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ORIGINAL ARTICLE

Design and evaluation of gastroretentive levofloxacin floating mini-tablets-in-capsule system for eradication of *Helicobacter pylori*

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Abstract Gastroretentive levofloxacin (LVF) floating mini-tablets for the eradication of *Helicobacter pylori* (*H. pylori*) were prepared using the matrix forming polymer hydroxypropyl methylcellulose (HPMC K100M), alone or with Carbopol 940P in different ratios by wet granulation technique. Buoyancy of mini-tablets was achieved by an addition of an effervescent mixture consisting of sodium bicarbonate and anhydrous citric acid to some formulations. The prepared mini-tablets were evaluated for weight variation, thickness, friability, hardness, drug content, *in vitro* buoyancy, water uptake and *in vitro* release. The optimized formula was subjected to further studies: FT-IR, DSC analysis and *in vivo* examination in healthy volunteers. The prepared mini-tablets exhibited satisfactory physicochemical characteristics. Incorporation of gas-generating agent improved the floating parameters. HPMC K100M mini-tablet formulation (F1) offered the best controlled drug release (>8 h) along with floating lag time <1 s and total floating time >24 h. The obtained DSC thermograms and FT-IR charts indicated that there is no positive evidence for the interaction between LVF and ingredients of the optimized formula. The *in vivo* test

Abbreviations: LVF, levofloxacin; *H. pylori*, *Helicobacter pylori*; HPMC, hydroxypropyl methylcellulose; FT-IR, Fourier transform infrared spectroscopy; DSC, differential scanning calorimetry; PVP, polyvinyl pyrrolidone; SI, swelling index

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confirmed the success of the optimized formula F1 in being retained in the stomach of the volunteers for more than 4 h. LVF floating mini-tablets based on HPMC K100M is a promising formulation for eradication of *H. pylori*.

1. Introduction

Helicobacter pylori (*H. pylori*) infection is the causative organism in chronic active gastritis, duodenal ulcers and gastric adenocarcinoma (Khalifa et al., 2010). This bacterium is highly adapted for colonization in the human stomach, the majority of these bacteria are free living in the gastric mucus layer although about 20% is in close contact with epithelial cells (Hessey et al., 1990). Antimicrobial resistance, patient's poor compliance with the antibiotic regimen, and drug-related side effects are said to be the major problems with eradication of *H. pylori* (Vakil, 2005). Levofloxacin (LVF) is a broad spectrum third-generation fluoroquinolone antibiotic (Kassab et al., 2010). Some studies have demonstrated that LVF has a remarkable *in vitro* activity against *H. pylori* when its strains are resistant to clarithromycin and metronidazole (Antos et al., 2006). These favorable results have been confirmed *in vivo*, indicating that most of the patients with both metronidazole and clarithromycin resistance are cured with the LVF-based regimen. LVF has shown promising results in different first-line triple regimens in several countries, with an eradication rate ranging from 72% to 96% (Gisbert and Pajares, 2010).

Complete eradication of *H. pylori* requires high concentrations of antibiotics to be maintained within gastric mucosa for prolonged period of time (Nayak et al., 2010). This approach can be achieved by preparing gastroretentive dosage forms that ensure prolonged drug release near the ecological niche of the bacterium (Bardonnet et al., 2006).

Floating drug delivery systems are those systems having a bulk density less than that of the gastric fluids and thus these systems remain buoyant for a prolonged period of time in the stomach without being affected by the gastric emptying rate. The drug is released slowly at the desired rate from the system and after release of the drug; the residual system is emptied from the stomach (Sharma et al., 2011). Most of the floating systems previously reported are single unit systems such as tablets and capsules. Multiple unit floating drug delivery systems, such as pellets or mini-tablets, show several advantages over monolithic ones, which include avoiding all or nothing emptying, more predictable drug release kinetics, less chance of localized mucosal damage and administration of units with different release profiles or containing incompatible substances (Ishak et al., 2007; Christian et al., 2011). Mini-tablets offer an alternative for pellets because of their relative ease of manufacturing. In addition, they offer dosage forms of equal dimensions and weight with smooth regular surface that could be obtained in a reproducible and continuous way. Mini-tablets could be either filled into hard capsules or compacted into bigger tablets (Lopes et al., 2006). In the present study, gastroretentive floating LVF mini-tablets, for the eradication of *H. pylori* were prepared and evaluated.

2. Materials and methods

2.1. Materials

Levofloxacin hemihydrate antibiotic (Zhejiang Apeloa Kangyu Pharmaceutical Co., Ltd., China). Methocel™ K100M Premium DC (Hydroxypropyl methyl cellulose), with an apparent viscosity 75,000–140,000 mPa s for a 2% solution in water at 20 °C (The Dow Chemical Company and Colorcon, Inc., USA). Carbopol® 940 NF polymer, with viscosity 40,000–60,000 mPa s (0.5% mucilage at 25 °C) (Lubrizol Advanced Materials, Inc., Calvert City, KY, USA). Barium sulfate for oral and rectal use (Commercial Firm for Chemicals and Pharmacies Supply, Turkey). Levoxin® (Amoun Pharmaceutical Co., Egypt). All other chemicals and solvents were of analytical grade.

2.2. Preparation of mini-tablets by wet granulation technique

Composition of mini-tablet formulations is listed in Table 1. All ingredients were weighed, and mixed using the geometric dilution technique except magnesium stearate. The mixture was granulated using isopropyl alcohol. Polyvinyl pyrrolidone (PVP) was added as a binder to the granulating solvent by 5% whenever needed. The obtained dough mass was passed through 1.4 mm mesh sieve to prepare the granules. The granules were dried at 60 °C in the thermostatic hot air oven. Dried granules were ground in a mortar and then sieved. Granules that passed sieve No. 45 (355 μm) were used. Magnesium stearate was then added as 2%. Mini-tablets, weighing 50 mg, were obtained using a single punch tablet press fitted with a 4 mm diameter concave punch. Each dose comprised 14 mini-tablets which are equivalent to 250 mg LVF.

2.3. Evaluation of the pre-compression parameters of powder mixtures

Pre-compression parameters: bulk density, tapped density, angle of repose, Carr's index and Hausner's ratio (Hadi et al., 2012), were measured.

2.4. Evaluation of the post-compression parameters of LVF mini-tablets

Compressed mini-tablets were characterized for weight variation, crushing strength, diameter, thickness and friability as follows:

2.4.1. Weight variation of mini-tablets

The weight variation test was conducted by weighing 20 randomly selected mini-tablets individually (Rao et al., 2012). The average weight and standard deviation were calculated.