Title: AN IMPROVED PROCESS FOR THE PREPARATION OF ESOMEPRAZOLE MAGNESIUM DIHYDRATE

Abstract: The present invention provides an improved process for the preparation of Esomeprazole magnesium dihydrate of formula (I) and its intermediates particularly 5-methoxy-2-[[4-methoxy-3 15-dimethyl-2-pyridinyl]-methyl][thio]-1H-benzimidazole (pro-chiral) compound of formula (II).
Designations under Rule 4.17:

- National search reports (Art. 21(3))
- Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2Q(i)).
AN IMPROVED PROCESS FOR THE PREPARATION OF ESOMEPRAZOLE MAGNESIUM DIHYDRATE

Field of the Invention

The present invention provides an improved process for the preparation of Esomeprazole magnesium dihydrate of formula (I) and its intermediates particularly 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]thio]-lH-benzimidazole (pro-chiral) compound of formula (II).

Background of the Invention

Esomeprazole is chemically known as (S)-5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl][sulfinyl]-lH-benzimidazole (hereinafter referred as "Esomeprazole") is the S-enantiomer of omeprazole. The magnesium salt of Esomeprazole hydrate is represented by Formula (I) is a proton-pump inhibitor developed as an oral treatment for peptic ulcer, gastroesophageal reflux disease (GERD), duodenal ulcer and esophagitis.
Esomeprazole magnesium is available in the US market under the brand name NEXIUM® as delayed-release capsules for oral administration. Each delayed-release capsule contains 20 mg or 40 mg of Esomeprazole (present as 22.3 mg or 44.5 mg of Esomeprazole magnesium trihydrate) in the form of enteric-coated pellets.

US 5,948,789 (1255/DEL/1995) discloses a process for the enantioselective synthesis of Esomeprazole by asymmetric oxidation of pro-chiral sulphide. In this patent the oxidation is carried out in an organic solvent with an oxidizing agent in the presence of a chiral titanium complex, optionally in the presence of a base, wherein the titanium complex has been generated in situ and it afforded either as a single enantiomer or enantiomerically enriched with S-isomer of omeprazole.


WO 96/001623 discloses a process for the preparation of optically enhanced Esomeprazole magnesium dihydrate by crystallising the Esomeprazole magnesium from a mixture of acetone and methanol.

WO 94/027988 discloses a process for the preparation of Esomeprazole magnesium dihydrate by adding aqueous solution of magnesium chloride to a
solution of Esomeprazole sodium in water. The product obtained by this procedure is an amorphous powder.

WO 01/036409 A1 disclosed that, pure anhydrous magnesium omeprazole is hygroscopic and it will readily absorb water from air until it reaches an equilibrium water content of about 5% to 8%, depending on the relative humidity of the air.


WO 09/047775 A2 (5419/CHENP/2007 A) discloses a process for the preparation of Esomeprazole magnesium dihydrate substantially free of Esomeprazole magnesium trihydrate. Accordingly the process utilizes chlorinated solvent for the preparation of Esomeprazole magnesium and it requires distillation of chlorinated solvent which is harmful to the environment.

WO 08/102145 (348/MUM/2007) discloses a process (Example-4) for preparing novel polymorphic Form II of 5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl]-methyl]thio]-IH- benzimidazole (pro-chiral) compound of formula (II) by crystallizing or recrystallizing crude 5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl]-methyl]thio]-IH-benzimidazole from ethyl acetate, cooling and isolating compound of formula (II), the polymorphic form of the isolated product is designated as Form II. This application further discloses the extraction
of compound of formula (II) with methylene dichloride before recrystallization. This application has certain drawbacks as it involves the use of hazardous solvents such as chlorinated solvent for the reaction as well as for extraction and the number of operations are also high to get the pro-chiral compound, which is very difficult in large scale preparation.

WO 08/087081 A1 discloses a process for the removal of organic solvent present in omeprazole magnesium by spraying omeprazole magnesium with stream of water. This patent also discloses that, during the process of removing residual organic solvent, amorphous nature of the compound was converted into crystalline compound. Moreover the method of removing residual organic solvent using stream of water needs additional infrastructure and special type of equipments and hence this is not feasible in the large scale preparation.

The reported method for the isolation of Esomeprazole magnesium dihydrate from methanol acetone medium resulted Esomeprazole magnesium dihydrate with higher level of residual solvent which is not acceptable as a drug product. The conventional method for the removal of residual solvent resulted in polymorphic modifications, in other words the use of conventional drying method afforded Esomeprazole Magnesium dihydrate contaminated with trihydrate. Hence there is a need for simple and commercially viable process to remove the residual solvents without any polymorphic modification of the final product.

The present inventors identified an improved process for the preparation of Esomeprazole magnesium dihydrate having pharmaceutically acceptable level of residual solvent particularly acetone by slurring Esomeprazole magnesium dihydrate having higher residual solvent such as acetone in water at low
temperature. This process is very simple, convenient for large scale preparation and it yields Esomeprazole magnesium dihydrate having pharmaceutically acceptable level of residual organic solvents without contamination of any other polymorphic forms. The present inventors also found that the trace amount of Esomeprazole magnesium trihydrate present in Esomeprazole magnesium dihydrate which is prepared by methods disclosed in the prior art are also removed by the process of the present invention.

The present inventors also identified an improved process for the preparation of Esomeprazole magnesium dihydrate without isolating potassium salt of Esomeprazole which simplifies the process operations and it avoids contaminations of polymorphs of potassium salt in the final product thereby increasing the yield and quality of the final product.

**Objectives of the Invention**

The main objective of the present invention is to provide an improved process for the preparation of Esomeprazole magnesium dihydrate of formula (I).

Another objective of the present invention is to provide an improved process for the preparation and isolation of Esomeprazole magnesium dihydrate having pharmaceutically acceptable level of residual organic solvents which is free from Esomeprazole magnesium trihydrate.

Still another objective of the present invention is to provide an improved process for the preparation of Esomeprazole magnesium dihydrate without isolating the corresponding potassium salt.
Yet another objective of the present invention is to provide an improved process for the isolation of 5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]thio]-H-benzimidazole of formula (II) using non-hazardous solvents.

Summary of the Invention:

Accordingly, the present invention provides an improved process for the preparation of Esomeprazole magnesium dihydrate of formula (I) having pharmaceutically acceptable level of residual organic solvents which is free from Esomeprazole magnesium trihydrate,

![Formula I](image)

which comprises the steps of:

a) condensing 2-chloromethyl-3,5-dimethyl-4-methoxy pyridine of formula (III) or its acid addition salt thereof

![III](image)

with 2-mercapto-5-methoxy benzimidazole of formula (IV)
IV

in presence of base and a solvent;

b) isolating 5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-thio]-H-benzimidazole compound of formula (II) (herein after pro chiral compound of formula (II)) using non-polar hydrocarbon solvent

5

\[
\text{Formula II}
\]

c) converting pro-chiral compound of formula (II) into Esomeprazole;
d) converting Esomeprazole to Esomeprazole potassium salt;
e) treating Esomeprazole potassium salt with a source of magnesium to isolate Esomeprazole Magnesium;
f) obtaining a solution of Esomeprazole magnesium in a solvent;
g) cooling the reaction solution;
h) mixing the solution of step g) with anti-solvent to yield Esomeprazole magnesium dihydrate;
i) treating Esomeprazole magnesium dihydrate obtained in step h) with water at Oto 10 °C; and

j) isolating Esomeprazole magnesium dihydrate.

wherein the improvement consists of one or more of the following

i) isolation of 5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-thio]-H-benzimidazole compound of formula (II) using non-polar hydrocarbon solvent by filtration,
ii) \textit{In situ} conversion of Esomeprazole potassium into Esomeprazole magnesium

iii) mixing the solution of step h) with anti-solvent at a temperature of 0-10 °C preferably at 0-5 °C to yield Esomeprazole magnesium dihydrate; and

iv) treating Esomeprazole magnesium dihydrate in water at a low temperature.

\textbf{Description of Drawings}

- Fig-1: PXRD of Esomeprazole Magnesium dihydrate obtained by following the process disclosed in example 5.

\textbf{Detailed Description of the Invention}

In an embodiment of the present invention, the base used in step (a) is selected from the group consisting of sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate and calcium carbonate preferably sodium carbonate.

In another embodiment of the present invention, the solvent used in step (a) is selected from alcohol, chlorinated solvents, ether or ketone, which is selected from methanol, ethanol, isopropyl alcohol, methylene dichloride, ethylene dichloride, chloroform, diethyl ether, isopropyl ether, acetone, methyl isobutyl ketone, preferably methanol, ethanol, isopropyl alcohol or mixtures thereof most preferably methanol.

In still another embodiment of the present invention, the acid addition salt of 2-chloromethyl-3,5-dimethyl-4-methoxy pyridine of formula (III) is selected
from inorganic or organic acid addition salt preferably hydrochloric acid, hydrobromic acid, hydroiodic acid, oxalic acid, fumaric acid more preferably hydrochloric acid.

In yet another embodiment of the present invention, the non-polar hydrocarbon solvent used for isolation of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-thio-lH-benzimidazole of formula (II) is toluene. The prior art process uses conventional method of extracting the product from the reaction mass and subsequent reaction without isolation or it required more operation to isolate the product, which affects the yield and quality of the product. On contrary, isolation of compound of formula (II) by the process of the present invention is simple, cost effective and the product can be isolated by simple filtration which is better in terms of large scale preparation and subsequent reaction gave Esomeprazole magnesium with increased yield having higher purity.

In one more embodiment of the present invention the conversion of prochiral compound of formula (II) in to Esomeprazole in step c) is carried out by following the process disclosed in the prior art or by using chiral oxidizing agent, wherein the chiral oxidizing agent is cumene hydroperoxide in combination with catalyst such as titanium isopropoxide or Vanadium complexes and (-)-diethyl-D-tartrate or oxidation by using (S)-camphor sulfonyl chloride and oxidising agent such as nitric acid, hydrogen peroxide, peracids, peresters, ozone, dinitrogen tetraoxide, iodosobenzene, N-halosuccinimide, 1-chlorobenzotriazole, tert-butyl hypo chloride, sodium hypochlorite, diazobicyclo-[2,2,2]-octane bromine complex, sodium metaper iodate, selenium dioxide, manganese dioxide, chromic acid, cericammonium nitrate, bromine, chlorine, and sulfuryl chloride in the presence of base such as N,N-diisopropylethylamine.
In one more embodiment of the present invention, the Esomeprazole obtained in step c) is converted into its potassium salt. The prior art process involves isolation of Esomeprazole potassium. As potassium salt of Esomeprazole was found to be more hygroscopic in nature, the isolation found to be difficult and yielded impure product due to degradation and require additional purification and thus the yield is reduced thereby increases the cost of production. Further, handling and storage of such hygroscopic material in large scale production involves tedious operation and it requires special infrastructure which is very difficult. On contrary the process of the present invention involves the preparation of Esomeprazole magnesium without isolating hygroscopic Esomeprazole potassium which resulted in increased yield with high purity. This further avoids the contamination of polymorphic impurities related to Esomeprazole potassium in the final Esomeprazole magnesium.

<table>
<thead>
<tr>
<th>Preparation method</th>
<th>Input (Kg)</th>
<th>Output (Kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preparation of Esomeprazole Magnesium by Isolating Esomeprazole potassium (Refer example number 2 and 3)</td>
<td>2</td>
<td>1.06</td>
</tr>
<tr>
<td>Preparation of Esomeprazole Magnesium without isolation of Esomeprazole potassium (Refer example number-4)</td>
<td>2</td>
<td>1.55</td>
</tr>
</tbody>
</table>

The above table clearly indicates that the yields are high if Esomeprazole magnesium prepared without isolating Esomeprazole potassium. In other words, *in-situ* conversion of Esomeprazole potassium into Esomeprazole magnesium resulted in higher yield.
In still another embodiment of the present invention, the magnesium source used for the preparation of Esomeprazole magnesium in step e) is selected from magnesium chloride, magnesium sulphate, magnesium hydroxide, magnesium methoxide or its hydrates and magnesium metal, preferably magnesium chloride hexahydrate. The obtained Esomeprazole magnesium was isolated by filtration from the reaction medium.

In yet another embodiment of the present invention, the isolated Esomeprazole magnesium was dissolved in a suitable solvent selected from methanol, ethanol, isopropanol or mixtures thereof, preferably methanol.

In one more embodiment of the present invention, the solution obtained in step f) is filtered to remove any insoluble materials or foreign particles. During the course of filtration filter aid selected from the group consisting of cationic polyacrylamide which is a copolymer of acrylamide and acryloyloxyethyltrimethyl ammonium chloride are optionally added to the reaction mass.

In still another embodiment of the present invention, the reaction solution of step g) was cooled to a temperature in the range of -5 to 15 °C and preferably 0-10 °C. Applicant identified that, this temperature plays a critical role in the preparation of Esomeprazole magnesium dihydrate. Further, the applicant also identified that, cooling to a temperature of 8-12 °C gave better result in small scale preparation however, 0-5 °C gave better result in large scale preparation. None of the prior art suggests or even motivates this temperature range.

In another embodiment of the present invention, the anti-solvent used in step h) is selected from the group consisting of ketone such as acetone, methyl
ethyl ketone, isobutyl methyl ketone, water or mixtures thereof preferably acetone. Accordingly the temperature of anti-solvent is cooled to reaction mass temperature before adding into the solution of Esomeprazole Magnesium in a solvent or *vice versa*.

Applicant performed an experiment by the process as disclosed in WO 94/027988 at low temperature yields only amorphous product of Esomeprazole magnesium.

The obtained product from (h) contains higher level of residual solvent which is not pharmaceutically acceptable and not suitable for commercialization.

Drying is a simple and easiest process to remove residual solvents from the drug substance. But in this case, the inventors found that it is very complicate because during drying, polymorphic modification is resulted in the Esomeprazole magnesium preferably the dihydrate is converted into trihydrate form, as a result of this, the final compound obtained after drying is Esomeprazole magnesium dihydrate contaminated with its trihydrate. Hence the conventional drying alone is not sufficient for large scale preparation.

The acceptable amounts for residual solvents in pharmaceuticals are related to the safety of the patient. Residual solvents in pharmaceuticals are defined as organic volatile chemicals that are used or produced in the manufacture of drug substances or excipients, or in the preparation of drug products. The solvents are not completely removed by practical manufacturing techniques. Appropriate selection of the solvent for the synthesis of drug substance may enhance the yield, or determine characteristics such as crystal form, purity and solubility. Therefore,
the solvent may sometimes be a critical parameter in the synthetic process. Since there is no therapeutic benefit from residual solvents, all residual solvents should be removed to the extent possible to meet product specifications, good manufacturing practices or other quality-based requirements. Drug products should contain no higher levels of residual solvents than can be supported by safety data.

Some solvents that are known to cause unacceptable toxicities (Class 1) should be avoided in the production of drug substances, excipients, or drug products unless their use can be strongly justified in a risk benefit assessment. Some solvents associated with less severe toxicity (Class 2) should be limited in order to protect patients from potential adverse effects. Ideally, less toxic solvents (Class 3) should be used where practical.

Hence there is a need for a simple and commercially viable, cost effective process for the preparation and isolation of Esomeprazole magnesium dihydrate having pharmaceutically acceptable level of residual organic solvent which is also free from Esomeprazole magnesium trihydrate.

In another embodiment of the present invention, treating Esomeprazole magnesium dihydrate with water in step i) is performed by adding Esomeprazole magnesium dihydrate to water and subsequent cooling the reaction mixture to 0-10 °C or by adding Esomeprazole magnesium dihydrate to pre-chilled water at 0-10 °C and subsequent stirring for a period of 15 minutes to 3 hours.

In yet another embodiment of the present invention water was cooled to temperature in the range of 0-10 °C more preferably 2-6 °C before the addition of
wet Esomeprazole magnesium dihydrate. The present inventors identified this
temperature plays a critical role in the preparation of Esomeprazole magnesium
dihydrate to remove the residual organic solvent from the drug substance without
any polymorphic modification. None of the prior art suggests or even motivates
the process of the present invention.

In still another embodiment of the present invention, nitrogen was also
purged during the water treatment to get Esomeprazole magnesium dihydrate
having pharmaceutically acceptable amount residual solvent and without
contamination of other polymorphic forms. Surprisingly, the applicant found that,
purging of nitrogen gas during water slurry enhances the reduction of residual
organic solvent in the final product. A comparative result of the content of
residual organic solvent before and after water slurry was provided in the example
part.

In still another embodiment of the present invention, nitrogen was also
purged during the water treatment to get Esomeprazole magnesium dihydrate
having pharmaceutically acceptable amount related substance and without
contamination of other polymorphic forms. Surprisingly, the applicant found that,
purging of nitrogen gas in water before slurry avoids the formation of N—oxide
impurity in the final product.

The starting materials used for the process of the present invention are
prepared by process as disclosed in the prior art or by following reaction scheme
as given below.
Scheme-1:

Scheme-2:

The present invention is illustrated with the following example, which should not be construed to limit the scope of the invention.
The reaction mixture was quenched with a solution of potassium hydroxide. The layers were separated and the aqueous layer pH was adjusted to 7-9 with 25% acetic acid in toluene. The layers were separated and the aqueous layer was re-extracted with toluene. To the combined organic layers potassium hydroxide (1.2 mol) was added at 40-45 °C under nitrogen. The reaction mass was cooled and ethyl acetate was added. The obtained product was filtered, washed with ethyl acetate and dried under vacuum afforded title compound. Yield: 60-75%; Purity: 94%

Example (3): Process for the preparation of Esomeprazole Magnesium dihydrate:

Potassium salt of Esomeprazole (1 mol) was dissolved in water at 20-35 °C and treated with activated carbon. The carbon was removed by filtration and washed the bed with water. To the filtrate was added a solution of MgCl$_2$·6H$_2$O in water. The obtained product was filtered and slurry washed with water. The crude wet Esomeprazole magnesium was dissolved in methanol and filtered through hyflo to remove insoluble material and washed with methanol. The filtrate was evaporated under vacuum till the residual volume of 1-3. To the residue acetone was added and cooled to -5 to 5 °C. The obtained product was filtered, washed with acetone then slurry washed with mixture of acetone and methanol (25:1), and dried under vacuum at 50-55 °C afforded the title compound. Purity: 99.5%
Conclusion:

<table>
<thead>
<tr>
<th>S. No</th>
<th>Condition</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Acetone addition at 0-5 °C into methanolic solution of Esomeprazole magnesium</td>
<td>Esomeprazole magnesium dihydrate free from trihydrate</td>
</tr>
<tr>
<td>2</td>
<td>Methanolic solution of Esomeprazole magnesium addition to Acetone at 0-5 °C</td>
<td>Esomeprazole magnesium dihydrate free from trihydrate</td>
</tr>
<tr>
<td>3</td>
<td>Acetone addition at 25-35 °C into methanolic solution of Esomeprazole magnesium</td>
<td>Esomeprazole magnesium dihydrate contaminated with trihydrate</td>
</tr>
</tbody>
</table>

The above table clearly indicates that, the addition of acetone to methanolic solution of Esomeprazole magnesium and vice-versa at 0-5 °C resulted in pure Esomeprazole magnesium dihydrate free from trihydrate.

Example (4): Process for the preparation of Esomeprazole magnesium without isolation of Esomeprazole potassium:

To a solution of titanium isopropoxide (0.3 mol) and (-)diethyl-D-tartrate (0.6 mol) in toluene, N,N-diisopropylethylamine (0.6 mol) and 5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-thio]-IH-benzimidazole (1 mol) were added and heated to 50-60 °C. The reaction mass was cooled and cumene hydroperoxide (1.05 mol) was added to the reaction mass and stirred. After completion of the reaction, a solution of potassium hydroxide was added to the reaction mass at 0-10 °C and stirred. The layers were separated and the aqueous layer pH was adjusted to 8-8.5 with acetic acid and in presence toluene. The layers were separated. To the toluene layer water was added and extracted with potassium hydroxide solution and the aqueous layer was treated with carbon at 25-35 °C. The carbon was removed by filtration, washed with water and cooled 0-5 °C. To the filtrate, a solution of MgCl₂·6H₂O in water was added and stirred at 0-5
The obtained product was filtered, washed with water and sucked dried. The wet Esomeprazole magnesium was slurry washed with water at 0-5 °C, filtered, washed with water and dried to obtain Esomeprazole magnesium. Moisture content: 12-20%.

**Example (5): Process for the preparation of Esomeprazole Magnesium dihydrate:**

To a solution of crude Esomeprazole magnesium in methanol, a solution of filter aid in methanol was added and stirred for 20-30 minutes. The reaction mass was filtered through hyflo, washed with methanol and the filtrate was evaporated under vacuum until 2-3 volume of residual volume of methanol. The residue was cooled and added into chilled acetone at 0-5 °C and stirred for 45-60 minutes, the obtained solid was filtered washed with chilled acetone, sucked dried under nitrogen. (Optionally the wet solid was purified with 4V of methanol and acetone) and dried under nitrogen afforded Esomeprazole magnesium dihydrate. The obtained wet solid was added to water at 2-6 °C under nitrogen, stirred at the same temperature, filtered and washed with water at 2-6 °C. Drying under vacuum afforded Esomeprazole magnesium dihydrate with pharmaceutically acceptable level of residual organic solvents preferably acetone which is not contaminated with any other polymorphic forms.

The following table illustrates the content of residual organic solvent preferably acetone before and after water slurry.

<table>
<thead>
<tr>
<th>S. No</th>
<th>Condition</th>
<th>Residual Acetone Content (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>before water slurry</td>
<td>14350</td>
</tr>
<tr>
<td>2</td>
<td>after water slurry</td>
<td>941</td>
</tr>
</tbody>
</table>
We claim:

1. An improved process for the preparation of Esomeprazole magnesium dihydrate of formula (I) having pharmaceutically acceptable level of residual organic solvents which is free from Esomeprazole magnesium trihydrate,

\[
\text{Formula I}
\]

which comprises the steps of:

a) converting prochiral compound of formula (II) into Esomeprazole;

\[
\text{Formula II}
\]

b) converting Esomeprazole to Esomeprazole potassium salt;

c) treating Esomeprazole potassium salt with source of magnesium to isolate Esomeprazole Magnesium;

d) dissolving Esomeprazole magnesium in a solvent at a temperature in the range of 0-10° C;
e) mixing the solution of step d) with anti-solvent at a temperature in the range of 0-10° C to yield Esomeprazole magnesium dihydrate;
f) treating Esomeprazole magnesium dihydrate obtained in step e) with water at Oto 10° C; and
g) isolating Esomeprazole magnesium dihydrate.

wherein the improvement consists of one or more of the following
i) \textit{In situ} conversion Esomeprazole potassium into Esomeprazole magnesium
ii) mixing the solution of step e) with anti-solvent at a temperature of 0-10 °C preferably at 0-5 °C to yield Esomeprazole magnesium dihydrate; and
iii) treating Esomeprazole magnesium dihydrate in water at low temperature.

2. The process according to the claim 1, wherein the solvent used in step d) is selected from the group consisting of methanol, ethanol, propanol, isopropanol and mixture thereof; preferably methanol

3. The process according to the claim 1, wherein the anti-solvent used in step e) is selected from the group consisting of acetone, methyl ethyl ketone, isobutyl methyl ketone; preferably acetone.

4. An improved process for the preparation of Esomeprazole magnesium, which comprises the steps of:

a) converting prochiral compound of formula (II) into Esomeprazole;
b) converting Esomeprazole to Esomeprazole potassium salt; and
c) treating Esomeprazole potassium salt with source of magnesium to form Esomeprazole Magnesium;

wherein the improvement consist of preparing Esomeprazole magnesium without isolation of Esomeprazole potassium salt obtained in step b).

5. An improved process for the preparation of Esomeprazole magnesium dihydrate free from acetone as residual organic solvent by treating Esomeprazole magnesium dihydrate in water at temperature in the range of 0-10 °C preferably 2-6 °C.

6. An improved process for the preparation prochiral compound of formula II,

which comprises the steps of:

a) condensing 2-chloromethyl-3,5-dimethyl-4-methoxy pyridine of formula (III) or its acid addition salt thereof
with 2-mercapto-5-methoxy benzimidazole of formula (IV)

b) isolating prochiral compound of formula (II) using toluene;

7. Use of prochiral compound of formula (II) prepared according to the claim 6 for the preparation of Esomeprazole magnesium and its hydrates.

8. An Esomeprazole magnesium dihydrate having less than 1500 ppm of residual acetone which is characterised by the PXRD as shown in Fig-1.
A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl.
C07D 401/12 (2006.01)

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)

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 practicable, search terms used)
CAPPLUS: Search on Esomeprazole magnesium dihydrate and Registry no. 217087-10-0

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
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<tr>
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<td>WO 2009/074997 A2 (LEE PHARMA LTD) 18&lt;sup&gt;th&lt;/sup&gt; June 2009 See (Description on pages 4-7, Examples 1-5, pages 7-12)</td>
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<td>x</td>
<td>US 2003/0004190 A1 (KRONSTROM A et al) 2&lt;sup&gt;nd&lt;/sup&gt; January 2003 See (Examples 1-8, pages 3-5 and claim 1)</td>
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<td>WO 2009/047775 A2 (HETERO DRUGS LIMITED) 16&lt;sup&gt;th&lt;/sup&gt; April 2009 See (Description pages 3-12 and example 4, page 15)</td>
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<td>WO 1998/054171 A1 (ASTRA AKTIEBOLAG) 3&lt;sup&gt;rd&lt;/sup&gt; December 1998 See (Examples 4-6, pages 13-16 and claim 5)</td>
<td>1, 2, 3, 5 and 8</td>
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<sup>*</sup> Further documents are listed in the continuation of Box C  <sup>X</sup> See patent family annex

* Special categories of cited documents:
  "A" document defining the general state of the art which is not considered to be of particular relevance
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"&" document member of the same patent family

Date of the actual completion of the international search  
29 November 2010

Date of mailing of the international search report  
06 DEC 2010

Name and mailing address of the ISA/AU

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Facsimile No. +61 2 6283 7999

Authorized officer
Will Findlay
AUSTRALIAN PATENT OFFICE
(ISO 9001 Quality Certified Service)
Telephone No: +61 2 6283 2018

Form PCT/ISA/2 10 (second sheet) (July 2009)
<table>
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<th>Relevant to claim No.</th>
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<tbody>
<tr>
<td>X</td>
<td>WO 2008/102145 A2 (CIPLA LIMITED) 28th August 2008 See (Examples 7-9)</td>
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<td>P, X</td>
<td>US 2010/0016370 A1 (TOPLAK CASAR R) 21st January 2010 See (Examples 1-4, pages 6 and 7)</td>
<td>1, 2, 3, 5 and 8</td>
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</table>
**INTERNATIONAL SEARCH REPORT**

**Box No. II** Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.,
   because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.
   because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.;
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

**Box No. II** Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

This International Application does not comply with the requirements of unity of invention because it does not relate to one invention or to a group of inventions so linked as to form a single general inventive concept.

   [Continued in Supplemental Box 1]

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☑ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1, 2, 3, 5 and 8

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.
Supplemental Box I
(To be used when the space in any of Boxes I to IV is not sufficient)

Continuation of Box No III:

In assessing whether there is more than one invention claimed, I have given consideration to those features which can be considered to potentially distinguish the claimed combination of features from the prior art. Where different claims have different distinguishing features they define different inventions.

This International Searching Authority has found that there are different inventions as follows:

Claims 1-3, 5 and 8 are directed to an improved process for the preparation of Esomeprazole magnesium dihydrate of formula I [see below] having pharmaceutically acceptable level of residual organic solvents and its crystal structure that is characterised by XRPD.

\[
\begin{align*}
\text{CH}_3 & \\
\text{O} & \\
\text{H}_3\text{C-} & \\
\text{N} & \\
\text{S-} & \\
\text{H}_2\text{C-} & \\
\text{O} & \\
\text{CH}_3 & \\
\text{Mg}^{2+}\text{H}_2\text{O} & \\
\end{align*}
\]

Formula I

It is considered that the process for the preparation of Esomeprazole magnesium dihydrate of formula I having pharmaceutically acceptable level of residual organic solvents comprises a first distinguishing feature.

Claim 4 is directed to an improved process for the preparation of Esomeprazole magnesium salt.

It is considered that the Esomeprazole and the defined improvements in preparation comprise a second distinguishing feature.

Claims 6 and 7 are directed to an improved process for the preparation of prochiral compound of formula II [see below].

\[
\begin{align*}
\text{CH}_3 & \\
\text{O} & \\
\text{H}_2\text{C-} & \\
\text{N} & \\
\text{S-} & \\
\text{H}_2\text{C-} & \\
\text{O} & \\
\text{CH}_3 & \\
\end{align*}
\]

Formula II

It is considered that the improved process for the preparation of formula II comprises a third distinguishing feature.

PCT Rule 13.2, first sentence, states that unity of invention is only fulfilled when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding special technical features. PCT Rule 13.2, second sentence, defines a special technical feature as a feature which makes a contribution over the prior art.

Each of the abovementioned groups of claims has a different distinguishing feature and they do not share any feature which could satisfy the requirement for being a special technical feature. Because there is no common special technical feature it follows that there is no technical relationship between the identified inventions. Therefore the claims do not satisfy the requirement of unity of invention a priori.
This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

<table>
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Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

END OF ANNEX