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Research paper

Preparation, characterization, and in vivo anti-ulcer evaluation of pantoprazole-loaded microparticles

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Abstract

Pantoprazole is an important drug in the treatment of acid-related disorders. This work concerns the preparation and characterization of gastro-resistant pantoprazole-loaded microparticles prepared using an O/O emulsification/solvent evaporation technique. The in vivo activity of the pantoprazole-loaded Eudragit® S100 microparticles was carried out in rats. Furthermore, tablets containing the microparticles were also investigated. Microparticles presented spherical and smooth morphologies (SEM) and they remained intact in the inner surface of tablets. DSC and IR analyses showed that pantoprazole was physically and molecularly dispersed in the polymer. In vivo anti-ulcer evaluation showed that the microparticles were able to protect rat stomachs against ulcer formation, while the drug aqueous solution did not present activity. Drug dissolution profiles from tablets demonstrated slower release than untabletted microparticles. Weibull equation was the best model for describing the drug release profiles from microparticles and tablets. As regards the acid protection, tablets showed a satisfactory drug protection in acid medium ($61.05 \pm 8.09\%$ after 30 min).
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Keywords: Microparticles; Pantoprazole; Emulsification/solvent evaporation; Polymer; Gastric resistance; Tablet; Release profile; In vivo ulcer evaluation

1. Introduction

Pantoprazole is an important drug in the treatment of acid-related disorders [1] and it is also very effective against *Helicobacter pylori* infections alone or associated to other drugs, like metronidazole, clarithromycin or amoxicillin [2,3]. This drug was the first water-soluble benzimidazole, 5-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-benzimidazole (Fig. 1), which could be administered intravenously in the form of sodium pantoprazole sesquihydrate. In low pH values, pantoprazole turns into a cationic sulfenamide, which is its active form [2,4]. This drug accumulates in the highly acidic environment of the parietal-cell canalicular lumen and it is activated. The active form, a tetracyclic cationic sulfenamide, reacts with thiol group of cysteines 813 and 822 of the transmembranal H^+/K^+ATPase [1,5]. This conversion must occur inside the gastric parietal cells, so pantoprazole must be absorbed intact by gastrointestinal tract [2].

Pantoprazole has several advantages compared to its analogues (e.g., omeprazole and lansoprazole) such as specific site of binding, greater stability in neutral pH environment, and longer duration of action [6]. Besides, it presents no potential to induce or inhibit the CYP 450 [1,2,7]. It is a more selective inhibitor of acid secretion than other proton pump inhibitors [8].

Due to the necessity to pass intact through the stomach for reaching the duodenum for absorption, the pantoprazole is formulated as solution for intravenous administration (lyophilized powder for reconstitution) or as gastric-resistant tablets (oral delayed-release dosage form). In the case of oral administration, the enteric coating prevents

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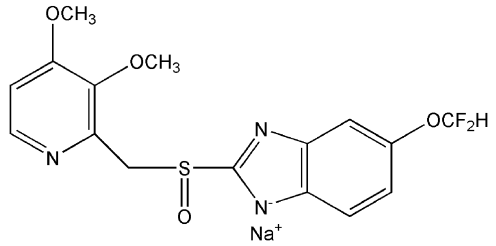

Fig. 1. Chemical structure of sodium pantoprazole.

pantoprazole from degradation in the gastric juice (at pH 1–2, pantoprazole degrades in few minutes) [9].

Up to now, no multiple-unit pharmaceutical dosage forms containing pantoprazole have been developed. As a general rule, the multiple-unit products show large and uniform distribution; they are less affected by pH and there is a minor risk of dose dumping [10]. Besides, these new drug delivery systems, as the polymeric microparticles, are also proposed to improve absorption, distribution, and bioavailability of acid labile drugs [11,12]. As they rapidly disperse in the gastrointestinal tract, they can maximize drug absorption, minimize side effects, and reduce variations in gastric emptying rates and intersubject variability [13].

The emulsification/solvent evaporation is a technique very well described in the literature [10,14] to prepare polymeric microparticles, which are useful for stabilizing drugs and to improve their distribution. This technique is an easy method, compatible with several polymers [15], and it is suitable for encapsulating both lipophilic and hydrophilic drugs [11]. Another advantage is the possibility of producing microparticles with a wide range of sizes, porosities, and shapes [16].

Eudragit® S100 is a gastro-resistant polymer used for colonic delivery, protecting drugs from pH of upper gastrointestinal tract [17]. This polymer is an anionic copolymer formed by methacrylic acid and methyl methacrylate (ratio 1:2). It is insoluble in acids and pure water, whereas it is soluble in aqueous solution presenting pH higher than 7 [18]. Microparticles prepared with this polymer can be tabletted, offering the advantages of the particulate-controlled release dosage forms [19].

Taking all the above into account, this study concerns the characterization of gastro-resistant microparticles containing sodium pantoprazole prepared using an O/O emulsification/solvent evaporation technique. Furthermore, the present study is devoted to evaluate the in vivo activity of the pantoprazole-loaded Eudragit® S100 microparticles. Additionally, tablets containing the pantoprazole microparticles were also prepared and characterized.

2. Methods

2.1. Materials

Pantoprazole sodium sesquihydrate was obtained from Henrifarma (São Paulo, Brazil). Eudragit® S100 was kindly given by Almapal® (São Paulo, Brazil produced by Rohm®, Germany). Sorbitan monooleate was obtained from Lipo Chemicals (New Jersey, USA) and mineral oil, USP grade, obtained from Fraccionata (Porto Alegre, Brazil). Acetonitrile, HPLC grade, was obtained from Fisher Chemicals (New Jersey, USA). All other chemicals were of analytical grade.

2.2. Preparation of microparticles

After dissolving the Eudragit® S100 (750 mg) in acetone (80 mL), pantoprazole sodium sesquihydrate (350 mg) was added. This suspension was emulsified (1000 rpm) with mineral oil (350 mL) containing sorbitan monooleate (1500 mg). The O/O emulsion was mechanically stirred for 2.5 h to remove the acetone. The microparticles were collected by vacuum filtration, washed with cyclohexane (2× 50 mL), and kept overnight in a desiccator.

2.3. Characterization of microparticles

2.3.1. Drug loading

An amount of the microparticles, equivalent to 10 mg of pantoprazole, was weighed and stirred with 40 mL of 0.05 M NaOH for 12 h. The volume was completed to 50 mL and drug concentration was determined after filtration (0.45 μm, Millipore®) by HPLC (Perkin-Elmer series 200; UV detector, $\lambda = 290$ nm, Shelton, USA), using a Waters® Nova Pak® column C_{18} (3.9×150 mm). Mobile phase consisted of acetonitrile/phosphate buffer, pH 7.4 (35:65 v/v).

HPLC method for pantoprazole quantification was validated [20]. Linearity (coefficient correlation) presented values higher than 0.99. The accuracy was $105 \pm 1\%$, the repeatability presented a RSD = 0.47, and the intermediate precision showed a RSD = 1.17. The detection limit was 0.5 μg/mL. To determine the reproducibility of the method and the drug purity, a liquid chromatographic system Shimadzu (LC-10ADVP, Kyoto, Japan) with a Diode Array Detector (SPD-M10AVP) was used.

2.3.2. Optical and electronic microscopies

The shape and the surface of the microparticles were analyzed by optical microscopy (Olympus®, Model BX-41, coupled with a photographic camera, Olympus®, Model PM-20, Tokyo, Japan) and scanning electronic microscopy (SEM) (Jeol Scanning Microscope JSM-5800®, Japan).

For optical microscopy analyses, samples were suspended in mineral oil. The SEM analyses were carried out using an accelerating voltage of 20 kV after they were gold sputtered (Jeol Jee 4B SVG-IN®, Peabody, USA).

2.3.3. Determination of surface area and pore diameter

The nitrogen adsorption–desorption isotherms of previous degassed organic solids, under vacuum at 40 °C, were determined at liquid nitrogen boiling point in a homemade

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