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Esomeprazole immediate release tablets: Gastric mucosa ex vivo permeation, absorption and antisecretory activity in conscious rats

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ABSTRACT

The aim of this work was to study the esomeprazole activity on the control of gastric secretion after administration of a novel immediate release tablet. The ex vivo permeation of esomeprazole across porcine gastric mucosa from immediate release tablets, containing sodium carbonate or magnesium oxide as alkalinizing agents, was firstly assessed. Pharmacokinetics and pharmacodynamics studies in conscious rats following the administration of immediate release tablets with sodium carbonate, in comparison with delayed-release tablets having the same formula, were also conducted. The results showed an important effect of sodium carbonate and magnesium oxide on the drug release, on the ex vivo trans-mucosal transport and the stability in acid environment. In particular, the presence of sodium carbonate in esomeprazole tablet formulation provided the maximum increase of the drug in vitro transport across the mucosa. Then, the absorption and the antisecretory activity of this proton pump inhibitor orally administered in rats as immediate release tablets containing Na_2CO_3, was superior but not significantly different compared to delayed-release tablets having the same formula. In the adopted animal model, an activity of esomeprazole from immediate release alkaline formulation was seen also in presence of partial gastric absorption allowing inhibition of proton pumps reached via systemic circulation. This esomeprazole immediate release formulation could be used for the on-demand treatment of acid-related disorders such as gastro-esophageal reflux disease.

1. Introduction

Esomeprazole (ESO), the (S)-configured enantiomer of omeprazole, is the first chiral non-racemic proton-pump inhibitor (PPI) used in the treatment of acid-related gastro-duodenal diseases [1,2]. Compared to the racemic form, esomeprazole given orally has a lower metabolic rate and systemic clearance, resulting in higher C_{max} and AUC values [3,4]. Esomeprazole proved to be more effective than omeprazole in maintaining the intra-gastric pH above 4.0, a condition promoting gastric mucosa healing [5].

Like all PPIs, for gastro-stability reasons ESO is orally administered in delayed-release enteric dosage forms [6,7]. It is absorbed in the small intestine and reaches the target parietal cells in the stomach via the bloodstream. ESO is activated in the secretory canaliculi of acid-secreting parietal cells to form a sulfenamide [8]. The activated form binds covalently to the sulfhydryl group of a cysteine present in the extracellular domain of the H^+/K^+-ATPase proton pump, thus inhibiting acid secretion. When the drug is given as delayed-release formulation, the release process causes a time lag in therapeutic effect. In fact, if the drug release occurred in the stomach, ESO would be degraded in the acidic environment, losing its activity.

Therefore, it is against common practice to orally administer a proton pump inhibitor in an immediate release dosage form. However, an immediate release oral formulation of omeprazole with sodium bicarbonate (Zegerid® powder; Santarus Inc., USA) has been registered. This omeprazole formulation with 30 mmol of sodium bicarbonate led to a rapid omeprazole absorption and quick onset of the anti-secretory effect [9,10]. Taken at bedtime, this product controlled nocturnal intra-gastric acidity significantly better than delayed-release PPIs [11]. The cited studies assumed that the omeprazole immediate release product given in association with sodium bicarbonate was absorbed by the proximal small intestine, similarly to delayed-release formulations. The presence of sodium bicarbonate was critical because it protected omeprazole from acid degradation favoring its absorption. In addition, sodium bicarbonate stimulates gastrin release, which leads to pump activation, allowing rapid inhibition of acid secretion [9].

In 2010 the FDA approved a fixed-dose combination product (Vimovo™), containing esomeprazole magnesium dihydrate and the

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non-steroidal anti-inflammatory naproxen in a single tablet, for the treatment of arthritis in patients at risk for NSAID-associated ulcers [12]. Vimovo is a multi-layer, delayed-release tablet combining an enteric-coated naproxen core and an immediate release esomeprazole magnesium layer surrounding the core [13].

Despite several papers found in the literature on PPI immediate release preparations, the transport of esomeprazole across the gastric mucosa as a function of pH or formulation has not yet been evidenced. In particular, the gastric behavior of esomeprazole that could explain the action of the immediate release tablets remains to be assessed.

Therefore, the aim of this work was firstly to study the ex vivo permeation of esomeprazole across porcine gastric mucosa by immediate release tablet formulations. Therefore, ESO immediate release tablets containing the alkalinizing agent sodium carbonate or magnesium oxide were manufactured. Subsequently, pharmacokinetics and pharmacodynamics studies from the formulations containing esomeprazole and sodium carbonate were conducted in conscious rats, in conditions that enabled the evidencing of the gastric availability and the anti-secretory activity of the PPI. Enteric-coated tablets having as a core the same immediate release formulation were tested for comparison purposes.

2. Materials and methods

2.1. Materials

Esomeprazole magnesium dihydrate (batch no. ESO0260710) and the reference standard (batch no. ESWS/11) were purchased from Hetero Drugs Limited (Hyderabad, India). Sodium carbonate (Na_2CO_3; MW 106), microcrystalline cellulose (Avicel® PH-102) and lactose were supplied by ACEF (Fiorenzuola d'Arda, PC, Italy). Heavy magnesium oxide (MgO) was purchased from Giusto Faravelli S.p.A. (Milan, Italy), croscarmellose sodium (Ac-Di-Sol®) was obtained from FMC BioPolymer (Philadelphia, PA, USA). Opadry® OY White and Eudragit L100-55 were supplied by Colorcon (Harleysville, PA, USA) and Evonik Pharma Polymers (Essen, Germany) respectively. All chemicals were pharmaceutical grade.

2.2. Methods

2.2.1. Tablet manufacturing

Powder blends (Table 1) were mixed in Turbula® for 15 min and tableted by direct compression on a tableting machine (EK, Korsh, Germany). Using the same formulation, 8 mm tablets (esomeprazole content 10 mg) and 2 mm tablets (1 mg per tablet) were manufactured.

In order to prepare delayed-release (DR) tablets, a portion of 2 mm esomeprazole IR tablets with Na_2CO_3 was film coated in a small rotating pan with an acid protective layer, using a dispersion of Opadry OY White (mixture of hydroxypropylmethyl cellulose, polyethylene glycol, talc and titanium dioxide) in 2-propanol/water (8:2 volume ratio). Then, a 5% (w/v) solution of Eudragit L100-55 in acetone/2-propanol/water (48.5:48.5:3 volume ratio) was applied over this film layer, until the coated tablets passed the gastro-resistance test according to Ph. Eur. specifications.

Table 1
Composition (% w/w) of esomeprazole immediate release tablets (IR).

	Tablet formulation		
	MgO	Na_2CO_3	Lactose
Esomeprazole magnesium $2H_2O$	11.5	8.1	11.5
Heavy MgO	83.8	–	–
Na_2CO_3	–	58.8	–
Lactose	–	–	83.8
AcDiSol®	4.7	3.7	4.7
Avicel® PH-102	–	29.4	–

2.2.2. In vitro drug release

USP dissolution apparatus IV with 12 mm diameter flow-through cell protected from light was employed for the IR and DR esomeprazole tablets. Simulated gastric fluid pH 1.2 without enzyme at 37 °C was used as dissolution medium for IR tablets, changing to phosphate buffer pH 6.8 after 2 h for DR tablets. The flow rate was set at 10 mL/min. At fixed time points, 10 mL samples were collected in a test tube containing 40 mL of borate buffer pH 11, Ph. Eur., to impair the drug acidic degradation. The samples were then filtered through a 0.45 μm membrane (CA 0.45 μm, LabService Analytica, Anzola dell'Emilia, BO, Italy) and analyzed by HPLC for the determination of esomeprazole content.

2.2.3. Esomeprazole tablet assay

An appropriate number of accurately weighed tablets were ground in a mortar. An amount of powder corresponding to the mean tablet weight (10 mg of ESO) was transferred to a 200 mL amber volumetric flask with 150 mL of Ph. Eur. borate buffer pH 11. The suspension was sonicated for 20 min, diluted to volume with borate buffer and filtered.

The ESO standard solution was prepared by transferring 11 mg of esomeprazole magnesium dihydrate standard powder (corresponding to 10 mg of esomeprazole) to a 200 mL amber volumetric flask with 10 mL of methanol, 10 mL of borate buffer pH 11 and 100 mL of distilled water. The suspension was sonicated until complete dissolution of the drug and then diluted to volume with distilled water.

The HPLC analysis was carried out using a Shimadzu Liquid Chromatograph LC-10AT apparatus with UV-VIS detector SPD-10 A set at 280 nm and a Supelcosil™ LC – 8 column 4.6 × 150 mm, 5 μm (Sigma-Aldrich, Buchs, Switzerland). The mobile phase was acetonitrile-phosphate buffer pH 7.6 (35:65) at 1.0 mL/min flow rate. The injection volume of the auto sampler (Model 542, ESA Inc., USA) was 20 μl. System suitability was assessed with the following results: theoretical plates 7033; peak symmetry 0.98; RSD 1.2% for 6 injections.

2.2.4. HPLC-MS/MS esomeprazole analysis in plasma

For the assay of esomeprazole in rat plasma, the HPLC–MS/MS method, reported by Hultman [14] and modified by Rossi [15], was adopted. Briefly, chromatographic separation was performed on an HP1200 Agilent LC system (Agilent Technologies, Santa Clara, CA, USA) equipped with an electrospray QTRAP 4000 mass spectrometer (AB SCIEX, Framingham, MA, USA). Separation was carried out using a Synergy Fusion C18 (50 × 2.1 mm, 4 μm) column (Phenomenex, Torrance, CA, USA) in the following conditions: mobile phase composed of 1 mL of formic acid, 100 mL of ammonium acetate 0.1 mol/L, 645 mL of degassed water pH 3.8, 200 mL of acetonitrile; flow-rate of 0.2 mL/min and injection volume of 5 μL. The mobile phase was filtered through a 0.45 μm cellulose membrane.

Solutions of esomeprazole magnesium dihydrate standard were freshly prepared before analysis by introducing an accurately weighed amount (5 mg) into a 10 mL volumetric flask, to which 8 mL of methanol was added. The flask was shaken until complete dissolution and brought to volume with methanol.

The Analyst software was used to control the system. Source parameters were optimized by infusion of esomeprazole standard solution (1 μg/mL): ESI voltage, 4.0 kV; declustering potential, 50 V; entrance potential, 10 V; source temperature, 350 °C. Quadrupoles were tuned to unit resolution. Full-scan mass spectra were acquired over the *m/z* 150–300 scan range, using a step size of 0.1 and a scan time of 2 ms. Production mass spectra of precursor ions ($[M + H]^+$) were recorded in the *m/z* 50–400 range, with collision-energy (CE) ramp ranging from 5 to 100 eV (medium nitrogen pressure). For quantitative purposes, experiments were performed under positive ion-selected reaction monitoring (PI-SRM) conditions using nitrogen as collision gas. The MRM transitions monitored were as follows: 346/180 (20 CE eV) and *m/z* 346/168 (30 CE eV) for esomeprazole.