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(54) Title: S-OMEPRAZOLE (ESOMEPRAZOLE INCLUSION COMPLEX WITH CYCLODEXTRINS

(57) Abstract: An inclusion complex comprises a substantially pure optical isomer of a benzimidazole compound and cyclodextrin. The complex preferably comprises S-omeprazole and β-cyclodextrin and is made by adding the cyclodextrin to an aqueous solution of the active material, and then isolating the complex from the solution.

S-OMEPRAZOLE (ESOMEPRAZOLE) INCLUSION COMPLEX WITH CYCLODEXTRINS

The present invention relates to an inclusion complex, particularly, but not exclusively to an inclusion complex of S-omeprazole, and to a method of making it.

The compound omeprazole (5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole) and therapeutically acceptable salts thereof are well known as effective gastric acid secretion inhibitors, and are useful as anti-ulcer agents. Omeprazole has two enantiomeric forms, the R and S- enantiomers, otherwise known as R-omeprazole and S-omeprazole, and normally exists as a racemic mixture. Certain optically pure salts of R and S omeprazole are described for example in US 5714504. The magnesium salt of S-omeprazole trihydrate is described in WO 98/54171, and S-omeprazole in a neutral, solid form (which can be in a partly or substantially crystalline state) is described in WO 98/28294. The optical isomers of omeprazole (in particular the S-enantiomer) are believed to possess certain advantages over the racemic form - for example, the optically pure salts of omeprazole disclosed in WO 94/27988 are said to have improved pharmacokinetic properties which give an improved therapeutic profile such as a lower degree of inter-individual variation. However, one particular problem with S-omeprazole, as with other similar benzimidazole compounds, is that it is not stable in its free form. Thus, for example, the compound is readily degraded by moisture and under neutral and acidic conditions. Previous approaches to providing a stable form of S-omeprazole have concentrated on the provision of alkali metal or alkaline earth metal salts of S-omeprazole (see WO 94/27988 and WO 98/54171), but these approaches are not entirely satisfactory since the salts *per se* are still liable to degradation. Another problem with S-omeprazole in its free form is that it is difficult to isolate. It can be

isolated as a trihydrate having about 13 to 15% moisture content, although this form has to be stored under refrigerated conditions to provide even limited stability.

We have now found that, surprisingly, S-omeprazole and related benzimidazoles can be provided in a form which is both stable and easily isolated and processed with minimal risk of degradation.

According to the present invention, there is provided an inclusion complex comprising a substantially pure optical isomer of a benzimidazole compound such as omeprazole, lansoprazole, pantoprazole or rabeprazole, and cyclodextrin. Preferably, the optically pure isomer is the S isomer and most preferably it is S-omeprazole. The cyclodextrin is preferably β-cyclodextrin.

The term "substantially pure optical isomer" in the context of the present invention means the S isomer when substantially free of the R isomer (or vice versa), preferably with an enantiomeric excess (e.e.) of 90% and more preferably 95% e.e.

In a further aspect, the invention provides a process for preparing an inclusion complex comprising a substantially pure optical isomer of a benzimidazole compound and cyclodextrin, which process comprises adding a cyclodextrin to an aqueous solution of a substantially pure optical isomer of a benzimidazole compound or a pharmaceutically acceptable salt thereof, and isolating the inclusion complex so formed from the solution. It is preferred to keep the solution at an alkaline pH throughout the process (i.e. a pH of above 7) so as to avoid any degradation of the active compound. The process is preferably used to prepare a β-cyclodextrin complex of S-omeprazole, but it can also be applied to other substituted benzimidazoles such as S-lansoprazole, S-pantoprazole and S-rabeprazole.

The present method enables S-omeprazole and the S isomers of other benzimidazole compounds to be prepared in a stable form, which form has much greater resistance to degradation than either the S isomers in their free form or as salts. The inclusion complex of the invention can be easily isolated in the form of a stable white powder by the present process, and this powder in turn has the advantage of excellent handleability. It can, for example, be processed easily and conveniently into

final dosage forms without the need to take special precautions to stabilise the active material during processing.

US 5399700 discloses a method for stabilising a racemic mixture of an acid-unstable compound such as omeprazole by forming an inclusion complex of racemic omeprazole with cyclodextrin. EP 1018340 A teaches a method of stabilising a racemic mixture of a benzimidazole compound by forming an inclusion compound comprising a racemic benzimidazole derivative with one or more amino acids and one or more cyclodextrins. However, it should be noted that both of these disclosures relate to racemic benzimidazoles and there is no teaching about either the S or R isomers. It is well known that the behaviour and properties of optically pure isomers (particularly in terms of stability) can vary markedly from that of the racemic compound. Thus, racemic omeprazole is a free powder having a high melting point, which can be purified by normal solvent crystallisation techniques, dried free of solvents and can be handled easily at room temperature and formulated into dosage forms. However, S-omeprazole is a low melting point solid which cannot be easily purified using solvent crystallisation methods since it has a tendency to hold the solvent molecule (as a solvate), thus drying the product becomes extremely difficult. S-omeprazole can be isolated from water only as a trihydrate (as noted above). Any attempt to further dry the product so that it is free of water results in decomposition of the product. The trihydrate form is stable only under refrigerated conditions, making it almost impossible for it to be formulated into dosage forms directly. There has been no previous disclosure of attempts to solve the stability problems associated with optical isomers (particularly the S-isomers) of the benzimidazoles in the manner disclosed by the present invention. Accordingly, an inclusion complex comprising the S isomer of a benzimidazole such as omeprazole and cyclodextrin is new. In particular, we have found that it is not necessary to use a benzimidazole amino acid derivative as described in EP 1018340 to obtain excellent stability of the S isomer.

In addition, whilst other known complexes of a pharmaceutically active material and cyclodextrin can be made even by physical mixing, slurrying, kneading together as a dough etc of the active substance and cyclodextrin in any proportion, these methods cannot be applied to a complex of S-omeprazole and cyclodextrin

owing to the stability problem. The present invention, however, provides a suitable process for preparing a complex of cyclodextrin with an unstable optical isomer of a benzimidazole compound, such as S-omeprazole.

The invention is described hereinafter with reference to S-omeprazole, it being understood that the invention also applies to the optical isomers of other benzimidazole compounds such as S-lansoprazole, S-pantoprazole and S-rabeprazole, and also to the R isomers of all these compounds.

S-omeprazole can be prepared by procedures well known in the art, such as those described and referred to in WO 94/27988. In forming the inclusion complex, the S-omeprazole can be used either in its free form or in the form of a pharmaceutically acceptable salt, such as the potassium salt.

It is possible to use any one of the cyclodextrins to form the inclusion complex, but we prefer to use β-cyclodextrin.

The proportion of S-omeprazole and cyclodextrin used is important in order to form a stable complex. We prefer to use a molar ratio of S-omeprazole to β-cyclodextrin in the range 1:1.5 to 1:5, with a ratio of 1:2 being particularly preferred. Reducing the amount of cyclodextrin much below these levels causes unwanted discoloration of the product to arise.

The process is preferably carried out under alkaline conditions by using an aqueous alkaline solution containing, for example, sodium hydroxide, to which the S-omeprazole is added. In principle, any alkaline substance can be employed so long as it does not interfere with the formation of the inclusion complex. Alkali metal hydroxides such as sodium hydroxide are particularly suitable. The S-omeprazole can be added to the alkaline solution either in solid form (such as a powder) or in the form of an aqueous solution. Preferably, the temperature of the solution is above at least 30°C, more preferably above 40°C. A temperature of around 45°C is ideal.

In the next stage, cyclodextrin, preferably as β-cyclodextrin, is added to the alkaline solution of S-omeprazole. It is preferred to add the cyclodextrin in small quantities over a period of about one hour. The mixture is preferably stirred thoroughly throughout the addition. The mixture is then preferably further diluted by the addition of water in order to provide a clear solution. The dilution ensures that the

cyclodextrin is completely dissolved and is entirely available for complex formation. Preferably, the dilution is at least 1 in 4 by volume of the initial solution. After dilution, the pH of the mixture is then checked and preferably adjusted to between 8 to 9. For example, this can be carried out using a 5% aqueous solution of boric acid, although other equivalent means can be used.

Preferably the mixture is then cooled, most preferably to around 5°C. Cooling enables maximum recovery of the product. The inclusion complex is then isolated. This can be done, for example, by filtering the complex from the cooled solution. The inclusion complex is thus isolated in the form of a white powder. The inclusion complex can be formulated into final dosage forms such as tablets, capsules and the like using standard excipients. A particularly preferred dosage formulation is that described in our publication WO 98/52564.

The following examples illustrate the invention:

Example 1

To an aqueous solution of sodium hydroxide (5.5 g NaOH in 1 litre) maintained at about 45°C is added an aqueous solution of potassium S-omeprazole (54 g in 200 ml). To this solution is further added β-cyclodextrin (495 g) in small quantities over a period of about 1 hour. The mass is then further diluted with 3.5 litres of water to obtain an almost clear solution. The pH of the mass is then adjusted to between 8 to 9 using a 5% aqueous solution of boric acid. The contents are cooled to 5°C and filtered to obtain 420 g of an inclusion complex of S-omeprazole with β-cyclodextrin. The complex contains about 10 to 14% of the active ingredient and is in the form of a white powder.

Example 2

To an aqueous solution of sodium hydroxide (12.5 g in 1 litre), maintained at about 45°C is added 45 g of S-omeprazole. To this solution is further added β-cyclodextrin (495 g) in small quantities over a period of about 1 hour. The mass is then further diluted with 3.5 litres of water to obtain an almost clear solution. The pH of the mass is then adjusted to between 8 to 10 using a 5% aqueous solution of boric acid. The contents are then cooled to 5°C and filtered to obtain 400 g of an

inclusion complex of S-omeprazole with β-cyclodextrin. The complex contains about 8 to 11% of the active ingredient and is in the form of a white powder.

CLAIMS:

1. An inclusion complex comprising a substantially pure optical isomer of a benzimidazole compound and cyclodextrin.

2. A complex according to claim 1 wherein said isomer is S-omeprazole.

3. A complex according to claim 1 or 2 wherein the cyclodextrin is β-cyclodextrin.

4. A pharmaceutical composition comprising an inclusion complex according to any of claims 1 to 3, and a pharmaceutically acceptable carrier therefor.

5. A process for preparing an inclusion complex according to any of claims 1 to 3, which process comprises adding a cyclodextrin to an aqueous solution of a substantially pure optical isomer of a benzimidazole compound or a pharmaceutically acceptable salt thereof, and isolating the inclusion complex so formed from the solution.

6. A process according to claim 5, wherein the aqueous solution is an aqueous alkaline solution.

7. A process according to claim 5 or 6 wherein before isolation of the inclusion complex, the process further comprises the steps of diluting the mixture containing the said complex and adjusting the pH.

8. A process according to claim 7, wherein the pH is adjusted to between 8 and 10 using an aqueous solution of boric acid.

9. A process according to any of claims 5 to 8, wherein the temperature of the solution/mixture is maintained at 45°C or above.

10. A process according to any of claims 5 to 9, wherein before isolation of the inclusion complex the mixture is cooled to 5°C or below.

11. A process for preparing an inclusion complex according to any of claims 1 to 3 substantially as described in Example 1 or Example 2.

12. Use of an inclusion complex according to any of claims 1 to 3 for the manufacture of a medicament for treating gastric acid-related diseases and gastro intestinal inflammatory diseases in animals and man, such as gastric ulcer, duodenal ulcer, reflux oesophagitis and gastritis.

INTERNATIONAL SEARCH REPORT

ational Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/4439 A61K31/724 //(A61K31/4439,31:724)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
BIOSIS, EPO-Internal, MEDLINE, EMBASE, PHARMAPROJECTS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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