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Short communication

Identification, isolation and characterization of new impurity in rabeprazole sodium

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ABSTRACT

Rabeprazole sodium [1] is a proton pump inhibitor, used as an antiulcerative. During the manufacturing of rabeprazole sodium, we observed an unknown impurity at levels 0.05–0.1% in HPLC analysis along with the known potential impurities. This new unknown impurity was isolated using preparative liquid chromatography. Based on the complete spectral analysis (^{1}H NMR, ^{13}C NMR, DEPT, Mass and IR), this new impurity was designated as 2-[[(3-methyl-4-(methylthio)-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole (methylthio impurity of rabeprazole). Impurity isolation, structure elucidation and probable formation mechanism was discussed.

1. Introduction

Rabeprazole sodium [1], chemically known as 2-[[(4-(3-methoxypropoxy)-3-methyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole, is a proton pump inhibitor and used as an antiulcerative. Several analytical methods have been reported in the literature for the determination of rabeprazole and its impurities [2–6]. During the preparation of rabeprazole sodium [7,8] (Fig. 1) one unknown impurity was detected consistently in HPLC analysis along with the potential known impurities (Fig. 2). The HPLC analysis of rabeprazole sample has been performed and described as in Section 2.2. As per regulatory requirement [9], new impurity present above 0.10% level in the drug substance need to be identified and characterized.

2. Experimental

2.1. Samples

The investigated samples of rabeprazole and known impurities were prepared in APL Research Centre (A unit of Aurobindo Pharma Limited, Hyderabad, India). Reagents used for analysis, i.e., ammonium acetate (AR grade), methanol (HPLC grade) and acetonitrile (HPLC grade) were obtained from Merck (India) Limited. Milli-Q grade water was used.

2.2. High performance liquid chromatography (analytical)

A Waters 2695 separation module equipped with 2996 photo diode array detector with Empower pro data handling system (Waters Corporation, Milford, MA, USA) was used. The analysis was carried out on YMC C8, 150 mm long, 4.6 mm i.d., and 5-μm particle size column. Mobile phase A consists a phosphate buffer (pH 7.6 ± 0.05) and acetonitrile in the ratio of 98:2 (v/v). The phosphate buffer was prepared by dissolving 3.2 g of dipotassium hydrogen phosphate and 0.85 g of potassium dihydrogen phosphate in 1000 mL of water and solution pH was adjusted to 7.6 ± 0.05 with 5N potassium hydroxide solution. Mobile phase B was acetonitrile. UV detection was at (set) 284 nm and flow rate 1.0 mL/min. Data acquisition time was 40 min. The gradient program as follows: time (min)/A (v/v):B (v/v); $T_{0.01}$/90:10, $T_{10.0}$/80:20, $T_{25.0}$/65:25, $T_{30.0}$/50:50, $T_{40.0}$/25:75, $T_{42.0}$/10:90, and $T_{50.0}$/10:90.

2.3. Isolation of impurity (methylthio impurity) by preparative HPLC

A Shimadzu LC-8A Preparative Liquid Chromatograph equipped with SPD-10A VP, UV–Vis detector (Shimadzu Corporation, Analytical Instruments Division, Japan), Symmetry C18 (250 mm long × 19 mm i.d.) preparative column packed with 7 μm parti-

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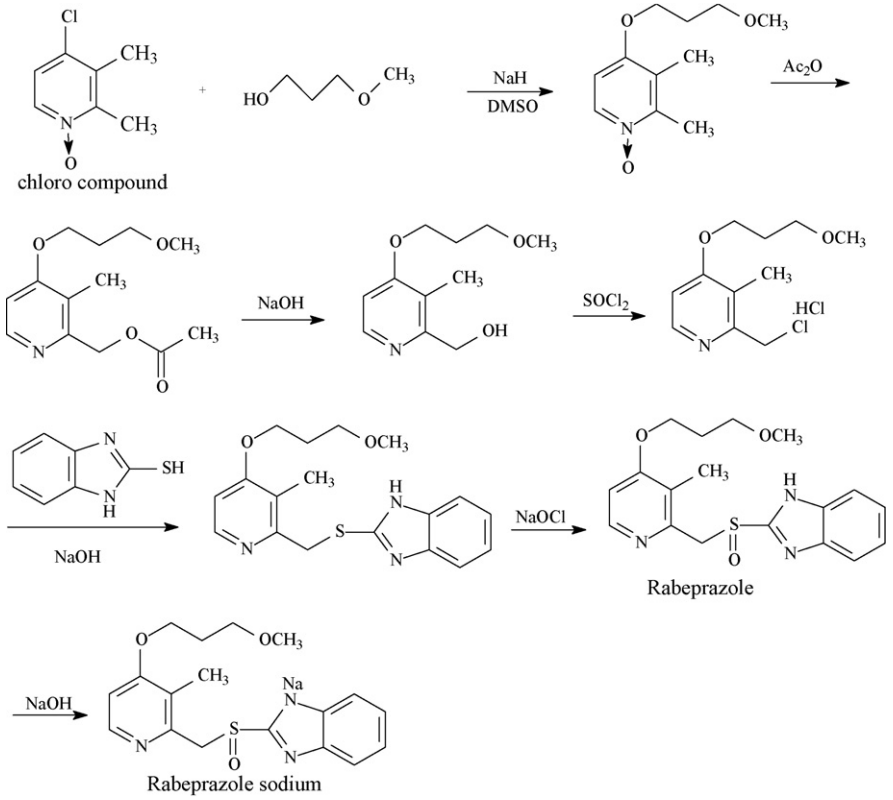

Fig. 1. Scheme for the synthesis of rabeprazole sodium.

cle size (Waters, USA) was used for isolation of new impurity. The mobile phase of (A) 0.1 M ammonium acetate solution and (B) methanol and acetonitrile are in the ratio of 70:30. Flow rate was kept at 20 mL/min and detection was carried out at 284 nm. The gradient program was as follows: time (min)/A (v/v):B (v/v); $T_{0-0.01}$/100% A; $T_{0.01-50}$/95% A: 5% of 75:25 B; T_{50-80}/90% A: 10% of 70:30 B; T_{80-100}/50% A: 50% of 30:70 B; $T_{100-110}$/100% A. Rabeprazole sodium samples containing the new impurity at ~0.1% level (determined by the method given in Section 2.2) were dissolved at 50 mg/mL in the mobile phase for the preparative HPLC. Injection volume is 10 mL. Peak cut criteria was set based on peak retention time. Fractions >95% purity were pooled together and concentrated by rotavapour to remove solvents. Concentrated fraction was passed through the preparative HPLC column using water as

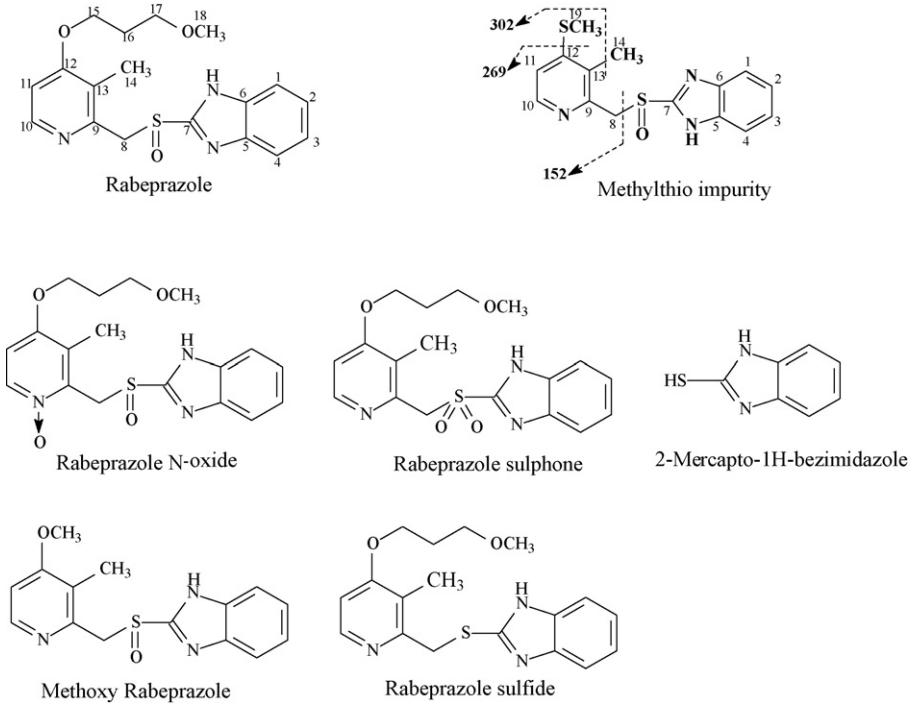

Fig. 2. Chemical structures of rabeprazole impurities.