

# Design and Development of a Stable Oral Dosage Form of Omeprazole, an Acid-Labile Model Drug, Via Combined Compression and Enteric Coating Techniques

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## INTRODUCTION

Acid-labile compounds present many challenges during manufacturing and production. A model drug, omeprazole, was selected in this investigation. Omeprazole, a substituted benzimidazole, is the first FDA-approved proton pump inhibitor which is used in treatment of GERD and peptic ulcer disease. Omeprazole, however, has poor stability. In solid state, omeprazole molecules are susceptible to heat, moisture, and to some degree, to light and organic solvents. In an aqueous solution or suspension, the stability of omeprazole is highly dependent on pH. As an acid-labile agent, omeprazole is susceptible to degradation in acidic and neutral media, while demonstrating acceptable stability at alkaline conditions. These properties pose significant challenges in designing a stable formulation of this drug. An oral dosage form of omeprazole should protect the drug molecules in such a way to improve the stability of omeprazole and insure its therapeutic efficiency.

## OBJECTIVES

To design a stable tablet formulation via combined compression and enteric coating techniques so that the omeprazole delivery system (i) withstands the gastric environment and releases the drug content in proximal intestine; (ii) remains stable over the period of stability testing in comparison to commercial omeprazole capsules.

## METHODOLOGY

### Excipient Selection

The selection of suitable excipients is a critical step when design of a stable formulation for an acid-labile drug is concerned. Several excipients were examined for possible interactions with omeprazole, including, microcrystalline cellulose (Avicel<sup>®</sup>, FMC Corp.), powdered cellulose (Arbocel<sup>®</sup>, JRS Pharma), sodium starch glycolate (Explotab<sup>®</sup>, JRS Pharma), Pregelatinized starch (Starch 1500, Colorcon), and mannitol (Mannidex, Cerestar, Inc.). Each excipient was dry-blended with omeprazole in the weight ratio of 2:1. Since degradation of omeprazole molecules takes place with distinct discoloration, all samples were examined at different time points for possible signs of degradation over the period of 30 days at ambient and 40 °C/ 75% RH conditions.

### Tablet Preparation

Tablet cores of omeprazole were prepared via dry-blending the suitable ingredients (binder and disintegrating agent, lubricated with magnesium stearate) and direct compression (F1). MgO was added to half of the tablet cores (F2) to investigate the effect of the alkalinizing agent on release and stability of the drug. The cores were further compression-coated using, more or less, the same ingredients as the cores, however void of omeprazole. The tablets were further enterically coated using an organic solution of Eudragit L100-55 (Figure 1).

### Dissolution Testing

The drug release was evaluated, as per the USP 28, at acid stage (pH=1.0) for 2 hours followed by buffer stage (pH=6.8), using apparatus-II at 75 rpm. The extent of omeprazole release was determined using HPLC analysis at 280 nm (Table 1). The results were compared to the commercial omeprazole capsules, regarded as the reference product.

Figure 1. Different steps in manufacturing the compression-coated tablet of omeprazole, (a) inner core containing omeprazole, (b) compression-coated tablet of omeprazole, (c) final tablet of omeprazole, compression-coated and enteric-coated, (d) a cross section of (c).

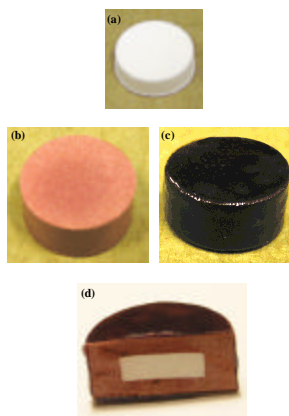


Table 1. The chromatographic conditions used in dissolution and stability testing of omeprazole dosage forms.

Stationary phase (analytical column)	Reverse C <sub>18</sub> column (4.6 mm × 150.0 mm, 5 μm)
Mobile phase	ACN: 0.05 M Na <sub>2</sub> HPO <sub>4</sub> , pH=8.5 (30/70, v/v)
Flow rate	0.7 mL/min
Detection wavelength	280 nm

### Stability Studies

The designed tablets and the commercial omeprazole capsules were individually placed in rubber-capped glass containers and were further stored at 2 different conditions, ambient environment and the stability chamber of 40 °C/ 75% RH. The stability of the dosage forms was investigated using HPLC analysis at 0, 7, 30, 60 and 90 days.

## RESULTS AND DISCUSSION

The compatibility study of the physical mixtures of omeprazole with various excipients revealed different range of instability over time. Acid-treated excipients such as MCC severely deteriorated drug stability as demonstrated through deep discoloration of the mixture (Figure 2). Other excipients showed different range of stability over time. In the dissolution testing, all dosage forms showed resistance to drug release at pH=1.0 (less than 1% drug release during the first 2 hours), while releasing over 85% of omeprazole at 10 minutes exposure to pH=6.8. However, after the maximum release was achieved, the concentration of omeprazole in the dissolution media did not remain at a plateau state and started to decrease (Figure 3). This is due to omeprazole degradation which occurs as the drug is being released to the dissolution medium. When the drug release is complete, degradation becomes the dominant process. The presence of MgO did not exhibit a significant effect in drug release between F1 and F2. The results of the stability studies are demonstrated in Figure 4. It appears that the stressed condition of 40°C/ 75% RH deteriorates the stability of all dosage forms as compared to their respective ambient conditions (p<0.05). This is more evident with commercial capsules. The presence of MgO at ambient conditions does not appear to enhance the stability of the formulations (p>0.05); however, at 40°C/ 75% RH, it improves the stability of F2 compared to F1 (p<0.05).

Figure 2. The appearance of selected physical mixtures of omeprazole at the time of mixing (left) and after 7 days storage at 40°C/ 75% RH (right), (a) plain omeprazole powder, (b) omeprazole and MCC, (c) omeprazole and sodium starch glycolate

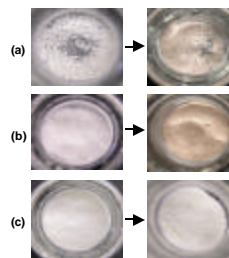


Figure 3. Dissolution profiles of the designed omeprazole tablets and of commercial capsules (n=3).

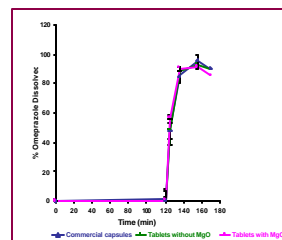
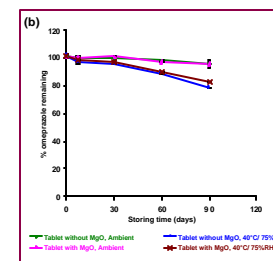
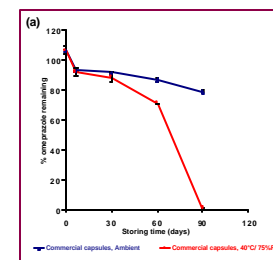


Figure 4. Remaining omeprazole content (%) over the period of stability testing (90 days) for (a) commercial capsules (reference product), (b) designed omeprazole tablets (n=3)



## CONCLUSIONS

Due to its extreme acid-lability, design of a stable oral formulation of omeprazole is challenging. The results demonstrate that upon selection of appropriate excipients, the application of both compression and enteric coating techniques, as an alternative to the currently used multiple coating approaches, can provide a stable formulation for a typical acid-labile compound. The compression-coat layer serves as a barrier to isolate the acid-labile drug from the deteriorating effect of the acidic enteric layers, while the enteric-coat protects the drug from the harsh gastric environment.

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