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SHORT COMMUNICATION

Assessment of the pharmaceutical quality of marketed enteric coated pantoprazole sodium sesquihydrate products

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Abstract Pantoprazole sodium sesquihydrate (PSS) is a proton pump inhibitor, used in acid-related disorders, like peptic ulcer and gastroesophageal reflux. Increasing the number of pantoprazole containing products in the market, raises questions of its efficacy and generic substitution. The pharmaceutical quality of 6 generic PSS enteric coated tablets in 2 local markets was assessed relative to the innovator product (pantozol®). Uniformity of dosage unit, disintegration and in vitro drug release were determined using United States pharmacopeia for delayed release tablets. The similarity factor (f2) was assessed using the FDA recommended approach (f2 similarity factor). The content uniformity of the innovator product was 98.39% of the labeled claim with RSD value of 1.08%, while the content of generic products ranged from 96.98% to 98.80% with RSD values of 1.24–2.19%. All the products showed no disintegration, cracks or swelling in 0.1 N HCl, except product 1, which showed complete disintegration after 20 min. However, the disintegration of all the products in phosphate buffer met USP requirements. Dissolution of tablets in 0.1 N HCl showed no drug release after 2 h except product 1 in which one tablet showed a drug release more than 10% at acid stage level A1. In addition, three tablets of this product showed dissolution of 45%, 48% and 69% at acid stage level A2. The similarity factor f2 of the products was between 71 and 74 indicating the similarity in dissolution profiles of all the products in accordance to FDA requirements, except product 1 in which f2 value was 18.67.

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1. Introduction

A generic drug is identical, or bioequivalent to a brand name drug in dosage form, safety, strength, route of administration, quality, performance characteristics and intended use. Although generic drugs are chemically identical to their branded counterparts, they are typically sold at substantial discounts from the branded price (Office of Generic Drugs, 2009). Drug companies must submit an abbreviated new drug application (ANDA) for approval to market a generic product. The ANDA process does not require the drug sponsor to repeat

costly animal and clinical research on ingredients or dosage forms already approved for safety and effectiveness (Office of Generic Drugs, 2009). To gain FDA approval, a generic drug must: contain the same active ingredients as the innovator drug, be identical in strength, dosage form, and route of administration, have the same use indications, be bioequivalent, meet the same batch requirements for identity, strength, purity, and quality and be manufactured under the same strict standards of FDA's good manufacturing practice regulations required for innovator products (Dighe, 1999; Meyer, 1999).

As defined in the USP, delayed-release drug products are dosage forms that release the drugs at a time later than immediately after administration (i.e., these drug products exhibit a lag time in quantifiable plasma concentrations). Typically, coatings (e.g., enteric coatings) are intended to delay the release of medication until the dosage form has passed through the acidic medium of the stomach (United States Pharmacopeia & National Formulary, 2004). A major aim of enteric coating is the protection of drugs that are sensitive or unstable at acidic pH (Liu et al., 2009; Brogmann and Beckert, 2001). This is particularly important for drugs such as enzymes (Keller et al., 2009) and proteins (Brogmann and Beckert, 2001), because these macromolecules are rapidly hydrolyzed and inactivated in acidic medium. Antibiotics are also rapidly degraded by gastric juices (Skinner et al., 1993; Bersanetti et al., 2005). Others, such as acidic drugs like NSAID's (e.g., diclofenac, valproic acid, or acetylsalicylic acid) need to be enteric coated to prevent local irritation of the stomach mucosa (Todd and Sorkin, 1988).

Pantoprazole, 5-(difluoromethoxy)-2-[(3,4-dimethoxypyridin-2-yl)methylsulfinyl]-3H-benzoimidazole, is a substituted benzimidazole derivative that inhibits gastric acid secretion by irreversibly binding the proton pump (H^+/K^+-ATPase) in the gastric parietal cells (Jungnickel, 2000). It is used for the treatment of gastrointestinal conditions particularly peptic ulceration, Zollinger–Ellison syndrome and reflux esophagitis (Cheer et al., 2003) and it is also very effective against *Helicobacter pylori* infections alone or associated to other drugs, like metronidazole, clarithromycin or amoxicillin (Cheer et al., 2003; Poole, 2001). Pantoprazole is unstable at low pH values. The highest stability of this drug is achieved at a pH value higher than 5.5. Therefore, Pantoprazole is commercially formulated as enteric coated tablets or capsules (Badwan et al., 2002).

The aim of this work was to compare the enteric efficacy of six generic products of coated pantoprazole sodium sesquihydrate Tablets in 2 local markets with the innovator product, and to evaluate these products according to United States pharmacopeia and food and drug administration guidelines.

2. Materials and methods

2.1. Materials

Tribasic sodium phosphate and Sodium hydroxide were purchased from E. Merck AB, Stockholm, Sweden. Hydrochloric acid 37% was supplied by BDH Laboratory Supplies, England. The innovator product (pantozol® (20.0 mg pantoprazole), Altana, Germany) and 6 generic pantoprazole sodium sesquihydrate enteric coated tablets were purchased from 2 local markets.

2.2. Methods

2.2.1. Tablet weight variation

Twenty tablets from each product were individually weighed on an analytical balance (Mettler, Switzerland). The average weight and relative standard deviation were reported.

2.2.2. Tablet thickness

The thickness was measured individually for 10 preweighed tablets by using a portable dial hand micrometer (Starrett, USA). The average, standard deviation and relative standard variation were reported.

2.2.3. Uniformity of dosage unit

Pantoprazole content was assessed according to the USP 27 requirements for content uniformity. Pantoprazole tablets were examined using UV Spectrophotometer (Labomed, Inc, USA), wavelength 295 nm. Individual tablets were placed in 100 ml volumetric flask and 70 ml of 0.1 N NaOH was added and the dispersion was sonicated to dissolve the tablet and then the volume was completed to 100 ml with 0.1 N NaOH. Five ml of the previously mentioned solution was placed in a 100 ml volumetric flask and the volume was completed with the same solvent.

2.2.4. Tablet disintegration

Disintegration of tablets was performed according to USP 27 "Disintegration Test" for delayed release dosage forms using a disintegration tester (Electrolab, India). A minimum of 6 tablets of each product were tested. One tablet of each product was placed in each of the six tubes of the basket. Then the apparatus was operated using 1 l of 0.1 N HCl maintained at 37 ± 2 °C for 1 h and using 1 l of 0.05 M phosphate buffer, pH 6.8, maintained at 37 ± 2 °C, for 30 min.

2.2.5. In vitro release studies

In vitro drug release was performed for the tablets according to the USP 27 "Dissolution procedure" for delayed release dosage forms. A minimum of 6 tablets of each product were tested. The dissolution of pantoprazole from the enteric coated tablets was monitored using an automated dissolution tester (LOGAN Instrument Corp, Somerset, NJ, USA) coupled to an automated sample collector (SP-100 peristaltic pump, Somerset, NJ, USA). The USP 27 (apparatus 2) paddle method was used at 75 rpm. The media used was 0.1 N HCl at a pH 1.2 and a volume of 750 ml for the first 2 h after which 250 ml of 0.2 M sodium phosphate, tribasic, was added to give a final pH of 6.8 and maintained at 37 ± 0.5 °C.

Pantoprazole release from each tablet (in the dissolution samples) was determined by UV spectrophotometer (UV-1800, Shimadzu, Tyoto, Japan) at WV 290 nm. Dissolution profiles for each product were compared to the innovator to determine the enteric coating efficacy of the generic products. The dissolution similarity was assessed using the FDA recommended approach (f2 similarity factor). The similarity factor is a logarithmic, reciprocal square root transformation of the sum of squared errors, and it serves as a measure of the similarity of two respective dissolution profiles:

$$f2 = 50\log\{[1 + 1/n\sum_{t=1}^{n}(RT - Tt)2] = 0.5.100\}$$