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The effect of the composition of a fixed dose combination on bioequivalence results

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ABSTRACT

The purpose of this work was to develop a new supergeneric product Meloxicam/Omeprazole. Such a combination brings a benefit in terms of decreasing side effects for the patients using meloxicam. The new combination is composed of a meloxicam powder blend (MPB) and omeprazole gastro-resistant pellets (OAP) in hard gelatin capsules. The main tasks were to select the excipients to keep the functional layer of OAP active and to prove the bioequivalence to the original products of meloxicam tablets together with omeprazole capsules. Although dissolution profiles similar to the original product were obtained, the unexpected results of omeprazole low bioavailability in the fed bioequivalence study (BES I) showed the necessity to investigate the formulation in greater depth. A modified more complex dissolution method was developed in order to understand the release of omeprazole under gastric conditions. This method revealed the degradation of omeprazole in the formulation when exposed to the fed conditions because of the increase in microenvironmental pH in the capsule caused by trisodium citrate, commonly used for improving solubility of meloxicam. This pH increase dissolved the gastro-resistant layer of OAP and caused the chemical degradation. To prevent this effect, a trisodium citrate-free formulation was developed. Reformulated capsules passed the repeated fed bioequivalence study (BES II).

1. Introduction

Fixed dose combinations (FDC) of drugs are very common for almost all therapeutic areas. Many different types are commercially available and the market shows a continuous growth of these products. There is a possibility to combine more active pharmaceutical ingredients (API) with different modes of pharmacological actions in a single dosing unit and thus optimize the treatment. The majority of the FDCs is composed of two API, some of them contain three and only some units have four API (Desai et al., 2013).

The frequented groups of diseases with an authorized indication of FDC are diabetes, HIV, cardiovascular diseases and some unspecified illnesses (Koo, 2010). The development of such FDC is useful in the management of these chronical diseases and support programs are usually submitted in the EU using the Article 10b of 2001/83/EC and in the US by the 505(b)(2) NDA route. An important developing group of FDC are oral dosage forms (Pudipeddi, 2010). The WHO Technical report No. 929, 2005 summarizes the principles of registration of FDC drugs used in medicinal prescription only. The development of FDC consisting of already registered medicinal products aims to show that these new formulations are bioequivalent to single-component drugs that are marketed (Guideline on clinical development of fixed combination medicinal products, 2017).

Non-steroidal anti-inflammatory drugs (NSAIDs) are frequently used for the treatment of chronic illnesses. Their indication is an inflammation and long term pain when dealing with arthritis, osteoarthritis and ankylosing spondylitis. Adverse gastrointestinal effects of NSAID, including inflammation, are bleeding, ulceration and perforation of the stomach, the small intestine and the large intestine – gastroenteropathy in short. NSAIDs reduce the inflammation by the inhibition of the prostaglandin enzyme cyclooxygenase (COX)-2. However, the inhibition of COX-1 enzyme leads to the inhibition of

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prostaglandins which have a protective effect on the gastric mucus layer. Additionally, most of the NSAIDs are weak acids and therefore have topical negative effects on gastric mucus (Gigante and Tagarro, 2012). Co-administration with proton pump inhibitors (PPI) which affect the final step of gastric acid production, reduce gastric acidity and therefore reduce the adverse effects caused by NSAIDs are very rational and this approach is described in the literature (Datto et al., 2013). A suitable drug is omeprazole, which is mainly used in the treatment of dyspepsia and peptic ulcer disease (Lanza et al., 2009; Engelhardt, 1996). In this study we describe the development of a new combination product of the NSAID meloxicam and the proton pump inhibitor omeprazole. Forming such products is very critical in terms of manufacturability and stability together with the capability to prove the required efficacy of drugs. In this case, APIs are chemically incompatible. NSAIDs like meloxicam are the acidic substances with pKA 3–5 (Luger et al., 1996) and proton pump inhibitors like omeprazole in acidic conditions below pH 5.0 rapidly degrade into two therapeutically ineffective species – sulphenic acid and sulphonamide. Due to this fact, the oral dosage forms of omeprazole must also be enterically coated. (Migoha et al., 2015; Storpirtis and Rodrigues, 1998; Li et al., 2013). For this reason it is absolutely necessary to find an enteric dosage form which allows isolating both APIs. For the preparation of such oral dosage forms, pharmaceutical technology offers especially multi-unit pellet systems (MUPS) and multilayer systems (MLS) (Desai et al., 2013). In terms of difficulty and availability with taking into account the original products, MUPS were selected notwithstanding a kind of modification where the compression was avoided. Starting materials for our combination product were the omeprazole pellets with an enteric layer (OAP) and meloxicam active ingredient in a powder blend (MPB). Handling with OAP during the preparation of the final dosage form with MPB, the retention of the proper function of the enteric layer was needed to be taken into consideration. MUPS are generally composed of pellets and a powder blend ready for tableting. Compression is in our case risky due to the possible damage of the coating layer caused by the negative effect of mechanical stress during the compression process, which is referred to in the literature (Abdul et al., 2010). The compression of coated pellets is challenging since ideally the compression should not have any effect on the individual behavior of pellet units (Dashevsky et al., 2004). The additional selection of tablet excipients improving the compression process, a sufficient degree of pellet plasticity, optimization of coating and the choice of an appropriate tablet shape are usually the additional technological requirements in order to develop multi-unit tablets containing coated pellets (Bodmeier, 1997; Dreu et al., 2011). To avoid a possible mechanical damage of the pellet layer and a consequent lower drug product efficacy, the hard gelatin capsules as a final dosage form were selected. The aim of this study was to prepare a fixed-dose combination of MPB/OAP in the form of hard gelatin capsules so that they successfully pass a bioequivalence study compared to the individual tablets/capsules of the reference product Losec® and Mobic® taken concomitantly.

2. Materials and methods

2.1. Materials

We purchased the required materials from the following suppliers: meloxicam from SUN Pharmaceutical Industries Ltd., (India), trisodium citrate from Jungbunzlauer Ladenburg (Germany), lactose monohydrate (Flowlac®) from Meggle (Germany), cellulose microcrystalline (Comprecel® M 102) from Mingtai (Taiwan), silica colloidal anhydrous (Aerosil® 200) from Evonik (Germany), crospovidone (Polyplasdone®) from ISP (Switzerland), magnesium stearate from Peter Greven (the Netherlands), omeprazole from Cadilla Healthcare Limited (India), lactose anhydrous from Domo (UK), sodium laurylsulphate from TensaChem (Belgium), disodium phosphate dodecahydrate from Jiangsu (China), hypromellose 2910/6 (Pharmacoat® 606) from Shin-Etsu (Germany), hydroxypropylcellulose (Klucel® EF Pharm) from Ashland (USA), sugar spheres (Suglets 850–1000 μm ®) from Colorcon (USA), macrogol from Croda (France), methacrylic acid – ethylacrylate copolymer (Eudragit® L30-D55) from Evonik (Germany), talc from Luzenac Pharma (Italy), and hard gelatinous capsules size 0 (type Coni-Snap) from Capsugel (Belgium).

2.2. Methods

2.2.1. Preparation of MPB

Meloxicam together with trisodium citrate were pre-blended in a Turbula homogenizer (T 10B, Willy A. Bachofen AG, Maschinenfabrik, Basel/Switzerland) for 5 min with 30 rotations per minute. The mixture was then sieved manually through a 0.63 mm sieve and blended again under the same conditions of 30 rpm for 10 min. Lactose monohydrate, cellulose microcrystalline, silica colloidal anhydrous and crospovidone were sieved through 1.0 mm on Frewit MS-LAB (Frewit SA, Switzerland) and then blended for 20 min with 30 rpm together with a mixture of meloxicam and trisodium citrate. Finally, magnesium stearate was added for the final 2 min of homogenization in the Turbula with 30 rpm. The batch size corresponded to 25 kg of powder blend and the quantitative composition complied to batch T1, Table 1.

Reformulated MPB citrate free (batch T2, Table 1) was produced in the same way only with one exception. Trisodium citrate was substituted with a part of lactosum monohydrate corresponding to one quarter of its whole amount in the pre-blending phase.

2.2.2. Preparation of OAP

Production of OAP is composed of three main steps – active coating (I), protective coating (II) and enteric coating (III). The suspension for active coating (I) was produced from two parts (IA and IB). The first one (IA) was the suspension of omeprazole, lactose anhydrous, sodium laurylsulphate and disodium phosphate dodecahydrate obtained by mixing all the components in purified water. The second one (IB) was a solution of hypromellose 2910/6 corresponding to one fifth of the whole amount and hydroxypropylcellulose produced by dispersing in hot purified water around 80 °C and subsequent cooling altogether for almost 3 h. These two parts (IA + IB) were mixed and used for coating inactive sugar spheres. Inactive spheres were preheated in 45 °C for around 5 min and then the active coating suspension was sprayed in a Wurster fluid-bed coater (CPCG 120 with 32″ Wurster, Glatt, Italy). The product temperature did not exceed 45 °C. The pellets were afterwards dried in the same equipment for approximately 30 min in temperatures below 45 °C. The second step, protective coating (II), was started by preparing the solution used for spraying. This solution was prepared by dispersing the rest of the hypromellose 2910/6 in hot purified water (60–80 °C) and subsequent cooling for almost 3 h. After spraying of the isolation layer on the pellets coated by the active layer, additional drying took place with temperatures below 45 °C and was applied for approximately 30 min. The last step, enteric coating (III), was started by preparing the dispersion. Firstly, macrogol was dissolved in purified water for 20 min (IIIA) and secondly the dispersion of purified water and Methacrylic acid – ethylacrylate copolymer Eudragit® L30-D55 was prepared by mixing them together for 10 min (IIIB). Parts IIIA and IIIB were mixed for 2 h and then the spraying started. All three parts of OAP coatings (I-III) were produced in mixing vessels (Ipros, Slovenia).

Spraying was done in all the steps (I–III) by using the spraying nozzles 1.8 mm and a spraying air pressure of 2 bars.