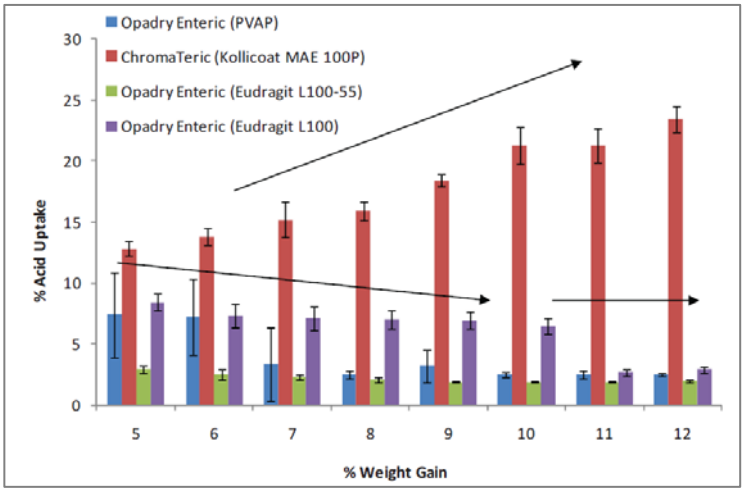


In pH 4.5 Acetate Buffer

The Eudragit-based and PVAP-based systems exhibited low acid uptake at all coating weight gains evaluated.

The Kollicoat MAE 100P-based coating, however, exceeded 10% acid uptake at all coating weight gains (Figure 2). The coating also appeared soft and tacky. The Kollicoat MAE 100P polymer is manufactured by partially neutralizing the enteric polymer dispersion with sodium hydroxide prior to spray drying.[2] The higher acid uptake may be attributed to at least partial solubility of the polymer and, correspondingly, greater permeability of the coating.

Figure 2. Acid Uptake of Placebo Tablets in pH 4.5 Acetate Buffer



In pH 5.1 and 5.5 Acetate Buffer

Placebo tablets coated with Opadry Enteric (PVAP) disintegrated in pH 5.1 and pH 5.5 acetate buffers. This can be explained by the lower dissolution trigger pH for PVAP (pH 5.0). As expected, due to the high acid uptake results in pH 4.5 buffer media (Table 4), the ChromaTeric (based on Kollicoat MAE 100P) coated tablets also disintegrated at pH 5.1 and pH 5.5.

However, at pH 5.1, low acid uptake was noted for placebo tablets coated with Opadry® Enteric, acrylic-based coating systems comprising Eudragit L100 or L100-55. The Eudragit L100-55 polymer starts to dissolve at pH 5.5, while the Eudragit L100 polymer starts to ionize and dissolve at a pH of 6.0.3 In lower pH media, these polymers will not ionize, hence they remain insoluble. This results in low acid uptake for coated tablets. As expected, only the Opadry Enteric (L100-based) film coating exhibited low acid uptake in media of pH 5.5. See Table 4 for acid uptake values of film coating systems based on Eudragit polymers in pH 5.1 and pH 5.5.

Table 4. Acid Uptake of Enteric Film Coatings at pH 5.1 and pH 5.5.

Coating Tablet Weight Gain (%)	% Acid Uptake for Enteric Coating Systems in pH 5.1 Sodium Acetate Buffer		%Acid Uptake for Enteric Coating Systems in pH 5.5 Sodium Acetate Buffer	
	Opadry Enteric (L100-55-based)	Opadry Enteric (L100-based)	Opadry Enteric (L100-55-based)	Opadry Enteric (L100-based)
5	15.0	8.8	Failed acid test	Failed acid test
6	14.0	7.7	Failed acid test	Failed acid test
7	13.8	4.5	Failed acid test	Failed acid test
8	8.3	2.6	Failed acid test	11.3
9	8.7	2.3	Failed acid test	12.4
10	6.4	2.2	Failed acid test	12.6
11	2.7	2.2	Failed acid test	4.6
12	2.8	2.4	Failed acid test	3.4

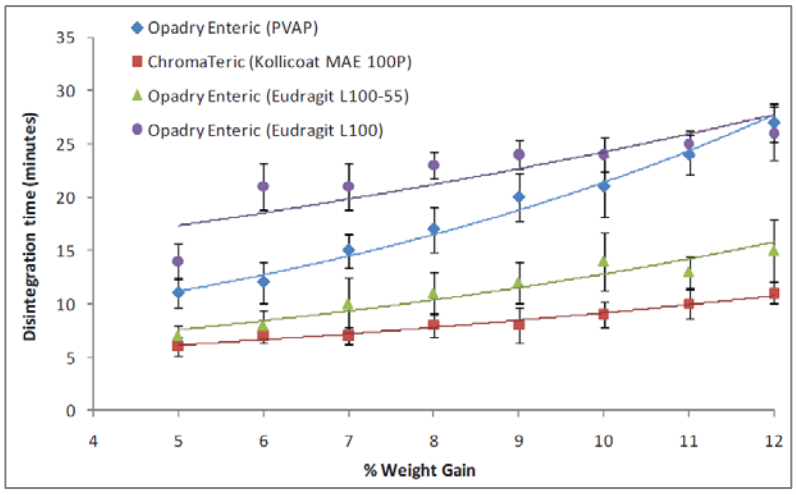
Effect of Enteric Coating Weight Gain on Acid Uptake

Acid uptake of the coated tablets in all tested media decreased with increased coating weight gain. Low acid uptake at higher enteric coating weight gains may be explained by the longer time required to solubilize a thicker film. This may also be attributed to a lower porosity, higher tortuosity and increased diffusion path length for the immersion fluid.4 This effect was observed until a certain minimum coating weight gain, after which the effect was less pronounced (Figures 1 & 2).

Disintegration Time (pH 6.8 Phosphate Buffer)

Uncoated placebo tablets disintegrated within 2-3 minutes. At pH 6.8, the solubility of all enteric polymers resulted in increased permeability of the coatings. Disintegration times increased with increasing weight gain; however, in all cases, disintegration times were less than 30 minutes as expected (See Figure **3**).

Figure 3. Tablet Disintegration in pH 6.8 Phosphate Buffer
(post-acid exposure: 0.1N HCl for 2 hours)



CONCLUSIONS

The pH trigger points of the enteric polymers influenced acid uptake and disintegration time of coated tablets. When applied using an organic solvent, the pre-neutralized ChromaTeric system did not provide enteric protection at intermediate pH (pH between 4.5-5.5). Whereas, coating systems based on PVAP or MAC polymers were resistant to intermediate pH media. Sustained resistance in this pH range is very important to maintain efficacy in fed states and gastric protection in patients treated with PPI or other enteric-coated products.

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