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Delayed release film coating applications on oral solid dosage forms of proton pump inhibitors: case studies

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Abstract

Background: Formulation of proton pump inhibitors (PPIs) into oral solid dosage forms is challenging because the drug molecules are acid-labile. The aim of this study is to evaluate different formulation strategies (monolithic and multiparticulates) for three PPI drugs, that is, rabeprazole sodium, lansoprazole, and esomeprazole magnesium, using delayed release film coating applications. *Method*: The core tablets of rabeprazole sodium were prepared using organic wet granulation method. Multiparticulates of lansoprazole and esomeprazole magnesium were prepared through drug layering of sugar spheres, using powder layering and suspension layering methods, respectively. Tablets and drug-layered multiparticulates were seal-coated, followed by delayed release film coating application, using Acryl-EZE®, aqueous acrylic enteric system. Multiparticulates were then filled into capsules. The final dosage forms were evaluated for physical properties, as well as in vitro dissolution testing in both compendial acid phase, 0.1N HCl (pH 1.2), and intermediate pH, acetate buffer (pH 4.5), followed by phosphate buffer, pH 6.8. The stability of the delayed release dosage forms was evaluated upon storage in accelerated conditions [40°C/75% relative humidity] for 3 months. *Results*: All dosage forms demonstrated excellent enteric protection in the acid phase, followed by rapid release in their respective buffer media. Moreover, the delayed release dosage forms remained stable under accelerated stability conditions for 3 months. *Conclusions*: Results showed that Acryl-EZE enteric coating systems provide excellent performance in both media (0.1N HCl and acetate buffer pH 4.5) for monolithic and multiparticulate dosage forms.

Key words: *Acryl-EZE®; drug layering; enteric coat; esomeprazole; lansoprazole; multiparticulates; powder layering; rabeprazole*

Introduction

Enteric film coating applications

The purpose of enteric film coating of an oral solid dosage form is to impart delayed drug release[1]. Delayed release dosage forms are defined as the one 'that releases a drug (or drugs) at a time other than promptly after administration'[2].

The enteric film coating is designed to resist the acidic environment of the stomach and starts to dissolve, leading to dosage form disintegration or drug release, in the higher pH environment of intestinal fluids. Therefore, the main reasons for using enteric coating on oral solid dosages are the following:

1. To protect the drug content of a pharmaceutical dosage form from the acidic environment of the gastric media, hence, improving the stability and bioavailability of the active ingredient;
2. To minimize bleeding or nausea by protecting the gastric mucosa from the irritating effects of some drugs such as nonsteroidal anti-inflammatory drug[3,4]; and
3. To deliver the drug to the lower segment of the intestine for site-specific drug delivery or local action. For example, enteric coated mesalamine tablets exert topical anti-inflammatory action in the distal intestine and the colon[5].

Most current enteric coating applications employ synthetic polymers as the main component of the coating

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composition. These polymers commonly referred to as polyacids carry acidic functional groups (such as ionizable carboxylic groups) on their structure. Therefore, they demonstrate pH-dependent solubility[1,3], which render them insoluble in gastric medium with low pH and dissolve in intestinal fluids with a higher pH. Several polymers are commonly used in enteric coating applications, such as cellulose acetate phthalate, cellulose acetate trimellitate, hydroxypropylmethylcellulose acetate succinate, hydroxypropylmethylcellulose phthalate, polyvinylacetate phthalate, and methacrylic acid/methylmethacrylate copolymers[1,6]. Natural polymers such as shellac[7] and rosin[8–11] have also been studied. Table 1 shows a list of enteric polymers and their respective threshold pH at which they start to dissolve.

The enteric polymers containing an ester structure may be susceptible to hydrolysis and degradation when exposed to humidity and elevated temperatures. Degradation of an enteric polymer can further lead to a substantial change in its functionality[1].

Important factors that may influence the behavior of enteric coated dosage forms[6] include the following:

1. type of the enteric polymer used and its threshold pH;
2. enteric coating composition (polymer, plasticizer, antitacking agents, and pigments);
3. core formulation, its swelling and disintegrant properties, and the nature of the drug in the dosage form;
4. presence of imperfections in the coating, such as fissures that can result in loss of integrity of the coating;
5. thickness of the film layers applied to the dosage form;
6. in vitro testing conditions, such as the composition, pH, ionic strength of dissolution media, and agitation intensity within the media; and
7. fed and fasted gastric conditions.

Table 1. Enteric polymers and their threshold pH[12,13].

Class	Enteric polymer	Threshold pH
Cellulosics	Cellulose acetate phthalate (CAP)	6.0
	Cellulose acetate trimellitate (CAT)	4.8
	Hydroxypropylmethylcellulose acetate succinate (HPMCAS)	5.5–6.8
	Hydroxypropylmethylcellulose phthalate (HPMCP)	5.0–5.5
Vinyls	Polyvinylacetate phthalate (PVAP)	5.0
Acrylics	Methacrylic acid copolymer, Type A, NF Methacrylic acid: methylmethacrylate (1:1)	6.0
	Methacrylic acid copolymer, Type C, NF Methacrylic acid: ethylacrylate (1:1)	5.5
	Methacrylic acid copolymer, Type B, NF Methacrylic acid: methylmethacrylate (1:2)	7.0
	Polymethylacrylate: polymethyl methacrylate: polymethacrylic acid) (7:3:1)	7.0
Natural polymers	Shellac	7.2
	Rosin	6.0

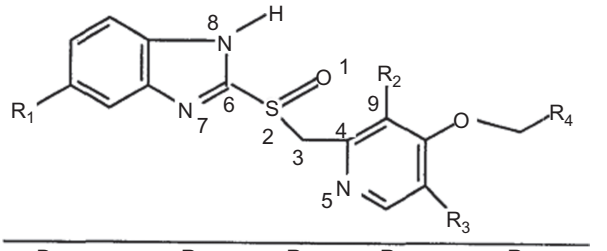
Enteric coating systems can be applied to various solid substrates such as crystals, granules, beads, tablets and capsules from organic solvent solutions, aqueous solutions and aqueous dispersions. The aqueous-based coating systems have attracted special attention because of environmental, toxicological and manufacturing safety advantages.

Because the performance of an enteric coated system is pH dependent, the release and absorption of the drug is significantly influenced by the gastrointestinal transit of such dosage form. There is a pH gradient through the gastrointestinal tract, progressively increasing from the stomach, pH 1–3[14] up to pH 4 during digestion, to a pH of 5–7 in the duodenum, and potentially to pH 8 in the distal ileum. As the enteric coated dosage form moves from the stomach to the duodenum, it is exposed to a marked change in the pH. Several factors, including: fed or fasted conditions, the presence of short-chain fatty acids, residues of bile acids, some disease states, or ingestion of certain drugs, such as antacids, may affect the intersubject, as well as the intrasubject pH variability in the gastrointestinal tract[3,15,16]. Therefore, drug release characteristics, in vivo performance and bioequivalency may not always be predictable.

It has been demonstrated that the type and design of the dosage form, that is, single unit (monolithic) or multiparticulates, may have different gastric emptying rates. In a multiparticulate system, the individually coated particles empty from the stomach in a more reproducible manner, as compared to a single enteric coated tablet, which may demonstrate a variable gastric transit time ranging from 0.5 to 12 hours[3]. Lansoprazole-delayed release multiparticulates have been reported to have better absorption properties compared to an enteric tablet[17]. Hence, in recent years, the focus has shifted toward designing enteric coated pellets or granules, which yield more reproducible drug release patterns[18,19].

Formulation of proton pump inhibitors

Proton pump inhibitors (PPIs) are substituted benzimidazoles (Figure 1) used for the treatment of acid-related gastroduodenal disorders by reducing gastric acid



Drug	R_1	R_2	R_3	R_4
Rabeprazole	H	CH_3	H	$CH_2CH_2OCH_3$
Lansoprazole	H	CH_3	H	CF_3
Omeprazole	OCH_3	CH_3	CH_3	H
Pantoprazole	$NCHF_2$	OCH_3	H	H

Figure 1. Chemical structures of proton pump inhibitors.

secretion[20–22]. PPIs are available as tablets, capsules, multiparticulates or multiple unit pellet system (MUPS), suspensions for oral administration, and as lyophilized powder (for reconstitution) for intravenous injection. The commonly used delayed release oral solid dosage forms of PPIs are listed in Table 2. These compounds are very sensitive to acidic environments[23,24] and undergo chemical degradation. As pH decreases, the rate of degradation increases; therefore, the acidic environment of the stomach causes significant decomposition of PPIs, leading to reduced bioavailability for these drugs. Consequently, most oral dosage forms of PPIs are formulated as delayed release systems, commonly in the form of enteric coated granules, tablets, and multiparticulates.

The degradation of PPIs manifests itself by significant discoloration, which tends to change over time[25]. Therefore, oral solid dosage forms containing the acid-labile PPIs are enteric coated. However, because the enteric polymers are acidic in nature, the stability of PPIs may be compromised during the enteric coating process and storage. Various studies[26,27] suggest the inclusion of an inert seal-coat on the PPI core formulation before enteric coating to separate the PPI from the enteric coating layer. The seal-coat is required to be inert, rapidly dissolve, or allow rapid disintegration of the core formulation upon dissolution of the enteric coating. Moreover, the seal-coat provides a smooth surface and mechanical strength to the core formulation, thereby improving the quality of the enteric coating[28]. It is often advantageous to add alkaline constituents in the core and/or the seal-coat to increase the stability of PPIs during manufacturing, storage and in gastric environment.

In the following three case studies, different formulation strategies and considerations for three model PPIs: rabeprazole sodium, lansoprazole, and esomeprazole magnesium are illustrated and discussed.

Case study 1: Delayed Release 20 mg Rabeprazole Sodium Tablets (Monolithic System)

Methods

Tablet preparation

Rabeprazole sodium tablets, using formulation shown in Table 3[29], were manufactured by a wet granulation method using ethanol in a high-shear granulator (GMX-10, Vector Corporation, Marion, IA, USA), followed by

Table 3. Rabeprazole sodium tablet formulation[29].

Ingredients	Supplier	%, w/w	mg/tablet
Rabeprazole sodium	Cadila Pharma, India	13.70	20.0
Powdered mannitol (Mannogem)	SPI Pharma, USA	27.40	40.0
Magnesium oxide USP, Heavy (Marinco OH)	Rohm and Haas, USA	42.46	62.0
Low-substituted hydroxypropylcellulose (L-HPC, LH-21)	Biddle Sawyer, New York, USA	13.36	19.5
Hydroxypropylcellulose (Klucel LF)	Ashland, USA	2.05	3.0
Magnesium stearate	Mallinckrodt, USA	1.03	1.5
Total		100.00	146.0

Table 2. Delayed release oral solid dosage forms of proton pump inhibitors.

PPI	Brand name	pKa	Aqueous solubility	Stability
Omeprazole	Losec, Prilosec	4.0	Very slightly soluble	10 minutes <pH 4 18 hours at pH 6.5
Lansoprazole	Zoton, Prevacid	4.0	Practically insoluble	0.5 hours at pH 5 18 hours at pH 7
Rabeprazole sodium	Pariet, Aciphex	5.0	Very soluble	Moisture sensitive
Pantoprazole sodium	Protonix	3.0	Freely soluble	2.8 hours at pH 5.0 220 hours at pH 7.8
Esomeprazole magnesium	Nexium	4.0	Very slightly soluble	19 hours at pH 6.8

drying in a fluid bed system (Flocoater FL-M-15, Vector Corporation). The dried granulation was lubricated with magnesium stearate before compression (Colton Model 2216, Vector Corporation). The tablets were evaluated for their physical properties including diameter, thickness, weight variation, content uniformity, breaking force (MultiCheck, Erweka, Heusenstamm, Germany) and friability (VanKel, Model 10,809, Cary, NC, USA).

Enteric film coating

Rabeprazole sodium tablets were then seal-coated using a dispersion of ethylcellulose/magnesium oxide (1:1) in absolute ethanol (as described by Saeki et al.[29]), followed by an aqueous enteric coating using a formulated methacrylic acid copolymer type C system (Acryl-EZE 93F, Colorcon, West Point, PA, USA). This grade of Acryl-EZE is a dry, dispersible powder, which contains plasticizers, detackifiers, neutralizing agents, processing aids, and/or pigments[30]. Both coating dispersions were prepared using low-shear mixing. The Acryl-EZE dispersion was passed through a 60-mesh screen (250 μm) before application (Table 4). The seal-coat layer was applied at a 1.37% theoretical weight gain (WG), followed by Acryl-EZE at various WGs of 8% to 14% in a partially perforated coating pan (LDCS-5, Vector Corporation). All coating process parameters are shown in Table 5.

Evaluation of delayed release rabeprazole sodium tablets

Integrity and liquid uptake of rabeprazole sodium tablets ($n = 6$) were tested in two different media, 0.1N HCl (pH 1.2) and USP acetate buffer (pH 4.5), to simulate a lower stomach pH in fasted conditions (pH 1.2) and a fed or PPI-treated stomach condition (pH 4.5). It has been shown that a multiple dose regimen of PPIs results in a decrease in gastric acid secretion with a subsequent elevation in gastric pH[31,32]. In this case study, the media uptake by rabeprazole sodium tablets was measured by weighing individually and placing the enteric coated tablets in a disintegration bath (Erweka ZT44) containing the media for 2 hours. Afterward, tablets were removed and inspected for bloating or discoloration. Tablets were then blotted dry and reweighed. The percent weight difference, before and after exposure to the media, was calculated and reported as media uptake values.

Drug release properties of the enteric coated tablets at various WGs were evaluated in a USP dissolution bath (Varian Inc., Cary, NC, USA), maintained at 37 ± 0.5°C, using apparatus II at 100 rpm. Tablets were placed in 1000 mL of either 0.1N HCl (pH 1.2) or acetate buffer (pH 4.5) for 2 hours, followed by USP phosphate buffer (pH 7.8). Drug release was measured using ultra high-performance liquid chromatography (HPLC) analysis (Waters Alliance 2695, UPLC, Milford, MA, USA), using a C_{18} column (Waters Acquity BEH C_{18}, 50 mm × 2.1 mm × 1.7 μm). The mobile-phase composition was phosphate buffer:acetonitrile (70:30), pH 7.0.

To evaluate the stability of rabeprazole sodium tablets, the delayed release dosage forms (coated with Acryl-EZE at 12% and 14% WG) were packed in high-density polyethylene (HDPE) bottles and stored at 40°C/75% relative humidity (RH) for 3 months.

Table 4. Coating dispersion preparation parameters for rabeprazole sodium tablets.

Parameter	Seal-coat layer	Enteric coat
Dispersion solids content (%)	10	20
Theoretical weight gain (%)	1.37	8.1–14.1
Powder (g)	20.55 Ethylcellulose 20.55 Magnesium oxide Total–41.1	81 Acryl-EZE
Deionized water (g)	N/A	324
Absolute ethanol (g)	369.9	N/A
Total dispersion (g)	411	405
Dispersion mixing time (minutes)	60	25

Table 5. Coating process parameters for seal layer and enteric coating of rabeprazole sodium tablets.

Parameter	Seal-coat 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 (m^3/h)	68	68
Pan rotational speed (rpm)	15	25
Atomization air pressure (bar)	1.3	1.3

Results and discussion

Tablets' physical properties including diameter, thickness, weight variation, content uniformity, breaking force and friability results are shown in Table 6. Media uptake values are reported in Table 7. Generally, the values less than 10% have been shown to correlate to acceptable dissolution performance (no drug release or degradation in the acid phase)[33,34]. Visual observation of the tablets after 2 hours in each media yielded no signs of discoloration of the tablets or dissolution media.

Table 6. Physical properties of the uncoated rabeprazole sodium tablets (20 mg).

Weight (mg)	144.5 ± 3.6
Breaking force (kp)	9.3 ± 0.8
Diameter (mm)	6.31 ± 0.03
Thickness (mm)	3.44 ± 0.05
Friability (%)	0.34 ± 0.01
Content uniformity (%)	101.8 ± 2.9

Table 7. Liquid uptake for enteric coated rabeprazole sodium tablets at various weight gains in two different media.

	Liquid uptake (%)	
Weight gain (%)	0.1N HCl	Acetate buffer, pH 4.5
8.1	4.35 ± 0.26	4.86 ± 0.52
10.1	4.76 ± 0.28	5.01 ± 0.28
12.1	3.81 ± 0.36	4.48 ± 0.23
14.1	3.48 ± 0.26	4.03 ± 0.24

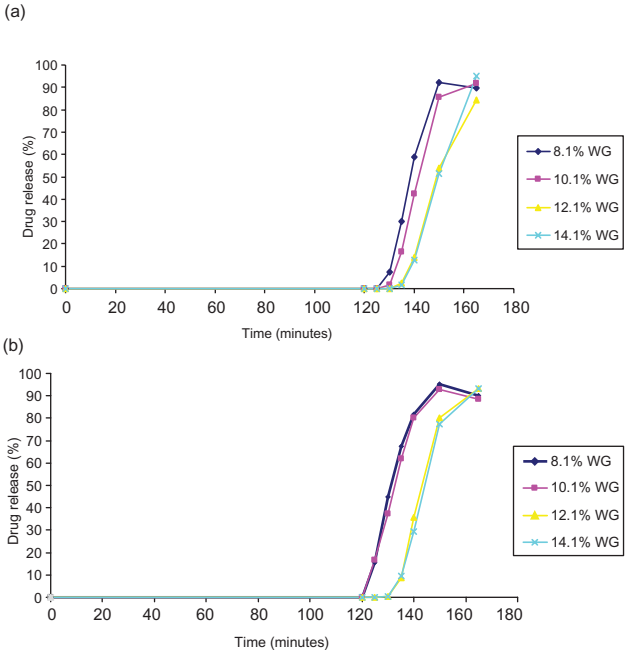


Figure 2. Drug release profiles of delayed release tablets of rabeprazole sodium in the acid phase followed by phosphate buffer, pH 7.8, (a) 0.1N HCl; (b) acetate buffer (pH 4.5).

Results of dissolution testing showed that different WGs of Acryl-EZE affected drug release profiles in the buffer phase, with higher WGs resulting in slightly slower release (Figure 2). All tablets had less than 10% drug release after 2 hours in both acid media, followed by rapid drug release (greater than 80% in 45 minutes) in the buffer phase (Figure 2). No degradants were detected in the chromatograms.

The stability data showed that the delayed release rabeprazole tablets remained stable over 3 months storage under accelerated conditions with the drug assay value of 99.0% and 101.5% for the tablets coated with Acryl-EZE 93F at 12% and 14% WG, respectively. Drug release profiles did not exhibit significant change upon stability testing in both acid media and buffer phase of this study.

Case study 2: Delayed Release 15 mg Lansoprazole Multiparticulates

Methods

Preparation of multiparticulates

It has been reported that binder solutions used for drug layering and excipients used for extrusion–spheronization are incompatible with lansoprazole[35]. In contrast, dry-powder layering has been shown to provide a more stable product for acid-labile drugs, such as lansoprazole[36]. In the following case study, delayed release multiparticulates of lansoprazole were prepared by dry-powder layering technology, followed by an aqueous enteric coating.

Lansoprazole was dry-powder layered (dusted) onto sugar spheres (SureSpheres®, drug layering substrate, 850–1000 µm, Colorcon) in a centrifugal fluid bed granulator (GPCG-1, Glatt Air Techniques Inc., Ramsey, NJ, USA). The dusting powder was applied while spraying a 3% (w/w) binder solution of hydroxypropylcellulose (HPC) (Shin-Etsu, Tokyo, Japan). The second dusting powder was applied to the pellets to enhance drug stability by providing a barrier between the drug layer and the subsequent enteric coating layer and to improve the physical properties of the granules. Table 8 outlines the composition and quantity of each ingredient in the powder-layering process[37]. The process parameters used for dry-powder layering are listed in Table 9.

The drug-layered pellets were fluid bed dried before enteric coating (Strea-1, Aeromatic Fielder, Niro Inc., Columbia, MD, USA) with Acryl-EZE 93F to a 26% theoretical WG. The coating dispersion was prepared using low-shear mixing, screened (60-mesh, 250 µm), and applied to the pellets using the processing parameters listed in Table 10. The pellets were manually filled in gelatin capsules, size 0 (Capsugel, Peapack, NJ, USA) (15 mg/300 mg pellets) for analysis.

Evaluation of delayed release lansoprazole capsules

Capsules were evaluated for drug assay using an ultra HPLC analysis (Waters Alliance 2965 UPLC) and a C_{18} column (Varian Pursuit C_{18}, 250 mm × 4.6 mm × 5 µm).

Table 8. Lansoprazole powder-layering formulation[37].

	Supplier	%, w/w	mg/g
Step #1: dusting powder			
Lansoprazole	Cadila Pharma, India	13.04	100
Magnesium carbonate	EDM Chemicals, USA	13.04	100
Sucrose	Domino Sugar, USA	13.04	100
Corn starch	Staley Starch, USA	13.04	100
Low-substituted hydroxypropylcellulose (L-HPC)	Biddle Sawyer, USA	13.04	100
Step #2: dusting powder			
Sucrose	Domino Sugar, USA	12.17	93
Corn starch	Staley Starch, USA	10.43	80
L-HPC	Biddle Sawyer, USA	10.43	80
Steps #1 and 2: aqueous binder solution			
Hydroxypropylcellulose (HPC)	Shin-Etsu, Japan	3.00	—
Total (solids)	—	101	753

Table 9. Powder-layering parameters for lansoprazole multiparticulates.

Parameters	Value
Batch size (g), SureSpheres (840–1000 µm)	2250
Rotor speed (rpm)	200
Binder spray rate (g/min)	20
Powder addition rate (g/min)	15
Inlet air temperature (°C)	55
Outlet air temperature (°C)	45
Bed temperature (°C)	45
Atomization air pressure (bar)	1.5
Air flap (%)	20
Air flow (m^3/h)	68–80
Total processing time (minutes)	113

Table 10. Enteric coating parameters for lansoprazole multiparticulates.

Parameters	Value
Batch size (g), 1190 µm drug layered pellets	500
Coating spray rate (g/min)	4.5
Inlet air temperature (°C)	44
Outlet air temperature (°C)	33
Bed temperature (°C)	32
Atomization air pressure (bar)	1.2
Total processing time (min)	144

The mobile-phase composition was water:acetonitrile:triethylamine (60:40:1), pH 7.0[38]. Dissolution testing was performed in a USP apparatus II (Varian Inc.) at 75 rpm, 37.0 ± 0.5°C. The dissolution testing (n = 6) was performed in 500 mL of acid phase for 1 hour, followed by phosphate buffer USP (pH 6.8). Lansoprazole release was measured using UV absorbance at 306 nm (Agilent 8453 spectrophotometer, Agilent Technologies, Inc., Santa Clara, CA, USA). Similar to rabeprazole sodium tablets, lansoprazole multiparticulates were also tested in two different media: 0.1N HCl (pH 1.2) and USP acetate buffer (pH 4.5). Furthermore, the capsules were packed in HDPE bottles and stored at 40°C/75% RH for 3 months to evaluate the stability of the formulations.

Results and discussion

Lansoprazole powder-layered pellets, prepared in a centrifugal fluid bed granulator, increased in size from 850–1000 to 1190–1410 µm, as determined through sieve analysis. No discoloration (degradation) was observed. Pellets appeared spherical, dense, had very few fines, and were therefore suitable for aqueous enteric coating. Lansoprazole pellets coated with Acryl-EZE 93F exhibited excellent enteric protection in acidic media (pH 1.2 and 4.5) and rapid drug release in phosphate buffer (pH 6.8). The results showed no drug release in either media at pH 1.2 or 4.5, followed by 80% release in phosphate buffer, pH 6.8, within 20 minutes (Figure 3). Stability data showed that lansoprazole-delayed release capsules remained stable over 3 months storage under accelerated conditions, with the drug assay value of 93.0%, meeting the USP specifications. In addition, there was no significant change in drug release upon stability testing in either acid media or buffer phase of this study.

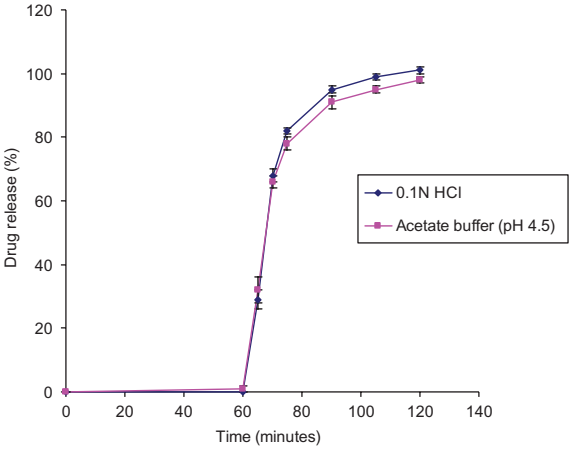


Figure 3. Drug release profiles of lansoprazole capsules in either 0.1N HCl or acetate buffer (pH 4.5), followed by buffer phase (pH 6.8).

Case study 3: Delayed Release Small Multiparticulates of Esomeprazole Magnesium Trihydrate (40 mg)

Methods

Preparation of delayed release multiparticulates

Formulation of delayed release multiparticulates involved drug layering, seal-coating, and enteric coating in a fluid bed coater (MP-2/3, Wurster setup, Niro, Inc., Columbia, MD, USA), using sugar spheres (45/60 mesh size, 250–355 μm) as starter seeds (Table 11). Drug-layering dispersion was prepared by dissolving a binder (hypromellose) and a wetting agent (polysorbate 80) in water, followed by addition of the drug (Table 11). The dispersion was refrigerated overnight to deaerate and sieved through a 60-mesh screen (250 μm) before the application. The screen retain was 0.36% (w/w) and the resulting dispersion had a pH of 9.0. The drug was applied onto the sugar spheres at a theoretical WG of 111.5% (w/w). An aqueous dispersion of the seal-coat, with a composition shown in Table 11[39], was prepared at 13% (w/w) solids and stored at ambient conditions overnight to deaerate, screened through a 60-mesh screen (250 μm) before application. The screen retain was 0.27% (w/w) and the dispersion had a pH of 9.1. The seal-coating composition was applied onto the drug-loaded beads to (44.4%, w/w WG). The seal-coated beads were then enteric coated, using Acryl-EZE 93A (a formulated coating system free of plasticizer) and triethyl citrate as the plasticizer. The enteric coating composition was prepared at 20% solids, screened through a 60-mesh (screen retain of 0.32%, w/w) and applied to the drug layered and seal-coated beads (61.5%, w/w WG). Because of the small size of the beads, the spray rate, air flow and product temperature were carefully monitored to ensure individual particle coating and to minimize potential agglomeration or electrostatic charge on the beads (Table 12). Controlling these parameters is of paramount importance when dealing with beads of small particle size, where coating imperfection may lead to variability in drug release. The coating application at each step proceeded with minimal agglomeration and electrostatic charge. The enteric-coated beads were then encapsulated in size 1 gelatin shells (Hawkins, Minneapolis, MN, USA), using an automatic bench top capsule filling machine (IN-CAP, Dott. Bonapace & C, Milano, Italy).

Evaluation of esomeprazole magnesium capsules

Capsules were evaluated for weight variation, drug assay and total impurities/degradation products using

Table 12. Process parameters for drug layering, seal-coating and enteric coating for esomeprazole multiparticulates.

Parameters	Drug layering	Seal-coating	Enteric-coating
Batch size (kg)	4.0	5.0	1.0
Inlet temperature (°C)	67	72	72
Product temperature (°C)	40	41	31.5
Outlet temperature (°C)	35–40	35–40	35–40
Air flow (m^3/h)	250	250	100
Atomization pressure (bar)	2.5	2.5	2.5
Flow rate (g/min)	56	58	32

Table 11. Formulation of esomeprazole multiparticulates (40 mg base)[39].

Ingredients	Supplier	%, w/w	mg/capsule
Sugar spheres (45/60 mesh size; 250–355 μm)	Mutchler Inc. (NP Pharm), USA	16.43	39.91
Drug layering			
Esomeprazole magnesium trihydrate	Kemprotec Ltd., UK	18.32	44.50
Hypromellose 2910 (HPMC, METHOCEL™ E6-LV)	Dow Chemical Company, USA	7.33	17.80
Polysorbate 80 (Tween 80)	Croda, USA	0.82	2.00
Seal-coating			
Hydroxypropylcellulose (HPC)(Klucel LF)	Ashland, USA	6.43	15.63
Talc	Luzenac, USA	11.61	28.20
Magnesium stearate	Mallinckrodt, USA	0.99	2.40
Enteric coating			
Acryl-EZE 93A	Colorcon, USA	34.56	83.95
Triethyl citrate (TEC)	Morflex, USA	3.47	8.43
Simethicone emulsion, USP	Dow Corning Corporation, USA	0.04	0.09
Total		100.00	242.91

ultra HPLC analysis (Waters Alliance 2965 UPLC), using a C_{18} column (Waters Acquity BEH C_{18}, 100 mm × 2.1 mm × 1.7 µm). The mobile-phase composition was phosphate buffer:acetonitrile (75:25), pH 7.6. To evaluate enteric protection, drug release was measured in a USP compliant bath (Varian Inc.), using apparatus II at 100 rpm. Capsules were placed in 500 mL of acid media, either 0.1N HCl (compendial acid phase) or acetate buffer USP, pH 4.5 (intermediate pH) for 2 hours, followed by dissolution testing in 900 mL phosphate buffer, pH 6.8. Currently, there is no official monograph for esomeprazole magnesium dosage forms in the USP. Therefore, the drug release criteria were specified as per the USP monograph for omeprazole delayed release capsules, that is, as less than 10% drug loss in the acid media followed by complete release of the drug (not less than 75% of the labeled amount) after 45 minutes in the buffer phase[38].

The capsules were packed in HDPE bottles and stored at 40°C/75% RH for 3 months to evaluate the stability of the formulations.

Results and discussion

Based on the results for 20 capsules, the weight was recorded as 313.44 ± 1.38 mg, representing 40 mg esomeprazole base. The values for drug assay and total impurities for esomeprazole capsules were determined as 104.0% and 0.1%, respectively. These values are in accordance with the USP monograph for delayed release omeprazole capsules.

The release profiles of esomeprazole capsules are displayed in Figure 4. The drug release in either media (0.1N HCl or acetate buffer, pH 4.5) was equal to or less than 2% after 2 hours, followed by complete release of the drug in phosphate buffer, pH 6.8. The values for $T_{75\%}$ in buffer (pH 6.8) were 23 and 18 minutes for the capsules pre-exposed to the 0.1N HCl and pH 4.5 media, respectively. The stability data showed that the product remained stable over 3 months in storage under accelerated conditions with the drug assay value of 96.2% and excellent enteric protection in both acid media under evaluation. There was no significant change in drug release upon stability testing, in either acid or buffer media.

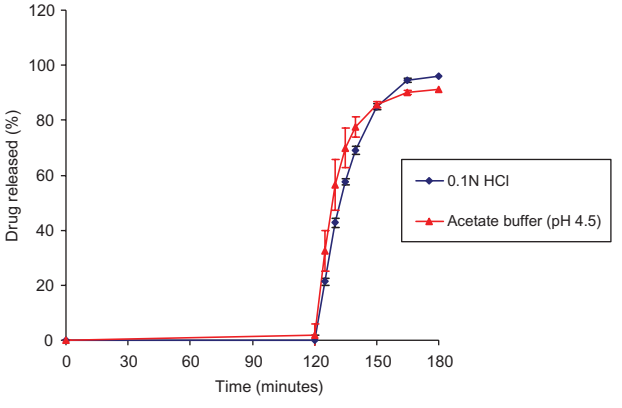


Figure 4. Release profiles for esomeprazole capsules containing enteric coated multiparticulates (40 mg base) in acid phase followed by buffer phase (pH 6.8).

General discussion

This study evaluated the delayed release film coating of various dosage forms of PPIs (tablets of rabeprazole sodium and multiparticulates of lansoprazole and esomeprazole magnesium) using Acryl-EZE enteric coating systems. Rabeprazole sodium tablets were prepared using an organic wet granulation method, followed by organic seal-coating application to prevent moisture entrapment in the core before aqueous enteric coating. This method may enhance the stability of the dosage form. For multiparticulates, both small (initial size of 250–355 µm) and large (850–1000 µm) sugar spheres were evaluated as the starting substrates. Careful coating process selection was required for coating of smaller substrates to reduce or prevent agglomeration of the multiparticulates. Lansoprazole multiparticulates were prepared using powder drug layering and seal-coating, followed by application of aqueous enteric coating, whereas multiparticulates of esomeprazole magnesium were prepared using aqueous drug layering and seal-coating applications, followed by aqueous enteric coating. These case studies indicated that various formulation methods had to be utilized to overcome potential degradation of challenging PPIs.

The amount of coating for each dosage form varied based on the starting size of the drug containing substrates, that is, the smaller substrates with larger surface area required higher WG of the enteric coating layers to render the desired gastroprotection. For instance, 8–14% WG of Acryl-EZE coating system onto rabeprazole sodium tablets was sufficient to ensure integrity of the dosage form in acidic media. On the contrary, multiparticulates of lansoprazole and esomeprazole magnesium required 26% and 61.5% WG of Acryl-EZE, respectively, to demonstrate satisfactory enteric protection.

To assess gastroprotection of the PPIs in the stomach of a patient with elevated gastric pH, the PPI dosage forms were subjected not only to 0.1N HCl (pH 1.2) but also to acetate buffer (pH 4.5) before dissolution testing in phosphate buffer. The results indicated that the PPI dosage forms formulated and studied here show excellent enteric coating protection in both media for 1–2

hours, followed by rapid release in the respective buffer media (Figures 2–4). In addition, stability data (drug assay and dissolution testing) for all dosage forms showed acceptable performance after 3 months of storage in 40°C/75% RH accelerated conditions.

Conclusions

PPIs are commonly used for the treatment of gastroduodenal disorders, but are highly sensitive to acidic media, and require careful formulation and enteric coating of their solid dosage forms. Here in this article, case studies were used to demonstrate typical core formulations and process applications of enteric coating for challenging drugs, such as rabeprazole sodium tablets, as well as lansoprazole and esomeprazole magnesium multiparticulates. Acryl-EZE enteric coating systems provided enteric protection in low and intermediate pH media, and complete release of the drug in higher pH environments. Results indicated that the formulations remained stable under accelerated ICH stability conditions for 3 months.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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