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(54) Title: NOVEL FORM OF *S*OMEPRAZOLE

(57) Abstract

The present invention relates to a novel form of the (–)–enantiomer of 5–methoxy–2– [[(4–methoxy–3,5–dimethyl–2–pyridinyl)–methyl]sulfinyl]–1H–benzimidazole, i.e *S*–omeprazole. More specifically, it relates to a novel form of the magnesium salt of the *S*–enantiomer of omeprazole trihydrate. The present invention also relates to processes for preparing such a form of the magnesium salt of *S*–omeprazole and pharmaceutical compositions containing it. Furthermore, the present invention also relates to new intermediates used in the process.

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NOVEL FORM OF *S*-OMEPRAZOLE

Field of the Invention

The present invention relates to a novel form of the (-)-enantiomer of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole, *i.e.* *S*-omeprazole. More specifically, it relates to a novel form of the magnesium salt of the *S*-enantiomer of omeprazole trihydrate. The present invention also relates to processes for preparing such a form of the magnesium salt of *S*-omeprazole and pharmaceutical compositions containing it. Furthermore, the present invention also relates to intermediates used in the process, and their preparation.

Background of the invention and prior art

The compound 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, having the generic name omeprazole, and therapeutically acceptable salts thereof, are described in EP 5129. The specific alkaline salts of omeprazole are disclosed in EP 124 495. Omeprazole is a proton pump inhibitor, i.e. effective in inhibiting gastric acid secretion, and is useful as an antiulcer agent. In a more general sense, omeprazole may be used for prevention and treatment of gastric-acid related diseases in mammals and especially in man.

Omeprazole is a sulfoxide and a chiral compound, wherein the sulfur atom being the stereogenic center. Thus, omeprazole is a racemic mixture of its two single enantiomers, the *R* and *S*-enantiomer of omeprazole, herein referred to as *R*-omeprazole and *S*-omeprazole. The absolute configurations of the enantiomers of omeprazole have been determined by an X-ray study of an N-alkylated derivative of the (+)-enantiomer in non-salt form. The (+)-enantiomer of the non-salt form and the (-)-enantiomer of the non-salt form were found to have *R* and *S* configuration, respectively, and the (+)-enantiomer of the magnesium salt and the (-)-enantiomer of the magnesium salt were also found to have *R*

and *S* configuration, respectively. The conditions for the optical rotation measurement for each of these enantiomers are described in WO 94/27988.

Certain salts of single enantiomers of omeprazole and their preparation are disclosed in WO 94/27988. These compounds have improved pharmacokinetic and metabolic properties which will give an improved therapeutic profile such as a lower degree of interindividual variation.

WO 96/02535 discloses a process for the preparation of the single enantiomers of omeprazole and salts thereof, and WO 96/01623 discloses a suitable tableted dosage forms of for instance magnesium salts of *R*- and *S*-omeprazole.

Brief description of the drawings

Figure 1 shows a X-ray powder diffractogram of the magnesium salt of *S*-omeprazole trihydrate prepared according to the present invention.

Figure 2 shows a X-ray powder diffractogram of the potassium salt of *S*-omeprazole prepared and used in the present application (See examples 2 and 3)

Figure 3 shows a X-ray powder diffractogram of a magnesium salt of *S*-omeprazole dihydrate prepared and used in the present application (See example 5)

Figure 4 shows a X-ray powder diffractogram of a magnesium salt of *S*-omeprazole dihydrate which is a polymorph of the dihydrate shown in Figure 3 (See Example 6). This magnesium salt of *S*-omeprazole dihydrate has been prepared and can be used in the preparation of the magnesium salt of *S*-omeprazole trihydrate according to the present invention.

Figure 5 shows X-ray powder diffractogram of the magnesium salt of *S*-omeprazole prepared according to example A in WO 96/01623 .

Description of the Invention

It has surprisingly been found that the magnesium salt of *S*-omeprazole occurs in a number of structurally different forms. It is an object of the present invention to provide a substantially pure magnesium salt of *S*-omeprazole trihydrate, hereinafter referred to as the compound of the invention. This trihydrate can be obtained as a well defined compound. The present invention also provides a process to obtain and a method of differentiating the magnesium salt of *S*-omeprazole trihydrate from other forms of magnesium salts of *S*-omeprazole.

The compound of the invention is advantageous because it is more stable than the corresponding magnesium salt compounds in prior art and is therefore easier to handle and store. The compound of the invention is also easier to characterize because it exists in a well defined state. Additionally, the compound of the invention is easier to synthesize in a reproducible manner and thereby easier to handle in a full scale production.

The magnesium salt of *S*-omeprazole trihydrate obtained according to the present invention is substantially free from magnesium salts of *R*-omeprazole. The magnesium salt of *S*-omeprazole trihydrate obtained according to the present invention is also substantially free from other forms of magnesium salts of *S*-omeprazole, such as the corresponding magnesium salt compounds described in prior art, and dihydrates used in the preparation of the trihydrate compound according to the present invention.

The compound of the invention is characterized by the positions and intensities of the major peaks in the X-ray powder diffractogram , but may also be characterized by conventional FT-IR spectroscopy. These characteristics are not exhibited by any other form of magnesium salt of *S*-omeprazole and accordingly, the magnesium salt of *S*-omeprazole trihydrate is easily distinguishable from any other crystal form of the magnesium salt of *S*-omeprazole disclosed in prior art. The compound of the invention is characterized by being

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