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Preparation of Pantoprazole 40 mg Delayed-release Tablets Exhibiting Good Stability and Drug-release Characteristics

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Introduction

This study describes the development of delayed-release pantoprazole (40 mg) tablets that exceeded compendial requirements with respect to drug release in simulated gastric juice (<10% after 2 hours) and buffer solution, pH = 6.8 (≥ 74% in 30 minutes) while demonstrating appropriate active pharmaceutical ingredient (API) stability. In each case, these criteria were designed to be met after submitting tablets to stability studies conducted under both standard and accelerated stability conditions.

Methods

Tablets containing pantoprazole sesquihydrate (equivalent to 40 mg of pantoprazole), and conforming to the formulation shown in Table 1, were prepared using a wet-granulation technique. Tablets were compressed to a target breaking force of 50–80 N.

Table 1
Formulation Used in Preparation of Pantoprazole 40 mg Tablets

Material Description	%w/w	mg/tablet
Pantoprazole sesquihydrate	29.1	45.1
Polyplasdone™ XL-10 crospovidone	6.45	10
Sodium carbonate	6.45	10
Mannitol	54.67	84.74
Plasdone™ K-90 povidone	2.58	4
Calcium stearate	0.75	1.16
TOTAL	**100**	**155**

Eight (8) kg of tablets prepared in this manner were subsequently seal coated with an Aquarius™ Prime film coating system (2% target weight gain) and then delayed-release coated with an Aquarius Control ENA film coating system (10 % target weight gain) using an O'Hara LabCoat I coating machine fitted with a 19" pan insert. The coating process conditions used are shown in Table 2.

Note: This work was presented at the Annual Meeting of the American Association of Pharmaceutical Scientists, October 14–18, 2012, Chicago, Illinois.

Table 2
Summaries of Coatings Conditions Used

Parameter	Process Settings	
	Seal Coating	Delayed-release Coating
Process air volume (cfm)	200	200
Inlet temperature (°C)	70	55
Bed temperature (°C)	41-43	38–42
Exhaust temperature (°C)	44-46	40–44
Dew point (°C)	14.5	14.5
Pan speed (rpm)	13	15
Atomizing air pressure (psi)	25	25
Pattern air pressure (psi)	35	35
Spray rate (g min^{-1})	30	30
Suspension solids (% w/w)	10	20

The delayed-release coated tablets were initially analyzed for drug content, moisture content, percent of drug released after two hours in simulated gastric juice (0.1 N HCl solution) and subsequently percent of drug released (up to 60 minutes, with quantities being noted every 15 minutes) in buffer solution, pH = 6.8. Samples of coated tablets were also filled into high-density polyethylene (HDPE) bottles (foil sealed), and set up for stability testing (using the storage conditions as shown in Tables 3 and 4). Samples were subsequently removed for testing at various time intervals (also as shown in Tables 3 and 4). At each time point, samples were analyzed in the same manner as the initial samples.

Results and Discussion

The moisture contents for the initial tablets, and for those stored for various periods of time under selected stability conditions, are summarized in Table 3, while the drug assay results are shown in Table 4.

Table 3
Summary of Moisture Content Results

Storage Time (months)	Moisture Content (% w/w)		
	25ºC/60% RH	30ºC/65% RH	40ºC/75% RH
Initial	5.7	5.7	5.7
1	5.2	5.6	5.5
2	-	5	5.6
3	5.3	5.1	5.6
4.5	-	5.3	-
6	5.5	5.6	-
9	5.5	-	-
12	5.3	-	-

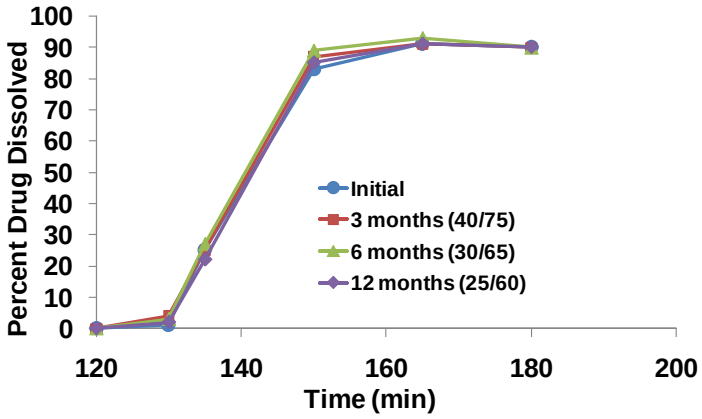
Table 4
Summary of Drug Assay Results

Storage Time (months)	Drug Assay (% w/w) 25°C/60% RH	30°C/65% RH	40°C/75% RH
Initial	96.1	96.1	96.1
1	96.6	95.7	95.9
2	-	96.1	95.8
3	95.7	96.3	96.3
4.5	-	96.2	-
6	96.1	96.1	-
9	95.9	-	-
12	95.7	-	-

These data indicate that there are essentially no moisture changes within the coated tablets, and that no decrease in drug assay has occurred during the course of the stability studies (uncoated tablets had a moisture content of 5.7%, and an assay result of 95.8%).

Drug dissolution data are shown in Figure 1. The dissolution media were analyzed for drug content after two hours in 0.1 N HCl, and subsequently after a further 60 minutes in buffer, pH = 6.8 (with intermediate samples being withdrawn for testing after 10, 15, 30 and 45 minutes).

Figure 1
Summary of drug release data in buffer solution, pH = 6.8



In each case, no drug release was detected after two hours of exposure to 0.1 N HCl solution, and the amount of drug released in buffer solution, pH = 6.8 exceeded compendial requirements in each case (Q value ≥ 75% after 45 minutes, with actual values being > 90% in each case).

Conclusions

The challenges in developing oral dosage forms containing proton pump inhibitors relate to achieving good stability (in which both moisture and interaction with the delayed-release coating can play an important role), and achieving appropriate functionality of the delayed-release coating (in terms of achieving good gastric resistance, as well as rapid release once the dosage form passes into the upper part of the small intestine).

The data presented in this study suggest that these objectives, with respect to the pantoprazole tablets, will be met.