**In vitro Permeation Studies of Esomeprazole through Gastric Pig Mucosa**

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**ABSTRACT SUMMARY**

The aim of this work was to study the *in vitro* permeation through pig gastric mucosa of an esomeprazole immediate release tablet to be used in a two pulse delivery system. The influence of alkalinizing excipients on the drug release and stability in acid environment was investigated. The presence of sodium carbonate in the formulation increases both the transport of esomeprazole through the mucosa and stability in the acid medium.

**INTRODUCTION**

Esomeprazole is a proton-pump inhibitor, used in the treatment of acid-related gastroduodenal diseases. Usually, it is orally administered as a delayed-release dosage form due to its very poor stability in the acid environment. Esomeprazole is absorbed in the small intestine and it reaches the stomach through the bloodstream, where the drug acts. This leads to a time lag in drug therapeutic effect.

The aim of this work was to study the transport through the pig gastric mucosa of esomeprazole from an immediate release tablet formulation. The influence of different buffering agents on the stability and permeation of the drug was investigated.

**EXPERIMENTAL METHODS**

**Tablet manufacturing**

8 mm tablets were manufactured using a tableting machine (EK, Korsh, Berlin, D) equipped with round shape punches. Each tablets contained 10 mg of esomeprazole, 80 mg of alkalinizing agents (MgO or Na₂CO₃) and 5 mg of croscarmellose sodium as disintegrating agents. Tablets made without alkalinizing agents and with lactose as a filler were used as reference.

Permeation experiments were carried out in Franz-type diffusion cells (Disa, Milan, I) with an exposed surface area of 2.8 cm². Pig gastric mucosa, with a thickness between 0.5 and 0.8 mm range, was used as membrane. The receptor phase was PBS. The tablets were deposited on the mucosa, donor side, containing different volumes of USP simulated gastric fluid without enzymes, namely 1, 3 and 5 ml.

The experiments lasted for 2 hours. 1 ml of PBS receptor phase was sampled at fixed times and replaced by fresh PBS. At the end of the experiment, the content of the donor compartment was recovered and stabilized using borate buffer (pH =11). The drug accumulated in the tissue was recovered by extracting the tissue with methanol for 2 hours.

**HPLC analysis**

HPLC analyses were performed using validated method, by a Shimadzu instrument (Shimadzu, Kyoto, J) and a Supelcosil LC – 8 column (Sigma-Aldrich, Buchs, CH). The UV detector was set at 280 nm. The mobile phase was a mixture of phosphate buffer (pH 7.6) and CH₃CN (65/35 v/v) pumped at 1.0 ml/min.

**RESULTS AND DISCUSSION**

The permeation profiles of esomeprazole from the immediate release tablets through pig gastric mucosa are shown in Figures 1-3.

In presence of Na₂CO₃, with 1 ml of simulated gastric fluid in the donor compartment, a flux of 0.109 ± 0.04 mg/cm²h was reached between 60 and 120 min (Figure 1). In the case of 3 ml and 5 ml the flux was higher (0.159 ± 0.03 mg/cm²h and 0.124 ± 0.05 mg/cm²h, respectively). After 2 hours, the pH of the medium in the donor side containing 5 ml of fluid was around 11.0. At the end of the experiment, the drug mass balance was about 97%. Anyway, the cumulative transport of
esomeprazole through the mucosa was not significantly different between the different volumes of the medium in the donor compartment.

In presence of MgO as alkalinizing agent (Figure 2), the transport of esomeprazole through the pig gastric mucosa was lower with respect to the tablet containing Na₂CO₃.

Moreover, the flux was higher in 1 and 3 ml fluid (0.1 ± 0.03 mg/cm²h and 0.09 ± 0.03 mg/cm²h) compared to 5 ml (0.05 ± 0.01 mg/cm²h). This last value was due to a greater degradation of esomeprazole in the donor environment where the pH was around 7.0.

In the absence of alkalinizing agent, the transport of esomeprazole was negligible and at the end of the permeation test, a low quantity of drug from the tissue (less than 0.1 mg) was recovered (Figure 3). In addition, the mass balance was very low likely due to the degradation of the drug in the acid environment.

CONCLUSION
The presence of the alkalinizing agent in the formulation increases the permeation of esomeprazole through the gastric pig mucosa as it reduces the degradation of the drug in the acid environment. Furthermore, from the permeation profiles it was observed that Na₂CO₃ showed an increased amount of drug permeated through the mucosa compared to MgO.

REFERENCES