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Aqueous Acrylic Enteric System

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Investigation of a Directly Compressible Pantoprazole Sodium Delayed Release Formulation

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Introduction

Pantoprazole sodium, a proton pump inhibitor (PPI) is used for the treatment of acid reflux and stomach ulcers. It is formulated as a delayed release tablet dosage form, using a pH-dependent polymeric coating to protect the drug from a highly acidic environment in the stomach, thereby avoiding degradation before in vivo absorption. PPIs also need protection from the slightly elevated acidic gastric conditions (pH 4.5), which mimics the stomach environment for patients on multiple dosage regimens or a fed state condition.

Due to poor flow and compressibility, pantoprazole sodium-based formulations are often granulated using non-aqueous solvent, then dried, milled, and compressed into tablets. Formulations usually include a super disintegrant to ensure the rapid release of drugs in the intestinal tract. These processing conditions such as exposure of API to solvents during granulation step, exposure to heat during drying/milling step, and formulation components such as the presence of super disintegrant may affect formulation stability including appearance, assay, impurities, and dissolution.

The purpose of this work was to design a robust and stable, enteric coated, directly compressible tablet formulation of pantoprazole sodium which can withstand the acidic condition of the stomach including elevated pH 4.5 and gets completely released in intestinal condition (pH 6.8).

Methods

Tablet Formulation

The composition of pantoprazole sodium enteric coated tablets, equivalent to 40 mg of pantoprazole is shown in Table 1. All ingredients were screened through 40# screen, blended for 10 minutes in drum blender, lubricated with magnesium stearate (previously screened through 60# screen) for additional 2 minutes, then compressed using a single rotary tablet press (Karnavati) fitted with 7.0 mm standard concave round D-tooling at 175 mg core weight.

Table 1. Formulation of Pantoprazole Sodium

Core Tablet Ingredients	%w/w	mg/dose
Pantoprazole sodium (equivalent to 40 mg pantoprazole)	25.7	45.0
StarTab, Directly Compressible Starch	68.1	119.1
Sodium bicarbonate	5.7	10.0
Magnesium stearate	0.5	0.9
Total	100	175.0

Testing of Physical Properties of Tablets

The tablet physical properties, such as weight and crushing strength, were measured on a Sotex Tablet Tester. Tablet friability at 25 rpm up to 100 rotations was determined using an Electrolab Friabilator.

Coating of Tablets

Pantoprazole tablets were seal-coated with an HPMC-based clear formulation of Opadry® Complete Film Coating System to 2.5% weight gain using 12% w/w solids in water. The seal-coated tablets were subsequently enteric coated with Acryl-EZE® Aqueous Acrylic Enteric System at 11% weight gain using 20% w/w solids in water. Tablet coating was performed in an 8.5-inch perforated coating pan (O'HARA Labcoat M5), using the coating parameters shown in Table 2.

Table 2. Coating Process Parameters

Parameter	Seal-coat	Enteric coat
Tablet load (g)	300	300
Weight gain (%w/w)	2.5	11
Atomization air pressure (bar)	1.2 – 1.3	0.8 – 0.9
Pattern air pressure (bar)	1.2 – 1.3	0.8 – 0.9
Pan speed (rpm)	10	11
Inlet air temperature (˚C)	61 – 63	39 – 41
Exhaust air temperature (˚C)	44 – 47	33 – 3
Bed temperature (˚C)	43 – 45	32 – 34
Air volume (m3/hr)	114	108
Spray rate (gm/min)	2 – 3	2 – 3

Enteric Performance Testing

The enteric protection performance of coated tablets (n=6) was evaluated using a USP disintegration bath (Electrolab, ED-2L) containing either 0.1 N HCl or acetate buffer pH 4.5 for 2 hours at 37 ± 2˚C. The tablets were inspected at the end of this test to check for any defects (bloating or swelling). Any excess surface moisture was gently blotted dry using a paper towel, and individual tablets were re-weighed. The percent uptake by the tablets was calculated. The time taken for all the tablets to disintegrate completely in pH 6.8 phosphate buffer, at 37.0˚C was also recorded.

Assay, Impurities and Dissolution

Tablets were evaluated for assay and organic impurities as per USP NF 37, and drug release was determined in a USP dissolution bath (Electrolab, EDT-08LX):

Acid Stage: 1000 mL of 0.1M HCl (or acetate buffer pH 4.5), 37.0±0.5ºC, apparatus II, 100 rpm.

Buffer Stage: 1000 mL of phosphate buffer pH 6.8, 37.0±0.5ºC, apparatus II at 100 rpm.

At the end of the acid stage, (120 min), dissolution testing was continued with the buffer stage and samples were withdrawn at 10, 20, 30, 45 and 60 min, then analyzed for the amount of pantoprazole released.

Stability Testing

Coated tablets were packaged in 75 cc HDPE bottles (Shriji Polymers, India) with desiccant, induction sealed, and screw capped. The packed tablets were subjected to stability evaluation for 3 months, at 30°C/65% RH and 40°C/75% RH storage conditions. The stability of enteric coated tablets was monitored by testing drug release, assay, impurities, and enteric performance as described above.

Microscopic Evaluation of Coated Tablets

Coated tablets were manually bisected using a pill-splitter, the film thickness of the enteric coat measured microscopically (Leica, S8APO) at 80 X magnification.

Results

Testing of Physical Properties of Powder Blend and Core Tablets

Pantoprazole sodium showed very poor flow properties (Carr's Index: 41.176%), however, a significant improvement in flow properties was observed with pantoprazole powder blend prepared with StarTab (Carr's index: 29.412%). The resulted powder blend further showed good flow on the rotary tablet press to produce tablets with low variation in tablet weight, hardness, and thickness. The physical parameters for the API alone, powder blend (API + StarTab) and compressed tablets are summarized in Table 3.

Table 3. Physical Properties of Powder Blends and Core Tablet

Parameters	API	API + StarTab
Powder Properties		
Bulk density (g/ml)	0.490	0.588
Tapped density (g/ml)	0.833	0.833
Compressibility index (%)	41.176	29.412
Hausner ratio	1.700	1.417
Tablet Properties		
Tablet weight variation (mg)	–	175 ± 5.00
Thickness (mm)	–	4.20 ± 0.05
Hardness (kP)	–	4.5 ± 1.00
Friability at 100 revolutions (%)	–	0.34
Friability at 200 revolutions (%)	–	0.66
DT in water (seconds)	–	40 to 45

Enteric Performance, Dissolution, Assay, Impurities Test

Enteric coated tablets of pantoprazole sodium remained intact (acid uptake < 10%) during the acid stage (0.1 M HCl and acetate buffer pH 4.5) up to 120 minutes each, followed by rapid disintegration (< 9 minutes) in the buffer stage (phosphate buffer pH 6.8). The results of accelerated stability studies up to 3 months showed no significant change in enteric performance (Table 4). Similar performance was obtained when enteric coated tablets were subjected to dissolution testing. Less than 10% drug was released up to 120 minutes in the acid stage (0.1N HCl and acetate buffer pH 4.5), whereas > 80% of the drug was released in the buffer stage (phosphate buffer pH 6.8) within the 45 minutes of dissolution (Figure 1 and 2). Assay content and total impurities for pantoprazole sodium tablets were 107.9% and 0.5% respectively. The formulation was stable at accelerated stability storage conditions as shown in Table 5.

Table 4. Enteric Performance Following Stability at 40°C/75% RH and 30°C/65% RH for 3 Months

Test	Initial	40°C/75%RH	30°C/65%RH
pH 1.2 (Acid stage)			
Acid uptake (0.1M HCL) for 2 h	4.8 to 7.0 %	4.5 to 5.3 %	5.1 to 7.0 %
Disintegration test in phosphate buffer pH 6.8 (USP)	8 to 10 min	7 to 11 min	7 to 10 min
pH 2.5 (Intermediate stage)			
Acid uptake (4.5 pH acetate buffer) for 2 h	9.2 to 9.6%	9.3 to 10.0 %	4.9 to 11.8 %
Disintegration test in phosphate buffer pH 6.8 (USP)	6 to 9 min	8 to 13 min	8 to 12 min

Table 5. Assay and Organic Impurity Results for Pantoprazole Sodium Delayed Release Tablet

Test	Limit	Initial	40°C/75% RH	30°C/65% RH
Assay as such (%)	90 – 110	107.90	101.50	107.20
Total impurities (%)	NMT 1.0	0.05	0.38	0.20

Figure 1: Dissolution Profile of Pantoprazole Sodium DR Tablets (Acid Stage: 0.1M HCl)

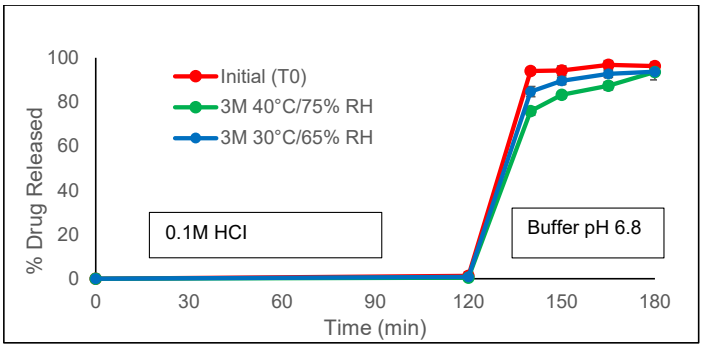
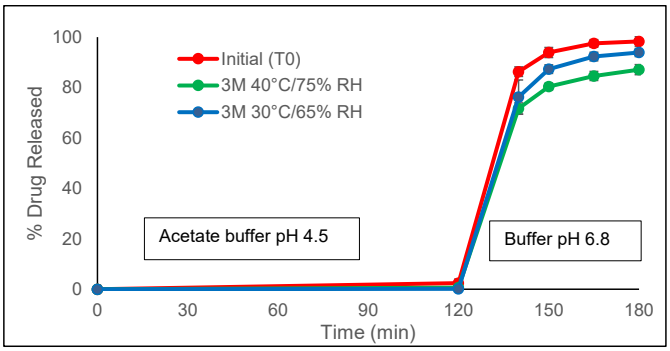


Figure 2. Dissolution Profile of Pantoprazole Sodium DR Tablets (Acid Stage: Acetate buffer pH 4.5)



Microscopic Evaluation of Coated Tablets

The microscopic evaluation indicated that the film thickness of the enteric coat layer is in the range of 65 – 100 µm. The face part of tablets showed higher film thickness (~ 100 µm) of the enteric coat as compared to the edge (~74 µm) and end part (~65 µm) of tablets. This range of enteric coat film thickness provides uniform coverage over different parts of the tablet surface which helps withstand the tablets in acid media.

Conclusions

Unique properties of StarTab associated with particle morphology and superior flow helped in directly compressible formulation of pantoprazole sodium, meeting all desired quality attributes for the powder blend and compressed tablets. These tablets were subsequently seal-coated with an Opadry coating system followed by an enteric system, Acryl-EZE, to achieve defect-free tablets. The tablets complied with USP drug release requirements, including intermediate pH protection, and demonstrated acceptable stability and performance at accelerated storage conditions. Pantoprazole sodium delayed release formulation was successfully developed using a direct compression method, consisting of StarTab in the core and Acryl-EZE II as an enteric coating.

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