Physicochemical characterization of enteric-coated Omeprazole pellets with and without a protective sub-coat

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Introduction
Omeprazole (5-methyl-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl][methyl]sulfonyl]-1H-benzimidazole), belongs to substituted benzimidazole class. Omeprazole binds selectively and irreversibly with gastric proton pump (H+/K+-ATPase enzyme system) at the parietal cell secretory membrane and inhibit both basal and stimulated acid secretion from the parietal cell, irrespective of the stimulus. Omeprazole is acid labile and degrades rapidly in the acidic environment of stomach or exposure to acidic conditions during formulation development and manufacturing. Thus, it is essential to protect drug against acid exposure during manufacturing and in the acidic environment of stomach by enteric coating to prevent its degradation in stomach and have protective measures during processing to enhance its storage stability, and increase its bioavailability and therapeutic efficacy after oral administration. In this study, we have evaluated the physiochemical stability and coating integrity of the enteric coated Omeprazole pellets obtained commercially or prepared by extrusion and spheronization, or use of non-pareil seeds or granulation followed by enteric coating with and/or without a protective sub-coat depending on formulation composition using four analytical methods including HPLC, NMR, DSC and fluorescent imaging.

Objective
To evaluate stability and coating integrity of enteric-coated Omeprazole formulations produced by extrusion-spheronization, sugar seed coating and granulation with and without application of sub-coat prior to enteric coating.

Method
Pellets containing Omeprazole were produced using both extrusion/spheronization and drug layering onto seeds followed by fluidization and coating with polymethacrylates. Stability of drug after storage following ICH guidelines (30°C ± 2°C/65% ± 5% H.R. 6 months) was determined using HPLC, DSC, NMR and fluorescent imaging.

a) NMR Analysis
Sample Preparation: All samples were analyzed in deuterated dimethylsulfoxide (dmsob-d6), by dissolving 20 mg material in 600μL dmsob-d6

1H-NMR spectra: Overview of entire spectra, with assignments

13C-NMR and COSY spectra:
Due to its structure, omeprazole has rather limited 1H-1H homonuclear correlations, which makes COSY spectra advantageous for formulations.

Sample A: Omeprazole purity in the formulation: 99.6%

Sample B: Omeprazole purity in the formulation: 99.5%

c) DSC Analysis
The melting points and/or transition temperatures for omeprazole, excipients, and omeprazole-based formulations were determined by DSC using a heating rate of 5°C/min up to 250°C.

b) HPLC Analysis
Sample Preparation: For each formulation, 10 mg of freshly-grinded powder was dissolved into 0.6 mL DMSO and 25 μL from each solution were injected into the chromatographic system. Elution was carried out on C18 column (4.6 mm x 25 cm) at a flow rate of 1 mL/min, with a mobile phase of phosphate buffer/ACN 3/1 (v/v) under the detection wavelength of 280 nm.

Sample A: Omeprazole purity in the formulation: 99.6%

Sample B: Omeprazole purity in the formulation: 99.5%

d) Fluorescent Imaging Analysis
The fluorescent imaging experiments were performed on a Leica DM4000B fluorescence microscope. Focusing was done using normal light, while imaging was performed using the L5 filter (excitation wavelength of 480 nm).

a) Extruded, spheronized and enteric coated (No sub-coat)

b) Sugar seed, drug layer and enteric coated (No sub-coat)

c) Sugar seed, drug layer, sub-coat and enteric coat

Summary and Conclusions
➢ Cross-sectioned pellets were subjected to fluorescence imaging that illustrated coating integrity and uniformity.
➢ HPLC and NMR results showed >99% of drug being present in all pellets. Three degradants were identified at levels of <1%.
➢ Representative DSC thermograms were also obtained all of which demonstrated stability to be stable.
➢ Analytical data showed that all pellets containing Omeprazole remained stable regardless of the coating conditions. Control of the pH environment within formulation, application of neutral sub-coat and enteric coating polymers all appear to provide options to produce stable product.

References
➢ Presented at AAPS 2012.